IPIC2023

INTERNATIONAL PRIMARY IMMUNODEFICIENCIES CONGRESS

DIAGNOSIS
AND CLINICAL CARE

NOVEMBER 8-10

ROTTERDAM,
THE NETHERLANDS

CONGRESS **REPORT**

ABOUT IPOPI

IPOPI is a non-profit international organisation and the leading advocate for primary inmmunodeficiency (PID) patients worldwide working in collaboration with patients, doctors, politicians, regulators, pharmaceutical industry and other relevant stakeholders.

IPOPI is the association of national PID patient organisations dedicated to improving awareness access to early diagnosis and optimal treatments for primery inmunodeficiency patients worldwide through global collaboration.

IPOPI has an increasing membership and currently represents 74 National Member Organisations spread all over the globe.

STRATEGIC PLAN 2021-2025

Our activities are carried out with a strategy-driven approach and geared towards the 4 following strategic objectives:

1 - **Improve access to early diagnosis and patient-centred care** through advocacy and awareness.

2 - **Build capacity and support IPOPI´s national member organisation** to improve living conditions for people living with PID.

3 - **Educate, promote knowledge and data sharing to increse understanding of PID,** improve clinical care and advance research.

4 - **Strenghten multi-stakeholder cooperation** to optimise all programmes and activities.

FIND US ONLINE

IPOPI is active on Facebook, Twitter, Linkedin and Instagram and we look forward to meeting you there as well!

@ IPOPI_INFO	@ IPOPI_PID	@ IPOPI_PID	ipopi.org
@ International Patient Organisation for Primary Immunodeficiencies			



الرابطة العربية لضعف المناعة الأولي
Arab Society for Primary Immunodeficiencies
ضعف المناعة
ARApid.org

ascia
australasian society of clinical immunology and allergy
www.allergy.org.au

ASID


BPIDG
Belgian Primary Immune Deficiency Group


Brazilian Group for Immunodeficiency
BRAGID

Care-for-Rare
Foundation

CEREDIH

British Society for Immunology
CIPN
Clinical Immunology Professional Network

CIS
Clinical Immunology Society


EUROPEAN SOCIETY OF
GENE & CELL THE A Y

EFCNI
european foundation for
the care of newborn infants

EFIS
European Federation of
Immunological Societies

ESID


FAIS
Federation of African Immunological Societies

FOCIS
Federation of Clinical
Immunology Societies
www.bcsnet.org

ICHS
INTERNATIONAL SOCIETY FOR COMPROMISED HOST

Immunodeficiency
Canada
Immunodéficience
Canada

INGID
for Immunodeficiencies


IPFA
international plasma
fractionation association

International Society for
Neonatal Screening

IUIS
Immunology
without
Borders
International Union of Immunological Societies

LASID
Latin American Society for Immunodeficiencies
Sociedad Latinoamericana de Inmunodeficiencias

LSAI
Lebanese Society of Allergy and Immunology


PERSATUAN ALERGI & IMUNOLOGI MALAYSIA
MSAI

Maroc
PID

nvvi
DUTCH SOCIETY FOR IMMUNOLOGY

nvii

PLASMA PROTEIN
THERAPEUTICS
ASSOCIATION



rita

SAAIS
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الجمعية السعودية للحساسية والربو والمناعة

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SPAIC
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ALERGOLOGIA E IMUNOLOGIA CLÍNICA

IPIC2023 ORGANISING COMMITTEE

• **Ms Martine Pergent,** Organising Committee President, IPOPI President.

• **Prof Tadej Avcin,** Head of Department of Allergology, Rheumatology and Clinical Immunology at the Children's Hospital, University Medical Centre Ljubljana, and Professor of Paediatrics at the University of Ljubljana, Faculty of Medicine, Slovenia.

• **Prof Fabio Candotti,** Professor of Medicine at the University of Lausanne and Head Physician in the Division of Immunology and Allergy of the Lausanne University Hospital, in Lausanne, Switzerland.

• **Prof Charlotte Cunningham-Rundles,** Professor of Immunology at the Mount Sinai School of Medicine in New York, US.

• **Dr Nahla Erwa,** Assistant Professor and Consultant Clinical Immunologist at Faculty of Medicine and Soba University Hospital, University of Khartoum, Sudan.

• **Prof Elie Haddad,** Clinical Scientist in Paediatric Immunology, Professor of Paediatrics at the University of Montreal, Canada.

• **Dr Pamela Lee,** Clinical Associate Professor Department of Paediatrics and Adolescent Medicine, LKS Faculty of Medicine, The University of Hong Kong.

• **Mr Bruce Lim,** IPOPI Vice-chair, Malaysia.

• **Dr Nizar Mahlaoui,** Scientific Committee President, Manager of the French National Reference Centre for Primary Immune Deficiencies (CEREDIH), France.

• **Mr Johan Prévot,** IPOPI Executive Director.

• **Prof Silvia Sánchez-Ramón,** Head of Immunology Dept., Consultant Clinical Immunologist and Associate Professor at the Hospital Clínico San Carlos, School of Medicine, Complutense University of Madrid.

• **Prof Gesmar Segundo,** Associate Professor at the Department of Pediatrics, Hospital de Clinicas, Federal University of Uberlandia, Brazil.

• **Prof Surjit Singh,** Head of the Paediatrics Department and Paediatric Allergy/Immunology Unit at PGIMER, Chandigarh, India.

• **Prof Martin van Hagen,** Internist-immunologist at the Department of Internal Medicine, head of section Clinical Immunology at the Erasmus MC in Rotterdam, Netherlands.

• **Dr Joris van Montfrans,** Paediatrician-immunologist at UMC Utrecht, Netherlands.

• **Ms Sarita Workman,** Specialist Sister in Immunology Research at the Royal Free London NHS Foundation Trust, United Kingdom.

IPIC2023 SCIENTIFIC COMMITTEE

• **Dr Nizar Mahlaoui,** Scientific Committee President, Manager of the French National Reference Center for Primary Immune Deficiencies (CEREDIH), France.

• **Prof Siobhan Burns,** Professor of Translational Immunology and Clinical Director for Immunity at the UCL Institute for Immunity and Transplantation, Royal Free London NHS Foundation Trust, United Kingdom.

• **Dr Virgil Dalm,** Internist-clinical immunologist in the Primary Immunodeficiency center at Erasmus MC University Medical Center, Netherlands.

• **Prof Alain Fischer,** Necker Enfants Malades Hospital. Inserm. Paris-Descartes University. Imagine Institute. Collège de France. Paris, France.

• **Prof Steven Holland,** Director of the Division of Intramural Research, National Institute of Allergy and Infectious Diseases, National Institutes of Health, USA.

• **Dr Narissara Suratannon,** Assistant Professor of the Division of Allergy and Immunology in the Department of Pediatrics, Faculty of Medicine, Chulalongkorn University, Thailand.

• **Prof Stuart Tangye,** Professor (Conjoint), School of Clinical Medicine, Faculty of Medicine and Health, UNSW Sydney, Australia.

• **Prof Klaus Warnatz,** Senior Physician, Head of Division of Immunodeficiency, Department of Rheumatology and Clinical Immunology and Center for Chronic Immunodeficiency (CCI), University Medical Centre Freiburg, Germany.

IPOPI EXECUTIVE COMMITTEE

• **Ms Martine Pergent** - President, France – IRIS

• **Mr Bruce Lim** - Vice-President, Malaysia – MyPOPI

• **Ms Otilia Stanga** - Treasurer, Romania – ARPID

• **Ms Roberta Anido Pena** - Argentina – AAPIDP

• **Ms Whitney Ayoub Goulstone** - Canada - ImmUnity Canada

• **Ms Jose Drabwell** - UK

• **Dr John Seymour** - USA – IDF

• **Dr Nizar Mahlaoui** (Ex Officio), - France - Chair of Medical Advisory Panel

• **Prof Martin Van Hagen** (Ex Officio), - Netherlands - Vice-Chair of Medical Advisory Panel

• **Mr Johan Prevot** (Ex Officio), - Belgium/Portugal - Executive Director

IPIC2023 | IPOPI CONGRESS REPORT

In the lively city of Rotterdam, IPIC2023, the International Primary Immunodeficiency Congress, unfolded as a convergence of expertise and experience dedicated to depicting the landscape of primary immunodeficiency (PID) care. The CME event, attended by nearly 900 professionals coming from more than 70 countries, pulsated with shared insights, innovative clinical research, and a profound commitment to improving patient outcomes.

Here, a summary is presented of the conference's main sessions, which served as fertile ground for experts and clinicians to delve deep into the intricacies of PID diagnosis, treatment modalities, and the holistic management of patients.

KEY MESSAGES

- **Shared Commitment to Patient Care Worldwide:** The overwhelming presence at the conference underscores a shared commitment to improving patient care on a global scale. Through collaborative efforts and shared knowledge, attendees demonstrated a dedication to advancing the field of PIDs for the betterment of patients worldwide.

- **Empowering Patient-Centred Approaches:** Throughout the conference, the emphasis on patient involvement and patient-centredness was evident. Recognizing the pivotal role of patients in shaping healthcare decisions and experiences, the conference emphasized the importance of access, advocacy, and inclusivity in providing ethical and effective care.

- **Advancements through Collaborative Efforts:** The conference highlighted the transformative power of successful collaborative efforts in propelling the field of PID forward. From newborn screening advancements to transplantation challenges and beyond, the collective expertise and cooperation of researchers, healthcare professionals, patients, and stakeholders are driving impactful advancements and improving outcomes for individuals affected by PIDs.

OPENING SESSION: INCLUDING KEYNOTE ADDRESS

Chaired by **Dr Nizar Mahlaoui** and **Ms Martine Pergent**

Opening remarks – **Ms Martine Pergent** and **Mr Johan Prévot**

KEYNOTE SPEECH

PIDs AS A MODEL OF SUCCESSFUL INTERNATIONAL SCIENTIFIC COLLABORATION - PROF MARTIN VAN HAGEN

- Overwhelming presence shows the shared commitment to improving patient care worldwide.
- Access remains a key word that resonates throughout the patient journey.
- Successful collaborative efforts propel the field of PID on a global scale.
- Tackling the rising Ig product shortages globally will require a large-scale collaborative effort.

Ms Martine Pergent, the president of IPOPI, opened the conference together with **Mr Johan Prévot,** IPOPI's executive director. They welcomed the audience to the vibrant and dynamic city of Rotterdam and highlighted that more participants had registered for IPIC 2023 than for any other past edition! The overwhelming presence of close to 900 attendees was considered a testimony of the shared commitment to improving patient care worldwide. A short introduction to IPOPI underscored its growing membership and shed light on the various regional initiatives that have recently been undertaken in Africa, Asia, Latin America, and Europe. Importantly, Ms Pergent stated that "access remains a key word that resonates throughout the patient journey". She concluded the welcoming address with words of gratitude, to everyone who helped made the conference possible, to all speakers and to all attendees from across the globe.

Prof Martin van Hagen provided the keynote speech in which successful international collaborations in the field of PIDs were showcased, based on concrete experiences from his position at the Erasmus Medical Center in Rotterdam, the Netherlands. He focused on the many successful initiatives between the hospital and various Asian collaborative universities in the form of clinical consulting, student exchange programs, joint PhD programmes and common research programmes. Importantly, the establishment of a regional network was shown to greatly promote and facilitate collaborations on a larger scale. Joint research programmes on primary immunodeficiencies, autoimmune retinal diseases and fibrosis, amongst others, have led to the publication of more than 50 scientific articles, underscoring the success of these collaborative efforts. A crucial need and opportunity for future collaboration lies in tackling the global shortage in immunoglobulin (Ig) products, the use and demand of which are rising worldwide.


MARTIN VAN HAGEN
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SESSION 2: MANAGEMENT OF NEUROLOGICAL MANIFESTATIONS IN PID

Chaired by **Dr Nizar Mahlaoui** and **Ms Martine Pergent**

Neurological manifestations: when to think about PID? – **Prof Mustafa Abdalla Mohamed Salih**

Mechanisms underlying neurodevelopmental deficits in PID – **Dr Aleksandra Badura**

Managing PID patients with neurological manifestations – **Prof Elie Haddad**

Patient testimony – **Mr Cédric Anchisi**

- Detection of an underlying PID implies combining careful physical examinations with functional or genetic testing to obtain a well-defined diagnosis.
- Animal models in which PIDs and their related phenotypes are mimicked are valuable tools to improve our mechanistic understanding of the disease.
- Timely diagnosis and establishment of optimal care are critical to ensure the best possible outcomes and prognoses.

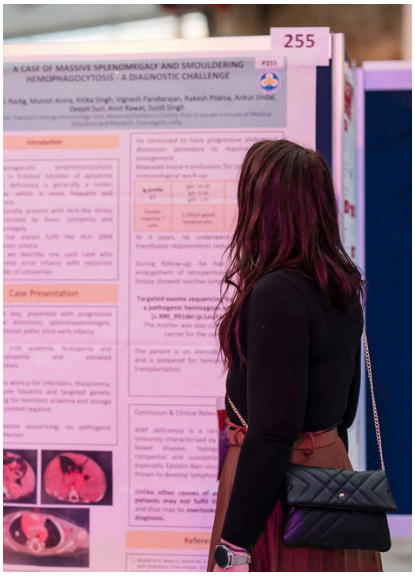
Prof Mustafa Abdalla Mohamed Salih opened the session with a broad introduction on neurological defects and symptoms related to PID. The majority of genetic disorders affecting the brain manifest in childhood as degenerative neurological disorders or neurobehavioral impairment. However, symptoms may also develop later in life and certain gene defects causing neurological abnormalities may only manifest as a PID in a secondary stage. While valuable clues can be obtained from careful physical examination to recognize the underlying PID, achieving a molecular diagnosis provides the most comprehensive understanding of a patient's disorder. Early recognition and treatment are critical to prevent or reduce future irreversible neurological sequelae. Using clinical case reports, an extensive overview of PIDs with associated or syndromic features and their clinical presentation was displayed: Ataxia-telangiectasia (AT), Nijmegen breakage syndrome, DiGeorge syndrome, CHARGE syndrome, Shwachman-Diamond syndrome, Chediac-Higashi syndrome, Hermansky-Pudlak syndrome type 2, Aicardi-Goutieres syndrome and Vici syndrome. A last case report highlighted the benefits of performing preimplantation genetic testing and subsequent in vitro fertilisation for affected families with a desire to have children.

Dr Aleksandra Badura provided insights on how neurodevelopmental deficits in PID are studied on a preclinical level, to better understand the mechanisms underlying such disorders. Her presentation focused on the overlap of autism spectrum disorder (ASD)-related risk genes and genes associated with PID. More specifically, the gene studied here was PIK3CD, for which certain mutations are causative of activated phosphoinositide 3 kinase delta syndrome (APDS). Visuomotor assessment tasks in humans, for which APDS patients typically underperform compared to neurotypical persons, were successfully translated to a mouse model based on eyeblink conditioning. Having developed this animal model, it is possible to study clinical observations in patients more in-depth. Ongoing work relating to differences in reaction to strong stimuli between neurotypical and non-neurotypical persons was shared, as were several hypotheses that are currently under investigation.

Prof Elie Haddad provided an immunologist's perspective on the management of PID patients with neurological manifestations, highlighting the difficulties experienced by both immunologists and neurologists in caring for patients with symptoms falling far out of their respective specialties. Concrete examples from clinical practice were discussed including, amongst others, (i) how to distinguish unrelated neurological events from PID-induced neurological events (e.g., stroke), (ii) how to approach a haemophagocytic lymphohistiocytosis (HLH) patient's requests for regular neurological check-ups, and (iii) ethical considerations of pursuing drastic treatment options (e.g.,haematopoietic stem cell transplantation (HSCT), gene therapy (GT)) when the patient has severe neurological impairments. In times, it may be challenging to agree on one clear management plan, which can cause the patient to experience feelings of uncertainty, confusion, and a general lack of

trust. Key to avoiding such situations are open communication and collaboration between the immunologist, the neurologist and the larger team. It is therefore important to acknowledge one's own limitations, both to medical colleagues and the patient, and keep collegiality and the patient's interests at the heart of all decisions.

The session was closed by **Mr Cédric Anchisi** who provided a testimony as father of a child affectedby AT and as president of ATEurope, a fund to finance research and provide families affected by AT with information and solutions. He stressed the need to shorten the time to diagnosis and referred to work from a team at the Imagine Institute in Paris, France, who developed two diagnostic assays to help detect AT promptly. To facilitate caregivers' search for appropriate and specialised help, the idea was raised to develop a PID-specific map-based overview of all known specialists in each country. Mr Anchisi reported on a registry of AT patients maintained by ATEurope providing useful insights regarding patient management, and underscored the need to develop uniform treatment guidelines. Lastly, the lack of time in a fast-progressing disease as AT was discussed, alongside suggestions on how to improve time efficiency in patient diagnosis, organisation of care, and the overall research processes. To end with a quote of Mr Anchisi: "From the perspective of families, time is above all hope. Let's work together to find ways to gain some."



SESSION 3: TRANSPLANTATION CHALLENGES IN PIDS

Chaired by **Prof Frank Staal** and **Ms Cynthia Olotch**

When to transplant adults or not: lessons from 20 years' experience – **Prof Emma Morris**

New transplantation techniques and technology – **Prof Andrew Gennery**

Management of psychological aspects before and after HSCT/GT – **Psychologist Mary Campbell**

Patient testimony – **Ms Elien Willems**

- HSCT is safe and effective in adulthood, with prognosis being impacted by the number of PID-related complications rather than age.
- Advancements in HSCT have significantly improved outcomes for patients transplanted with a mismatched donor, resulting in a negligible difference compared to matched donors.
- Psychological support is crucial throughout the transplantation journey and the bidirectional relationship between mental and physical health should be well-recognized.

Prof Emma Morris introduced the topic of transplantation in adult PID patients, stating that when there is the potential for curative therapy, it should be properly explored. Adult patients may not have undergone transplantation during childhood due to various reasons such as a late diagnosis, a previously unknown genetic cause, or a previous lack in donor. Timing plays a major role in a patient's HSCT-related prognosis. Accordingly, HSCT is best performed when patients have demonstrated a severe clinical phenotype, but before they have developed too many complications. Several studies convincingly showed that HSCT is safe and effective in adulthood, with prognosis being impacted by the number of PID-related complications and the level of organ damage rather than age. While CVID is the most common type of PID in adults, only a small number of HSCT studies have been performed, showing poor outcomes. Therefore, Prof Morris and her team are currently running a clinical trial investigating specific biomarkers to better understand which CVID patients are most likely to benefit from HSCT. Further improvements are expected with optimisation of patient selection, patient preparation, conditioning regimen and peri-HSCT management.

Taking a closer look at HSCT performed in SCID patients, **Prof Andrew Gennery** showcased that with the most recent advancements in HSCT no difference in outcome can be observed based on the patient's age at transplantation, the type of donor, the SCID genotype or the conditioning regimen. However, active infection at the time of transplantation was found to negatively impact overall survival, while early detection of SCID via NBS was shown to have a significantly positive effect on patient outcome. Two novel techniques were described that have drastically changed the transplantation landscape, for SCID and other PIDs as the achieved results for mismatched versus matched donors are now comparable. The first advancement is based on the administration of cyclophosphamide post transplantation which predominantly targets alloreactive T cells. The second approach to help reduce graft versus host disease (GVHD) is based on depletion of T-cell receptor (TCR)αβ/CD19 cells with retainment of TCRγδ cells.

Psychologist Mary Campbell provided insights into the effects of transplantation on patients' mental health, with a focus on the adult patient population. The bidirectional relationship between mental and physical health is well described, thus necessitating the need to thoroughly consider both. However, very little data is available on mental health and quality of life (QoL) in PID patients in general, let alone for patients undergoing transplantation. The limited number of studies performed do indicate reduced psychological wellness in patients both shortly after transplantation and in long-term follow-up. The latter is characterised by higher rates of anxiety and depression compared to the general population. Psychological support should be provided throughout the patient's journey; before, during and after transplantation. It must be recognized that this is no linear process but rather a winding pathway, meaning that patients may experience new or increased challenges related to the HSCT later in life. Helpful tools and guidelines for accessing psychological support were provided and the value of collaboration between the treating physician and psychology services was underscored.

The session was closed by **Ms Elien Willems** who provided a powerful testimony as a patient who has undergone HSCT and lived through severe complications and psychological struggles. Her story shed light on the extreme hardships that can sometimes be associated with such an invasive procedure, and the long journey to recovery. Fortunately, she has now made a full recovery and is enjoying life to the fullest, celebrating two birthdays every year.

SESSION 4: ANALYSE "THIS" COMPLEX CASE STUDIES

Chaired by **Prof Stephen Jolles** and **Dr Nizar Mahlaoui**

The use of JAK/STAT in PIDs – **Dr Carsten Speckmann**

Actinopathies management "when actin is not acting" – **Prof Fabio Candotti**

It's all in the genes: Monogenic vs polygenic manifestations – **Prof Alain Fischer**

- JAK inhibitors used in the management of patients with activated JAK/STAT signalling seem to be effective and should be considered for peri-transplant use.
- Data is largely lacking on advanced therapies for immuno-actinopathies, yet promising results have been obtained for WAS patients undergoing HSCT or gene therapy.
- Genetic intricacies and external factors influencing the genotype-phenotype relationship underlie the clinical presentation of PID patients.

In this session, complex patient cases encountered in clinical practice were presented. **Dr Carsten Speckmann** introduced the JAK/STAT pathway and gave an overview of the different types of PID-associated gene variants in this signalling pathway. A patient case of a girl with a gain-of-function (GOF) mutation in STAT1 causing severe disease and death at the age of 14 years exemplified the significant burden of this type of PID. The broader issue of poor outcomes for HSCT in these patients was emphasized, and the potential benefits of using JAK inhibitors prior to HSCT was discussed. While no JAK inhibitors are currently licensed for use in PIDs, off-label usage is increasingly common. Based on the results of a multi-centre retrospective study in patients with activated JAK/STAT signalling, JAK inhibitors seem to be effective and are considered promising for peri-transplant management. Further evaluation of JAK inhibitors in randomised clinical trials is paramount, as well as the formulation of treatment consensus guidelines.

Prof Fabio Candotti explained the crucial role of the protein actin for the cytoskeletal structure of a cell, and showcased how a variety of gene variants can impact its proper assembly, disassembly, production and functioning. From the presented list of immuno-actinopathies and their related clinical features it is clear that these disorders can present very differently. Nonetheless, typical commonalities include (i) recurrent infections, (ii) atopy, autoimmune or autoinflammatory symptoms, (iii) presence of lymphopenia and/or hypogammaglobulinemia, (iv) cell migration and/or chemotaxis defects and (v) neutropenia and/or thrombocytopenia. While overall clinical management for these disorders is similar to that of other PIDs, there is little data on the effectiveness of immunosuppression therapy or HSCT. For Wiskott-Aldrich Syndrome (WAS) however, recent studies show good survival rates for patients treated by HSCT as well as by gene therapy.

A range of case studies were presented by **Prof Alain Fischer** to guide the audience through the genetic peculiarities of certain PIDs. Firstly, defects in one single gene can cause multiple different phenotypes. This may be due to (i) certain genetic variants causing a loss in function as opposed to a gain in function, (ii) biallelic versus monoallelic mutations, (iii) different mutations causing varying degrees of disease severity, or (iv) incomplete penetrance. Secondly, 20% of PID-causative defects affect various organs apart from the immune system, resulting in a syndromic phenotype. Thirdly, the same phenotype can be caused by mutations in different genes, as is the case for several variants in key molecules involved in Ebstein Barr virus (EBV) infection control. Lastly, PIDs without germline mutations but rather somatic mutations or caused by anti-cytokine neutralising antibodies have been described. While genetic analysis is key in PID patient management, it becomes clear that interpretation of the results can be complex and external factors such as epigenetics or environmental influences may heavily impact the observed clinical phenotype.

SESSION 5: REGIONAL DIAGNOSIS AND CLINICAL CHALLENGES SESSION

Chaired by **Dr Pamela Lee** and **Ms Otilia Stanga**

APSID lecture – **Prof Surjit Singh**

ASID lecture – **Dr Leila Jeddane**

CIS lecture – **Prof Elie Haddad**

ESID lecture – **Prof Fabio Candotti**

LASID lecture – **Prof Gesmar Segundo**

SEAPID lecture – **Dr Narissara Suratannon**

- Access to universal and affordable plasma-derived immunoglobulin products remains a major hurdle in Latin America, Africa and Asia.
- Global challenges include limited access to gene therapy for PID treatment and the need for tailored clinical services catering to adult patients, including smooth transitions from paediatric to adult care.
- Significant progress has been made worldwide in terms of disease awareness, advancements in diagnostic technologies, collaborative networking and improved training facilities and opportunities.
- Exciting progress in NBS programmes signifies a brighter future with improved early detection and enhanced survival rates for PIDs.

In Session 5 we heard from representatives of the medical societies for PIDs worldwide who shared the region-specific challenges and progresses in PID diagnosis and management. One significant challenge, underscored by several representatives, was the heterogeneity of healthcare access, diagnostic capabilities, and treatment options for the different countries of the region. In the Asia Pacific region this was exemplified by the disparity of available advanced treatment options such as HSCT and gene therapy, as illustrated by **Prof Surjit Singh** from the Asia Pacific Society of Immunodeficiencies (APSID). Importantly, access to universal and affordable plasma-derived immunoglobulin products was identified as a major hurdle in Latin America, Africa and Asia.

A common challenge in regions with many low- and middle-income countries (LMIC) was the need for improved large-scale patient registries. This was evident in the African region, where despite long term efforts limitations in funding have prevented the establishment of a regional registry. Interestingly, **Prof Fabio Candotti** from the European Society for Immunodeficiency (ESID) highlighted its patient registry as regional success, aiding in estimating disease burden and identifying novel disease-associated genes.

A global challenge which was highlighted by the European region is the limited access to gene therapy despite relevant scientific advancements, and the need for innovative approaches to overcome regulatory and reimbursement obstacles. Likewise, **Dr Narissara Suratannon** representing the South East Asia Primary Immunodeficiency Network (SEAPID) identified a need for increased availability of specific services for adult PID patients and effective practices for transitioning from paediatric to adult services, which are issues that extend beyond the region and are pertinent worldwide.

Successes in PID care were often linked to increased disease awareness, advancements in diagnostic technologies, collaborative networking and improved training facilities and opportunities. As such, the Asian region has witnessed an increase in diagnostic expertise and genetic diagnostic facilities, resulting in access to next-generation sequencing technology and consequent successful identification of novel rare disorders.

In Africa, the “A project” training initiative organised by the African Society of Immunodeficiencies (ASID), represented by **Dr Leila Jeddane,** has demonstrated positive outcomes. It resulted in improved diagnoses, the establishment of patient support associations, and increased availability of diagnostic tools. This one-day training program is organised in four to six African countries annually, encompassing clinical projects of various levels, nurse projects, and biological training projects. The countries where the A project has been implemented showcased tangible improvements, including a gradual increase

in diagnoses, the formation of patient support associations, and enhanced access to diagnostic tools and specialized consultations, as exemplified in Senegal.

Significant global progress is evident in the advancement of NBS programmes. In Asia, strides are being taken with several countries initiating pilot programs to enhance early detection. Meanwhile, **Prof Gesmar Segundo** from the Latin American Society for Immunodeficiencies (LASID) explained that in Brazil the initiation of NBS for SCID in 2010 has evolved into a nationwide program for screening 50 diseases under federal law, with full implementation effective from July 2023 in the federal district and planned expansion to other states by 2025. The impact of NBS extends to North America, where its pivotal success is underscored by the notable improvement in survival rates following HSCT for SCID cases diagnosed early through NBS as outlined by **Prof Elie Haddad** from the Clinical Immunology Society for North America (CIS).

Overall, despite the evident differences in regional circumstances and realities, many common concerns and priorities emerged. The session further underscored the importance of a collective global approach to address these challenges and build on shared successes for the benefit of patients with primary immunodeficiencies worldwide.

SESSION 6: MANAGING MALIGNANCIES IN PIDS

Chaired by **Prof Klaus Warnatz** and **Ms Jose Drabwell**

Diagnosing malignancies in PID: Getting it right and learning from what went wrong

– **Prof Charlotte Cunningham-Rundles**

Common features of primary and secondary immunodeficiency – **Prof Markus Seidel**

Check point blockers and repurposing cancer drugs: what can we learn from the oncology field?

– **Prof Aurélien Marabelle**

A nurse's perspective – **Ms Emily Carne**

- Cautious interpreting of histological findings and PET scans for lymphoma diagnosis is needed in PID patients to avoid potential misdiagnosis.
- Malignancy and autoimmune diseases in "secondary" immunodeficiency patients may in fact be manifestations of an underlying PID.
- Immune checkpoint inhibitors are successful anti-cancer therapies because of their polyclonal nature, and ability to induce anti-tumour immune memory and cross the blood-brain barrier.
- With a rapid increase in SID patient referrals, timely recognition of malignancy risks and warning signs by nurses is crucial, along proper multidisciplinary collaboration.

Prof Charlotte Cunningham-Rundles addressed the association between PIDs and lymphomas, focusing on the challenges in diagnosis and treatment. She highlighted data from registries and studies indicating the elevated risk of lymphoma in immune-deficient patients, particularly those with common variable immune deficiency (CVID). It was emphasized that the type of immune deficiency can influence the type of cancer that develops. Prof Cunningham-Rundles discussed the difficulties in diagnosing immune deficiency-related lymphomas, including misleading histological appearances and PET scans due to abnormal B cell clonality and chronic lymphocyte activation. Genetic factors contributing to lymphoma development in PID patients were explored and the challenge of distinguishing PID-related lymphomas from secondary lymphomas arising post-chemotherapy was addressed. Despite the complexities, Prof Cunningham-Rundles highlighted that most patients with primary immune defects respond well to standard chemotherapy treatments.

Prof Markus Seidel delved into the complex landscape of secondary immune deficiency (SID) and immune dysregulation, with a focus on their implications in malignancies. Secondary immune dysregulation was hereby underscored to be an important extension to the usual SID paradigm. Prof Seidel discussed the diverse aetiology of secondary immune deficiency and immune dysregulation (SIRD), including drug-induced, functional, and exogenous causes. He highlighted the

significance of vigilance in diagnosis, as well as the need to consider both quantitative and functional aspects of immune deficiency. The commonalities and distinctions between secondary and primary immune deficiencies were outlined, taking note of SIDs' temporary nature and the potential for restoration upon eliminating the underlying cause. Finally, the difficulty of distinguishing primary from secondary immune deficiencies was stressed, particularly in the context of malignancies and autoimmune diseases. It is therefore important to consider the possibility of an underlying PID, of which the malignancy or autoimmune disease may be a first manifestation.

Prof Aurélien Marabelle discussed the revolution in the field of oncology due to the development of immunotherapies. He explained that the focus has shifted from targeting cancer cells to stimulating the immune system to fight cancer. He highlighted the success of immune checkpoint inhibitors, such as anti-PD1 and anti-CTLA4 antibodies, in generating durable responses and improving overall survival in various cancer types owing to their polyclonal nature, immune memory induction, and ability to cross the blood-brain barrier (BBB). He also discussed the importance of biomarkers, such as PD-L1 expression and tumour mutational burden, in predicting response to immunotherapy rather than histological characterisation of the tumour. Prof Marabelle also mentioned the emergence of chimeric antigen receptor (CAR) T cell therapy and bispecific T cell engagers as promising treatments for certain cancers. He discussed the challenges of managing immune-related adverse events and the phenomenon of hyperprogression, the counterintuitive acceleration of disease, in some patients. Finally, the diversity of immunotherapies currently being developed was highlighted, including mRNA-based vaccines, small molecules, oncolytic viruses, and antibody-drug conjugates.

Ms Emily Carne provided the nursing perspective on managing malignancy in patients with immune deficiencies. She emphasized the need for individualized care and close monitoring of patients, as well as the importance of recognizing potential risk factors for cancer. Ms Carne discussed the role of nurses in listening to patients' concerns and identifying early symptoms or clues that may require further investigation. She also highlighted the importance of collaboration with other healthcare professionals and ensuring that patients receive appropriate cancer screening based on their individual risk factors. The role of general care in the infusion clinic to better support and guide patients was outlined, with an emphasis on encouraging vigilance without inducing fear. Lastly, it was recommended to be mindful of the additional risks relating to the rapidly changing patient cohort, with an increasing number of SID patients warranting even better recognition of cancer risk and warning signs as well as enhanced collaboration between specialities.

SESSION 7: PID CARE – DO WE REALLY HAVE THE CHOICE?

Chaired by **Prof Elie Haddad** and **Ms Martine Pergent**

Invited panellists:
Prof James Taylor
Ms Mary Louise Daly
Prof Surjit Singh
Prof Alain Fischer
Prof Cornelis Boersma
Mr Matthew Harold
Prof Ana Hidalgo-Simon

- Striking a delicate balance between medical expertise and patient autonomy is essential in navigating complex clinical decisions.
- Recognizing and respecting cultural, socioeconomic, and logistical factors is crucial for providing ethical and effective patient care.
- By integrating diverse perspectives and fostering audience interaction, this ethics session serves as a dynamic forum for collective learning, enriching clinical practice with comprehensive insights and shared wisdom.

This session created the opportunity for physicians to share real-life challenges, dilemmas, and ethical considerations encountered in their practices. A diverse panel of healthcare professionals, an ethicist, a patient representative, a regulator, and an industry expert were presented with 3 clinical cases to consider, with this year's theme being HSCT. Together with the audience they navigated through complex decisions, emphasizing the nuanced balance between medical expertise, patient choice, economic constraints, and healthcare facility limitations.

[1] The first case, presented by **Prof Elie Haddad** involved a one-year-old boy with HLH and severe neurological and systemic manifestations. The neurologist indicated that the functional prognosis was catastrophic, with the patient potentially experiencing severe disabilities. The medical team and transplant team were not in favour of performing a transplantation, but the parents insisted on it as they believed it was the only chance for their child's survival.

The panellists engaged in a discussion about whether the transplantation could be refused, considering the parents' wishes, and whether it should be refused based on medical reasons and the potential strain on limited healthcare resources. They also acknowledged the parents' desire to do everything possible for their child and the importance of hope in such situations. The need for ongoing discussions and support for the parents was emphasized, as well as the potential long-term impact on the family and the child's quality of life. The importance of counselling and supporting the parents in understanding the best interests of their child was underscored. Measured through a polling system, the majority of participants in the audience and the panellists agreed that the transplantation should be refused due to medical reasons and the potential impact on other patients.

[2] The second case, provided by **Prof Surjit Singh,** involved a three-year-old boy diagnosed with X- linked agammaglobulinemia (XLA). The parents had been providing immunoglobulin replacement therapy, but due to financial constraints, they were unable to continue. They sought help from local health authorities and were given some support, but it was not enough. One immunologist suggested HSCT as a curative option but highlighted that it was still considered experimental and carried risks, including a small but definite risk of death. The ethical dilemma was whether to continue with suboptimal immunoglobulin therapy or pursue transplantation with its associated risks.

The panellists were divided in their opinions, with some advising against transplantation due to the inefficient benefits-risk profile, while others suggested initiating the transplantation process and exploring potential donors. Interestingly, when asked what the audience would advise in their role as clinician, and what they would do as parent of the child, the answers differed. While 47% of clinicians would consider initiating HSCT, as parent only 30% would opt for HSCT. The panel considered the one-time cost of the transplant, which was clarified to be similar to 5 years of immunoglobulin replacement therapy in India, and the possibility of crowdfunding and government support for the transplant was mentioned to raise funds. The ethical dilemma of balancing the cost and potential benefits of the transplant was discussed, as well as the

importance of considering the individual patient's circumstances and the potential impact on their quality of life. The need for further research and clinical studies to assess the efficacy of transplantation in resource-limited settings was also highlighted. The discussion emphasized the importance of open communication, informed consent, and involving the patient and their family in the decision-making process.

[3] A third complex case was introduced by **Prof Alain Fischer** which involved a seven-month-old patient diagnosed with perforin deficiency, necessitating urgent transplantation. The parents, migrants with low socioeconomic status and cultural barriers, initially refused therapy. After numerous consultations and transcultural mediations, the parents eventually accepted the diagnosis and treatment, with the father as the donor. However, multiple logistical delays ensued, leading to the tragic death of the patient.

The discussion highlighted the challenges of reconciling differences in decision-making timeframes between medical teams and families, particularly in emergency situations. Panellists emphasized the paramount importance of prioritizing the child's well-being while acknowledging the cultural, logistical, and legal complexities involved. Opinions varied regarding the extent to which medical professionals should intervene in cases where parents may not fully comprehend or accept the recommended treatment. Some suggested a more assertive approach, while others emphasized the need for building trust, engaging cultural and religious support, and respecting the parents' autonomy in decision-making. Examples from various cultural contexts highlighted the nuanced nature of medical decision-making and underscored the importance of cultural sensitivity and humility in providing patient-centred care.

Overall, the discussions highlighted the complex nature of medical ethics and the need to consider various factors, including medical indications, resource availability, patient preferences, and long-term outcomes. The participants emphasized the importance of counselling and support for the parents in making informed decisions and considering the quality of life for the child. The meeting also touched upon the need for accurate information and guidance for families facing difficult medical decisions.

YOUNG PID INVESTIGATORS: POSTER WINNER'S SESSION

Chaired by **Dr T Alba Cano** and **Ms Martine Pergent**

Poster 1: "Deep Reinforcement Learning for Adaptive Treatment Optimization in Severe Combined Immunodeficiency (SCID)" – **Mr Rifaldy Fajar**

Poster 2: "Impact of COVID-19 pandemic on clinical care of patients and Psychosocial health of affected families with Chronic Granulomatous Disease: An observational study from North India" – **Dr Prabal Barman**

Poster 3: "Malignities and lymphoproliferations in children with primary immune deficiency: a single center experience" – **Dr Kaplan Sarikavak Sibel**

With this session attention is given to upcoming PID investigators who submitted excellent research in a poster format. The authors of the three best posters were invited to share their work through a short lecture, next to their posters being featured in the winner section.

Mr Rifaldy Fajar was introduced as the first winner of this year's poster award. He presented his research on deep reinforcement learning for adaptive treatment optimisation in SCID. The study aimed to create an adaptive framework that learns from patient data and clinical outcomes to provide personalised treatment recommendations. The research utilised a comprehensive dataset and developed a custom deep neural network architecture for the deep reinforcement learning model. The results showed an impressive success rate of 93.5% in delivering effective treatment recommendations across various patient scenarios.

Dr Prabal Barman, the second winner, presented his study on the impact of the COVID-19 pandemic on the clinical care and psychological profile of families with chronic granulomatous disease (CGD) in India. The study highlighted the challenges faced by parents and caregivers of CGD patients during the pandemic, including the shift to teleconsultations, vulnerability to COVID-19, and limited access to healthcare. The results showed elevated levels of stress, anxiety, and distress among parents and caregivers. The study emphasized the importance of addressing the psychosocial concerns of these families and the need for further research on psychological interventions.

Dr Sibel Kaplan Sarikavak, the third winner, presented a study on malignancies and lymphoproliferation in children with PID. The study aimed to evaluate the frequency, types, and prognosis of malignancies and lymphoproliferation in PID patients. The results showed that immune dysregulation disease was the most common subtype of PID associated with malignancy, followed by ataxia-telangiectasia and predominantly antibody deficiency. The study highlighted the importance of timely recognition and management of these conditions to provide holistic treatment for PID patients.

SESSION 8: CLINICAL LIFE ODYSSEY OF PIDS

Chaired by **Prof Anna Sediva** and **Ms Roberta Anido de Pena**

Lost in transition: How to improve transition care from childhood/teenagehood to adulthood – **Prof Siobhan Burns**

Pregnancy and PID! – **Dr Elise Mallart**

Transition adulthood to elderly – **Dr Virgil Dalm**

Emergency wards, ICU and PIDs – **Dr Nahla Erwa**

- Disease-specific guidelines for transition care in PIDs are scarce, and existing protocols often neglect patient perspectives.
- Physiological changes to the immune system occur during pregnancy, which increase the risk of infections in PID patients. Appropriate prophylactic measures can help mitigate these risks.
- Both immunological and non-immunological age-related factors can impact the presentation of PIDs in older patients and should be considered for optimal patient management.
- Severe infection necessitating ICU admission should alert the physician and function as a PID warning sign.

Prof Siobhan Burns introduced the challenges and strategies surrounding the transition of adolescent and young adult patients from paediatric to adult healthcare systems. She emphasized the importance of a purposeful and planned transition process that addresses not only the medical aspects but also the psychosocial and educational needs of patients. Transition was explained to extend beyond a simple transfer appointment and requires a gradual process that begins as early as ages 12 to 14 and continues until young adults achieve independence in adult-centred care. Key steps were highlighted in successful transition, including assessing readiness, planning for transfer, and monitoring the acquisition of self-management skills. Prof Burns also provided insights into transition practices across Europe, noting variations in timing and approach. While most centres have transition processes in place, challenges such as difficulty finding specialist adult centres and lack of disease-specific guidelines were identified. Additionally, she underscored the importance of understanding the patient perspective and the need for more research in patient-reported outcomes.

Dr Elise Mallart delivered a compelling presentation on the intersection of PIDs and pregnancy, shedding light on the challenges and outcomes associated with maternal health in this relatively understudied area. She began by highlighting the physiological changes that occur during pregnancy, emphasizing the intricate balance needed to accommodate the foetus while maintaining maternal health, especially in the context of immune dysregulation seen in PID patients. A study was presented, which collected data from patients with various types of PIDs who had experienced at least one pregnancy

with the aim to assess the risks, outcomes, and management of pregnancy in PID patients. Key findings revealed that while successful pregnancies were achievable in PID patients, there were notable risk factors associated with poor outcomes, such as a history of severe infections before pregnancy. Additionally, the study highlighted the importance of optimizing prophylactic measures during pregnancy to mitigate the risk of infections and improve pregnancy outcomes. Dr Mallart concluded by emphasizing the need for close collaboration between obstetricians, midwives, and expert centres specializing in PID management to ensure comprehensive care for pregnant PID patients.

Dr Virgil Dalm addressed the unique challenges and considerations involved in caring for elderly patients with PIDs. He delved into the topic by sharing a case study of a 70-year-old patient with suspected PID, highlighting the complexities and diagnostic challenges in older individuals presenting with recurrent infections. Through the case study and data from patient registries, Dr Dalm underscored the significance of PID in the elderly population, with a notable proportion of patients above the age of 65 exhibiting primary antibody deficiencies. He emphasized the importance of considering age-related changes in the immune system, such as immunosenescence, as well as non-immunological factors such as malnutrition, which can impact both the presentation and management of PIDs in older patients. The potential impact of age on treatment options and preferences was discussed with the recommendation to apply personalized approaches that consider comorbidities, medication interactions, and the risk of adverse events in elderly patients receiving immunomodulatory treatments. To this end, Dr Dalm advocated for multidimensional geriatric assessments in older patients with PIDs, involving interdisciplinary teams to address physical, mental, and social domains of care.

Dr Nahla Erwa delivered a thought-provoking lecture on the intersection of PIDs and intensive care units (ICUs). Through case examples, she highlighted the diverse presentations and diagnostic challenges associated with PID patients encountered in the ICU and illustrated the significant impact of immunodeficiencies on patient outcomes within the ICU environment. She emphasized the need for early recognition and intervention as well as heightened awareness and clinical suspicion to identify PID patients presenting with severe infections or other critical conditions requiring ICU admission. Through a review of existing literature and research findings, Dr Erwa explored the role of ICU admissions as potential warning signs for underlying PID, advocating for increased awareness and screening efforts in these settings. She also discussed the challenges and opportunities for implementing transition care programs for PID patients moving between ICU and other healthcare settings, emphasizing the need for collaborative efforts between healthcare providers and patient organisations.

CLOSING SESSION

Chaired by **Dr Nizar Mahlaoui**

Closure Talk: The future perspectives of PIDs and possible challenges ahead – **Prof Charlotte Cunningham-Rundles**

Closing Remarks – **Ms Martine Pergent**

Prof Charlotte Cunningham-Rundles delivered an insightful closing lecture, highlighting significant advancements and challenges in the field of PID. She began by acknowledging the remarkable progress made in the last decade, including increased visibility of immune deficiencies, advancements in laboratory diagnostics and genetics, and the introduction of newborn screening. She emphasized the importance of registries in pooling data for comprehensive analysis and fostering collaborative research. Next, Prof Cunningham-Rundles discussed the expansion of genetic knowledge, with numerous

new gene variants being found to be associated with PID development, reflecting ongoing research and discovery in the field. She also praised initiatives like IPOPI's PID Life Index website and the development of smartphone apps for phenotypic classification, facilitating accessibility to information.
New treatments, particularly biologics, were highlighted as a significant development, although accessibility remains a challenge, especially in underserved regions. The transition of care from paediatric to adult medicine was identified as an area needing improvement, alongside the implementation of molecular diagnostics and the use of artificial intelligence in healthcare. The lecture underscored the necessity of addressing challenges such as delayed diagnosis, global disparity in molecular diagnostics availability and limitations of access to advanced but also first-line treatments. Prof Cunningham-Rundles advocated for the repurposing of medications and leveraging electronic medical records and artificial intelligence to improve patient care and enhance diagnostic capabilities.

In conclusion, she emphasized the importance of collaborative efforts, continued research, and innovative approaches to overcome challenges and further advance the field of primary immunodeficiencies.

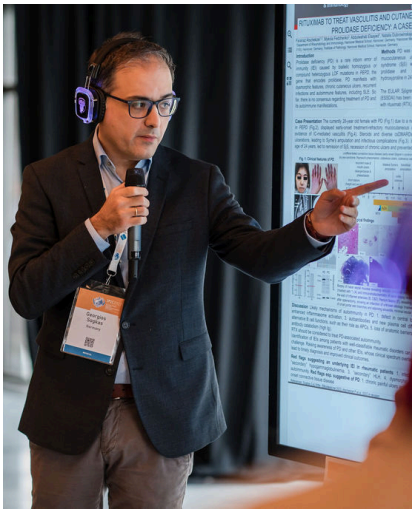
The conference was closed by **Ms Martine Pergent,** who expressed gratitude to all involved in the success of the event. She highlighted the diversity of perspectives presented at the conference, including those of physicians, nurses, experts, and patients, underscoring the importance of such varied viewpoints in advancing patient care.

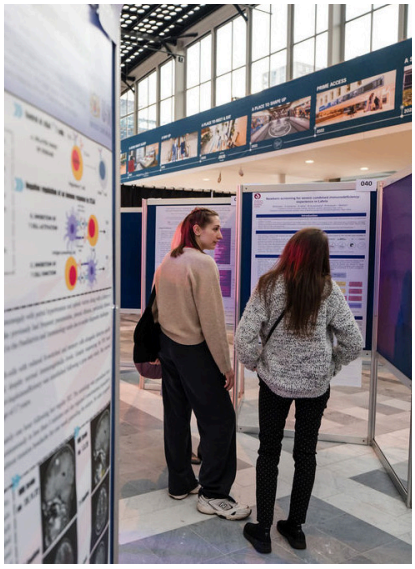
Finally, the next IPIC edition was announced to take place in Prague, 5-7 November 2025. See you there...!


WISKOTT-ALDRICH
SYNDROME
APDS
DELTA SYNDROME


MARKUS SEIDEL


EMILY CAR





APDS	Activated phosphoinositide 3 kinase delta syndrome
APSID	Asia Pacific Society of Immunodeficiencies
ASD	Autism spectrum disorder
ASID	African Society of Immunodeficiencies
AT	Ataxia Telangiectasia
BBB	Blood-brain barrier
CAR	Chimeric antigen receptor
CGD	Chronic granulomatous disease
CHARGE	Coloboma, Heart defects, Atresia of the choanae, Retardation of growth and/or development, Genitourinary abnormalities, and Ear anomalies
CID	Combined immune deficiency
CIS	Clinical Immunology Society for North America
CTLA-4	Cytotoxic T-lymphocyte-associated protein 4
CVID	Common variable immune deficiency
EBV	Ebstein Barr virus
ESID	European Society for Immunodeficiencies
GOF	Gain-of-function
GT	Gene therapy
GVHD	Graft versus host disease
HLH	Haemophagocytic lymphohistiocytosis
HSCT	Haematopoietic stem cell transplantation
ICU	Intensive care unit
Ig	Immunoglobulin
IPIC	International Primary Immunodeficiencies Congress
IPOPI	International Patient Organisation for Primary Immunodeficiencies
JAK	Janus kinase
LASID	Latin American Society for Immunodeficiencies

LMIC	Low- and middle-income countries
NGS	Next generation sequencing
PD1	Programmed cell death protein 1
PD-L1	Programmed death-ligand 1
PID	Primary immunodeficiency
PKU	Phenylketonuria
QoL	Quality of life
SCID	Severe combined immunodeficiency
SEAPID	South East Asia Primary Immunodeficiency Network
SID	Secondary Immunodeficiency
SIRD	Secondary immune deficiency and immune dysregulation
STAT	Signal transducer and activator of transcription
TCR	T-cell receptor
WAS	Wiskott Aldrich syndrome
WGS	Whole genome sequencing
XLA	X-linked agammaglobulinaemia

IPIC2023 APPROVED ABSTRACTS

1 - DIAGNOSIS AND NEWBORN SCREENING ADVANCES

2 - AUTOINFLAMMATION AND AUTOIMMUNITY

3 - GENETIC DIAGNOSIS AND OTHER BASIC RESEARCH

4 - PID ENVIRONMENT AND QUALITY OF LIFE

5 - MALIGNANCY IN PIDS

6 - NEUROLOGICAL AND OTHER TYPES OF COMORBIDITIES OF PIDS

7 - PID TREATMENT ADVANCES (TARGETED THERAPIES, CURATIVE THERAPIES, NOVEL IMMUNOGLOBULINS...)

8 - COVID-19 AND OTHER INFECTIOUS AGENTS

9 - BASIC AND TRANSLATIONAL RESEARCH FINDINGS

10 - CASE STUDIES, CLINICAL PRESENTATION AND IMMUNOLOGICAL PARAMETERS

11 - THE NURSES PERSPECTIVES ON PID DIAGNOSIS AND MANAGEMENT

12 - OTHER TOPICS

POSTER WINNERS

1ST PLACE: **Rifaldy Fajar.** "Deep Reinforcement Learning for Adaptive Treatment Optimization in Severe Combined Immunodeficiency (SCID)."

2ND PLACE: **Prabal Barman.** "Impact of COVID-19 pandemic on clinical care of patients and Psychosocial health of affected families with Chronic Granulomatous Disease: An observational study from North India."

3RD PLACE: **Sibel Kaplan Sarikavak.** "Malignities and lymphoproliferations in children with primary immune deficiency – a single center experience."

POSTER 157 - DEEP REINFORCEMENT LEARNING FOR ADAPTIVE TREATMENT OPTIMIZATION IN SEVERE COMBINED IMMUNODEFICIENCY (SCID)

AUTHORS

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Biography:
Rifaldy Fajar is a doctoral student in Computational Biology and Medicine at Yogyakarta State University. His research primarily revolves around computational immunology and the integration of artificial intelligence (AI) and machine learning (ML) in medicine. With a keen interest in leveraging computational approaches to unravel the intricacies of the immune system, Rifaldy's work focuses on developing ML-based models for predicting immunological outcomes in various diseases. He has been awarded research grants by the Ministry of Research and Technology of Indonesia, recognizing his contributions to applying ML techniques to advance medical research. Rifaldy actively engages in scientific conferences and workshops, aiming to foster collaborations and contribute to cutting-edge developments in computational immunology and the application of AI in medicine.

Objective: Severe combined immunodeficiency (SCID) is a rare, life-threatening primary immunodeficiency disorder characterized by profound impairment of T cell function. Optimal treatment decisions for SCID patients, such as hematopoietic stem cell transplantation (HSCT) or gene therapy, are challenging due to the complex interplay of genetic, clinical, and immunological factors. This research presents a pioneering research approach that utilizes deep reinforcement learning (DRL) to optimize treatment selection in SCID. The aim is to develop an adaptive framework that learns from patient data and clinical outcomes to provide personalized treatment recommendations, maximizing long-term efficacy and minimizing risks.

Method: We compiled a comprehensive dataset from a multi-center cohort of 300 SCID patients, encompassing diverse clinical records, high-resolution genetic profiles, immune cell phenotyping data, treatment modalities, and long-term outcomes. The dataset included information from leading SCID research centers and major clinical databases, ensuring its reliability and representativeness. A DRL agent was constructed using a customized deep neural network architecture, incorporating both convolutional and recurrent layers. The value network estimated long-term treatment outcomes, while the policy network determined treatment selection based on the predicted values. The DRL agent was trained using a combination of supervised learning and reinforcement learning techniques, optimizing for cumulative treatment efficacy over time. The training process involved extensive simulation of various treatment scenarios and iterative updates to the agent's policy based on rewards and penalties obtained from the simulated outcomes.

Results: Our DRL-based adaptive treatment optimization framework demonstrated exceptional results in SCID treatment selection. The trained DRL agent achieved an average success rate of 90% in selecting the most effective treatment strategy for SCID patients. By continuously learning from patient data and adapting its treatment recommendations, the framework outperformed traditional treatment guidelines, resulting in a 25% improvement in long-term treatment efficacy. Moreover, the agent showcased the ability to adapt to individual patient characteristics and dynamically adjust treatment strategies in response to evolving clinical conditions.

Conclusion: Deep reinforcement learning presents a groundbreaking approach for adaptive treatment optimization in severe combined immunodeficiency (SCID). Our research demonstrates the effectiveness of a DRL-based framework in learning from a comprehensive dataset and optimizing treatment selection for SCID patients. By integrating clinical, genetic, and immunological information from a multi-center cohort, the DRL agent provides personalized treatment recommendations, maximizing long-term efficacy while minimizing risks. This approach has the potential to revolutionize clinical decision-making in SCID and pave the way for precision medicine strategies in primary immunodeficiencies management.

POSTER 75 - IMPACT OF COVID-19 PANDEMIC ON CLINICAL CARE OF PATIENTS AND PSYCHOSOCIAL HEALTH OF AFFECTED FAMILIES WITH CHRONIC GRANULOMATOUS DISEASE: AN OBSERVATIONAL STUDY FROM NORTH INDIA

AUTHORS

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Biography:
Dr Prabal Barman completed his graduation (MBBS) from Gauhati Medical College, Guwahati, Assam, India (2015) and post-graduation (MD) in Paediatrics from Advanced Paediatrics Centre, Post Graduate Institute of Medical Education and Research, Chandigarh, India (2020). He is currently pursuing a 3-year post-doctoral (DM) training programme in Paediatric Clinical Immunology and Rheumatology at the Advanced Paediatrics Centre, Post Graduate Institute of Medical Education and Research, Chandigarh, India and is likely to complete it in December 2023. This is the first, and till date the only, such post-doctoral training course in Paediatric Rheumatology in India.
He aspires to continue in an academic institute after his training and has 12 publications till date in reputed journals. In addition to medicine, he has a keen interest in extra-curricular activities and has a Bachelor's degree in Indian classical music (Vocal) and a Diploma in Water and Oil painting.

Objective: Day-to-day clinical management of patients with inborn errors of immunity, including chronic granulomatous disease (CGD), has been affected by the Coronavirus disease-2019 (COVID-19) pandemic. There is a dearth of information on impact of this pandemic on clinical care of children with CGD and psychological profile of the caretakers. We aimed to describe the difficulties and psychological status of parents/caregivers of children with CGD during COVID- 19 pandemic, from the perspective of a developing country. We also report the clinical manifestations of COVID-19 infection and its resultant complications in our cohort of CGD from North India.

Design and methods: Case records of patients with CGD and concomitant COVID-19 infection/complications attending Pediatric Immunodeficiency Clinic of our Institute were analyzed in detail. Parents and caretakers of CGD patients (n = 21) and 21 healthy adults with similar ages and genders, were also evaluated on the following scales and questionnaires: COVID-19 Fear Scale (FCV 19S), Impact of Event Scale (IES-R), Depression, Anxiety, and Stress Scale (DASS 21), Preventive COVID-19 Behavior Scale (PCV 19BS) and a 'COVID-19 Psychological wellbeing questionnaire'.

Results: Among the 101 patients with CGD followed up at our Centre, 5 children developed infection/complications associated with COVID-19. Four of these children had a mild clinical course, while 1 child developed features of multisystem inflammatory syndrome in children (MISC) requiring intravenous glucocorticoids.
Median age of the parents/caregivers was 41.76 years (range: 28-60 years). Male: female ratio was 2:1. In the study group, 71.4% had higher IES-R, DASS21, FCV 19S and PCV 19BS scores. The caregivers had a high prevalence of stress, anxiety, avoidance behavior, and depression compared to controls ($p < 0.001$). Sub-group analysis revealed that parents/caregivers having intermediate level education, elementary occupation, and low-income were more stressed than those who were graduate/post graduates or those who were skilled professionals and had a higher income ($p < 0.05$).
Conclusion: Children with CGD have had predominantly mild infection with COVID-19; however, caregivers/parents of these children were at risk of developing psychological distress. COVID- 19 pandemic has brought to light the importance of patients' and caretakers' mental health which needs periodic assessment and appropriate interventions. Future studies should evaluate psychological interventions such as psychoeducation, cognitive behavioural therapy, counselling and family therapy, and socio-economic risk factors with a larger sample size in patients with CGD and their caregivers/parents.

POSTER 112 - MALIGNITIES AND LYMPHOPROLIFERATIONS IN CHILDREN WITH PRIMARY IMMUNE DEFICIENCY - A SINGLE CENTER EXPERIENCE

AUTHORS

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1 MD- Hacettepe University School of Medicine, 2008-2014

2 Pediatrics- Hacettepe University, 2015-2019

Work experience:

2014-2015: General practitioner, Diyarbakır Child Health and Diseases Hospital, Diyarbakır, Turkey

2019-2021: Pediatrician, Silvan State Hospital, Diyarbakir, Turkey

PRESENTATION DETAILS

Poster presentation

1. *Kaplan S, Kuskonmaz B, Soyer O, Aytaç S, Gümrük F. (2018). When to Suspect Systemic Mastocytosis? Blood, 132, 5826. https://doi.org/10.1182/blood-2018-99-119809.*
2. *Kaplan S, Gökmirza Ozdemir P, Turkyilmaz Ucar O, Cakmak E, Yazıcıoğu M. A Case of Airborne Allergic Contact Dermatitis. Poster Session, 28th National Allergy and Clinical Immunology Congress, 0201, Antalya, 2021.*
3. *Kaplan S, Turkyilmaz Ucar O, Gökmirza Ozdemir P, Eren T, Yazıcıoğu M. Successful Desensitization With Vincristine In A Child Case. Poster Session, 3.Young Pediatric Allergists Symposium,6110, Online, 2021.*
4. *Cakmak E, Gökmirza Ozdemir P, Gökdemir P, Turkyilmaz Ucar O, Kaplan S, Yazıcıoğu M. A Rare Type of CTFR mutation in an Asthmatic Case. Poster Session, 15th pediatric allergy and asthma congress, P-048 , Mugla 2021*
5. *Turkyilmaz Ucar O, Cakmak E, Gökmirza Ozdemir P, Gökdemir P, Kaplan S, Yazıcıoğu M. Dry Skin And Laseration: Eczema Or Not? 15th pediatric allergy and asthma congress, P- 002 , Mugla, 2021.*

PUBLICATION DETAILS:

1.Tanır Başaranoğlu S, Kaplan S, Aykaç K, Özsürekçi Y, Cengiz AB, Kara A, Ceyhan M. (Department of Pediatrics, Hacettepe University Faculty of Medicine, Ankara, Turkey). Clinical evaluation of 423 pediatric patients with skin rashes. Çocuk Sağlığı ve Hastalıkları Dergisi 2017; 60: 46-51.

Although the frequency of studies on malignancies accompanying primary immunodeficiencies (PID) has increased, very few studies examine cases of PID with non-neoplastic lymphoproliferation. In this paper, we aimed to present lymphoproliferation and the types of malignancies that we encountered in immunodeficient patients. Among 550 primary immunodeficiency patients followed in Basaksehir Cam and Sakura city hospital, 17 (3,0%) patients who developed malignancy or non-neoplastic lymphoproliferation were included in the study. The demographic, clinical characteristics and prognosis of patients were evaluated. The mean age at diagnosis of primary immunodeficiency was 7,6± 3,1 years. Eight of the patients had immune dysregulatory disease (MAGT1, NFAT, ITK=2, STX11, PIK3R1, Munc, LRBA), five of them had combined immunodeficiency with DNA repair defect (ataxia-telangiectasia) (AT), three patient had antibody deficiency (E47,VAV1, no genetic mutationon), and one had the phagocytic disease (chronic granulomatous disease) (CGD). Lymphoma was detected in nine (52,9%) patients and lymphoblastic leukemia were in two (11,7%) patients, retinoblastoma in one patient (5,8%), and craniopharyngioma in one patient (5,8%), Rhabdomyoma is also detected in a patient with lymphoma. Lymphoproliferation was detected in seven (46,6%) patients. Eleven patients with malignancy received chemotherapy (CT) and five of them also underwent bone marrow transplantation. One patient with retinoblastoma received both chemotherapy and radiotherapy. One patient with craniopharyngioma underwent surgery. Two patients diagnosed with NFAT and E47 deficiency had only lymphoproliferation, these patients were treated with rituximab and underwent bone marrow transplantation. Despite treatments, 4 patients had excitus.Although the limited number of our patients, our study is important in terms of the underlying immunodeficiency diversity. AT and CVID are reported as the most common causes in the lit-

erature, but ın our study, the most common malignancy developing PID subclass in our study was immune dysregulation syndromes. In addition, our study contributes to the literature in terms of being careful in terms of PID and malignancy in patients with immune dysregulation. Due to the high mortality rate of malignancy in PID, early diagnosis with a multidisciplinary approach can protect patients.Completing the immune workup with next generation sequencing, such as whole exome sequencing, will offer better genetic diagnosis and counseling.

DIAGNOSIS AND NEWBORN SCREENING ADVANCES

POSTER 32 - SEVERE COMBINED IMMUNODEFICIENCY (SCID) SCREENING FOR PREMATURE INFANTS QUALITY IMPROVEMENT PROJECT

AUTHORS

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AFFILIATIONS

[1]Association of Public Health Laboratories, [2]University of Wisconsin-Madison, [3]Newborn Screening Laboratory at Wisconsin State Laboratory of Hygiene

Biography:
Ruthanne Sheller is a Manger for the Newborn Screening Technical assistance and Evaluation Program (NewSTEPs) at the Association of Public Health Laboratories (APHL). Ruthanne provides subject matter expertise and technical assistance to newborn screening programs, supporting these programs with the adoption of new conditions and quality improvement initiatives. She received her Master's in Public Health and Bachelor of Science degree in Community Health from the University of Maryland, College Park. She recently earned a Lean Six Sigma Green Belt certificate through the University of Michigan. Prior to her current position, she worked as a Senior Research Assistant, supporting early detection and intervention research at Kennedy Krieger Institute.

Background: Newborn screening (NBS) for Severe Combined Immunodeficiency (SCID) by measurement of T-cell receptor excision circles (TRECs) successfully identifies newborns with SCID and severe T-cell lymphopenia as intended. At the same time, the screening programs face the challenge of false positive results, especially a disproportionally high number in the premature newborn population. Generally, these false-positive results are due to the relative immaturity of a premature newborn's immune system and T- cell development at the time of newborn screening. As a result of the high number of screen-positive results in this population, premature infants are often screened multiple times or undergo unnecessary diagnostic testing in efforts to clarify or resolve the screening results. NBS programs throughout the country have reported concerns about how best to perform SCID screening and follow-up in this population to reduce clinical burden, while maintaining high quality performance metrics.

Objective: To better understand TREC values and SCID screening outcomes in premature newborns and elucidate evidence-based SCID screening practices that reduce unnecessary follow-up activities in premature infants.

Method and Design: De-identified individual SCID newborn screening data and aggregate SCID screening data were collected by APHL through funding from the Immune Deficiency Foundation from seven states for babies born between 2018 and 2020. Relevant statistics were performed on data pooled from these states to quantify screening performance metrics
and clinical impact on various groupings of newborns, categorized by neonatal intensive care unit (NICU) status, gestational age, and birth weight. Data was normalized using multiples-of-the- median (MoM) of Quantification Cycle (Cq) values or TREC values in order to allow for aggregation of data across states.

Results: The analysis is currently underway. Average and median TREC values, along with ranges, will be assessed in an effort to graphically represent the relationship between TREC values and both birth weight and gestational ages. Analyses will evaluate SCID
screening presumptive positive results and associated follow-up actions and outcomes, grouped by distinct gestational age/birth weight categories.

Conclusion: Our project will assess the association between SCID screening false positive rate and gestational ages/birth weights, and ultimately identify best practices that either
reduce the SCID screening false positive rate or provide more appropriate recommendations for follow-up of screen-positive results in the premature newborn population.

POSTER 40 - NEWBORN SCREENING FOR SEVERE COMBINED IMMUNODEFICIENCY: EXPERIENCE IN LATVIA

AUTHORS

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AFFILIATIONS

[1]Children's Clinical University Hospital

Biography:
Master's Degree of Natural Sciences in Biomedicine.

Clinical laboratory geneticist at the Metabolic and Newborn screening Department of Laboratory in Children's Clinical University Hospital in Riga, Latvia for almost seven years.

In charge of newborn screening and selective screening of IEM, especially in protein glycosylation analysis and partly in organic acid analysis.

Objective: Severe combined immunodeficiency (SCID) is a group of rare inherited disorders that causes disfunction of immune system. Newborns with SCID may appear healthy at birth, first symptoms can manifest when child have serious infections and organ damages. Early diagnosis and treatment can prevent disability, death and improve life quality.
Design and method: Since 1st April 2023 screening for SCID was included in Latvian national Newborn screening program. SCID screening is based on DNA extraction from dried blood spot samples, using real-time PCR for the semi quantitative determination of TREC (T-cell receptor excision circle) and KREC (Kappa-deleting recombination excision circle). Absence or low levels of TREC and KREC may indicate SCID. The quality of DNA and amplification reaction was confirmed using the beta-globin as an internal control determination in each sample.

Results: Since newborn screening for SCID was implemented, initial cut-off value for TREC and KREC were based on literature review and published data. Value of beta-globin, recommended by reagent kit manufacturer, was decided to accept. Samples with beta-globin below cut-off value were defined invalid and were retested. Samples with TREC and/or KREC values below cut-off values and beta-globin above cut-off were retested from the same material. After reanalyzing, samples with low levels of TREC and/or KREC were defined "positive" and recalled repeating the test from another material or referred to a Children's Clinical University Hospital to an immunologist for further observation and diagnosis. About 30% of newborns should be recalled to repeat the screening after first test due to low TREC and KREC values. These results suggest that TREC and KREC copy number could differ between utilized methods and population consequently laboratory should establish they own cut-off values to reduce false- positive results and recall rates.

Conclusions: Newborn screening for SCID is opportunity to improve life expectancy and quality. Although setting the norms of TREC and KREC values for Latvian population and establishment of our own algorithm for SCID screening to avoid unnecessary recalls is an urgent need.

POSTER 58 - PARADIGM SHIFT IN DIAGNOSIS OF INBORN ERRORS OF IMMUNITY- ENCOURAGING OUTCOMES OF COMMUNITY-DIRECTED INTERVENTIONS

AUTHORS

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AFFILIATIONS

[1]Advanced Centre For Immunology & Rheumatology, [2]Government Medical College, [3]All India Institute of Medical Sciences

Biography:
Degrees: MBBS, MD (Pediatrics), DM (Pediatric Clinical Immunology), FESID (Advanced Immunology & Stem Cell Transplantation)
Affiliation: Advanced Centre for Immunology & Rheumatology
Position: Pediatric Immunologist, President, NIAPIDS, Nepal

Objective: To study the effect of various community-directed interventions on the diagnosis and management of inborn errors of immunity (IEIs) in Nepal

Methods: Dedicated pediatric clinical immunology services became available in Nepal in August 2020. From this date to December 2021, the rate of diagnosis of IEIs was assessed. Separate web- based community- and health-care provider-directed surveys were conducted to assess the baseline awareness regarding IEIs. Community-directed interventions were implemented from January 2022 up to May 2023. Interventions (number) applied included immunology-oriented national health camps (6), social media promotions (38), local language articles (9), audio-visual clips (17), interviews (9), conference talks (3), classes for pediatricians (18) and society registration (2). The rate of diagnosis of IEIs was reassessed for this period. Post-intervention web-based surveys were conducted to evaluate the change in awareness regarding IEIs.

Results: Twenty-four patients (M: F=1.4:1) were diagnosed from August 2020 to December 2021. The genetic diagnosis was established in 12 patients. Regular intravenous immunoglobulin replacement (IGRT) could be initiated in only 2 of the 8 patients with humoral immunodeficiencies. Hematopoietic stem cell transplantation (HSCT) could not be expedited for any patients. Baseline awareness regarding IEIs among the general public and physicians was 2.1% and 17.3%, respectively.
From January 2022 to May 2023, 89 patients (M: F=1.3:1) with IEIs were diagnosed. Of these, 59 patients were confirmed genetically. IGRT was initiated in 12 patients. Four children are undergoing HSCT in this period. Post-intervention awareness regarding IEIs among the general public and physicians was 7.1% and 39.2% respectively. In this period, we also diagnosed some rare and newly identified immunodeficiencies like various NLRP3 defects, PSMB8 defect, ARPC1B deficiency, MECOM deficiency, haploinsufficiency of A20, C1QA deficiency, RIPK1 deficiency, X-linked inhibitor of apoptosis protein deficiency, and STAT1-GOF defect to quote a few. A scientific society for clinical immunology in Nepal (www.niapids.org) was established.
Nepalese chapter of IPOPI (NePOPII) was also registered. Advocacy for patients' rights with government and philanthropic organizations has begun in the interventional period.

Conclusions: Notable increments in the diagnosis of IEIs and awareness among physicians were observed after community-directed interventions regarding awareness of IEIs. The study reinforces the need for further interventions for mass scale increment of awareness of IEIs. Logistic constraints coupled with a lack of awareness of IEIs among laity and pediatrician accounted for missed diagnoses, late diagnoses, and poor outcomes in resource-limited settings.

POSTER 85 - THE PIDCAP PROJECT: DEVELOPING A WARNING-SIGN-BASED ALGORITHM FOR USE IN AN ELECTRONIC HEALTH RECORD SCREENING TOOL FOR INBORN ERRORS OF IMMUNITY SCREENING

AUTHORS

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AFFILIATIONS

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Biography:
I am a pediatrician passionate about immunology, rare diseases, and humanizing medicine at Vall d'Hebron Hospital in Barcelona since 2013. In 2016, I had the opportunity to undergo training abroad with Dr. Haddad at a renowned immunology center in Canada. Since July 2017, I have been part of Dr. Soler's team, where I have the privilege of caring for patients with immune deficiencies and their families. Additionally, I collaborate on various research projects within the same research group, where I oversee the advanced immunology laboratory and work on digital transformation and research involving digital tools.

Objective: To establish inborn errors of immunity (IEI) warning signs (WS) for a rule-based algorithm in an electronic health record (EHR) screening tool ("PIDCAP"), thereby raising clinical suspicion of IEI by highlighting high-risk patients in primary care workstations via matching ICD-10-CM codes.
Design:

A literature review to determine a list of IEI WS alongside their suggested weighting by the algorithm, followed by a DELPHI-like survey of each WS's perceived relevance in the clinical suspicion of an underlying IEI.

Method: The algorithm was developed in three phases. First, a local taskforce identified risk factors of IEI by literature review, then collaborated with 8 local experts to decide upon an initial selection of adult/pediatric WS and their weighting. Next, a panel of experts among immunologists and primary care physicians rated the perceived significance of each WS on a 1-to-4 scale via survey. To maintain WS's inclusion, a cut-off score of 3+ on 50% of the votes was established. Finally, the local task force translated to ICD-10-CM coding.

Results: Of 22 total participants, 16 answered the pediatric survey and 10 the adult survey (4 answered both) – Fig.1-2. Of the 28 WS featured in the survey for pediatric and 22 for adult patients, 27 and 22, respectively, achieved the cut-off score. The remaining WS were amended based on survey comments and their ability to be coded. Following a review of all 68,000 ICD-10-CM codes, 3385 relating to the pediatric WS and 3497 relating to the adult WS were identified and implemented for use by the algorithm, which was able to be utilized by the PIDCAP tool in real- world testing within a primary care center in Catalonia.

Conclusions: With the results of the survey, we were able to refine a list of WS for IEI that considers both the opinions of specialized immunologists and primary care physicians. This expands the classic '10 WS of Primary Immunodeficiency' in a way that is based on the opinion of those that are intimately familiar with the realities of real-world presentation and coding of IEI patients. We were able to assign coding per WS, allowing for the implementation of the PIDCAP tool into the primary care workstation – a good first step for any artificial intelligence model with a similar EHR-screening design. The project is currently active with an ongoing algorithm validation in IEI cohort and pilot study for the application to the general population in primary care.

POSTER 97 - HIGH-DIMENSIONAL IMMUNOPHENOTYPING OF T CD4+ CELLS IN COMMON VARIABLE IMMUNODEFICIENCY

AUTHORS

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AFFILIATIONS

[1]Servicio Inmunología Hospital Clínico San Carlos

Biography:
Graduated in Biology from the University of Vigo. From the early years in the career I have always been interested in the world of health biology, above all it called me special attention to understand and decipher what were the underlying biological mechanisms in different diseases. In third year I studied Immunology, and for me it was a great discovery and I really realized that I wanted to pursue this passionate field.

At the moment I am doing the residency at the Immunology Service of the San Carlos Clinical Hospital in Madrid where I combine the routine work of the laboratory with a research activity.

Background: Common variable immunodeficiency (CVID) is the most common clinical primary immunodeficiency, characterized by a defect in B cell differentiation which leads to hypogammaglobulinemia. However, alterations in the function of T cells have also been described, affecting the T-B cell interaction. T cell defects could explain the defective antibody production, but also the development of other complications, such virus infection, gastrointestinal disease, autoimmunity or inflammation.

Aims: In this study, we assessed a new flow cytometry panel for the diagnosis of CVID patients.

Methods: We studied 12 CVID patients and 10 healthy controls (HC) for CD4+ T lymphocytes subsets. Twelve-color flow cytometry panel and analysis of circulating lymphocytes was made. Results were analyzed by U de Mann-Whitney statistical test.

Results & Conclusions: We observed a decrease in CD4+ T lymphocytes and naïve CD4+ T cells in CVID patients compared with HC ($p<0.05$ and $p<0.01$, respectively). The percentage of effector memory (EM) CD4+ T cells was significantly higher in CVID patients than HC ($p<0.01$). An increase in T helper 1 (Th1) lymphocytes in CVID was also observed ($p<0.01$). One CVID patient had diminished regulatory T (Treg) cells and a marked expansion of Th1 lymphocytes which might explain the development of autoimmunity and GLILD in this patient.
Our data show that the analysis of CD4+ T lymphocytes by flow cytometry provides valuable diagnostic information in CVID patients, which, added to the classical diagnostic criteria, could increase diagnostic efficiency with clinical relevance.

POSTER 100 - INBORN ERRORS OF IMMUNITY IN THE HIMALAYAN REGION – A MULTI-CENTER STUDY

AUTHORS

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AFFILIATIONS

[1]Government Medical College, [2]Advanced Centre for Immunology & Rheumatology, [3]All India Institute of Medical Sciences

Biography:
The presenting author is a young immunologist currently working to establish pediatric clinical immunology services in resource-limited settings. The author has more than 50 publications in various peer-reviewed international journals.

Objectives: To describe the spectrum of inborn errors of immunity (IEIs) in the Himalayan region.

Methods: Patients with IEIs belonging to Nepal, Bhutan, and Indian Himalayan regions who were diagnosed from August 2020 to May 2023 were included. Patients with variant-proven IEI were grouped according to the 2022 International Union of Immunological Societies (IUIS) Classification. The European Society of Immunodeficiencies criteria were used for clinical diagnoses of IEIs.

Results: During 2.8 years of study duration, 159 patients were diagnosed to have IEIs. Of these, genetic testing could be performed in 97 patients (62%). Antibody deficiency was the most common (21%) group of IEIs diagnosed [diseases diagnosed include common variable immune deficiency, X-linked agammaglobulinemia, specific antibody deficiency]. Disorders of phagocyte function or number were the second most (18%) common [chronic granulomatous disease, leukocyte adhesion deficiency, congenital neutropenias, GATA-binding factor 2 deficiency].
Combined immunodeficiencies (including severe combine immunodeficicency) were diagnosed in 13%. Disorders of immune regulation were noted in 12% patients [activated phosphoinositide 3-kinase δ syndrome, familial hemophagocytic lymphohistiocytosis syndromes, autoimmune lymphoproliferative syndromes, cytotoxic T-lymphocyte-associated protein-4 deficiency haploinsufficiency, syndrome of immune dysregulation, polyendocrinopathy, enteropathy, X- linked). Complement defects were noted in 7%. Autoinflammatory diseases were diagnosed in 6% [Blau syndrome, adenosine deaminase 2 deficiency, nucleotide-binding and oligomerization domain-like receptor family pyrin domain-containing 3 inflammasomapathy, tumor necrosis factor-receptor associated periodic syndrome, haploinsufficiency of A20, receptor-interacting serine/threonine-protein kinase 1 deficiency]. Disorders of innate/intrinsic immunity were noted in 5% patients.
Regular antimicrobial prophylaxis could be administered in all patients. Contrastingly, regular immunoglobulin replacement therapy (IgRT) could be arranged in only one-fourth of patients with humoral and combined immunodeficiencies. Targeted therapy in the form of mammalian target of rapamycin or Janus kinase inhibitors was used in 6 patients. Logistics for performing a hematopoietic stem cell transplantation (HSCT) could be arranged in only 4 patients.

Conclusions: Our study highlights enhanced diagnosis of a wide spectrum of IEIs in our region. Greater awareness and increasing availability of immunological/genetic testing are the notable factors resulting in improved diagnostic rates of IEIs. However, significant hurdles impede the optimal management of these patients. Regular IgRT and routine employment of HSCT for management of IEIs is specifically hindered given the significant costs associated which are to be borne by the patients' caregivers in the absence of universal health insurance or federal support. Besides, only a few targeted therapeutic agents are available at affordable costs in our region.

POSTER 120 - PERFORMANCE EVALUATION OF THE COMPLEMENT C1Q TURBIDIMETRIC ASSAY ON THE BINDING SITE OPTILITE® ANALYSER

AUTHORS

Iliev V[1], Gavrilas I[1], Malin G[1], Nelson A[2], Kalass S[3], Bell I[1], Allen S[1], Zhang Y[2], Willrich M[3], Lakos G[1]

AFFILIATIONS

[1]The Binding Site, Part Of Thermo Fisher Scientific, [2]University of Iowa, Molecular Otolaryngology & Renal Research Laboratories, [3]Mayo Clinic BioPharma Department of Laboratory Medicine and Pathology

Biography:
Born in Bulgaria, he moved to the UK in 2013 to pursue his higher education. Victor obtained his BSc in Virology from the University of Glasgow, where he consequently did his PhD at the Centre for Virus Research. His academic research revolved around the characterization of molecular spatiotemporal events of cellular innate immunity to early Herpes Simplex 1 infection. Following this, he began working in a CRO, where he was involved in the post-marketing surveillance of a COVID-19 vaccine and Regulatory Authority reporting. From there, Victor move to Birmingham and began working for the Binding Site, where he works as a Medical Science Liaison and specializes in complement assay development.

Objective: The objective of this study was to assess the analytical and clinical performance of the complement C1q antigen turbidimetric assay (in development by The Binding Site, part of Thermo Fisher Scientific) for the automated Optilite® analyser.

Design and method: All analytical performance studies were performed based upon CLSI guidelines: precision (EP5-A3:2014), linearity (EP06-ED2:2020), matrix comparison (EP09C- ED3:2018), interference and cross-reactivity (EP07-ED3:2018).
The clinical performance of the Optilite C1q assay was assessed on 233 serum samples from patients with immunological disorders (e.g., complement deficiency, systemic lupus erythematosus [SLE], glomerulonephritis and other systemic autoimmune diseases), including a sub-cohort on complement (C5) inhibitor therapy. Optilite CH50 results were generated on all patient samples.
Optilite C1q results were compared to those generated with the Human Complement C1q BINDARID™ Radial Immunodiffusion Kit (C1q RID) on 150 serum samples.

Results: A twenty-day precision study showed total precision CV% of ≤3.8%. Additionally, between instrument and between lot precisions were ≤1.5% and ≤2.1%, respectively. Linearity was demonstrated over a range of 7.52 - 523.88 mg/L with deviation from linearity of <10%. The matrix comparison study showed equivalency between serum, EDTA plasma and lithium heparin plasma matrices. The assay exhibited no significant assay interference effects when tested with Intralipid (200 mg/dL), bilirubin (400 mg/L), triglyceride (1500 mg/dL), and haemoglobin (10 g/L). No significant cross reactivity was observed with analytes of relevance: C3 (1.65 g/L), C4 (0.41 g/L).
C1q concentration was low in 34.6% of patients with glomerulonephritis and in 15.9% of patients with SLE (without kidney involvement), whereas in patients with other immunological disorders, such as rheumatoid arthritis and Sjögren's syndrome, only 7.2% had low C1q levels. Of these 74% also had low CH50 levels, exhibiting a strong correlation between C1q and CH50 levels.
Conversely, C1q concentrations were normal in 17 out of 23 patients with inherited complement factor deficiencies (other than C1q), and in 19 out of 23 patients who were on complement (C5) inhibitor therapy.
Optilite C1q assay results were 87.3% concordant with the C1q RID assay. Quantitative comparison demonstrated a Passing Bablok slope of 1.00, and a Bland-Altman bias of
+13.78%.

Conclusions: In conclusion, these initial performance results show that the complement C1q antigen turbidimetric assay for the Optilite analyser has the potential to provide reliable, precise and clinically relevant results for C1q concentration in human serum, EDTA plasma and lithium heparin plasma on a fully automated platform.

POSTER 121 - PERFORMANCE EVALUATION OF THE COMPLEMENT C2 TURBIDIMETRIC ASSAY ON THE BINDING SITE OPTILITE® ANALYSER

AUTHORS

Iliev V[1], Fisher J[1], Edwards D[1], Mulla A[1], Malin G[1], Nelson A[2], Kalass S[3], Adersen T[4], Bell I[1], Allen S[1], Hegel J[4], Zhang Y[2], Willrich M[3], Lakos G[1]

AFFILIATIONS

[1]The Binding Site, Part Of Thermo Fisher Scientific, [2]University of Iowa, Molecular Otolaryngology & Renal Research Laboratories, [3]Mayo Clinic BioPharma Department of Laboratory Medicine and Pathology, [4]Labor Berlin – Charité Vivantes Services GmbH

Biography:
Born in Bulgaria, he moved to the UK in 2013 to pursue his higher education. Victor obtained his BSc in Virology from the University of Glasgow, where he consequently did his PhD at the Centre for Virus Research. His academic research revolved around the characterization of molecular spatiotemporal events of cellular innate immunity to early Herpes Simplex 1 infection. Following this, he began working in a CRO, where he was involved in the post-marketing surveillance of a COVID-19 vaccine and Regulatory Authority reporting. From there, Victor move to Birmingham and began working for the Binding Site, where he works as a Medical Science Liaison and specializes in complement assay development.

Objective: The objective of this study was to assess the analytical and clinical performance of the complement C2 antigen turbidimetric assay (in development by The Binding Site, part of Thermo Fisher Scientific) for the automated Optilite® analyser.

Design and method: All analytical performance studies were performed based upon CLSI guidelines: precision (EP5-A3:2014), linearity (EP06-ED2:2020), matrix comparison (EP09C- ED3:2018), interference and cross-reactivity (EP07-ED3:2018).
The clinical performance of the Optilite C2 assay was assessed on 279 serum samples from patients with immunological disorders (e.g., complement deficiency, systemic lupus erythematosus [SLE], glomerulonephritis and other systemic autoimmune diseases), including a sub-cohort on complement (C5) inhibitor therapy. Optilite CH50 results were generated on all samples.
Optilite C2 results were compared to those generated with the Human Complement C2 Kit for use on SPAPLUS® (SPAplus C2) on 204 serum and EDTA plasma samples.
Results. A twenty-day precision study showed total precision CV% of ≤5.7%. Additionally, between instrument and between lot precisions were ≤5.5% and ≤3.7%, respectively. Linearity was demonstrated over a range of 1.99 - 40.45 mg/L with deviation from linearity <10%. Matrix comparison study showed equivalency between serum and EDTA plasma. The assay exhibited no significant interference effects when tested with Intralipid (200 mg/dL), bilirubin (400 mg/L), triglyceride (1500 mg/dL), and haemoglobin (10 g/L). No significant cross reactivity was observed with analytes of relevance: C3 (2.92 g/L), IgG3 (1946.31 mg/L), factor B (535.91 mg/L).
C2 concentration was low in 3.9% of patients with glomerulonephritis and in 15.9% of patients with SLE (with no kidney involvement), whereas in patients with other immunological disorders, such as rheumatoid arthritis, only 5.6% had low C2 levels. Of these, 90.5% also had low CH50 levels, demonstrating a very strong correlation between C2 and CH50. C2 concentration was undetectable in the only C2 homozygous deficient patient and was low in 41.7% of C2 heterozygotes. On the other hand, C2 levels were normal in all patients with inherited complement factor deficiencies (other than C2), and in 22 out of 23 patients on C5 inhibitor therapy. Optilite C2 assay results were 95.1% concordant with the SPAplus C2 assay. Quantitative comparison demonstrated a Passing Bablok slope of 1.07 and Bland-Altman bias of +9.5%.

Conclusions: These initial performance results show that the complement C2 antigen turbidimetric assay for the Optilite analyser has the potential to provide reliable, precise and clinically relevant results for C2 concentration in human serum and EDTA plasma on a fully automated platform.

POSTER 153 - POINT-OF-CARE LATERAL FLOW DETECTION OF VIABLE ESCHERICHIA COLI O157:H7 USING AN IMPROVED PROPIDIUM MONOAZIDE-RECOMBINASE POLYMERASE AMPLIFICATION METHOD

AUTHORS

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AFFILIATIONS

[1]RMIT University, Australia

Biography:
Growing up in the second-most populated country, India, Alka is passionate about public health and well-being. She has completed her Bachelor of Biotechnology from Panjab University, Chandigarh, India. She also received her first-class Master's degree in research from the same University. She moved to Australia in 2015 and gave birth to two beautiful princesses. Alka is pursuing Ph.D. in Applied Biology and Biotechnology from RMIT University, under the supervision of Prof. Andy Ball. She has developed and assessed a point-of-care molecular detection assay for waterborne and foodborne pathogens in her Ph.D. project. She also worked on an additional project in collaboration with EPA, Victoria. While this journey, she has developed her interest in water research and providing a safe and clean environment to the public. She is also working with EPA Victoria as a Lab research officer in the GardenSafe program. She hopes to use the skills and experience she has gained to make her career in the water and environment industry.

Escherichia coli O157:H7 is a leading cause of food-associated outbreaks worldwide. The detection of viable and viable but non-culturable (VBNC) E. coli O157:H7 is a crucial step in food safety procedures which directly connected to public health. To date, the most applied detection methods for E. coli O157:H7 in the VBNC state represent Traditional culture-dependent approaches based on the combination of enumeration of culturable cells with differential staining and direct microscopy count using a LIVE/DEAD bacterial viability kit to identify metabolically active cells and cells assumed to be VBNC. The traditional culture- dependent methods are lengthy and laborious. Recently, recombinase polymerase amplification (RPA) has been reported for the detection of E. coli O157:H7 from various food matrices.
However, there is no study reported for the differential detection of viable and no-viable E. coli O157:H7 in food and water. Therefore, our lab group has developed the RPA method for the detection of viable E. coli O157:H7 through integration with propidium monoazide (PMA).
Initially, two primer sets, targeting two different genes (rfbE and stx) were selected, and DNA amplification by RPA combined with PMA treatment was assessed. Subsequently, one primer set, targeting the rfbE gene was found to enable the sensitive detection of viable E. coli O157:H7. The optimised and validated viable RPA assay integrated with paper-based lateral flow (LF) detection was then applied to commercial beverage samples spiked with E. coli O157:H7, including milk, apple juice, and drinking water. The detection limit of the assay was found to be 102 CFU/mL for VBNC cells from both pure culture and all matrices. pH values 3 to 11 were found to have no significant effect on the efficacy of the PMAxx-RPA-LFA assay. The PMAxx-RPA method was completed at 39o C within 40 min. This study introduces a rapid, robust, reliable, and reproducible method for the detection of viable bacterial counts. In conclusion, the optimised PMAxx-RPA assay can be used by the food and beverage industry, government, and public sectors in quality assurance to reduce public health risks related to E. coli O157:H7.

POSTER 262 - THE EXPANDED NEWBORN SCREENING FOR INBORN ERRORS OF IMMUNITY IN TUSCANY, ITALY

AUTHORS

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AFFILIATIONS

[1]Immunology Unit, Meyer Children's Hospital, Irccs - University Of Florence

Biography:
Resident in pediatrics.

Expert in:
- invasive infectious disease in children
- Inborn errors of immunity: newborn screening
- vaccination

Objective: Inborn errors of immunity (IEIs) now comprise 485 inherited disorders characterized by increased susceptibility to invasive infectious diseases, systemic autoimmunity and susceptibility to malignant forms, constituting a group of diseases with high morbidity and mortality rates in the first years of life. Diagnosis before the appearance of one of these complications revolutionizes the prognosis of these children. Severe combined immunodeficiency (SCID) is definitely the most severe form of IEI and is the main target of most neonatal screening strategy for primary immunodeficiencies worldwide. However, all those immunological defects that meet the term 'actionable' recently used to refer to all IEIs for which early and urgent specialist intervention leading to a significant and demonstrable improvement in prognosis is necessary and useful may be worthy of a neonatal screening programme. The objective of this study is to evaluate the results of the expanded NBS strategy for IEIs, comparing the results obtained with already described NBS practices worldwide in terms of accuracy, defined by the rate of genetic diagnoses made, and sustainability, defined by the rate of recalls made.

Design and methods: This is a single-centre retrospective study collecting data from all live-born infants in Tuscany from October 2018 to October 2022. The blood drop collected at birth was tested both by tandem mass analysis for the detection of ADA and PNP metabolites and by molecular PCR assay to quantify the expression of TRECs (T-cell receptors circles) and KRECs (kappa-deleting recombination excision circles).

Results: The recall rates obtained for TRECs (0.031%) and KRECs (0.074%) in this study are comparable with data available in the literature to date. Among these recalls, we identified 35 cases of transient but severe B-cell (85.7%) or T-cell (14.3%) lymphopenia followed up with short follow-up and 10 cases with confirmed genetic diagnosis by Next Generation Sequencing (NGS) or Chromosomal Microarray (CMA) techniques, resulting in a rate of genetic diagnosis of IEIs of 1/9.431 live infants.

Conclusion: The expanded NBS strategy improves diagnostic accuracy for IEIs, while still maintaining sustainable and comparable recall rates compared to narrower NBS programmes. Comparing studies of equal extension and with the same recall range performed, the rate of genetic diagnosis of IEIs to our knowledge is the highest ever described.

AUTOINFLAMMATION AND AUTOIMMUNITY

POSTER 17 - RHEUMATOLOGICAL MANIFESTATIONS IN PRIMARY IMMUNE DEFICIENCY PATIENTS

AUTHORS

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AFFILIATIONS

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Biography:
Nasrullayeva Gulnara is a professor of prediatri from 2004 and Head of Research Immunology Laboratory in Azerbaijan Medical University from 2005. She has more than 200 publications in the local and International journals in the pediatric, immunology and genetic fields.

Background and aims: Primary immunodeficiency (PID) is a severe congenital pathology manifested by damage to many organs and systems (nervous, cardiovascular, respiratory system, thymus, joint and skin). Arthritis is a frequent symptom of PID occurs in 10–30% of patients with hypogammaglobulinemia and usually appears in large joints. In this study, we report rheumatological manifestations in patients with PID.

Methods: In 2010-2023, 149 patients with various types of PID were identified at the Azerbaijan Medical University. The main complaints were the respiratory tract infections, ataxia, telangiectasia, thymus aplasia, congenital heart disease, arthritis, skin wounds. The clinical and instrumental examination, CBC, blood chemistry, serological, immunological and genetic analysis was performed.

Results: Rheumatological manifestations as arthritis, vasculitis, sclerosis were observed in 16 (11%) patients: agammaglobulinemia (BLNK gene mutation)-1, XLA-4 patients, Kabuki syndrome-1, immune dysregulation-2, CGD-2, HIES-4 and 2 patients with WAS disease. Knee, ankle, elbow joints, spine and facial bones were damaged. Initially, 3 patients were suspected by bone tuberculosis and 2 patients - by rheumatoid arthritis, but genetic analysis in all 16 patients confirmed the PID diagnosis. The IVIG replacement therapy show positive effect and clinical improvement. Although CRP and ASO were elevated in all patients, RF and ANA were negative. That is typical for patients with humoral PID and decreased immunoglobulin synthesis.

Conclusion: The arthritis in frequently ill children raises suspicion about the PID. The diagnosis of PID can be confirmed by immunological and genetic testing. Timely and correct immunological treatment eliminates joint pain and can prevent patients from becoming disabled.

POSTER 21 - IS PFAPA SYNDROME AT THE BEGINNING OF A PATHWAY TO BEHCET'S DISEASE?

AUTHORS

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AFFILIATIONS

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Biography:
Prof Dr. Sara Sebnem KILIC completed her pediatric specialty training at Uludağ University Faculty of Medicine between 1991-1996. She went on to complete a Pediatric Immunology specialty at Hacettepe University between 1997-1999. She founded the Department of Pediatric Immunology at Uludağ University, Medical, in 2000. In this center, she diagnosed and treated patients with primary and secondary immunodeficiencies. She has provided genetic counseling to families with primary immunodeficiency, ensuring the birth of healthy babies. She provided this service to her patients by collaborating with international centers during periods when molecular tests could be limited.

Dr. KILIC, who received her Pediatric Rheumatology specialty certificate in 2011, is also a faculty member of the Department of Translational Medicine and takes part in doctoral program training.

Dr. KILIC has 117 international publications with 5020 citations and has an H index factor of 37 (WEB OF SCIENCE).

Background: Periodic fever, aphthous stomatitis, pharyngitis, and adenitis (PFAPA) is a disorder of innate immunity and IL-1 plays an essential role in Th1 activation. Behçet disease is characterized by recurrent oral aphthae and various systemic manifestations.

Methods: This study included 150 cases between the ages of 2-18, including 60 with PFAPA syndrome, 30 with Juvenile Behçet's Disease, and 60 healthy volunteers. The data of the patients were reviewed retrospectively. All subjects with PFAPA syndrome or Juvenile Behçet's disease and in the control group were asked to fill out a PedsQL questionnaire form with their parents.

Results: The mean age of diagnosis in the PFAPA group is 29 months, whereas it is 114 months in the Juvenile Behçet group. The average age of diagnosis in the Behçet group is significantly higher than that of the PFAPA group ($p<0.001$). The mean attack duration was longer in males than in females with PFAPA syndrome ($p=0.015<0.05$). The prevalence of lymphadenopathy in the neck was higher among PFAPA patients than in the Behcet and control groups ($p<0.001$). PFAPA and Behçet's patients had a higher fever rate than the control group, followed by aphthous ulcers. Painful skin lesions, redness in the eyes, uveitis, testicular pain, and genital ulcers were observed more frequently in Behçet patients compared to the PFAPA and control groups ($p<0.001$). The prevalence of a family history of PFAPA was found to be statistically higher in PFAPA patients compared to the other groups ($p<0.001$). The prevalence of a history of tonsillectomy was higher in PFAPA and Behçet patients compared to the control group ($p=0.027<0.05$). While Behçet patients had significantly lower mean values of ANS ($p=0.010<0.05$), CRP ($p<0.001$), and serum amyloid A ($p<0.001$) compared to PFAPA patients. HLA-B51 positivity exhibited the highest prevalence among all study groups in the Behçet patient group, with a rate of 35.59%.
In juvenile Behcet's and PFAPA patients, the total scale score of the PedsQL Questionnaire form was lower than in the control patients. According to the ROC analysis of the poor survival predictive value of the patient groups, ETP was <74.60 in the PFAPA group; ETP was <72.50 in the juvenile Behçet group.

Conclusions: Patients with Pfapa syndrome and Behcet's disease have some similarities, including aphthous stomatitis, articular symptoms and fever, although their clinical severity is different. Further studies are needed to determine whether Pfapa syndrome is at the beginning of a pathway to Behcet's disease in some patients.

POSTER 47 - DYSIMMUNITY IN COMMON VARIABLE IMMUNODEFICIENCY IS ASSOCIATED WITH ALTERATIONS IN ORAL, RESPIRATORY, AND INTESTINAL MICROBIOTA

AUTHORS

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AFFILIATIONS

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Biography:
Dr. Cabañero is a fifth-year resident in the Internal Medicine department at La Fe Hospital. She is currently conducting her doctoral thesis on Common Variable Immunodeficiency and dysimmunity. Dr. Cabañero has made significant contributions to the field, with several articles published in the prestigious journal Frontiers in Immunology. In addition, she has completed a clinical rotation in the Clinical Immunology department at John Radcliffe Hospital in Oxford. This experience has provided her with valuable insights and exposure to cutting-edge research and clinical practices in the field of immunology. Dr. Cabañero's diverse background and expertise make her a valuable asset in the field of primary immunodeficiencies.

Objectives: Common variable immunodeficiency (CVID) is the most common symptomatic primary immunodeficiency characterized by decreased immunoglobulins and recurrent infections. Its aetiology remains unknown, and some patients present severe non-infectious autoimmune or inflammatory complications with elevated associated morbimortality. Recently, intestinal dysbiosis has been proposed as a driver of immune dysregulation.

Materials and Methods: We assessed the oral, respiratory, and gastrointestinal microbiota of 41 CVID patients (24 with dysimmune and 17 with infection complications) and 15 healthy volunteers using 16S rRNA gene sequencing to explore bacterial biomarkers and associations between microbiome profiles and CVID phenotypes (Fig.1).

Results: Profound differences in the composition of the microbiota in saliva, sputum, and stool were detected between dysimmune CVID patients and healthy individuals. Globally, respiratory species diversity and faecal bacterial richness were lower in CVID individuals with immune complications (Table 1 and Fig.2). Despite a single species could not be identified as a robust predictor of dysimmunity, a combination of around 5-7 bacterial species in each type of sample could predict this severe phenotype with an accuracy of around 90% in our population (Fig.3).

Conclusions: Our study provides new insights into these previously unexplored but highly interrelated ecological niches among themselves and with patient profiles. Our data suggest that this disease-related systemic dysbiosis could be implicated in the immune dysregulation associated with severe cases of CVID.

POSTER 65 - CASE REPORT OF TWO PATIENTS HAVING IMMUNE CHECKPOINT DEFICIENCIES PRESENTED WITH AUTOIMMUNITY AND LYMPHOPROLIFERATION

AUTHORS

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Biography:
Dr Noor Zakirah binti Noordin is a medical officer pursuing paediatrics as her speciality. She obtained her medical degree in 2016 and is currently in her second year of postgraduate training. She developed a special interest in immunology after given a chance to be part of the clinical immunology unit in the paediatrics department, Universiti Putra Malaysia.

Introduction: Cytotoxic T-lymphocyte antigen-4 (CTLA4) is a negative regulator of T-cell immune responses, known as immune checkpoint. CTLA4 insufficiency results in immune dysregulation syndrome, characterized by autoimmune diseases, infections, and lymphoproliferation. Inheritance is by autosomal dominant with incomplete penetrance. Here, we describe two patients with autoimmune manifestations and lymphoproliferative disease who were labelled as systemic lupus erythematosus (SLE) and autoimmune lymphoproliferative syndrome (ALPS), respectively. Both later were found to have CTLA-4 haploinsufficiency.

Case Presentation: A 17-year-old girl was well from birth until age 11 years when she developed skin rashes, bicytopenia and splenomegaly. Unfortunately, she defaulted follow up. At age 15, she presented with syncopal attack, bruises and cutaneous lupus. No hair loss, joint pain, eye symptom, recurrent fever or infections. Examination showed oral ulcers and splenomegaly. Investigations revealed pancytopenia, positive direct Coomb's test, hypocomplementemia and raised ESR. ANA, anti-dsDNA and ENA were negative. She was treated as seronegative SLE with prednisolone and hydroxychloroquine. However, her splenomegaly and bicytopenia persisted.
Bone marrow examination showed normal marrow. Further immunological workup revealed low T- and B-cells, hypogammaglobulinemia, reduced lymphocyte proliferation to mitogen and poor antibody response towards pneumococcal vaccine. Double-negative T-cells (DNT) was not elevated. Genetic testing was consistent with CTLA4 haploinsufficiency.

A 10-year-old boy presented with spontaneous bruising of both lower limbs at age 2 years. Clinical examination was unremarkable apart from the bruises. Blood count showed severe thrombocytopenia. He was diagnosed with immune thrombocytopenic purpura and was given a course of intravenous immunoglobulin (IVIG). After 2 months, he developed recurrent thrombocytopenia and responded well to IVIG. His symptoms recurred at 8 years old when he had lower limbs bruises, multiple lymphadenopathies and hepatosplenomegaly. Investigations revealed thrombocytopenia, neutropenia and lymphopenia. Direct Coomb's test and ANA were positive. DNT was reported as elevated. He was treated as ALPS. Further immunological workup showed normal T- and B-cells and immunoglobulin levels, but reduced lymphocyte proliferation to mitogen and poor antibody response towards pneumococcal vaccine. Bone marrow examination showed hypercellular marrow. Genetic testing was consistent with CTLA4 haploinsufficiency.

Conclusions: CTLA4 haploinsufficiency can present with multitude manifestations. Recognition of this disease is crucial to institute appropriate therapy and prevention of complication associated with the disease.

POSTER 69 - HEPATIC INVOLVEMENT IN PATIENTS WITH COMMON VARIABLE IMMUNODEFICIENCY: A SINGLE-CENTER EXPERIENCE

AUTHORS

Evcen R[1], Esen H[2], Çölkesen F[1], Sadi Aykan F[1], Kılınç M[1], Yılmaz Ergün Ü[1], Akkuş F[1], Önalan T[1], Kahraman S[1], Gerek M[1], Yıldız E[3], Kökbudak N[2], Arslan Ş[1]

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Biography:
I was born in Adana, Turkey, in 1988 and attended Ankara University for my medical degree. Necmettin Erbakan University's Department of Internal Diseases was where I specialized. After four years as an internal medicine specialist in various institutions, I began my fellowship at Necmettin Erbakan University's Division of Clinical Immunology and Allergy in Konya, where I am still enrolled. My professional interests include primary and secondary immunodeficiency, as well as the relationship between immunodeficiency and autoimmunity. I am a married man with two young kids.

Background: Common variable immunodeficiency (CVID) is the most common symptomatic primary immunodeficiency in adults, characterized by antibody deficiency, recurrent bacterial infections, and autoimmunity. Nodular regenerative hyperplasia (NRH) is the most typical form of liver involvement in CVID. We aimed to evaluate the histological and immune features and outcomes of hepatic clinical participation in patients with CVID.

Materials and Methods: The medical records of 72 patients with CVID were reviewed retrospectively. In laboratory findings, a complete blood count, liver enzyme levels, hepatitis virus serologies, autoimmune hepatitis markers, and serum immunoglobulin levels were examined. In addition, liver radiological imaging and upper gastrointestinal endoscopy findings were evaluated. Liver biopsy specimens were obtained from seven patients with evidence of liver involvement and examined by two experienced histopathologists specializing in liver histology. Immunohistochemical staining was performed to identify immune cell infiltration.

Results: 72 patients with a median age of 38 (22–77) and 47% (n = 34) women were included in the study. Seven patients (1 male, 6 female) with elevated transaminase levels (n = 4) and splenomegaly (n = 3) were considered significant in terms of liver disease findings. A liver biopsy was performed on these patients to evaluate the histopathological reflections of the results. The mean age of patients with liver disease was 37.8 (±11.2). The sex ratio, splenomegaly, switched memory B cells, and low CD4+/CD8+ ratios differed statistically between patients with and without liver disease ($p<0.05$). Autoimmune diseases were more common in patients with liver disease than those without: 85.6% vs. 40%;$p = 0.041$ (Table 3).
Autoimmune complications of CVID in 7 patients who underwent liver biopsy included immune thrombocytopenic purpura, Evans syndrome, autoimmune hemolytic anemia, and inflammatory bowel disease. Histological analysis revealed non-fibrosing structural abnormalities consistent with NRH in 43% of CVIDs with liver disease. According to the biopsy findings, there were different levels of CD4+, CD8+, and CD16+ positivity (Figure 1). On the other hand, CD21+, CD56+, and CD138+ positivities were not detected in any of the patients in the biopsies.

Conclusions: Due to the heterogeneity of liver disease, all CVID patients should undergo routine liver examinations. This may help identify liver involvement promptly, monitor its progression and select suitable patients for liver biopsy. Results indicated that cytotoxic T lymphocytes that target sinusoidal cells contribute to the pathogenesis of NRH. Understanding the etiology and pathophysiology may improve the prognosis by facilitating early diagnosis and the selection of appropriate treatments.

POSTER 78 - CURRENT EPIDEMIOLOGY OF ACTIVATED PHOSPHOINOSITIDE 3- KINASE δ SYNDROME IN A NATIONAL RETROSPCTIVE STUDY IN ITALY

AUTHORS

Giardino G[1], De Rosa A[1], Lougaris V[2], Conti F[3], Costagliola G[4], Marzollo A[5], Rivalta B[6], Santilli V[6], Marinoni M[7], Martire B[8], Cancrini C[6], Tommasini A[9], Badolato R[2], Pignata C[1]

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Biography:
Dr. Giuliana Giardino has been working in the field of Primary Immunodeficiencies (PIDs) during the last 14 years and in July 2017, she completed her residency program in Pediatrics with a thesis focused on Severe Combined Immunodeficiencies. She also completed a PhD program aimed at the characterization of novel aspect of the pathogenesis and treatment of already known immunodeficiency, diagnosed conventionally or through Next Generation Sequencing.
During this period, she has been involved in the writing of more than 70 papers published on peer-reviewed journals, in more than 10 cases as first or last Author, 6 book chapters and many abstracts for national and international congresses. She has attended the CIS Summer School, the 4th Workshop on PIDs and the IAPIDS School. In September 2016, she started an observership at Great Ormond Street Hospital under the supervision of Prof. Bobby Gaspar.
She had the opportunity to improve her knowledge on the management and approach to patients undergoing bone marrow transplantation or gene therapy for different PIDs. During this period, she has been involved in an audit on the long-term follow-up of patients with Di George Syndrome in which she analyzed clinical and laboratory features of 486 patients in follow-up at velocardiofacial clinic at Great Ormond Street Hospital between 2004 and 2017. Two abstracts on this subject have been accepted for the ESID congress and a manuscript has very been accepted for publication in the prestigious journal 'Blood'. Moreover, she took part to the writing of a Review article on "Risk factors predisposing to the development of hypogammaglobulinemia and infections post-Rituximab" accepted for the publication on International Review of Immunology, and to the writing of an abstract accepted for the Clinical Immunology Society congress. During her time at UCL/GOSH, she has also been involved in a couple of research projects. She has taken part in a research project looking the thymic defects in adenosine deaminase deficiency. She executed a number of important assays and she made a major contribution to a manuscript that was recently published. She has also taken part in another research project looking at the migration of haematopoietic stem cells across the blood brain barrier. During these years she developed a well-established experience on the study of thymus and T cell development in human and mouse models in different forms of primary immunodeficiencies, developed through the direct collaboration with the major experts in the field including Luigi Notarangelo, Claudio Pignata, Graham Davies and Bobby Gaspar and documented by peer reviewed publications. She has been working as assistant professor at Federico II University since July 2019. She is involved both in clinical and laboratory activities. She has been recently awarded a 450000 euro grant from the Italian Ministry of Health for a project on the characterization of the variability of clinical manifestations in 22q11.2DS. She is involved in this project as PI. As for the clinical duties she is involved in the management of over 200 patients with different Inborn errors of immunity in follow up at the Department of Translational Medical Sciences – Pediatric section at Federico II University of Naples.

Objective: Activated Phosphoinositide 3-Kinase Delta Syndrome (APDS 1/2) is a recently described form of inborn error of immunity (IEI) caused by heterozygous mutations in PIK3CD or PIK3R1 genes, respectively encoding leukocyte-restricted catalytic p110δ subunit, and the ubiquitously expressed regulatory p85α subunit of the phosphoinositide 3-kinase δ (PI3Kδ). The aim of the study is to define the epidemiology of APDS in Italy and to characterize the clinical and laboratory features and the presenting signs of the syndrome in a cohort of Italian patients.

Design and method: Patients affected with APDS in follow up at centers of the Italian Network for Primary Immunodeficiencies (IPINet) were included in the study. The diagnosis of APDS was based on clinical and laboratory features and confirmed at genetic level. Clinical and laboratory data was collected using a Case Report Form.

Results and conclusions: A total of 23 patients, 14 females, affected with APDS1/2 were identified. In 19 patients a pathogenetic mutation of either PIK3CD or PIK3R1 gene was identified while 4 patients carried a variant of uncertain significance (VUS). These patients were defined as APDS-like. The cohort included 9 familial cases from 3 families. All the family members are included in this cohort. The age at diagnosis was available for 20 patients. The average age at diagnosis was 17 years and 8 months, ranging from 20 months to 49 years. The most common presenting signs were

infections: recurrent lower respiratory tract infections in 74% (17/23) and upper respiratory infections in 69.5% (16/23). Non-malignant lymphoproliferation was observed in 69.5% (16/23). Gastrointestinal involvement, including colitis, Chron disease, intestinal lymphoid hyperplasia, celiac disease, and gastroesophageal reflux, was also quite common, being present in 39% (9/23) of the patients. The other features are summarized in table 1.
Overall, 13 patients received Ig replacement therapy, either intravenously or subcutaneously. Eight patients received antimicrobial prophylaxis, 9 patients received immunosuppressive drugs including sirolimus (5 patients) and corticosteroids (4 patients). Four patients received a PI3Kδ inhibitor (leniolisib). One patient underwent hematopoietic stem cell transplantation.

In conclusion, the analysis of 23 APDS patients identified by IPINet centers showed that presenting signs of the diseases included infections and immune signs of dysregulation mainly lymphadenopathy. A better characterization of a large cohort of patients will allow to identify the warning signs leading to a more precocious diagnosis that may improve the management of this condition and to provide the access to available treatments for patients.

POSTER 84 - SYSTEMIC CHRONIC NON-CLONAL LYMPHOPROLIFERATION IN INBORN ERRORS OF IMMUNITY: NATURAL HISTORY, RISK OF LYMPHOMA, AND AUTOIMMUNE MANIFESTATIONS

AUTHORS

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Biography:
Beatrice Rivalta is a pediatrician who is currently in the final year of her PhD program in "Immunology, Molecular Medicine, and Applied Biotechnology" at the University of Rome Tor Vergata. Her doctoral thesis is focused on lymphoproliferation in inborn errors of immunity (IEIs).

Additionally, she is actively involved in the Immunology Department of the Bambino Gesù Children's Hospital taking care of diagnosis and follow up of children with IEIs.

Introduction: Systemic chronic non-clonal lymphoproliferation (LPD) can manifest as an initial symptom of inborn errors of immunity (IEIs) or arise subsequently. However, limited data are available regarding the management, progression of the disease, and risk factors associated with malignant degeneration.

Methods: We retrospectively included patients with IEIs and LPD and/or lymphoma in follow-up at the Bambino Gesù Children Hospital of Rome and IRCCS Azienda Ospedaliero-Universitaria di Bologna from 1996 to 2022.

Results: We included a total of 47 patients. The median age at the symptoms onset was 7 years (0.1-53 years), and the median age at the IEIs diagnosis was 14 years (0.5-60 years), with a median diagnostic delay of 3 years (0-30 years). At the onset 53% of patients presented lymphoproliferation and 34% had isolated lymphoproliferation. Among them, 21.3% at the onset of symptoms and 29.8% at the IEIs diagnosis were over 18 years old. 25.5% were diagnosed with Common Variable Immunodeficiency (CVID), 40.4% received a genetic diagnosis, 8.5% Autoimmune Lymphoproliferative Syndrome (ALPS), and 8.5% Activated PI3K delta Syndrome (APDS). After a median follow-up of 10 years from the IEI diagnosis, 31.9% of patients developed lymphoma (53.3% Hodgkin Lymphoma), and 46.8% developed autoimmune (AI) and/or autoinflammatory disorders. 43% of patients received immunomodulant therapies.
Patients who developed lymphoma were less likely to have AI and/or autoinflammatory manifestations compared to those without malignant lymphoproliferation (20.0% vs. 59.4%; p=0.015). Additionally, patients with lymphoma more frequently received antibiotic prophylaxis throughout the course of their disease (73.3% vs. 15.6%; p=0.001). Patients with AI and autoinflammation less frequently exhibited lymphoproliferation at the onset of the disease (46.7% vs. 72%; p=0.006) and presented a higher frequency of gastrointestinal and endocrinological complaints. Furthermore, we observed significantly lower total lymphocyte, CD3+CD4+, CD3+CD8+, and CD16+56+ counts in AI patients at the onset of the disease, along with a higher percentage of CD3+CD4+ central memory cells.

Conclusions: LPD can manifest as an underlying feature of IEIs even in adulthood. These patients face a significant risk of developing lymphoma. It is crucial to conduct a comprehensive immune evaluation and establish multidisciplinary diagnostic approaches to ensure appropriate follow-up and tailored treatments. In this study, we identified an inverse association between the development of lymphoma and the presence of autoimmune/autoinflammatory manifestations. Expanding the cohort will allow to further validate these findings and to identify additional markers of disease evolution.

POSTER 89 - A PARADOXICAL ENDEAVOR IN GENETIC SYNDROMES OF NON- MUSCULAR ACTIN: ABSENCE OF THE TYPICAL ACTINOPATHY IMMUNE DYSREGULATION

AUTHORS

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Biography:
Jorge Diogo Silva is currently a Medical Genetics Resident and Ph.D. researcher at the Centro Hospitalar e Universitário de Santo António. Throughout his career, he has engaged in several research activities, such as an Internship at Harvard Medical School/Massachusetts General Hospital and a continuous collaboration at the Life and Health Science Research Institute (ICVS; Braga, Portugal). He has pursued his Ph.D. studies on the topic of Neurogenetics, where he explored the usefulness of nematode models to study neurogenetic diseases, in both fundamental and translational perspectives, and has undertaken post-graduate training in Clinical Trial Regulation and Biostatistics. He has presented his work in several international meetings, having been awarded several scholarships and prizes for his research. He has also collaborated in research studies in both Fundamental and Clinical Medicine, currently with published work in Human Genetics, Epigenetics, Stem Cell Research, Neuroscience and Clinical Neurology. He currently has internationally funded research projects and supervises master and doctoral students. Moreover, he is involved in teaching activities for both medical, psychology and post-graduate students, in the areas of Genetics and Neurosciences. His goal is to synergistically bridge the areas of clinical care, medical research and teaching.

Objectives: actinopathies are a group of monogenic disorders characterized by defects in actin remodeling, usually associated with immune dysregulation. Interestingly, while all implicated actinopathy genes influence cytoskeletal dynamics, pathogenic variants in genes coding for non-muscular actin itself (ACTB and ACTG1) have never been definitively linked to an immunogenetic condition. Monoallelic loss-of-function in these genes is, however, well- established as a cause of Baraitser-Winter syndrome (BWS), an extremely rare neurodevelopmental disorder. Here, we provide the first objective assessment of the immunological phenotype of BWS patients, which was so far uncharacterized.

Design and methods: we retrospectively reviewed all cases of ACTB or ACTG1-associated BWS from a tertiary hospital center in Portugal. Demographic, clinical, and genetic data were collected. Deep immune phenotyping with assessment of cellular and antibody immunity through standard diagnostic techniques was performed.

Results: we characterized 6 cases of BWS (2 male, 4 female), with ages ranging from 2 to 24 years-old. Four patients had likely pathogenic/pathogenic variants in ACTB, and 2 in ACTG1. Clinically, all 6 patients had significant dysmorphic features and developmental delay/intellectual disability. None of the patients had any history of recurrent infection, autoimmunity or autoinflammatory features, blood cell dyscrasias, or hematological malignancies. Remarkably, no significant abnormalities were detected in any patient when it comes to the immunological phenotype. Specifically, we observed no changes in granulocyte number or function (oxidative burst and phagocytic ability), lymphocyte subpopulations and activation, autoantibodies (anti- nuclear, cytoplasmic, actin and neutrophil), and complement function.

Conclusions: while it might seem paradoxical, loss-of-function in actin-coding genes apparently does not cause immune dysregulation. This is in contrast to the well-established immunogenetic conditions where disruption of the actin cytoskeleton is a central hallmark. A possible explanation is that haploinsufficiency of actin is not sufficiently deleterious for white blood cells, as most actinopathies follow autosomal recessive patterns, but mostly affects neuronal cells during development. In conclusion, we provide preliminary evidence of absence of immune dysfunction in the extremely rare non-muscular actinopathies.

POSTER 92 - CHARACTERIZATION OF REGULATORY T CELL SUBSETS IN COMMON VARIABLE IMMUNODEFICIENCY (CVID) SUBJECTS

AUTHORS

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Biography:
Dr. Veronica De Rosa has a prominent role in the field of immunological and epigenetic studies, with unique expertise in ex-vivo and in vitro experimental approaches with primary human T cells. Dr. De Rosa consolidated her fully independent research group (Laboratory of Immunology at the IEOS) that is currently composed of two postdoctoral CNR fellows, one PhD student and two biotechnology students. Her transition towards autonomy has been facilitated by the support from research grants that she had been awarded in the last years. In the last years, she acquired a strong expertise in the study of the molecular and epigenetic mechanisms that control T cell tolerance, in health and immune-related disorders (multiple sclerosis, type 1 diabetes, cancer), as testified by her publication records in the field.

Background & Rationale: Common variable immunodeficiency (CVID) is the most common symptomatic primary immunodeficiency, characterized by both infectious and noninfectious manifestations. Although the hallmark of CVID is represented by the increased susceptibility to severe and/or recurrent infections, up to 50% patients develop additional non-infectious complications including autoimmune manifestations, granulomatous diseases, lymphoproliferation and malignancy. Autoimmunity is most frequently associated to CVID, suggesting the existence of common pathophysiologic mechanisms underlying the immune dysregulation of both these conditions; among them, altered T-cell homeostasis has been identified as an interesting contributing factor.
Since alterations in T cell homeostasis are permissive for the breaking of immune self-tolerance, we hypothesized that the complex immunological picture of CVID subjects with autoimmunity originates from an altered generation and/or function of Forkhead-box-p3 (Foxp3)+CD4+CD25+ regulatory T cells (Tregs), the subset able to prevent autoimmunity and uncontrolled inflammation and modulate immune homeostasis during infection and cancer. Among the different Foxp3+ Tregs, there is a distinct subpopulation expressing the Foxp3 exon 2 (Foxp3E2) splicing variants, necessary for their induction and functional stability.

Objectives: We evaluated by FACS analysis the frequency of Tregs in peripheral blood mononuclear cells (PBMCs) purified from CVID, CVID plus autoimmunity (CVID/AI), or Healthy subjects (HS). We analyzed the two most common Treg populations: Foxp3+Tregs (expressing all the splicing variants) and Foxp3Exon2+Tregs (expressing the splicing variants containing the exon 2). On these subsets, we measured the expression of Treg-cell lineage markers (CD69, CD31, CD45RA, CD71, CTLA-4, GITR, PD-1), ki67 (readout of proliferation), p-S6 (which reveals their metabolic asset), the expression of chemokine receptors and integrin (such as CD62L and CCR7). Moreover, we assessed the suppressive capacity of Tregs in terms of inhibition of conventional T cell (Tconv) proliferation. Finally, we evaluated the methylation status at the level of Foxp3 promoter and enhancer, through the MethCore analysis, a tool able to identify combinations of methylated CpGs common to epiallele families.

Results & conclusion: CVID/AI subjects display a reduced frequency of Foxp3Exon2+ Tregs compared either with HS or CVID, testified by a decrease of the Foxp3E2+/Foxp3+ ratio. This associates with a distinct immune phenotype characterized by an augmented expression levels of PD1 and CTLA4 and decrease of GITR. Moreover, both CVID and CVID/AI Tregs display a reduced suppressive capacity compared with HS. The integration of these results with the MethCore analysis will unveil whether an altered epigenetic regulation of Foxp3 could underlie the onset of autoimmunity in CVID/AI subjects.

POSTER 187 - GASTROINTESTINAL DISEASE IN CVID: THE UTILITY OF THE DUODENAL LYMPHOGRAM

AUTHORS

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AFFILIATIONS

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Biography:
2013-2019: Graduated in Medicine (University of the Basque Country UPV-EHU)

2021-2023: Inmunology resident (Hospital Clínico San Carlos)

Objectives: Common variable immunodeficiency (CVID) is the most common symptomatic primary immunodeficiency in adults. It is characterized by dysregulation of the immune system with hypogammaglobulinemia and recurrent infections. CVID can be associated with gastrointestinal manifestations that can cause alterations in the duodenal mucosa, as occurs in celiac disease (CD). The duodenal lymphogram analyzes subpopulations of intraepithelial lymphocytes: total intraepithelial lymphocytes IELST , TCR-ɣđ+ IELS and CD3- IELS, and it is a complementary tool for the diagnosis of CD. The objective of the study is to compare the duodenal lymphogram of patients with CVID who associate gastrointestinal clinic, celiac patients and healthy controls (without digestive pathology).

Design and methods: A prospective study was performed in 30 patients: 10 patients with CVID and gastrointestinal symptoms, 80% on a gluten-containing diet (GD); 10 celiac patients on GD and 10 healthy controls (HC). The duodenal lymphogram study was performed in duodenal biopsy samples by flow cytometry. The cut-off points were: IELST ≥15%; TCR- ɣđ+≥15%; and CD3-≤6%. Statistical analysis was performed using Kruskal-Wallis nonparametric test ($p<0.05$).

Results: Preliminary results show that celiac patients presented significantly higher IELST values than those observed in HC [19.5 (10.76) vs 10 (6.5), $p<0.05$] and in CVID patients [6 (5.25) $p<0.05$], with no significant differences observed between HC and CVID patients. When comparing TCR-ɣđ+, the medians obtained in celiac patients were significantly higher than in HC [26.5 (14) vs 6 (5.2), $p<0.05$], and than in CVID patients (7.5 (8.25), $p<0.05$). On the contrary, CD3- were significantly lower in celiac patients compared to those obtained in healthy controls [1.5 (3) vs 21 (12.75), $p<0.05$]. It should be noted that no significant differences in CD3- were observed between celiac patients and patients with CVID [6.5 (14.5), $p>0.05$], being in both groups much lower than those obtained in healthy patients.

Conclusions: Our preliminary results show a decrease in CD3- levels in the group of patients with CVID and in celiac patients compared to healthy controls. This suggests that both groups present active duodenal mucosal damage. However, to find a clear association between CVID and celiac disease, a larger sample size is needed, as well as to assess other parameters that influence the subpopulations studied in the duodenal lymphogram.

POSTER 202 - IMMUNE DYSREGULATION IN CHILDREN WITH DOWN SYNDROME AND JANUS KINASE INHIBITION AS TARGETED THERAPY

AUTHORS

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AFFILIATIONS

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Endocrinology and Nephrology Section. Santander, Cantabria, Spain., [5]Immunology Unit. University Hospital Virgen del Rocío, Seville, Spain, [6]Universitary Hospital La Princesa, Madrid, Spain, [7]Pediatric Infectious Diseases, Rheumatology and Immunology Unit, Hospital Universitario Virgen del Rocío, Instituto de Biomedicina de Sevilla, IBiS/ Universidad de Sevilla/CSIC, Red de Investigación Translacional en Infectología Pediátrica RITIP, Seville, Spain

Biography:
I graduated in Biotechnology and studied a Master in Health Biotechnology at the University Pablo de Olavide (UPO) in Seville in 2010-2012. During my PhD at the Institute of Biomedicine of Seville (IBiS), I studied Cytomegalovirus infection in solid organ transplant patients at low (seropositive recipient) and high (seronegative recipient) risk of CMV infection. I identified the CMV-specific cellular and humoral immune responses conferring protection against CMV organ disease. I published several manuscripts on this topic and successfully defended my PhD thesis entitled "CMV-specific immune response and its relationship with the protection against CMV infection for the design of a vaccine" in 2016, with the highest honors (cum laude) from the University of Seville. I completed a 16- months postdoctoral internship (Feb 1st 2017- June 31 2018) at the University of Rochester (NY, USA) in the laboratory of the Professor Martinez- Sobrido studying influenza virus, pathogen-host interactions and vaccine development using in vitro and in vivo approaches. In May 2019, I joined to the Inborn Errors of Immunity Lab at IBiS to study Primary Immunodeficiencies (PIDs). I am currently in the third year of the Sara Borrell contract (Instituto de Salud Carlos III). My studies focus on immune dysregulation syndromes caused by dysfunction in the STAT1 and STAT3 proteins and other immune defects associated to high susceptibility to infections or autoimmunity (eg. ACT1, ELF4 deficiencies, or Down Syndrome).

Objective: Down Syndrome (DS) has shown to be associated with inflammatory and autoimmune processes. In particular, there is a subset of DS patients who shares clinical manifestations with Signal-Transducer and Activator of Transcription 1 gain-of-function (STAT1 GOF) patients, also presenting IFN hypersensitivity, increased levels of STAT1 and its phosphorylated form (pSTAT1). As Janus Kinase (JAK) inhibition has been a successful treatment for STAT1 GOF patients and its potential and effectiveness in DS has not been explored yet, we here propose the study of JAK inhibitors, Baricitinib or Ruxolitinib, as a targeted therapeutic approach for a selected subgroup of DS patients with IFN hypersensitivity and clinical manifestations similar to the those STAT1 GOF patients.

Design and methods: Flow cytometry was performed to quantify IFN subunit receptors (IFNR) in monocytes as well as STAT1 and pSTAT1 levels in CD14 (monocytes), CD3, CD4 and CD8 T cells from DS individuals, STAT1 GOF patients and healthy controls (HC). In parallel, PBMCs were stimulated with IFN α/γ, and transcription levels of STAT1, CxCL10, SOCS1 and PD-L1 were evaluated by RT-PCR. Expression levels of IFN-response genes were quantified by nCounter FLEX (NanoString) platform. CXCL10 protein production and secretion levels were evaluated by ELISA and levels of different cytokines on serum were measured by Luminex assay.

Results: We confirmed in DS individuals an increased gene dosage of IFN R1 and IFN R2. Furthermore, similar to STAT1 GOF patients some DS individuals have increased STAT1 and pSTAT1 levels after IFN stimulation compared to HC in CD14+ and CD3+, CD4+, CD8+ T cells. STAT1 and CXCL10 expression and IL-6, IL-7, IP-10, TNF proteins on serum were higher in most DS patients compared to HC. We also observed that ex vivo JAK inhibition was effective reducing this IFN hypersensitivity in DS cells similar to STAT1 GOF patients' cells.

Conclusions: JAK1/2 inhibitor Baricitinib or Ruxolitinib might represent a promising targeted therapy for a selected subgroup of DS with inflammatory and/or infectious manifestations aiming to reduce comorbidities and improve the quality of life of affected children and adults as well as their caregivers.

POSTER 226 - THE PREVALENCE OF AUTOIMMUNE DISEASE IN PATIENTS WITH COMMON VARIABLE IMMUNE DEFICIENCY

AUTHORS

Lishchuk-Yakymovych K[1], Chopyak V[1], Bondarenko A[2], Derkach M[3], Hilfanova A[2], Nazarenko L[4], Zlotnikova O[5]

AFFILIATIONS

[1]Danylo Halytsky Lviv National Medical University, Department of Clinical Immunology and Allergology, [2]International European University, Department of Pediatrics, Immunology, Infectious and Rare Diseases, [3]Center of Allergology, Pulmonology and Immunology, [4]Regional Children's Hospital of Cherkassy, [5]Kyiv City Children Clinical Hospital # 1,

Biography:
Khrystyna Lishchuk-Yakymovych

In 1997 finished specialized school in Lviv (Ukraine)
During 1997-2003 - studied at Danylo Halytsky Lviv national medical university, specialty: general medicine, qualification: medicine.
During 01.08.2003-30.06.2004 - internship at the General therapy department of Danylo Halytsky Lviv National Medical University. Certificate of the Ministry of Healthcare conferred with the qualification of a physician.
She got her PhD degree in the specialties "Clinical Immunology and Allergology" in 2011 and got an academic title of Associate Professor of Medicine in 2013.
She has been involved in the clinical research in rheumatology, therapy, allergy and immunology since 2005.

Main research directions:
- *Development of a modern concept of cellular and humoral immunological, genetic and epigenetic regulatory mechanisms of the development of primary and secondary systemic vasculitis*
- *Management of systemic vasculitis regarding etiological, pathogenetic, morphological, clinical and statistical criteria;*
- *Introduction into the clinical practice of high-dose regimens of immunoglobulin therapy for the treatment of autoimmune, allergic, and immunodeficiency diseases;*
- *Study of immunopathological syndromes: cryopathy, eosinophilia, hyperimmunocomplex, hypocomplementary, antiphospholipid syndrome, syndrome of activated herpetic infections.*

Prior experience in scientific publishing:
2022 - Member of the working group of the Ministry of Healthcare of Ukraine on preparation the state program " Common variable immunodeficiency" and "Hereditary Angioedema (HAE)" Member of the editorial board of the
"Alergologia Polska – Polish Journal of Allergology"
"Allergy Practice"
Since 2015 is an expert of the Department of Healthcare of the Lviv State Administration in Immunology and Allergology
Member of Ukrainian Society of Immunologists, Allergists and Immunorehabilitation. Member of European Academy of Allergy and Clinical Immunology (EAACI).
Member of Polish Allergology Organisation.
Authored 142 published scientific works, 3 textbooks, 2 patents for a utility model. h-index Google scholar: 23
h-index Scopus: 2
h-index Web of Science: 7

Awards:
- *Diploma of the Ministry of Health of Ukraine for significant scientific and practical contribution to the development of healthcare in Ukraine*
- *Diploma of the Department of Healthcare of the Lviv Regional State Administration*

Background: Common variable immunodeficiency (CVID) is the commonest clinically significant primary immunodeficiency. Its prevalence is estimated as 1:25,000-1:50,000 with men and women being equally affected. The age of onset is variable, most patients are diagnosed in childhood or between the ages of 20 and 40 years.
The aim of the study was to assess the frequency and features of autoimmune disorders among the Ukrainian population of patients with CVID.

Materials and methods: Of a total 74 patients with diagnosed CVID were included and medical cards were analyzed. Data was retrieved on different autoimmune disorders.

Results: In total 24 patients with autoimmune diseases were identified among 74 patients with CVID (32.4%). Among them 6 patients suffered from polymyositis (PM) including antisynthetase syndrome (ASS), 9 suffered from lupus, 6 patients had mixed connective tissue disease and 12 patients had rheumatoid arthritis. In 14 patients, the disease was manifested by immune cytopenia (10 - thrombocytopenia, 1 – neutropenia, 3 – haemolytic anemia) and one patient suffered from antiphospholipid syndrome. Among other autoimmune disorders inflammatory bowel disease (2), celiac disease (1), alopecia (1), multiple sclerosis (1) were observed.
Patients with CVID and autoimmune diseases were of older age at CVID diagnosis than patients with CVID only.
Significant immunophenotypic differences was found between patients with autoimmune diseases associated with CVID in comparison to the patients without autoimmune disorder and CVID regarding CD19+ B-cells, the regulatory T-cells, median IgA or IgG levels, a tendency of lower memory B- cells and especially IgM+ memory B- cells. Genetic studies were performed in 10 patients - pathogenic mutations were detected in 7 of them (2 – TACI, 2 – CTLA4, 1- PIC3CD, 1- PIC3R1).
In all cases with SLE and RA the diagnosis were made 3-4 years before the diagnosis of CVID, in the other eight cases, the patient had suffered from recurrent infections in the ten years on the base of autoimmune diagnosis. In patient with ASS, the autoimmune disorder was diagnosed 6 years before CVID.
The patients received prednisone and azathioprine without significant efficacy. Treatment with high doses of IVIG and cessation of methotrexate led to a decreased episodes of recurrent infections and improvement of autoimmune processes.

Conclusions: CVID was accompanied by autoimmune phenomena in one third of the patients with a wide range of manifestations, in significant number of cases autoimmune diseases manifested earlier than the development of an infectious syndrome.

POSTER 239 - ENTEROPATHY IN DUTCH COMMON VARIABLE IMMUNODEFICIENCY COHORT

AUTHORS

Juliana N[1], Severs M[1], Abdelmoumen A[1], van Montfrans J[1], Ellerbroek P[1], Dalm V[2], de Bree G[3], Bouma G[3], Oldenburg B[1], Leavis H[1]

AFFILIATIONS

[1]University Medical Center Utrecht, [2]Erasmus Medical Center, [3]Amsterdam University Medical Center

Biography:
Helen Leavis is a clinical scientist and associate professor at the Department of Rheumatology and Clinical Immunology of the UMC Utrecht. Her specific clinical and scientific interest is the understanding disease mechanisms and treatment of inflammatory complications in CVID and applications of artificial intelligence in IEI.

Objectives: In common variable immunodeficiency (CVID) immune dysregulation results in significant morbidity. Little information is available regarding different manifestations and optimal treatment. Here we describe clinical characteristics, endoscopy, histopathology and treatment response of CVID enteropathy (CVID-E) in 3 teaching hospitals.

Design and methods: All CVID patients provided written informed consent. We collected, retrospectively, gender, age and start of enteropathy symptoms, age at CVID diagnosis, reports of endoscopy and histopathology, enteropathy related symptoms and the immunosuppressive medication (IS).
Treatment response was defined as remission, response, need for step-up, and unknown. Descriptive statistics were used to study associations.

Results: 32 of 82 patients had enteropathy. The average age of this group was 45.4 (13.5 SD) and the mean age of CVID diagnosis was 31.7 (16.7 SD). The age at first presentation of enteropathy was 30.9 years (14.6 SD). 50% of patients were female. 90.6% had other complications, 81.3% other inflammatory manifestations: lymphoproliferation (43.8%), splenomegaly (34.4%) and autoimmune disease (37.5%). Bronchiectasis occurred in 68.8%. Two patients had a solid malignancy and one lymphoma. We compared CVID-E treated with IS to those untreated.
Autoimmune cytopenia, and bronchiectasis were significantly more prevalent in CVID-E treated with IS, than those without IS: 23.5% vs 0% ($P<0.05$) and 82.4% vs 46.7% ($p<0.01$) respectively. 30 patients underwent endoscopy, 90.6% coloscopy and 78.1% gastroscopy. The most common histopathologic findings consisted of IBD-like colitis (n=10) and IEL (n=9). Other findings of note were lymphocytic (n=3), microscopic (n=2) or collagenic colitis (n=1) and apoptotic enteritis (n=1).
53.1% of patients received IS for CVID-E. 14 received local corticosteroids (CS), 12 systemic CS, 15 DMARDs (methotrexate, azathioprine, mesalazine, baricitinib, mycophenolate, tacrolimus and sulfasalazine), 6 biologicals (adalimumab, infliximab and ustekinumab) and 6 had combined therapy. These 17 patients underwent 64 treatments. Local CS therapy did not result in remission. 9/17 (52.9%) of patients needed more than 2 systemic drugs. DMARD monotherapy achieved remission/response in 6 of 13 patients (46.2%). The best results concerning combined therapy in this cohort consisted of combinations of DMARD(s) and systemic CS, and combinations of DMARD(s) and TNF-alpha inhibitors (TNFi).

Conclusions: CVID-E is strongly associated with other inflammatory complications and bronchiectasis, especially in CVID-E on IS. This cohort consists of the largest series reporting on treatment efficacy in CVID-E. We found combination treatment and DMARD monotherapy to be most effective. Additionally, TNFi seem to have a good clinical response in patients with CVID enteropathy, especially when combined with other treatments.

POSTER 253 - A SIGNIFICANT PROPORTION OF CHILDREN WITH EARLY ONSET AUTOIMMUNE CYTOPENIA HAS UNDERLYING INBORN ERRORS OF IMMUNITY: AN EXPERIENCE FROM A TERTIARY CARE CENTRE IN NORTH INDIA

AUTHORS

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AFFILIATIONS

[1]Allergy Immunology Unit, Department of Pediatrics, Postgraduate Institute of Medical Education and Research, [2]Department of Pediatrics, Government Medical College, [3]Department of Pediatrics, Christian Medical College

Biography:
Dr Pallavi L Nadig completed her MBBS from Bangalore Medical College and Research Institute, Bangalore, Karnataka, India in 2015 and her MD in Pediatrics from the Post Graduate Institute of Medical Education and Research (PGIMER), Chandigarh, India in the year 2018.
She is currently pursuing her post-doctoral three-year fellowship in Pediatric Clinical Immunology and Rheumatology from PGIMER, Chandigarh, India, under the mentorship of Prof Surjit Singh.

Background: Autoimmune cytopenias (AIC) results from immune-mediated destruction of blood cells, which can be due to primary or secondary causes. Corticosteroids remain the cornerstone in managing children with AIC; however, it is a nonspecific immune-suppressive strategy.
Recently, with a more understanding of molecular and genetic aetiologies, AICs are being increasingly identified as presenting symptoms of certain Primary immunodeficiencies (PIDs).

Objective: To describe the spectrum of PIDs with AIC as the presenting manifestation from a tertiary care centre in Northern India.

Design and methods: We prospectively screened 30 children presenting with AIC to the Allergy Immunology unit, for probable underlying immunodeficiency between January 2018- March 2023.

Results: Of the 30 children with a suspected PID with AIC at the presentation, 14 (46%) children had a genetic mutation in known PID genes; 5 (16.7%) were suspected to have an underlying PID based on clinical phenotype; the rest of the 11 patients had no known mutation in PID genes. Our cohort had Autoimmune lymphoproliferative syndrome (ALPS) (n=3); Lipopolysaccharide-responsive and beige-like anchor protein (LRBA) deficiency (n=2); severe combined immunodeficiency [SCID, n=2; STIM1 defect (1), PNP defect (1)]; X-linked inhibitor of apoptosis (XIAP) deficiency (n=2); activated Phosphoinositide 3-kinase δ syndrome [APDS (n=1)]; CD40L defect (n=1); DOCK8 defect (n=1), KMT2D mutation [Kabuki syndrome (n=1)].
We observed that a history of recurrent infections was present in 7/30 (23%) patients and 18/30 (60%) had evidence of lymphoproliferation. Only 5/30 (16.7%) patients had hypogammaglobulinemia and low T cell count.
Among those with a proven PID, corticosteroid was the first-line agent used (n=8/ 14, 57%). Other agents included Mycophenolate mofetil (MMF) (n=6, 42%); Azathioprine (n=3, 21%); Sirolimus [n=7/14, 50%; ALPS (2); LRBA (1); STIM1 defect (1), SCID (1) APDS(1), Kabuki
syndrome (1)]; and Rituximab [n=1, 11.7%; ALPS (1)]. Complete remission of AIHA was achieved with Corticosteroid alone (n=3, 21%); IVIg with corticosteroids (n=1, 7%); and MMF (n=3, 21%). Seven patients administered with sirolimus achieved either partial or complete remission. The patient with DOCK 8 mutation had a refractory AIHA and was planned for hematopoietic stem cell transplantation.

Conclusions: Experience gained from our cohort showed a prevalence of IEI in patients with autoimmune cytopenias of ≈ 50% with variable severity in various PIDs with variable treatment responsiveness. This study also shows clinical improvement with targeted therapy, implying the need to elucidate the underlying genetic cause in patients with secondary AIC.

POSTER 257 - IDENTIFICATION OF VARIANTS IN GENES ASSOCIATED WITH AUTOINFLAMMATORY DISORDERS IN PSORIATIC ARTHRITIS: A CASE-CONTROL STUDY

AUTHORS

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[1]Department of Rheumatology and Immunology, Hannover Medical School, Hannover, Germany, [2]Hannover Medical School, Cluster of Excellence RESIST (EXC 2155), Hannover

Biography:
Georgios Sogkas completed his medical degree at the University of Thessaly (Larissa, Greece) and after that moved for postgraduate studies to Oxford (University of Oxford, UK; MSc in Integrated Immunology) and then to Hannover (Hannover Biomedical Research School, Germany; PhD in Immunology). He specialized in Internal Medicine and Rheumatology as well as in Clinical Immunology at the Hannover University Hospital. Since 2021 he works as a consultant Rheumatologist and Immunologist at the outpatient clinic of the Department of Rheumatology and Immunology at the Hannover University Hospital. His main research focus is the investigation of the mechanisms of immune dysregulation in inborn errors of immunity and their pathogenic relevance in systemic rheumatic disorders.

Objectives: Genetic risk factors for psoriatic arthritis (PsA) include innate immunity genes. This together with the fact that PsA is a seronegative disease without clear adaptive immune correlate suggests the autoinflammatory immunopathogenesis of PsA. Here, we investigated the autoinflammatory genetic background of PsA focusing on genes associated with autoinflammatory disorders.

Methods: Patients with PsA visiting the outpatient clinics of the Hannover University hospital underwent targeted next-generation sequencing (N=120), searching for variations in genes linked with inborn errors of immunity classified as autoinflammatory disorders (AIDs). Deleteriousness of rare variants was evaluated through in silico analysis.

Results: We identified 45 germline predicted deleterious variants in 37 out of 120 (30.8%) patients with PsA, which all were monoallelic. Relatively common were variants in AP1S3, PLCG2, NOD2 and NLRP12. A total of 25/45 variants, found in 20 out of 120 (16.7%) patients, were localised in genes associated with autosomal dominant (AD) disorders. Clinical features associating with detection of AD-AIDs-associated variants included pustular psoriasis or a coexisting inflammatory bowel disease (IBD). Further, detection of AD-AIDs-associated variants correlated with higher CRP values and higher activity of PsA.

Conclusions: Approximately 30% of patients with PsA harboured at least one variant in a gene associated with an AID, suggesting an autoinflammatory disease mechanism in this patient subgroup. Detection of variants in genes linked to AD-AIDs may explain extra-articular manifestations of PsA, such as pustular psoriasis and IBD and may define a PsA subgroup with treatment refractory disease.

POSTER 263 - AUTOINFLAMMATORY DISEASES IN UKRAINE

AUTHORS

Stepanovskyy Y[1], Bondarenko A[1], Hilfanova A[1]

AFFILIATIONS

[1]International European University, Medical School, [2]Ukrainian Association of Pediatric Immunology

Biography:
Dr. Yuriy Stepanovskyy, M.D., Ph.D., associate professor of the Department of Pediatrics, immunology, infectious and rare diseases (International European University)

Executive director of the Ukrainian Association of Pediatric Immunology

Area of interest: autoinflammatory diseases, Kawasaki diseases, factitious fever in children

Background: To date, more than 25 patients with monogenic/polygenic systemic autoinflammatory diseases (SAIDs) were diagnosed in Ukraine (FMF, CAPS, HIDS, TRAPS, DADA2, SAVI, Schnizler-syndrome, Aicardi-Gourières-syndrome, CRMO, SAMD9L, and undefined periodic fever syndromes) and more than 130 patients with PFAPA-syndrome. Being one of the largest European countries, the Ukrainian cluster of SAIDs was poorly represented on the world map. Despite the small number of diagnosed patients and all challenges that today faces in Ukraine, the communities of pediatric immunologists and patients organizations prepared a solid base for the sustainable development of the autoinflammatory diseases line (genetic diagnostics, medication supply, governmental support of treatment programs, and international cooperation).

Objective: To describe the current situation with SAIDs in Ukraine, to look on from the “helicopter view position” and to determine the burdens, achievements, and perspectives.

Design and methods: We prospectively screened 30 children presenting with AIC to the Allergy Immunology unit, for probable underlying immunodeficiency between January 2018- March 2023.

Results: The analysis was based on the Ukrainian National Registry of primary immunodeficiencies involving more than 1360 patients. The diagnostic has been based on genetic verification or clinical/laboratory-recognized criteria. We compared clinical data and genetic characteristics with published data. We expect that hundreds of patients in Ukraine are non-diagnosed following the statistics. The average delay with diagnosis was 5 to 7 years. The clinical picture of Ukrainian patients was similar to those described in medical literature, and the genetic landscape showed both common and novel variants. About 30% of patients with “classical’’ presentations of autoinflammatory conditions had negative genetic results.

Conclusions: The achievement of high importance is the state registration of anakinra (generic formula). The official presence in Ukraine of canakinumab, etanercept, adalimumab, tocilizumab, tofacitinib, ruxolitinib, and other medicines (original or generics) that can be used for SAIDs is of great benefit for future management of patients with SAIDs. Assembling pediatric and adult state support programs would give patients the green light to transition from childhood to adulthood. The possibility of a fast-track registration process for orphan treatment is another benefit. At the same time, we conclude that full-scale russian aggression against Ukraine pushed back our efforts for many years, with the outflow of patients and devastating impact of the Ukrainian healthcare system.

GENETIC DIAGNOSIS AND OTHER BASIC RESEARCH

POSTER 46 - DIAGNOSTIC YIELD OF GENOME-WIDE GENETIC TESTING IN 640 INDEX CASES WITH INBORN ERRORS OF IMMUNITY

AUTHORS

Gauck D[1], Sturm M[1], Brecht I[2], Grasshoff U[1], Beck-Wödl S[1], Hansmann S[3], Samba S[3], Wasiliew P[3], Welzel T[3,4], Holzer U[2], Keck B[5], Kehrer M[1], Riess O[1,6], Skokowa J[7], Kümmerle- Deschner J[3], Haack T[1,6]

AFFILIATIONS

[1]Institute for Medical Genetics and Applied Genomics, University of Tübingen, [2]Department of Pediatric Hematology and Oncology, University Children's Hospital, University of Tübingen, [3]Department of Pediatrics, Division of Pediatric Rheumatology and autoinflammation reference center Tübingen (arcT), University Hospital Tübingen, [4]Pediatric Pharmacology and Pharmacometrics, University Children's Hospital Basel, University of Basel, [5]Department of Pediatrics, Diakonie Hospital Schwäbisch-Hall, [6]Center for Rare diseases, University of Tübingen, [7]Department of Oncology, Hematology, Clinical Immunology, and Rheumatology, University Hospital Tübingen

Biography:
My name is Darja Gauck and I am an academic staff member at the Institute of Medical Genetics and Applied Genomics based in Tübingen for seven years. I have been specializing in IEI for several years, analyzing genomic data in diagnostic and scientific context. I am also attending an educational program to become a specialist in human geneticist. I graduated from the Technical University of Dortmund in 2017 with a master's degree in chemical biology.

Objective: Human Inborn Errors of Immunity (IEI) constitute a heterogeneous group of genetic disorders associated with a variety of clinical manifestations, including autoinflammation, increased susceptibility to infections, autoimmunity, and malignancy. In the era of precision medicine, defining the molecular bases of IEI is essential not only for counseling of patients and their families, but also for developing targeted treatment. In this report we provide an overview of the diagnostic yield in a cohort of patients with a suspected clinical diagnosis of IEI.

Design and method: We investigated 662 patients from 640 families with suspected IEI referred for genetic testing from more than 20 clinical centers. Sequencing libraries were generated from genomic DNA for genome (TruSeq DNA PCR-free kit) or exome (TWIST Custom Exome IMGAG V2/SureSelectXT Human All Exon kits V6-7) sequencing and prepared libraries were sequenced for exome as paired-end reads on a NovaSeq6000 System (Illumina). Data analysis was conducted using an in-house bioinformatics pipeline optimized for single nucleotide variant, copy number variant (CNV) as well as structural variant (SV) detection.

Results and conclusions: A firm genetic diagnosis was established in 11% (n=73) of cases. For another 19% (n=113) of patients, variants of uncertain significance were identified in known IEI genes and 2% (n=11) in suspected candidate genes. In 71% (n=465), the underlying genetic cause of IEI remained unsolved. We have identified 203 unique variants in 105 genes. Notably, 52.7% of the variants (n=107) were private and had not been previously listed in public databases (ClinVar, HGMD). Proportionally, 59.8% of these variants were reported as variants of unknown significance. This study provides insights into the diagnostic yield of IEIs in a multi- center setting and highlights the challenges of diagnosing these heterogenic disorders. Since the majority of identified variants are novel, our results once more emphasize the necessity of functional validation studies as well as structured reporting of genomic variation in publicly accessible repositories.

POSTER 53 - CASPASE-10 MUTATIONS IN AUTOIMMUNE LYMPHOPROLIFERATIVE SYNDROME: END OF THE STORY

AUTHORS

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AFFILIATIONS

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Biography:
Filippo Consonni is a Medical Doctor and researcher attending the last year (5th) of a Residency program in Pediatrics at University of Florence, Florence, Italy.

During his formation, Dr. Consonni has built a strong research interest in the management of children affected by Inborn Errors of Immunity (IEI), with a special focus on Primary Immune Regulatory Disorders (PIRDs, such as STAT3-gain-of-function, IPEX and ALPS). On a clinical level, he has a 2-year experience in pediatric immuno-hematology, dealing with pediatric cytopenia and hematopoietic stem cell transplantation (HSCT).

His goal is to translate molecular research on PIRDs from bench to the clinical side: with this aim he is currently pursuing a research fellowship at the Laboratory of Immunogenetics of pediatric autoimmune diseases at Institut Imagine (Paris, France), directed by Dr. Fréderic Rieux-Laucat, focusing on the genetic determinants of ALPS.

Objective: Autoimmune lymphoproliferative syndrome (ALPS) is a primary disorder of lymphocyte homeostasis, leading to chronic lymphoproliferation and hematologic autoimmunity. The main genetic defects reported in ALPS involve FAS (ALPS-FAS) and FASLG (ALPS- FASLG). Caspase-10 (CASP10) variants have also been associated to ALPS, though their causative role is still debated due to their high frequency in the general population. In this study, we aimed to assess the impact of known CASP10 variants on lymphocyte apoptosis and on CASP10 protein expression.

Design: Carriers of known CASP10 mutations were retrospectively retrieved using our in-house Imagine "Polyweb" bioinformatic tool (including samples of > 70,000 subjects that underwent genetic testing at our Institute). Lymphocyte apoptosis function and CASP10 protein expression were assessed in each recruited subject and compared to healthy controls and to ALPS-FAS patients bearing mutations in FAS extracellular (FAS ECD) or intracellular (FAS ICD) domains.

Method: CASP10 mutations were confirmed by Sanger sequencing. Lymphocyte apoptosis assay was repeatedly performed both on CD3/CD28- and Staphylococcal enterotoxin type E (SEE)-stimulated T blasts, using a well described and routinely used apoptosis assay. CASP10 protein expression was assessed on T blasts by Western blot. Data were analyzed using FlowJoTM and GraphPad Prism software.

Results: We retrieved 3 individuals carrying one of the following controversial CASP10 variants in a homozygous state (CASP10 HMZ): p.C401LfsX15 (c.1202-1208 del), p.V410I (c.1228 G>A) and p.Y446C (c.1337 A>G). Each homozygous individual was coupled to a heterozygous carrier of the same mutation (CASP10 HTZ). Clinical and laboratory features of the 6 included subjects were highly variable (of note, 2 individuals were healthy) but in any case, not consistent with ALPS (Table 1). Upon stimulation with optimal dosage of Apo1.3 (a FAS agonist), no differences in FAS- mediated apoptosis were detected between subjects with any type of CASP10 variant and healthy controls. As expected, FAS ECD and ICD patients displayed an impairment of FAS- mediated apoptosis (Figure 1A-B). CASP10 protein expression was reduced in heterozygous and absent in homozygous carriers of p.C401LfsX15 mutation respectively, while it was comparable to healthy controls in all other included subjects (Figure 1C).

Conclusion: CASP10 is dispensable for FAS-mediated apoptosis. Despite an undetectable CASP10 protein expression, there is no impact on lymphocyte apoptosis and on individuals' clinical and laboratory phenotype. This study thereby rules out an apoptosis-related function of the previously described CASP10 variants in patients with ALPS.

POSTER 55 - A CASE DIAGNOSED WITH ARTEMIS MUTATION IN ADULTHOOD

AUTHORS

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Biography:
I was born in Konya,Turkey in 1984 and obtained my medical degree at Selçuk University in Konya. My specialization was in the Department of Chest Diseases at the Necmettin Erbakan University. After working for 7 years as a specialist in pulmonology, tuberculosis and intensive care departments in a public hospital,I started and still attending my fellowship at Necmettin Erbakan University in Divison of Clinical İmmunology and Allergy in Konya. Professionally, I am interested in primary and secondary immunodeficiencies, interstitial lung diseases and severe asthma. I am maried and amother of two young children.

Introduction: VDJ recombination that occurs during early phases of maturation of T- and B-cells is among fundamental steps in maturation of these cells. This process is mediated by various enzymes/proteins (1). One of these is Artemis nuclear protein encoded by DCLRE1C gene, which is important for T- and B-cell development and a fundamental component of non- homologous end joining (NHEJ) pathway (2).

Case: A 20-year-old female patient admitted with recurrent warts on fingertips (Figure-1). She had received local treatment for warts on fingertips at 3-4 years of age. Two years ago, she was operated by a plastic surgeon in another center for development of anal-genital warts that impaired her gait. She then received laser treatment due to recurrent warts. The patient admitted to our clinic for refractory warts. Older sister of the patient had been found to have DCLRE1C mutation while being investigated due to presence of refractory warts and then developed lymphoma. She had deceased while being followed-up in department of hematology. On admission, the patient had no pathological physical examination finding other than scars left by warts on fingertips and anal-genital warts. Patient had normal complete blood count and biochemistry results. Results of immunological tests are summarized in Table-1. Genetic testing revealed DCLER1C homozygous mutation. IVIG therapy at a dose of 500 mg/kg three times a week was initiated for the patient. The patient has been followed-up for development of malignancies and radiosensitivity and local treatment for refractory warts is carried out in cooperation with department of dermatology.

Discussion: NHEJ is the major mechanism for repair of double strand formed during class switch recombination (3). It is known that, as a result of Artemis (DCLRE1C) mutation involved in this pathway, clinical phenotypes varying from clinically atypical severe combined immunodeficiency to antibody deficiency alone may occur. These cases have been known to have predisposition to radiosensitivity and malignancies (4,5). The present case is conspicuous regarding a case of combined immunodeficiency that reached to adulthood.

POSTER 62 - CARMIL2 MUTATION IN A SENEGALESE CHILD : NEED COLLABORATION FOR TAKE CARE PATIENT AND HIS FAMILY

AUTHORS

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Biography:
Dermatologue-Venereologue
Master Immunology-Infectiology
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Introduction: We report the case of a Senegalese child in who was found to have a CARMIL2 mutation following the development of disseminated molluscum contagiosum skin lesions.

Observation: This was a 10-year-old child from a 3rd-degree consanguineous marriage with 5 brothers and sisters. He was seen in consultation for cutaneous lesions of molluscum contagiosium evolving since the age of 2. These lesions were unusual in that they were diffuse all over the body, large in size and becoming tumoral, frequently superinfected with bacteria, and recurred after often mutilating surgery. The child's blood count showed a constant hypereosinophilia of over 5000 elements/mm3. There was no lymphopenia and total IgE was normal. Lymphocyte immunophenotyping with CD3, CD4, CD8, CD19, CD20, CD16 and CD56 markers was normal. Genetic mutation testing using whole exom sequencing identified the CARMIL2 mutation. The child's treatment required an allogeneic bone marrow transplant. Unfortunately, this treatment is unavailable in Senegal, making this child's future rather bleak.

Conclusion: CARMIL2 is a rarely described mutation, and the only treatment is allogeneic bone marrow transplant, which is non-existent in Senegal. This fact, which we underline through this case, makes it essential to seek collaboration in the treatment of our patients in order to improve their survival.

POSTER 71 - A NOVEL SPI1 MUTATION IN A PATIENT WITH AGAMMAGLOBULINEMIA

AUTHORS

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Biography:
Jelena Ljubicic is MD and PhD student at Faculty of Medicine, University of Belgrade, Serbia. She is also a junior researcher at Institute of Molecular Genetics and Genetic Engineering, interested in primary immunodeficiences and malignancies in patients with PID.

Introduction: Agammaglobulinemia is a primary immunodeficiency characterized by a low number or absence of mature B lymphocytes and consequently by immunoglobulin deficiency. In 2021, six patients with pathogenic variants in SPI1 gene associated with agammaglobulinemia type 10 (PU.MA) were described for the first time. This gene encodes the pioneer transcription factor PU.1, which plays an important role in the differentiation of B lymphocytes, monocytes, and conventional dendritic cells. Here we present a female patient with a novel mutation in SPI1 gene which has not been previously found in patients with PU.MA.

Case description: A 37-year-old female patient with frequent middle ear infections in early childhood was diagnosed with agammaglobulinemia at the age of 15 when she started immunoglobulin replacement therapy (IgRT). One year later, an allogeneic hematopoietic stem cell transplant from a healthy sibling donor was performed. Unfortunately, chimerism analysis found no DNA material from the donor in the patient's blood, suggesting graft rejection, so she remained dependent on antibody replacement therapy. Years later, she was diagnosed with protein-losing enteropathy, and despite escalating doses of IgRT, IgG levels remained low.
Subsequently, the patient developed persistent COVID -19 viremia and bacterial meningoencephalitis. Clinical exome sequencing using the TruSight (Illumina) panel was performed and in comparision with the human reference genome (hg19), has revealed a heterozygous mutation in exon 4 of the SPI1 gene. This mutation is characterized by the insertion of 2 nucleotides (c.441dup), a reading frame shift, and the insertion of a premature stop codon. According to the American College of Medical Genetics and Genomics, this mutation is described as a likely pathogenic-class 2 (PVS1_Very Strong).

Conclusion: From analysis of previous literature, we concluded that the mutant sequence in exon 4 encodes the PEST region of the pioneer transcription factor PU.1, which is responsible for interaction with other transcription factors. Immunophenotyping of peripheral blood cells did not reveal CD19+ B cells, suggesting that a differentiation arrest may have developed between the prepro-B and pro-B stages, where there is a high requirement for PU.1 activity. Next- generation sequencing can be a very useful tool to uncover the causes of rare primary immunodeficiencies, but further analysis is needed to explain the relationship between patient genotype and clinical presentation.

POSTER 87 - NOVEL IMMUNODEFICIENCY CAUSED BY HOMOZYGOUS MUTATION IN SOLUTE CARRIER FAMILY 19 MEMBER 1 ENCODING THE REDUCED FOLATE CARRIER

AUTHORS

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AFFILIATIONS

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Biography:
The presenting author started his career as a paediatrics since 2006 in Japan. He received PhD in 2017. Since 2019, he has been working in the Hospital for Sick Children for the analysis of inborn errors of immunity.

Objective: Folates are essential for de novo synthesis of purine and pyrimidines during DNA and RNA synthesis as well as normal tissue growth and development. Genetic aberrations affecting metabolic pathways can lead to primary immunodeficiency. Notably, the Reduced Folate Carrier (RFC), encoded by the SLC19A1 gene, transports folate in addition to cyclic dinucleotides (CDN), so called ‘danger signals’ that trigger activation of the Stimulator of Interferon Genes (STING) pathway required for orchestrating immune responses. Here, we report on two distantly related patients with recurrent fever, oral aphthous lesions, immunological, hematological, and neurological abnormalities, whose genetic investigations revealed RFC to be a novel Mendelian cause of immunodeficiency.

Design and method: Patient data was reviewed retrospectively and prospectively in accordance with Research Ethics Board protocols. Extensive immune evaluations, including flow cytometric analysis of lymphocyte subpopulations and assay of T cell function were performed. Whole exome sequencing (WES) followed by Sanger confirmation were employed to identify the genetic abnormality in the patients and segregation in family members. To determine functional significance, structural modelling and cellular and molecular studies using patient primary cells and HEK293T cell lines (wild-type and mutant) were performed. Folic acid was administered to both patients in an attempt to overcome the defects in RFC function.

Results and Conclusions: WES identified a novel homozygous mutation in SLC19A1, c.1042G>A (p.G348R), encoding RFC, in our patients. Structural modelling studies indicate that the G348R amino acid change alters the transmembrane domain tertiary structure, disrupting the integration of RFC into the lipid-bilayer and leading to loss-of-function. Indeed, cells expressing the mutant RFC demonstrated reduced cGAMP-dependent phosphorylation of STING, as well as dampened NF- kB activation and impaired induction of IFN-beta transcription. These results were similarly reflected in patient cells. Evaluation of lymphocyte subpopulations revealed low CD4+ T cells and CD19+ B cells. Moreover, CD24hi cells were reduced in resting and un-switched memory cells. In vitro responses to phytohemagglutinin were depressed. Folic acid supplementation rapidly normalized platelet counts and improved anemia. Hair and skin discoloration, mouth lesions, and chronic diarrhea also improved. In contrast, neurological and developmental issues remained unchanged. In summary, we report for the first time, two patients with primary immunodeficiency caused by a homozygous missense mutation in SLC19A1 with recurrent infection, hematological abnormalities, skin, hair, and neurological disorders, which were partially reversible by folic acid supplementation.

POSTER 91 - TNFRSF13B MUTATIONS IN COMMON VARIABLE IMMUNODEFICIENCY: CORRELATION OR CAUSATION?

AUTHORS

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AFFILIATIONS

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Biography:
Fresh undergraduate working as Intern doctor in Maharajgunj Medical Campus, Tribhuwan University Teaching Hospital, Nepal with profound interest in Neuroimmunology.

Background: CVID is continuously evolving with new genes being discovered at an exponential rate and precision medicine being the road ahead. With studies emerging across the globe, they have reported varying frequency and types of mutations of TNFRSF13B/TACI in CVID and increasing non-infectious manifestations of it.

Objective: To report different mutations in TNFRSF13B encoding transmembrane activator and calcium- modulating cyclophilin ligand interactor(TACI) in common variable immunodeficiency(CVID) and to review clinical phenotypes associated with them.

Design and method: This systematic review was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta analyses (PRISMA) guidelines. Article selection was performed by searching the MEDLINE (PubMed), Google Scholar, Scopus, Web of Science and EMBASE using predefined search strategy from inception till May 27, 2023. The search strategy was not limited by study design but only for articles in the English language.

Results: A total of 1443 CVID patients from eight full-text articles were included in the analysis. 720 of them were from North America, 644 from Europe, 26 from South America, and 53 from Asia. Proportion of CVID patients carrying at least one TNFRSF13B mutation ranged from 6.25% and 21%. Twelve distinct mutations (C104R, S144X, A181E, S194X, R202H, ins204A, P251L, p.R72H , p.V220A, P42T, C172Y, c.61+1G>T) were found, with C104R being the most prevalent. Conflicting evidence was reported regarding causal relationships of C104R and A181E variants in CVID patients. Autoimmune disease was found in 31-46% with autoimmune thrombocytopenia being most common. Lymphoproliferative disorders were reported in 60% of cases with splenomegaly being most common.

Conclusions: TACI mutations significantly raise the risk of autoimmunity and lymphoid hyperplasia in CVID. Despite the fact that the C104R mutation had previously been recognized as a disease- associated mutation, recent studies reported that its frequency was not significantly different from that of healthy individuals. To further corroborate results, larger studies must be replicated across multiple settings.

POSTER 94 - NOVEL HYPERMORPHIC VARIANTS IN IRF2BP2 IDENTIFIED IN PATIENTS WITH COMMON VARIABLE IMMUNODEFICIENCY AND AUTOIMMUNITY

AUTHORS

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Biography:
Dr Faranaz Atschekzei is a Principal Investigator who has successfully researched immunogenetics at the MHH Clinic for Rheumatology and Immunology for a decade. Her research group focuses on the molecular genetics of primary immunodeficiencies and how epigenetic factors influence immunodeficiency diseases. Primary immunodeficiencies are congenital and often genetically determined defects of the immune system that manifest themselves in childhood or even in adolescence or adulthood. Dr Atschekzei's research group is investigating the molecular basis of the disease in order to enable patients with these heterogeneous diseases to receive a very individual and targeted therapy soon.

The nuclear IRF2BP2 protein (IFN regulatory factor 2 binding protein 2) was initially identified as a transcriptional corepressor dependent on Interferon regulatory factor-2 (IRF-2). Its coding gene IRF2BP2 has been described as ubiquitously expressed in normal and tumour cells and tissues, suggesting a potential role for this transcriptional cofactor in different cell signalling pathways. Variants in IRF2BP2 have recently been reported in familial CVID, immune dysregulation, and inflammatory conditions.

This study investigated three rare novel variants identified in patients with primary antibody deficiency and autoimmunity by whole exome-sequencing (WES). Following transient overexpression of EGFP-fused mutants in HEK293 cells and transfection in Jurkat cell lines, we used fluorescence microscopy, real-time PCR and Western blotting to analyze their effects on IRF2BP2 expression, subcellular localization, nuclear translocation of IRF2, and the transcriptional activation of NFkB1(p50) following stimulation.

We found altered IRF2BP2 mRNA and protein expression levels in the mutants compared to the wildtype after IRF2BP2 overexpression. In confocal fluorescence microscopy, variants located in the C-terminal RING finger domain showed an irregular aggregate formation and distribution instead of the expected nuclear localization when compared to the variants in the N-terminal zinc finger domain and their wildtype counterpart. Immunoblotting revealed an impaired IRF2 and NFκB1 (p50) nuclear localization in the mutants compared to the IRF2BP2 wildtype counterpart. LPS stimulation reduced both the expression and localization of IRF2BP2 to the nucleus.

Our data provide additional evidence for the clinical significance of IRF2BP2 mutations in the pathogenesis of immunodeficiency and immune dysregulation. It suggests an impairment of the nuclear translocation of IRF2 and NFκB1 (p50) due to the upregulation of IRF2BP2, which may affect specific gene expressions involved in immune regulation.

POSTER 98 - COEXISTENCE OF TWO PATHOGENIC TACI AND ARTEMIS GENE DEFECTS IN A PATIENT PRESENTING WITH GRANULOMATOUS SKIN LESIONS

AUTHORS

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AFFILIATIONS

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Biography:
Seda Tunca, born in 1985 in Siverek, Turkey . Diyarbakır Anatolian High School and Harran University School of Medicine. She recevied her MD degree in 2010. She completed pediatric residency in 2015 at Health Sciences University Tepecik Training and Research Hospital and pediatric allergy and immunology fellowship in 2020 and currently at Celal Bayar University School of Medicine.

Introduction: ARTEMIS (DCLRE1C) is an endonucleolytic enzyme involved in non-homologous double-strand DNA break repair and V(D)J recombination. Amorphic Artemis mutations cause T-B-NK+ severe combined immunodeficiency (SCID). The transmembrane activator and CAML (calcium-modulator and cyclophilin-ligand) interaction (TACI) protein is a member of the TNF- like receptor family. A patient with both TACI and ARTEMIS gene mutations is presented.

Case presentation: The patient who is an 11-year-old male, presented with ulcerated skin lesions on the face, trunk and extremities that had persisted for 5 years. The patient's growth and development were normal for his age, and there was no previous history of recurrent sinopulmonary or other system infections. IgG, IgM and IgA values were found to be low for age. A heterozygous (p.Cys104Arg, c.310T>C) mutation in the TACI gene was detected in the sequence analysis of the patient, who was followed up with a prediagnosis of common variable immunodeficiency (CVID) with isolated skin granulomas. Regular IVIG treatment was started with no improvement of the lesions. During follow-up, he began to have severe clinical symptoms such as recurrent upper and lower respiratory tract infections, total alopecia and progression of the skin lesions, which were not fully explained by the heterozygous TACI mutation. Reevaluation of the patient with targeted next-generation sequence analysis (Ion AmpliSeq™ Primary Immune Deficiency Research Panel) showed a homozygous mutation in the DCLRE1C (ARTEMIS) gene.

Conclusions: Multiple genetic defects may coexist in patients with atypical onset and clinical course. Molecular examinations are important in reaching a definitive diagnosis. Reporting new clinical findings will help identify the phenotypes associated with TACI and ARTEMIS mutations.

POSTER 109 - NOVEL GENETIC VARIANTS IN HEREDITARY ANGIOEDEMA: A COHORT STUDY FROM THE PAST 30 YEARS IN A SINGLE SPANISH HOSPITAL

AUTHORS

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Biography:
MD. Andrea Ferranti is a medical graduate from the University of Monterrey, Mexico, currently in the third year of specialization in Immunology in Cáceres, Spain. Her primary focus lies in expanding her expertise in the diagnosis, treatment, and management of immune-related disorders. Participating in medical congresses and presenting her findings offers her the opportunity to share knowledge, exchange ideas with colleagues, and learn from other experts in the field. Through clinical work and research, she aims to contribute to the advancement of medical science and enhance patient outcomes.

Objective: The aim of this study was to analyze and report the genetic variants found in 20 patients from 8 Spanish families diagnosed with hereditary angioedema due to C1 inhibitor deficiency (HAE- C1inh), within the population of Cáceres, Extremadura, and establish a genotype-phenotype correlation.

Design and method: Clinical and laboratory data were collected at Hospital Universitario in Cáceres, serving a population of 400,000. Patients were recruited between 1993 and 2023. Demographic data, clinical information, treatment, C1-inhibitor (C1-inh) levels, and function were compared among patients with different SERPING1 gene mutations. DNA was analyzed using Next Generation Sequencing (NGS) and multiplex ligation-dependent probe amplification (MLPA).

Results: Clinically relevant mutations in the SERPING1 gene were identified in eight families. These included six missense mutations, one large duplication, and one nonsense variant. Some variants were already described in publications and/or genomic databases, while others are novel (c.599C>T, c.1193T>A) [Table 1].

The missense variant found in family 3 (c.599C>T) is in exon 4, classified as of uncertain significance (VUS) by the predictors tool. It showed segregation with levels and function of C1 inhibitor. However, three out of six members were asymptomatic. Interestingly, in the second generation, the proband's nieces had an earlier age of onset. The proband is currently undergoing long-term prophylaxis (LTP) with Danazole.

In family 6, a missense variant (c.1193T>A) located in exon 7 was found. This variant was predicted to be pathogenic and was present in the father, correlating with C1inh levels and function. The proband is receiving LTP treatment with tranexamic acid.

In family 2, no variants were identified through NGS, but MLPA revealed a duplication affecting at least exons 5 and 6. The proband has experienced poor disease control and requires LTP treatment with Lanadelumab. The father died presumably because of laryngeal angioedema.

Conclusions: Hereditary angioedema (HAE) is a rare and potentially life-threatening genetic disorder caused by mutations in the SERPING1 gene. So far, over 700 pathogenic variants have been described. However, mutations often go undetected (10%), and additional methods such as long-range PCR and MLPA are necessary for comprehensive analysis. Missense variants were the most common, followed by a gross duplication and a nonsense variant. Two novel missense variants were identified. No duplication variant affecting both 5 and 6 exons have been described in the literature so far. The study highlighted the diversity in the course and age of onset of HAE-C1inh, indicating variable expressivity within the condition.

POSTER 110 - EXPANDING C-X-C CHEMOKINE RECEPTOR 4 VARIANT LANDSCAPE IN WARTS, HYPOGAMMAGLOBULINEMIA, INFECTIONS, MYELOKATHEXIS (WHIM) SYNDROME: INTEGRATING CLINICAL AND FUNCTIONAL DATA FOR VARIANT INTERPRETATION

AUTHORS

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AFFILIATIONS

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Biography:
Katarina Zmajkovicova is a group leader at X4 Pharmaceuticals. The research of her team focuses on chronic neutropenias, in particular WHIM syndrome. She completed Master of Biomedical Sciences at Katholieke Universiteit Leuven, Belgium and obtained PhD degree in Molecular Biology at the University of Vienna, Austria. Katarina has long-standing interest in cellular signaling with the focus on mechanistic understanding of disease pathology and mode- of-action of small molecule drugs.

Objective: Warts, Hypogammaglobulinemia, Infections, Myelokathexis (WHIM) syndrome is a rare immunodeficiency disease typically caused by gain-of-function variants in C-terminus of CXCR4. Due to variable clinical presentations, genetic testing for CXCR4 variants can aid with diagnosis of WHIM syndrome. As of February 2023, 35 CXCR4 variants in patients with WHIM syndrome were identified via publications, ClinVar, and Invitae/PATH4WARD genetic screening initiative. Most of these CXCR4 variants were categorized as variants of uncertain significance (VUS) and were not informative for clinical decision-making. We aimed to expand knowledge of genetic landscape in WHIM syndrome and reclassify potential disease-causing variants by Sherloc/American College of Medical Genetics and the Association for Molecular Pathology (ACMG-AMP) criteria.

Design and Method: Literature, databases (Clinvar, GnomAD), and genetic testing programs (Invitae) were used to collect information on CXCR4 variants (ie, phenotype, de novo occurrence, variant and phenotype segregation within family pedigree, number of independent cases/pedigrees, and allele frequency). CXCR4 variants identified were tested in a pipeline of in vitro assays. CXCR4 internalization responses in CXCR4 variant-expressing cells stimulated with C-X-C chemokine ligand 12 (CXCL12) was used to assess pathogenicity.

Results: The 35 identified CXCR4 variants were interpreted in collaboration with Invitae using Sherloc/refined ACMG-AMP criteria. Absence in general population (GnomAD), segregation with disease, de novo occurrence, and reports of multiple unrelated cases were factors that conferred most pathogenic points for CXCR4 variant classification. In vitro functional testing of 31/35 identified variants showed that all 31 exhibited substantially impaired internalization across a range of CXCL12 concentrations, in line with previous reports of known pathogenic CXCR4 variants. By integrating genetic, clinical, and functional data, we reclassified 14 CXCR4 variants: 4 from VUS to pathogenic (P), 7 from VUS to likely pathogenic (LP), and 3 from LP to P, resulting in 20 variants being recognized as LP or P for WHIM syndrome (Figure). The remaining 15 CXCR4 variants could not be reclassified due to limited clinical and family history data, which leaves the possibility that these VUSs are disease causing.

Conclusions: We showed the value of functional in vitro testing and detailed variant workup in resolving the pathogenic potential of variants, especially in cases when clinical information is insufficient for confident variant interpretation. These data improve understanding of genetic landscape in WHIM syndrome and support the molecular diagnostic process for patients.

Nykamp K, et al. Genet Med. 2017;19(10):1105-1117.

POSTER 117 - LINKED HYPER-IMMUNOGLOBULIN M SYNDROME HARBORING A UNIQUE AND NOVEL CD40-LIGAND GENE MUTATION, A CASE REPORT STUDY

AUTHORS

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AFFILIATIONS

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Biography:
- Dr. Abhishek Mohanty Is currently the Program Director and Head, Centre for Biorepository and Biobanking, HCG (Health Care Global) Cancer Hospitals, Bangalore. Prior to this Dr.
Mohanty served as Principal Research Officer and Head of Research, at prestigious Rajiv Gandhi Cancer Hospital and Research Institute (RGCIRC), Delhi. He is also the Regional Director (South-India) for Biobanking India Foundation (BBIF).

- Dr. Mohanty was also the founder Head of Molecular Oncology Division at MVR Cancer Hospital and Research Institute, Calicut, Kerala. Dr. Abhishek Mohanty received his Doctorate in Biochemistry from Indian Institute of Science, Bangalore, India and has post-doctoral fellowships from Ottawa Heart Institute, Ottawa, Canada and from the Institute of Stem Cell & Regenerative Medicine (INSTEM-NCBS, Bangalore),

- Dr. Abhishek has more than 12 years of teaching, research and molecular oncology and translational research and oncology experience and has more than 30 publications in peer reviewed international journals. Dr. Abhishek has authored a Book chapter in Springer Nature and holds two patents, one Indian and one US patent. He serves in the editorial board of many peer reviewed international journals like Human Gene and Frontiers in Immunology, PLOS ONE
JCCS etc.

- Dr .Mohanty's is driven by his passion to expand the concept and the quint essence of tumor and bio-banking in the conduct of medical and clinical /translational cancer research owing to advent of -omics science (genomics, transcriptomics, proteomics, metabolomics) and the ability of omics to develop large electronic databases that store huge amounts of information (big data) associated with patient clinics leading to cancer biomarker and drug discovery for early diagnosis ,better prognosis and prevention of multifactorial diseases like cancer.

Objective: The immune system is activated by the protein CD40L, also known as the CD40 ligand and is essential for controlling a variety of immunological responses. Multiple disorders including X-linked hyper-IgM syndrome have been linked to CD40L mutations.
The X-linked Hyper-IgM (X-HIGM, HIGM1) syndrome is a rare variant of the HIGM resulting out of mutations in the gene encoding for the membrane glycoprotein CD40 ligand or CD154 protein (CD40L, CD154, or gp39), mainly expressed on the surface of activated T cells and platelets.
The CD40L, member of the TNF (tumor necrosis factor) super family interacts with its receptor, CD40 expressed on B cells, macrophages, and dendritic cells. For illuminating their underlying mechanisms and creating new therapeutic approaches, it is crucial to comprehend the structural and functional effects of these alterations.

Design and method: In the present study, we investigated the molecular defects underlying such a PID in a patient presenting with clinical history of pneumonia and acute respiratory distress syndrome (ARDS) at 7 months of age and diagnosed as transient hypogammaglobulinemia with decreased levels of IgG and increased levels of IgM.
RESULTS: We have identified a novel and yet to be reported, frame shift deletion of a single base pair (c.229delA) in exon 2 (p.Arg77AspfsTer6) of the CD40L gene ensuing the premature truncation of the protein by 6 amino acids by targeted gene sequencing.

Conclusions: The frame shift mutation identified as a CD40L variant was found to be pathogenic which was also validated by Sanger sequencing. The in-silico analysis of c.229 del A mutation also predicted the change to be pathological affecting the structure and function of the CD40L (CD40L, CD154) & its protein-protein interaction properties. To examine the effects of CD40L mutations on its structure and dynamics, we used molecular dynamics (MD) simulations. Using the Pymol software, we created six mutant models (each with a single amino acid change) to mimic clinically significant mutations found in individuals with the CD40l deficiency.

These mutations affect the portion of the cd40l protein that is soluble and interacts with the cd40 receptor and result in altered amino acids that have different physiological properties based on the r group. The G144E mutation's rmsd plot depicts the mutant structure have more deviation compared to the wild-type structure which may lead to the structure instability. This mutation is close to the cd40l active site, which aids in the interaction between the cd40l and cd40 receptor.

POSTER 124 - APPLYING WES TECHNIQUE FOR DIAGNOSIS CHRONIC GRANULOMATOUS DISEASE IN VIETNAMESE PATIENTS

AUTHORS

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Biography:
I, Nguyen Thi Phuong Mai, have completed my PhD. in 2018 at Institute of Genome Research, Vietnam Academic of Science and Technology in Hanoi, Vietnam. I'm a vice-head of Human Genetics Department in National Children's Hospital. I have published more than 30 papers in reputed journals. I'm interested in applying molecular techniques for research and diagnosis some genetic diseases especially primary immuno deficiencies

Chronic granulomatous disease (CGD) is a rare primary immunodeficiency disorder (PID) due to genetic defects in the NADPH oxidase of phagocytes. Affected patients become susceptible to infections such as pneumonia, diarrhea, and skin ulcer types. The patients require life-long treatment with prophylactic antibiotics, anti fungals, or hematopoietic stem cell transplantation (HSCT) therapy.

Patients: Six patients from different Vietnamese families were collected for genetic analysis at Allergy, Immunology, and Rheumatology Department, Vietnam National Hospital Pediatrics. They were diagnosed with CGD by flow cytometry test with the conversion of dihydrorhodamine (DHR) 123 to rhodamine 123.

Methods: We performed whole exome sequencing (WES) as a tool for detecting novel mutations. The mutations were confirmed by the Sanger sequencing method in patients and their families. The influence of the mutations was predicted with the in silico analysis tools: PROVEAN, SIFT, PolyPhen 2, Mutation Taster, and MaxEntScan. Results: In this study, five mutations were found in six unrelated patients with CGD from different Vietnamese families. Three novel pathogenic mutations were detected including one mutation (c.45+2 T>G) in the CYBB gene and two mutations (c.187_188insA and c.289G>C) in the NCF2 gene.

Conclusions: Our results of CGD-related mutations contribute to the general understanding of the etiology of the disease and emphasize that WES sequencing can be used as a tool to help to diagnose carriers as well as assist in genetic counseling and prenatal screening.

POSTER 132 - HOMOZYGOUS MUTATION IN TNFRSF13B (CODING FOR TACI) IN AN ASYMPTOMATIC PATIENT WITH HYPOGAMMAGLOBULINEMIA

AUTHORS

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Biography:
A 29-year-old doctor educated in Ecuador. I am currently a third year resident of Immunology in Cáceres/Spain. Wife, mother of two and passionate about medicine and science. Languages: Spanish / English.

Objective: The genetic cause of Common Variable Immunodeficiency (CVID) is unknown in 70% of cases. About 10% percent of patients carry heterozygous mutations in the TNFRSF13B gene, which codes for TACI. This protein promotes the differentiation of plasma cells and acts as a mediator in the isotype change of immunoglobulins. This study was developed to characterize an asimptomatically man with hypogammaglobulinemia produced in the context of a not described mutation in TNFRSF13B.

Methods: We collected clinical data and performed immunological and genetical tests in order to categorize the patient.

Results: A 37 year old man with no relevant family history was referred to the Immunology service due to a casual finding of hypogammaglobulinemia. He started at the age of 2 years with recurrent tonsillitis and otitis until he was tonsillectomized at 5 years. In adulthood he remains asymptomatic. In a 2010 low levels of total proteins were found in serum, what makes us think that hypogammaglobulinemia was already present. The other biochemical and inmunological parameters remain normal. Secondary causes of hypogammaglobulinemia were ruled out: renal or digestive protein-loss syndromes, drug causes, and lymphoproliferative processes. In the genetic study, an homozygous complex variant was detected in TNFRSF13B located in exon 4-5. It codes for TACI (Transmembrane Activator and Calcium-modulator and cyclophilin ligand Interactor). Although its exact nature is unknown, it involves an inversion of intron 3 and exons 4-5. It is expected to result in an absent or interrupted protein product. This variant has not been reported in the literature. However, there is a pathogenic mutation (p.Ala181Glu) described in the same location, associated with Common Variable Immunodeficiency. This suggests that this region has clinical relevance and that the affected variants could cause disease.

Conclusion: An asymptomatic patient with panhypogammaglobulinemia with a normal number of memory B lymphocytes and a good response to vaccines shows a complex mutation not previously described in a pathogenic area of TNFRSF13B. However, he does not meet criteria for the diagnosis of CVID. It would be interesting to know the allelic dosage and penetrance of these genetic variants. And thus have a clearer vision of why some patients present just analytical findings and others develop illness.

POSTER 139 - DOUBLE-NEGATIVE T CELLS IN INBORN ERRORS OF IMMUNITY WITH AUTOIMMUNE LYMPHOPROLIFERATIVE SYNDROME-LIKE PHENOTYPE

AUTHORS

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Biography:
Mahnaz Jamee is a medical doctor and research fellow performing research in the field of inborn errors of immunity. After graduation from Alborz University of Medical Sciences, she was enrolled in a research assistantship position at Research Institute for Children's Health, Shahid Beheshti University of Medical Sciences. She won a research fellowship grant from EAACI and EFIS-IL for a lab placement at Leiden University Medical Center. She is interested in monogenic immune dysregulation disorders and T cell immunodeficiencies.

Objective: Elevated DNT cell is a historical hallmark for the diagnosis of autoimmune lymphoproliferative syndrome. However, they may also be compromised in ALPS-like patients, consequently contributing to the diagnosis delay and hindering disease-specific monitoring of ALPS-like disorders.

Design and Method: In this cross-sectional study, patients with ALPS-like defects who gave consent for participation were recruited. Following thorough history taking, immunophenotyping for lymphocyte subsets was performed using BD FACS CaliburTM flow cytometer and the results were compared to normal range for ages.

Results: Fifteen ALPS-like patients (60% male and 40% female) at a median (IQR) age of 14.0 (7.6-21.8) years were enrolled. Most patients (8, 53.3%) were born to consanguineous parents. Family history of immunodeficiency was present in 8 (53.3%) patients. First presentations of IEI occurred at a median (IQR) age of 18 (4-36) months and comprised of neurologic (4, 26.7%), hematologic (3, 20%), infectious (3, 20%), lymphoproliferative (3, 20%), and autoimmune (2, 13.3%) disorders. Clinical and molecular diagnoses were established in 8.0 (4.0-17.0) and 9.5 (5.0-20.9) years, respectively. Molecular defects were observed in these genes: LRBA (3, 20%), CTLA-4 (2, 13.3%), BACH2 (2, 13.3%), AIRE (2, 13.3%), and FOXP3, IL2RB, DEF6, RASGRP1, PIK3CD, and PIK3R1 each in one patient (6.7%).
The most common manifestations were infections in 14 (93.3%) patients [mainly in upper (8, 53.3%) and lower (7, 46.7%) respiratory tract] and autoimmune disorders in 12 (80%) patients [autoimmune cytopenia (7, 46.7%), autoimmune endocrinopathy (5, 33.3%), IBD and autoimmune enteropathy (3, 20%), cutaneous disorders (3, 20%)]. Ten patients (66.7%) suffered from lymphoproliferations.

The median (IQR) count of leukocytes and lymphocytes were 7160 (3690-12600) and 3266 (2257-5370) cells/mm3, respectively. The median (IQR) absolute counts of lymphocyte subsets were as follows: T CD3+: 2085 (1487-4222), T CD4+: 979 (852-2138), T CD8+: 886 (357-1720),
TCRαβ+CD3+CD4+CD8+: 2050 (1261-3937), and DNT: 18 (11-36) cells/mm3. Compared to normal ranges for ages, low lymphocytes, low T CD3+, low T CD4+, low T CD8+, and reversed T CD4+/T CD8+ ratio each were observed in 3 (20%) patients. Only one patient
with FOXP3 mutation had an elevated level of DNT cells.

Treatments at the time of study included intravenous immunoglobulin (8, 53.3%), prophylactic antibiotics (8, 53.3%), steroids (6, 40%), and monoclonal antibodies (4, 26.7%).

Conclusions: Most ALPS-like patients manifested normal DNT cell count. For a small subgroup of patients with high DNT cells, ALPS-like genes may be the underlying etiology and should be included in the diagnostic genetic panel.

POSTER 140 - DIAGNOSTIC IMPROVEMENTS BY WHOLE GENOME SEQUENCING AND OPTICAL GENOME MAPPING IN DETECTION OF NEW DISEASE- CAUSING STRUCTURAL VARIANTS IN INBORN ERRORS OF IMMUNITY

AUTHORS

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Biography:
-study of medicine (Marburg University)
-study of chemistry (Marburg University)
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Objective: Today nearly 500 causative genes have been described in Inborn Errors of Immunity (IEI), however, after Panel-or Exome sequencing no genetic diagnosis can be made in 70-90% of affected patients.
Using a combination of different diagnostic methods, Whole Exome Sequencing (WES), Whole Genome Sequencing (WGS) and Optical Genome Mapping (OGM), we aim to improve the diagnostic yield in patients with suspected IEI by detection of the full spectrum of genetic alterations like single nucleotide variants (SNVs) and Structural variants (SVs) including copy number alterations, insertions or inversions affecting function of known or new genes in IEI.

Design: Patients with suspected IEI that meet the European Society for Immunodeficiencies (ESID) criteria are eligible for the study. Patients with non-conclusive results after routine diagnostic procedures were included.
A holistic reanalysis of WES/WGS data as well as OGM was performed for detection of potentially causative SNVs and SVs. After classification, functional analysis of potentially pathogenic variants takes place.

Method: WES/ WGS was conducted using standard short-read sequencing techniques.
For OGM, ultra-high molecular weight DNA was extracted from frozen blood and labelled using DLE1 enzyme. Total molecule data of 1500 Gb DNA was collected and filtered for a minimum fragment size of 300kb for de novo assembly. During comparison to the hg38 reference, variants with an allele frequency <1% compared to a reference data set were reconsidered.

Results: In our growing cohort of patients, we were able to detect causative variants by reanalysis of WES/WGS data sets. By detecting a disease-causing homozygous variant (p.(R281W)) in STING1 we could confirm an autosomal-recessive inheritance pattern of SAVI (STING- associated vasculopathy) previously reported to follow autosomal dominant inheritance (Wan et al., 2022). Further, segregation analysis in a large family presenting with diverse symptoms of A20 haploinsufficiency allowed classification of a heterozygous variant in TNFAIP3 c.751G>A p.(Gly251Ser) as disease causing (class 4), formerly classified as variant of uncertain significance. As an example, for a larger rearrangement, a de novo deletion at chromosome 3 (3p21.31) with a size of 834kb has been identified in a patient with an autoinflammatory phenotype. It affects around 33 genes including ARIH2, which acts as negative regulator of the NLRP3 inflammasome. Haploinsufficiency of this gene might explain the phenotype. Further variants of uncertain significance have been identified, which require functional analysis.

Conclusions: The combination of WES/ WGS and OGM can improve the detection of disease-causing variants and allows further investigations to understand potential pathomechanisms.

POSTER 145 - EARLY DIAGNOSIS OF HYPER-IGE SYNDROME USING WHOLE EXOME SEQUENCING - A CASE REPORT

AUTHORS

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Biography:
My name is Luiza, I have a degree in Biomedical Science, a specialty in molecular diagnosis and I'm currently working on my master degree on the biotechnology program of Faculdades Pequeno Príncipe.

I worked with the DHR test to diagnose children with chronic granulomatous disease for 3 years during my undergraduate studies. In my master project I investigate PIDs by NGS sequencing in children under 4 years admitted in the biggest Brazilian pediatric only hospital.

Objective: Describe the clinical and immunological manifestations of a patient diagnosed with Hyper IgE Syndrome due to STAT3 mutation (STAT3-HIES) at an early age.

Design and method: A case report based on clinical and laboratory data collection of medical records and Whole Exome Sequencing (WES) analyses.

Results: A 3-months-old girl was transferred to our specialized pediatric hospital for the treatment of sepsis due to Staphylococcus aureus. While recovering from sepsis, she developed pneumonia, followed by otitis, diarrhea and urinary tract infection. From the tracheal aspirate culture, it was identified Moraxella catarrhalis and Acinetobacter ursingii, Pseudomonas aeruginosa was identified in the ear secretion culture and Candida tropicalis was isolated in the urine culture. The hemogram revealed leukocytosis (24,270cells/uL), with eosinophil count of 5,097cells/uL. Immunoglobulin evaluation revealed high IgE for age (237UI/mL) while the other classes maintained in the reference range. The patient was diagnosed with spongiotic dermatitis based on immunohistochemical examination in skin biopsy when she was 5 months old. The mother reported that the child's symptoms started when she was 15 days old, with diarrhea, otitis and dermatitis. Since then, she presented with recurrent otitis and 3 episodes of pneumonia. The patient's parents are not consanguineous and both parents and the older sibling are healthy.
To aid in the diagnosis of HIES, in 1999 Bodo Grimbacher developed an identification methodology of warning signs for this syndrome, with symptom-based scoring. According to this methodology, individuals who score >15 are considered likely to have a genotype of HIES. When applying the Grimbacher classification, the proband scored 30 by the time our Immunology team evaluated her, demonstrating a phenotype highly compatible with the syndrome (Figure 1).
Genetic investigation based on exome analysis identified the heterozygous variant c.1144C>T (p.R382W) in STAT3, one of the genes that cause HIES. The variant was classified as pathogenic following the ACMG criteria and was not identified in the child's sister nor in her parents' DNA.
Genetic evaluation combined with clinical and laboratorial data, permitted the diagnosis of autosomal dominant HIES in a patient younger than 2 years old.

Conclusions: The variant identified in the proband is one of the most commonly found on the HIES-AD patients, however, the average age at diagnosis in the literature is 4-5 years. In the case presented, the clinical suspicion added to the access to genetic evaluation allowed earlier diagnosis, which is essential to a better quality of life and longer survival.

POSTER 166 - IKZF1 GENE DEFECTS - DIVERSE CLINICAL SPECTRUM

AUTHORS

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Takci S, Esenboga S, Gonc N, Yigit S. Persistent hypoglycemia caused by umbilical arterial catheterization. J Pediatr Endocrinol Metab. 2011;24(11-12):1081-3.

Introduction: Ikaros zinc finger 1 (IKZF1 or Ikaros) is a hematopoietic zinc finger DNA-binding transcription factor that plays an important role in the differentiation of lymphocytes and myeloid cells. While somatic IKZF1 mutations have been shown to be important in the etiology of B-cell-derived acute lymphoblastic leukemia and poor prognosis in patients, recently, loss-of-function germline heterozygous mutations in IKAROS have been identified as the cause of two distinct inborn errors of immunity (IEI) diseases: mutations acting by haploinsufficiency present with a CVID- like phenotype characterized primarily by increased susceptibility to infections, whereas mutations acting in a dominant negative fashion present with a combined immunodeficiency phenotype.
The clinical, laboratory, and genetic features of patients who were followed up on in our clinic and were found to have an IKZF1 gene variant were discussed in this study.

Results: A mutation or polymorphism in the IKZF1 gene was identified in seven patients, three of whom were adults and five of whom were children. Table 1 summarizes the patients' demographic, clinical, laboratory, and genetic features.

Discussion: Variants associated with haploinsufficiency or dominant-negative mechanisms, as well as penetrance/expression differences affecting specific functions of IKAROS, are associated with common variable immunodeficiency, combined immunodeficiency, or hematologic (such as primary ALL), rheumatologic, and dermatological phenotypes, as seen in the patients. A genetic diagnosis is necessary to provide patient-focused guidance concerning the risk of infections, autoimmune, inflammation, or susceptibility to cancer, which should be accompanied by disease-specific surveillance.

POSTER 169 - CURRENT GENETIC DEFECTS IN COMMON VARIABLE IMMUNE DEFICIENCY PATIENTS ON THE GEOGRAPHY BETWEEN EUROPE AND ASIA

AUTHORS

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Biography:
I'm working as a fellow Ege University, Faculty of Medicine, Department of Pediatric Immunology.

Identification of the causes of monogenetic common variable immune deficiency (CVID) patients has rapidly increased in the last years by means of worldwide availability of appropriate genetic diagnostic methods. However, up to date, very limited numbers of reports demostrating the role of geography, ethnicity and consanguinity have been published. Here, we reported the first study of Turkish CVID patients and compared them with the results of three countries from America, Europe and Asia. A total of 100 children diagnosed as CVID according to the criteria of European Society for Immunodeficiencies were enrolled and they were genetically analyzed by using Targeted Next Generation Sequencing and Whole Exome Sequencing. The median age of our patients was 5.8 years (range, 3.0-16.0 years) at clinical diagnosis and 9.0 years (range, 4.8-21.0 years) at the time of genetic diagnosis. The consanguianity rate was 24%. Disease- causing pathogenic mutations were defined in 40% of patients in a total of 17 different genes.
Sixteen of 40 identified mutations were novel (40%). We determined 18 surface molecular defects, 10 cytosolic defects, 9 nuclear defects and 3 others. In our cohort, the most common gene was TACI (15/40 in mutation identified cases and 15/100 in all cases) followed by the others such as PLCγ2, LRBA, TCF3 and STAT1. In contrast to our expectations, our results were more similar to American and European population rather than Asians, although we also have high consanguinity rates and live on the geography between Europe and Asia. Genetic investigation is a great challenge, because of the complexity and heterogenity of the disease and each country has to know their own current genetic landscape in CVID for a better and successful management of the patients.

POSTER 170 - IN-SILICO ANALYSES OF ALL STAT3 MISSENSE VARIANTS LEADING TO EXPLORE DIVERGENT AD-HIES CLINICAL PHENOTYPES

AUTHORS

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Biography:
MANSOURI Mariam, I am 28 years old, currently I am a PhD student, I am working on an immune deficiency called hyperimmunoglobulin E syndrome, through my thesis I am trying to make a phenotype-genotype correlation to explain the diversity of clinical pictures of each patient suffering from the same syndrome.

Autosomal dominant hyper-IgE syndrome (AD-HIES) is linked to dominant negative mutations of the STAT3 protein whose molecular basis for dysfunction is unclear and presenting with a variety of clinical manifestations with only supportive treatment. To establish the relationship between the impact of STAT3 mutations in different domains and the severity of the clinical manifestations, 105 STAT3 mutations were analyzed for their impact on protein stability, flexibility, function, and binding affinity using in Silico approaches. Our results showed that 73% of the studied mutations have an impact on the physicochemical properties of the protein, altering the stability, flexibility and function to varying degrees. In particular, mutations affecting the DNA binding domain (DBD) and the Src Homology 2 (SH2) have a significant impact on the protein structure and disrupt its interaction either with DNA or other STAT3 to form a heterodomain complex, leading to severe clinical phenotypes. Collectively, this study suggests that there is a close relationship between the domain involving the mutation, the degree of variation in the properties of the protein and the degree of loss of function ranging from partial loss to complete loss, explaining the variability of clinical manifestations between mild and severe.

POSTER 172 - UNRAVELING THE P293L MUTATION IN STAT1 GENE: IMPLICATIONS FOR SUSCEPTIBILITY TO CANDIDA INFECTIONS AND IN SILICO PREDICTIONS OF FUNCTIONAL IMPACT

AUTHORS

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Background: Mutations in the STAT1 gene have been associated with a range of immunodeficiencies, including a predisposition to recurrent fungal infections such as candidiasis. We present a case report of an 8-year-old girl with a genetic predisposition to Candida infections and the detection of a P293L mutation in the STAT1 protein via Sanger sequencing.

Case Presentation: The patient presented with recurrent and severe Candida infections, including oral thrush and cutaneous candidiasis. Sanger sequencing of the STAT1 gene identified a heterozygous missense mutation, resulting in the substitution of a proline residue with a leucine residue at position 293 (P293L). To assess the potential functional impact of this mutation, in silico prediction tools were employed. Methods: Various computational algorithms and bioinformatics tools were utilized to predict the potential effects of the P293L mutation on the structure and function of the STAT1 protein. These tools evaluated factors such as protein stability, flexibility, pathogenicity, and binding affinity.

Results: In silico analysis indicated that the P293L mutation in the STAT1 protein may disrupt its structural stability and hinder its interactions with other proteins involved in immune signaling pathways. Moreover, the mutation was predicted to affect the protein's DNA-binding domain, potentially compromising its ability to regulate gene expression and modulate immune responses.

Conclusion: The identification of the P293L mutation in the STAT1 gene in our patient sheds light on the underlying genetic basis of her susceptibility to Candida infections. In silico predictions suggest that this mutation may contribute to an impaired immune response against Candida species. Further functional studies and genetic counseling are warranted to validate the pathogenicity of the mutation and guide appropriate clinical management and therapeutic interventions for the patient.

POSTER 174 - COMPLEX MOLECULAR DIAGNOSIS IN SUSPECTED PRIMARY IMMUNODEFICIENCY IN NEONATAL PATIENT: AGAMMAGLOBULINEMIA, DYSKERATOSIS CONGENITA OR SOMETHING ELSE?

AUTHORS

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Biography:
Biochemistry graduate from Complutense University of Madrid. Resident in Immunology in Hospital Universitario Gregorio Marañón.

Objective: Here we present a one-year-old infant followed up by Paediatric Immunology Unit due to anaemia, neutropenia, agammaglobulinemia and severe B-cell deficiency. Also, the history of severe infections (Pseudomonas aeruginosa) and others syndromic symptoms (oesophageal atresia, delayed development) were an alert sign pointing to possible immunodeficiency.
Genetic testing performing a Next Generation Sequencing-based bone marrow failure-targeted gene panel allowed the detection of a germinal heterozygous allelic variant in WRAP53 gene (c.1564dup; p.Ala522Glyfs*8) associated with dyskeratosis congenita (autosomal recessive).
However, the variant was classified as a variant of uncertain significance in clinical databases and the genotype wasn't consistent with the inheritance pattern.

The chromosomal study didn't identify any alterations; but the study on telomere length showed telomere shortening. Lymphoproliferation capacity in vitro in response to phytohemagglutinin (PHA) were lower in the patient than those observed in control patient.

Family genetic study showed that the patient's mother also carriers the mutation in WRAP53 gene and telomere shortening, but she doesn't show clinical criteria for dyskeratosis congenita.
Hence, it was decided to perform the genetic study by clinical exome to continue the diagnosis of the immune-mediated pathology.

Design and method: Genomic DNA was isolated from peripheral blood and Next Generation Sequencing was performed using a clinical exome solution (4727 genes, Sophia Genetics). Genes associated with dyskeratosis congenita and a panel of genes associated with immune-mediated diseases were differentially analysed.
Results: The clinical exome study has identified a heterozygous variant in TCF3 gene (c.1663G>A; p. Glu555Lys) which was previously described as pathogenic for Agammaglobulinemia type 8A in databases.

The TCF3 gene encodes two protein isoforms, E12 and E47, which work as critical transcription factors in development regulation of B cells. The identified variant is in a highly conserved site of isoform E47 encoding the DNA-binding domain (Figure 1).

Conclusions: Agammaglobulinemia type 8 is characterized by panhypogammaglobulinemia, decreased circulating B-cells level and maturation blockade in pre-B stage in bone marrow. Therefore, the genotype and phenotype are compatible with the molecular diagnosis of agammaglobulinemia type 8 in our patient.
However, some clinical and analytical findings identified aren't related to what has been describe in association with agammaglobulinemia type 8.

In this moment, it is unknown if there is an association between the TCF3 variant and the previously identified WRAP53 variant and the telomere shortening.

POSTER 182 - A SIMPLE ASSAY FOR IDENTIFYING INNATE IMMUNE DEFECTS UPSTREAM OF NF-KB – A CASE REPORT

AUTHORS

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Biography:
Biochemist. PhD work at the EMBL Heidelberg (1995-1999). Postdoc at CSHL and EMBL (1999-2001). Patent attorney exams 2005 (DE) and 2007 (EP). Patent attorney at Sandoz from 2005 to 2019. Self-employed patent attorney at ScrIPtum and IP Manager at the TU Dresden.

We suggest a simple non-invasive point-of-care (POC) diagnostic assay which should allow the identification of individuals who have a defect in a signaling pathway upstream of NF-kB.
In this case report we show that activators of toll-like-receptors (TLRs) produce an observable inflammatory response (red spot, “erythema”) when administered onto the skin of an immunocompetent individual in the context of a skin prick test. We suggest that this readout will allow for a simple diagnostic assay, as it will be missing in patients with corresponding inborn errors of signaling pathways upstream of NF-kB. We suggest that this simple assay will allow population-wide screens for individuals with a TLR loss-of-function, as well as for individuals with defects further downstream, such as interleukin-1 receptor-associated kinase 4 (IRAK4)- or MYD88-deficiency. Thus, we expect that activators of signaling pathways upstream of NF-kB will become useful tools for future diagnostic routine testing in a point-of-care (POC) setting.

POSTER 185 - WALDMANN'S DISEASE IN A PATIENT WITH A MUTATION IN THE RASGRP1 GENE.

AUTHORS

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Introduction and objectives: Waldmann's disease is characterized by primary intestinal lymphangiectasia, with protein-losing enteropathy, lymphopenia and hypogammaglobulinemia. We present the clinical case of a 36- year-old woman with a history of viral and bacterial recurrent respiratory infections since childhood, associated to chronic asthenia and diarrhea, with subsequent diagnosis of duodenal lymphangiectasia in 2004. The patient had no symptoms or signs of serositis or edema at present.

Method: The immunological study showed moderate IgG and IgM hypogammaglobulinemia (416 and 18 mg/dL, respectively), specific polysaccharide antibody deficiency, CD4+ T-cell lymphocytopenia (197 cells/uL) and C4 hypocomplementemia (9.6 mg/dL). From the beginning of our study, we had the clinical suspicion of an underlying primary immunodeficiency related to her clinical and analytical-immunological history, so clinical exome study was requested.

Results: The clinical exome study revealed a heterozygous variant in the splicing site of the RASGRP1 gene (c.327-1C>T) (NM_005739.3) classified as probably pathogenic and associated with a defect in Ras-mediated activation of T and B lymphocytes. The product encoded by this gene acts as a guanine nucleotide exchanger, activating the Ras protein, which in turn leads to the activation of the Ras-MAPK pathway, of great importance in the survival, development and destruction of T cells. Alterations in this gene are related to a type of recessively inherited immunodeficiency (OMIM:618534) described in patients with associated clinical and analytical features shared by the patient.

Conclusions: The finding of the described mutation confirms our hypothesis of the underlying immunodeficiency presented by the patient. The RASGRP1 gene is involved in cytoskeletal remodeling pathways, with actin filaments being one of the main components of the cytoskeleton. These filaments are involved in multiple cellular functions and there is increasing evidence linking actin cytoskeleton defects to autoinflammatory diseases and primary immunodeficiencies, representing a new perspective in the field of immunology. Functional studies are necessary to know the contribution of these variants to the mechanisms of the disease and thus be able to make therapeutic decisions and personalized follow-up.

POSTER 192 - SKIN BARRIER DEFECTS ASSOCIATED WITH IMMUNODEFICIENCY AND ERYTHRODERMA

AUTHORS

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SKIN BARRIER DEFECTS ASSOCIATED WITH IMMUNODEFICIENCY AND ERYTHRODERMA

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Introduction: Erythroderma is a potentially fatal condition marked by extensive erythroderma and exfoliation.It is generally seen in the neonatal period. Skin disorders such as atopic dermatitis, seborrheic dermatitis, psoriasis, mastocytosis, ichthyosis, bullous congenital ichthyosiform erythroderma, staphylococcal scalded skin syndrome, drug usage, Netherton syndrome, Omenn syndrome, and multiple carboxylase deficiency are the diseases included in the differential diagnosis.
Defects in proteins involved in skin barrier integrity and function, such as filaggrin and desmoglein, can cause severe atopic dermatitis. Filaggrin is a protein found in the stratum corneum, and its absence increases the fragility and permeability of the stratum corneum. Desmoglein 1 is important in tissue adhesion. SPINK5 gene defects causes LEKTI deficiency named Netherton syndrome, which is characterized by disturbed skin homeostasis with the detachment of stratum corneum leading to the breakdown of the skin barrier and easy penetration of microorganisms and allergens.
Here we present the skin phenotype, allergic manifestations and immunological findings of our patients with skin barrier defects.

Results: A total of 8 patients were included with age range 16 months-11 years and varying degrees of skin involvement and immunodeficiency. All patients presented with erytroderma in the early periods of life. Seven suffered from recurrent infections including sepsis, diarrhea, urinary tract infections and abscess. 6 of the 8 patients had food allergy. All patients had eosinophilia nad increased IgE. Low levels of IgG was present in 3 patients, absolute numbers of lymphocyte subsets were all within normal ranges. All patients were given immunoglobulin replacement therapy.
Table 1 summarizes the patients' demographic, clinical and laboratory features.

Discussion: Elucidating the etiology of erythroderma in the newborn period is not always simple. Severe atopic dermatitis, Omenn syndrome, Wiskott-Aldrich syndrome, Hyper IgE syndrome are primary immunodeficiencies most commonly presenting with skin findings. Besides, genes important for skin barrier function may be affected without causing a systemic immunodeficieny. There is no cure for skin barrier defects; the primary lines of therapy are supportive with immunoglobulin replacement therapy and prophylaxis with antimicrobial agents. All patients should be provided moisturizing products to maintain the skin barrier and prevent secondary infections.

POSTER 193 - HETEROZYGOUS MUTATION IN TREX1 GENE IN A PATIENT WITH RETINAL VASCULOPATHY, CEREBRAL LEUKOENCEPHALOPATHY AND SYSTEMIC MANIFESTATIONS, A CASE REPORT

AUTHORS

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AFFILIATIONS

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Biography:
Medicine degree in "Universidad de Cuenca" Immunology medical second-year-Resident in HGUGM.

Objective: To describe a 56-year-old male who presented with weakness in the right lower limb for four years which required recent hospital admission due to walking inability. On the CT scan, it was observed superficial and deep white matter nonspecific lesions. The brain biopsy was not compatible with demyelinating or tumoral disease. Blood tests showed remarkable increase in acute phase reactants and anemia associated to chronic disease.
A month later, the patient had iliocolitis and colonic perforation with a torpid recovery. He also had Cytomegalovirus infection, recurrent fever and severe pleural effusion. Pleural biopsy showed chronic necrotizing granulomatous inflammatory process, suggestive of pulmonary sarcoidosis.
Furthermore, he started presenting behavioral complains like: irritability, aggressiveness, apathy, global brain dysfunction and cognitive decline. Moreover, he developed asymptomatic vascular retinopathy with retinal exudates.
As family background, his father and two paternal uncles had died of alleged brain tumor, with no availability of clinical records. Surprisingly his paternal grandparents died of natural causes at old age.
Hence, it was decided to perform a genetic study to continue the diagnosis of the suspected immune-mediated pathology.
Method: Genomic DNA was isolated from peripheral blood and next generation sequencing was performed using a clinical exome solution.

Results: In the genetic study, it was identified a monoallelic frameshift mutation in the C-terminal domain of the TREX1 gene, p.Val235Glyfs*6. This variant has been previously described in clinical databases as a pathogenic mutation for Retinal Vasculopathy with Cerebral Leukoencephalopathy and Systemic manifestations (RVCL-S): a rare autosomal dominant disease that could justify the underlying pathology on this patient. Frameshift variants in C- terminal domain result in the codification of truncated TREX1 proteins with altered interaction with the endoplasmic reticulum and dysregulation of oligosaccharyltransferase activity.

Conclusions: Clinical phenotype and genotype of the patient are compatible with diagnosis of RVCL-S. Although, there is some evidence in the literature about systemic inflammation and immune-dysregulation in association with this syndrome, there is not enough published data about its contribution to pulmonary sarcoidosis. The patient's therapeutic options are limited and overall there is a poor prognosis associated with this disorder. Further studies of the immunological profile, as the interferon score, would be useful to identify potential targeted treatments.
Variant segregation analysis in the family is recommended in order to detect potential affected members. It will also help to clarify the inheritance patter in the family, since no cases of germinal mosaicism have been described so far in RVCL-S.

POSTER 196 - GENETIC DIVERSITY IN PEDIATRIC CVID PATIENTS – A SINGLE CENTER REPORT

AUTHORS

Bataneant M[1,2], Chirita-Emandi A[1,2], Pantea C[2], Baica M[2], Boeriu E[1,2], Urtila P[1,2]

AFFILIATIONS

[1]University Of Medicine And Pharmacy "Victor Babes"" , [2]"Louis Turcanu" Emergency Clinical Hospital for Children

Biography:
PhD Senior pediatrician, working with PID patients.

Introduction: Common variable immunodeficiency (CVID) is one of the most diagnosed primary immunodeficiencies (PIDs) defined by a marked decrease in serum IgG, decreased IgA and/or IgM, poor antibody responses to vaccines and/or decreased switched memory B cells, and exclusion of defined causes of hypogammaglobulinaemia. So far, a monogenic cause has been identified in 2–10% of patients with CVID.
Objective: To evaluate the genetic background in pediatric patients who fulfilled CVID criteria. Material and methods: We analyzed 14 patients aged between 4-18 years, diagnosed with CVID in the IIIrd Pediatric Clinic, Timisoara between 2000-2022. In 7 patients we performed PID gene panel, in 7 patients WES and in 2 patients WGS.

Results: We identified a monogenic cause of CVID in 8 patients (57,1%): TACI-1 case, NFKB1- 2 cases, LRBA-2 cases, Kabuki syndrome-1 case, APDS1-1 case and CARD11GOF-1 case. In all children the disease started before age of 10 years. The time from the diagnoses to genetic investigation was: immediately: 2 cases, 1-3 years: 2 cases, 4-7 years: 4 cases, 8-10 years: 2
cases and >10 years: 4 cases.

Conclusion: CVID is a remarkably genetically heterogeneous syndrome, single-gene defects do clearly underlie the immune defect in at least 50% percent of our cases. Therefore we consider that all children diagnosed with CVID should be genetically tested. This is important to guide treatment and follow-up, to support genetic counselling and reproductive options.

POSTER 204 - APPROACHES TO FAMILY TESTING FOR AUTOSOMAL DOMINANT INBORN ERRORS OF IMMUNITY IN EUROPE: RESULTS OF A BLINDED SURVEY

AUTHORS

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Biography:
Jo Luscombe has a PhD in Molecular Cardiology from Université Catholique de Louvain and extensive medical communications agency experience. Jo now works in Medical Affairs as Director of Scientific Engagement at Pharming Group NV.

Objective: Inborn errors of immunity (IEIs) are a group of 485 rare and underdiagnosed genetic disorders that may cause morbidity and mortality from infancy. In an affected family, variable penetrance and expressivity results in wide phenotypic heterogeneity. Family testing may allow early diagnosis, even in pre-symptomatic individuals, raising awareness of potential risks, and facilitating early intervention; however, increased legislation on patient confidentiality and difficult ethical considerations can leave clinicians with unpalatable decisions. This study aimed to determine the approaches to genetic testing of family members of an individual affected by activated phosphoinositide 3-kinase delta syndrome (APDS), an autosomal dominant IEI.

Design and methods: A blinded survey was conducted with immunologists (IMs), paediatric immunologists (PIMs), haematologists (HAs), haematologic oncologists (HOs), general internists (GIs) and other specialties (Os) who were working in centres managing patients with IEIs in Germany, France, Italy, Spain and the UK, and had spent ≥2 years in their current role. A hypothetical scenario, in which participants were asked to imagine that one of their patients with an IEI was diagnosed with APDS, was used to query approaches to family testing.

Results: Survey participants (N=151, n≥30 per country) were 46% IMs, 17% GIs, 11% HOs, 10% HAs, 7% PIMs and 9% Os. Overall, 62% of participants indicated that all family members would be informed of an APDS diagnosis in the family, regardless of whether the family members were their patients; 23% would inform family members only if they were their patients (Figure 1). PIMs were more likely to inform all family members than other specialists (91% of PIMs vs 71% of IMs, 58% of GIs, 53% of HAs, 46% of Os and 35% of HOs). Irrespective of whether participants would ensure all family members were informed vs only those that were their patients, most participants would either recommend that family members seek, or ensure they were offered genetic testing (Figure 2). If a licensed therapy was available to treat APDS, 85% of participants indicated that they would be more likely to refer a potential APDS patient for genetic testing and 7% of participants said they would be more likely to screen first-degree relatives.

Conclusion: Significant variance exists in physician approaches to testing of family members of a patient with an IEI, which may contribute towards underdiagnosis. With genetic testing becoming more accessible, affected families may benefit from more open dialogue and counselling around the ethical challenges of family testing.

POSTER 210 - IMMUNOLOGICAL PROFILE IN SWACHMAN-DIAMOND LIKE SYNDROME DUE TO SRP-RECEPTOR MUTATION

AUTHORS

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Biography:
Consultant Clinical Immunologist at the Hospital Universitario Clínico San Carlos

Swachman-Diamond syndrome is characterized by complex and multi-organ symptoms. Mutations in SBDS account for the majority of cases, other genes such as EFL1 or SRP54 have also been reported, even so, a percentage close to 10% do not present a known genetic mutation and the differences in the clinical and immunological profile in each mutation are not well defined.
We present the case of a 24-year-old woman with a mutation in the SRP protein receptor. The patient debuted in the first months of life with severe neutropenia (<100 cells/ul) and various serious infectious clinical pictures such as peritonitis, orbital cellulitis and various episodes of pneumonia. The genetic study showed a mutation of the SRPR gene, c.1390C>G, with autosomal dominant inheritance. This protein is responsible for the recognition of endoplasmic reticulum signals, participating in the targeting and translocation of secretory and membrane proteins.
Recently published studies show a pathogenic role for this mutation in vitro and in zebrafish models, also, the different in silico algorithms predict an important impact on both the structure and the function of the protein. However, there is no clinical scientific evidence of these patients. We present the clinical data found associated with this mutation, with special emphasis on the immunological profile.

POSTER 220 - EXPLOITING THE GENOTYPE-PHENOTYPE CORRELATION IN WHIM SYNDROME MAY GUIDE THE CLINICAL MANAGEMENT

AUTHORS

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AFFILIATIONS

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Biography:
Laura Dotta is a Pediatric Immunologist at the Department of Pediatrics of Spedali Civili of Brescia and researcher at the Department of Clinical and Experimental Sciencies of University of Brescia in the field of Inborn Errors of Immunity.

Background and objective: Warts, hypogammaglobulinemia, infections, and myelokathexis (WHIM) syndrome is an ultra-rare inborn error of immunity predominantly caused by heterozygous gain-of-function mutations in the chemokine receptor CXCR4. The disregulated receptor signaling and enhanced chemotactic response of CXCR4 to its ligand CXCL12 determines neutrophil sequestration in the bone marrow (myelokathexis) and abnormal trafficking of lymphocytes in primary immune organs, thus explaining peripheral panleukopenia and susceptibilty to infections. More than 60% of WHIM patients carry the R334X or S338X variants, but the phenotypic presentation is extremely variable both in patients with different genotype and patients with the same mutation. Recently, the in vitro functional characterization of CXCR4-WHIM variants has shown the correlations between the entity of CXCR4 internalization defect and the severity of neutropenia, lymphopenia, and the recurrence of infections. However, we have recently reported that the novel WHIM Leu317fsX3 mutation impairs CXCR4 downregulation but reduces other signaling events -including ERK1/2 phosphorylation, calcium mobilization, and chemotaxis. Material and method: data were retrospectively analyzed from medical records to investigate any genotype-phenotype similarities in the cohort of 22 patients who were diagnosed at our Center with WHIM syndrome.

Results: 16/22 patients (73%) harbored missense mutations (R334X, S338X, G336X), while 6/22 patients (27%) frameshift mutations. Media age at onset was of 2,24 years for patients with missense mutations, with media absolute neutrophil count (ANC) of 80 cells/uL, and 3,37 years for patients with frameshifts mutations, with media ANC of 170 cells/uL, respectively.
Lymphopenia was present in all patients with missense mutations but lacked in 4/6 patients with frameshifts variants. 10/16 patients (62,5%) and 5/6 patients (83%) had warts, 8/16 (50%) and 2/6 (33%) patients had hypogammaglobulinemia, 12/16 patients (75%) had major infection at onset (meningitis, pneumonia) at a median age of 1,9 years, while 5/6 patients (83%) had less severe respiratory or cutaneous infections at a median age of 3 years. We recorded tetralogy of Fallot (3/22), autoimmunity (3/22, autoimmune haemolytic anemia, arthritis, vitiligo), and neurological manifestations (6/22 with cerebellar malformation, mild neuromotor and/or psychopathological dysfunction; 2/22 epilepsy) only in patients with missense mutations.

Conclusion: WHIM syndrome largely varies in the severity of immunodeficiency and autoimmune manifestations. However, the characterization of the genotype-phenotype correlation in larger cohort is warranted to guide the clinicians in the patient's management and improve supportive treatment and/or access to target therapies as the experimental CXCR4 antagonists plerixafor/mavorixafor.

POSTER 221 - GENETIC EVALUATION OF GATA2 DEFICIENCY

AUTHORS

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AFFILIATIONS

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Biography:
My name is Pantea Cristina-Loredana, I have completed MD (Pediatrics) in October 2022 and I am a resident physician in 1st year of training in Medical Genetics at the “Louis Đurcanu” Children’s Emergency Clinical Hospital in Timisoara, Romania.

Objectives: GATA binding protein 2 (GATA2) is a key component in hematopoiesis. GATA2 deficiency (OMIM#614172) can associate: cytopenias, susceptibility to infection with mycobacteria, HPV, histoplasmosis, alveolar proteinosis, myelodysplastic syndrome/acute myeloid leukemia/chronic leukemia myelomonocytic, lymphedema. Symptoms can range from life-threatening bone marrow failure, immunodeficiency and/or myeloid malignancy, to no obvious phenotype even in old age. We aim to present a case of neutropenia associated with GATA2 deficiency.

Design and methods: Clinical, imagistic, interdisciplinary assessments and genetic testing (WES) were performed for the patient.

Results: 15 years old female presents with: bronchial hyperreactivity, supraventricular tachycardia, mild recurrent neutropenia (first detected at age of 5, which varied between 980 and 1270 neutrophils Bone Marrow Biopsy detects hypocellularity, small atypical megakaryocytes, and neutropenia. Results of genetic testing: WES showed two de novo, heterozygous, pathogenic variants in GATA2 gene (NM_032638.4:c.1081C>T) and in CFTR gene (NM_000492.3:c.1521_1523del) in the patient’s blood.

Conclusion: The pathogenic variant in the GATA2 gene is associated with GATA2 deficiency which is classified as an immunodeficiency primary phagocytic, with autosomal dominant transmission, part of the congenital marrow failure syndromes.

POSTER 251 - DIVERSE CLINICAL AND IMMUNOLOGICAL PHENOTYPE IN PATIENTS WITH TACI MUTATIONS

AUTHORS

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AFFILIATIONS

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Biography:
Anastasiia Bondarenko graduated from the Bogomolets National Medical University in 2000. After completing the internship, received the qualification of a Pediatric Infectious Disease specialist. During 2001-2005 PhD student at the Department of Paediatric Infectious Diseases and Paediatric Immunology, Research work "Age-dependent peculiarities of meningitis in children (etiology, epidemiology, clinical features, diagnostics)". Since 2007 – Pediatric Immunologist at the Kiev Children's Clinical Hospital. In 2005 - 2012 Assistant Professor, in 2012-2020 Associate Professor, in 2020-2022 Full Professor at Shupyk National Medical Academy for Postgraduate Education, Department of Paediatric Infectious Diseases and Paediatric Immunology. Since 2022 - Head of the Department of Pediatrics, Immunology, Infectious and Rare Diseases at International European University (Kyiv, Ukraine).

Board Member of the All-Ukrainian Association of Pediatric Immunology – since 2010. Board Member of the Public Organization "Rare Immune Diseases" (National patient's organization for Primary Immune Deficiency, NMO of IPOPI) – since 2014. President of International Interdisciplinary Association of Medical Professionals (IIAMP) – since 2020. Chair of Procurement Support expert Group in MOH of Ukraine for patients with primary immunodeficiencies.

Background: Monoallelic or biallelic mutations in TNFRSF13 gene encoding TACI have been reported as the most common genetic defects in patients with common variable immunodeficiency (CVID). However, these mutations are also found in 1–2% of the general population. The aim of our study was to evaluate the clinical and immunological correlations in Ukrainian cohort of patients with detected mutations in TNFRSF13 gene.
Materials and Methods: The study included 17 individuals from 7 families in which mutations were identified in TNFRSF13B gene. The age of the patients ranged from 6 to 44 years, male/female: 9/8. In 16 patients mutations were detected in panel sequencing for 407 PID- associated genes, and in one patient in WES. Three patients carried homozygous mutations (c.204dupA (p.Leu69Thrfs*12), c.492C>G (p.Tyr164*)-2) and fourteen carried single heterozygous mutations. Pathogenic mutations were detected in 8 patients, likely pathogenic in 7 and VUS in 2 patients. The reason for genetic testing were PID criteria either ELVIS or GARFIELD or Family follow-up. In one patient, the mutation in TNFRSF13 was combined with the mutation in the BTK gene consistent with XLA, so he was excluded from the clinical evaluation.

Results: Only one from 16 patients with TACI mutations met ESID diagnostic criteria for CVID, other 9 patients had clinical signs of PID and 6 patients were asymptomatic. Five patients had recurrent upper respiratory, skin or intestine infections, one had herpetic encephalitis; in three patients lymphoproliferative syndrome was predominant. Asthma, drug and insect allergia were noted in three patient and autoimmunity observed in four patients. The most characteristic laboratory sign was persistent leukopenia (37.5%), in one patient associated with immune thrombocytopenia, four patients showed mild lymphopenia and moderate hypogammaglobulinemia limited to IgG (4.5-5 g/l) or impaired response to vaccines, one patient had a partial IgA deficiency. Six patients tested as part of Family follow-up aged 10 to 44 years were asymptomatic, 5 of them were heterozygous carriers of pathogenic or likely pathogenic mutations and one - homozygous pathogenic mutation c.204dupA (p.Leu69Thrfs*12). The most frequently detected likely pathogenic mutation was c.542C>A (p.Ala181Glu) identified in 6 patients from 4 independent families.

Conclusions: Testing of family members revealed a significant percentage of asymptomatic patients. The relatively mild clinical and laboratory abnormalities and different phenotype within the same family indicates the complex role of various co-factors in the development of immunodeficiency in TACI defects. Genetic diagnosis at a preclinical stage allows clinical and immunological monitoring.

POSTER 252 - AN IRF2BP2 MUTATION IN A PEDIATRIC PATIENT WITH COMMON VARIABLE IMMUNODEFICIENCY

AUTHORS

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AFFILIATIONS

[1]Selcuk University Medical Faculty, Department of Pediatrics, Division of Immunology and Allergy

Biography:
Dr. Hasibe Artac is a Professor of Pediatrics and Director of the Pediatric Immunology and Allergy Division at Selcuk University Medical Faculty, in Konya, Turkey. She is certified by European Allergy and Clinical Immunology (EAACI) in Pediatric Allergy and Immunology (2011). Dr. Artac's primary research focus is the oversight of clinical trials of patients with primary immunodeficiency. She is actively involved in clinical trials. Dr. Artac has received numerous awards including the Turkish National Society of Allergy and Clinical Immunology, ESID Travel Grant (2007), and EAACI (2023). She belongs to numerous professional organizations including the ESID and EAACI. She has authored over 50 articles in peer-reviewed journals. Dr. Artac received her MD (1999) at the Selcuk University School of Medicine in Konya. He trained in pediatric Immunology and Allergy at the Akdeniz University School of Medicine in Antalya.

Background: IFN regulatory factor-2 binding protein 2 (IRF2BP2) is an important new transcriptional cofactor that interacts with IFN regulatory factor 2 (IRF-2) and an IRF-2- dependent transcriptional repressor. IRF2BP2 plays a role in different cellular functions, including apoptosis, survival, and cell differentiation. In this study, we report a case with common variable immune deficiency (CVID) which has a heterozygous variant in the IRF2BP2 gene.

Case report: A 13-year-old girl was evaluated for immunodeficiency due to recurrent sinusitis and tonsillitis for a year. She suffered from a chronic cough for 3 months. She was hospitalized with lobar pneumonia and bronchiectasis. She was the second child of consanguineous parents. On physical examination, there was no growth and development retardation. Immunological screening of the patient demonstrated agammaglobulinemia with low total memory B and class-switching memory B cells. Specific antibody responses to Rubella and hepatitis B were low. T and B lymphocyte counts and T cell responses to PHA were normal. Exome sequencing identified a heterozygous mutation in IRF2BP2 (c.112C>T:pArg38Cys). We analyzed the IRF2BP2 variant to be deleterious (CADD score, 24.9; PolyPhen-2 score,0.999) with in-silico prediction tools. On follow-up, pancytopenia occurred secondary to acute viral infection and resolved in 2 weeks. She has maintained good infection control with antibiotic prophylaxis and immunoglobulin replacement therapy.

Discussion: To our knowledge, this case is the youngest CVID who had been diagnosed with IRF2BP2 in the literature. The low percentage of total memory and switched memory B cells in the proband suggested that IRF2BP2 might have had a role in the development or survival of memory B cells. Functional studies are needed about the critical role of IRF2BP2 protein in B cell maturation and humoral immune responses.

POSTER 258 - A PATIENT-BASED STAT3 L387R GAIN-OF-FUNCTION VARIANT MURINE MODEL

AUTHORS

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[1]Erasmus Medical Center, Internal Medicine, Division of Clinical Immunology, [2]Chulalongkorn University, Microbiology, Faculty of Medicine, [3]Chulalongkorn University, Physiology, Faculty of Medicine, [4]Erasmus University Medical Center, Pathology, Division of Bioinformatics, [5]Erasmus University Medical Center, Immunology, Laboratory Medical Immunology

Biography:
Zijun Zhou graduated from the University of South China, Department of Pharmacy in 2015. After obtaining her bachelor in science degree, she continued her studies in the master program of Guangdong Pharmaceutical University in the Department of Pathology and Physiology and graduated in 2019. During her masters, she focused her research on the molecular mechanism behind the carcinogenesis of cancers and angiogenesis by utilizing chemical compounds on in vivo cell line models as well as genetically engineered mice models. Her three-year master training resulted in 5 publications as first author or co-author. She is currently a member of the PhD program at the Department of Immunology, Erasmus Medical Center, Rotterdam, Netherlands. Her PhD projects focus on exploring genetic defects underlying the mechanism of Primary Immunodeficiencies (PID) by means of gene editing and patient-specific mice model generation.. (Z.Z Zhou (0000-0001-8761-7828) (orcid.org))

Objective: Patients with autosomal dominant germline STAT3 gain-of-function (GOF) variants develop immune regulatory disorders with a broad spectrum of clinical presentations. Here, we describe the clinical phenotype of a family with a novel heterozygous STAT3 (c.1160T>G, p.L387R) variant. We evaluated the immunological phenotype associated with this variant. To further evaluate the role of this novel STAT3 GOF variant we generated a mice with the Stat3 L387R variant using CRISPR-Cas9 technology.

Design & Methods: The immunologic phenotype was studied by flow cytometry. The STAT3 variant was functionally validated using HEK293 cells overexpressing the STAT3 variant and mobility shift assays. Stat3 L386R GOF mice were generated by CRISPR-Cas9 editing.

Results: The STAT3 L387R variant was identified in a Dutch family. The clinical spectrum of the six affected family members included recurrent bacterial and viral infections, hypogammaglobulinemia, hearing loss, dermatitis, interstitial lung disease, immune thrombocytopenia, splenomegaly, retinal vasculitis with severe macular edema, and diabetes mellitus. Patients had decreased frequency of naïve CD4+T lymphocytes, increased Th17 T lymphocytes and elevated levels of STAT3-regulated cytokines in the serum. In STAT3- transduced HEK293 cells, STAT3 phosphorylation, and SOCS3 mRNA induction were higher in cells carrying L387R variant upon IFN-α and IL-6 activation in comparison to HEK cells expressing wild-type (WT) STAT3. Accordingly, the transcriptional and DNA binding activity of L387R STAT3 construct were stronger than that of WT STAT3. In our mouse model, the percentage of Stat3 L387R/L384R mice (HOMs) that were delivered was much lower (4.7%) than for WT (30.6%) or Stat3 +/L387R mice (HETs) (64.6%). Furthermore, all HOMs died after birth. Around 25% of HETs had dermatitis, and ocular defects were seen in approximately 3% of them. HETs had lower weight than WT mice at older age (>20w) and significant splenomegaly. CD4+ Th1 cell skewing and lymphoproliferation were observed in the splenocytes of HETs.
Moreover, mRNA expression of Socs3, a downstream target gene of Stat3, was significantly higher in the splenic tissues of HETs.

Conclusion: In conclusion, we identified an activating heterozygous STAT3 variant in a family with immune dysregulation and additional noninfectious complications. Even without immune challenging, the mouse model with pathogenic patient-specific STAT3 L387R variant reveals distinguished pathological phenotypes similar to the patients. Our findings stress the importance of generating patient-related mutant animal models to allow in-depth studies leading to expanded knowledge on the mechanisms of disease pathogenesis in STAT3 GOF syndrome.

POSTER 261 - WHOLE EXOME SEQUENCING ENABLES CVID METAMORPHOSIS TO DIFFERENT INBORN ERRORS OF IMMUNITY

AUTHORS

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AFFILIATIONS

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Biography:
Resident in Pediatrics, expert in genetic diagnostic for IEIs, in respiratory infectious disease in children.

Objective: Common variable immunodeficiency (CVID) represents the umbrella definition of all those clinical forms characterised by increased susceptibility to infections, autoimmune or autoinflammatory manifestations, lymphoproliferation, atopy and neoplasms. Recognised laboratory criteria are hypogammaglobulinaemia, absence or loss of specific antibody response and possible B memory defect. Whole Exome Sequencing (WES) has proven to be an effective tool for the discovery of genetic defects in patients with primary immunodeficiencies; however, its application is limited in the context of CVID. The aim of this study was to recruit a cohort of paediatric and adolescent patients with CVID and characterize them clinically, immunologically and genetically.

Design and methods: Pediatric and adolescent patients followed for CVID were enrolled in this study (CVIDOME), conducted within the framework of the Bando Salute Toscana 2018 Research Project. Clinical data were collected from electronic medical records. The genetic variants identified were compared with the latest update on genetic causes of immunodeficiency and dysregulation of the International Union of Immunological Societies (IUIS) 2022.

Results: Thirty-seven patients were enrolled; the clinical data made it possible to classify them into asymptomatic patients, patients with increased susceptibility to infection and patients who also had complications such as autoimmune disease, autoinflammation or atopy. Based on the results of the cytofluorimetric analysis, we divided the patients into different groups according to the European consensus classification CVID (EUROclass). Through exome analysis, we identified genetic variants in 50% of the patients, including known genetic variants in SLC39A7, NLRP12, TNFRSF13B, PRKCD, PLCG2, RFXANK, NFKB1, CARD11, STAT3 and new variants
in SPI1, CR2, NFKB1 and NFKB2. In some cases, genetic analysis allowed a more accurate definition of the immune defect, making it possible to adjust treatment and follow-up.

Conclusion: The discovery of the genetic defects underlying CVID is crucial to improve the understanding of the immune system, compare with highly specialized centres, perform homogeneous population studies and enable better clinical management of patients. A genetic diagnosis can also provide relevant prognostic information, direct the clinician towards a more tailored-made therapy, and enable genetic counselling. If a genetic variant is not identified, second-reading the exome, in light of the continuous updates of the IUIS classification, has been crucial.

POSTER 265 - MOLECULAR CHARACTERIZATION OF INBORN ERRORS OF IMMUNITY (OR PRIMARY IMMUNODEFICIENCIES) USING GENOME SEQUENCING – FIRST FINDINGS OF THE LATVIAN COUNCIL OF SCIENCE PROJECT

AUTHORS

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AFFILIATIONS

[1]Riga Stradiņš University , [2]Children's Clinical University Hospital , [3]University of Tartu, [4]Pauls Stradins Clinical University Hospital

Biography:
PhD student at Riga Stradiņš University, specializing in the field of genetics related to inborn errors of immunity

Background: Inborn errors of immunity (IEI) or Primary immunodeficiencies (PIs) encompass a diverse group of inherited immune system disorders with variable phenotypes. Despite advances in exome sequencing, the diagnostic yield for primary immunodeficiency (PIs) cases remains low, ranging from 15% to 70%. This study aims to identify molecular causes of clinically diagnosed PIs patients with a particular emphasis of predominately antibody deficiencies through the application of genome sequencing.

Materials and methods: A total of 33 PIs probands, comprising 22 cases of predominantly antibody deficiencies and 11 cases of other clinically identified PIs, underwent genome sequencing. Nucleotide and copy number variations in a PID gene panel (n=565) were analyzed using seqr. The analysis primarily focused on coding regions, as well as intronic variants with a spliceAI score >0.2. The identified variants were classified based on the American College of Medical Genetics and Genomics (ACMG) criteria.

Results: Molecular causes of PID were identified in five patients (15%): in NRAS, SH2D1A, NR2F1, STAT1 and ADA2 genes. Additionally, four patients presented variants of uncertain significance in NLRP1, MPO, IKBKB and BACH2 genes. In one individual, biallelic TET2 variant was detected in the blood, but it remains unclear whether this variant is a clonal somatic mutation or a germline variant. In 23 patients, no genetic cause associated to PIs could be identified even using genome sequencing.

Conclusion: Genome sequencing proves to be a valuable tool for identifying the genetic causes of PIs. However, the diagnostic yield remains low.
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PID ENVIRONMENT AND QUALITY OF LIFE

POSTER 41 - DISEASE BURDEN FOR PATIENTS WITH PRIMARY IMMUNODEFICIENCY DISEASES - A COMPARATIVE STUDY

AUTHORS

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Biography:
I am a health professional from India, who is presently involved in Academics, Research and Clinical decision making.

Background: In addition to the deleterious effect on health, there is considerable economic and psychosocial morbidity associated with primary immunodeficiency diseases (PID). Also, the cost of a late diagnosis frequently results in a heavy disease burden on the patient. The objective of this study was to collect and analyze data on patients with PID in the state of Kerala, India, to indirectly estimate the burden of the disease.

Methods: An observational, longitudinal, and comparative study was conducted. A total of 44 patients were included and grouped according to the updated classification of PID.

Results: The median time elapsed from the onset of symptoms to the reference and diagnosis by a tertiary hospital was of 2.17 (IQR = 6.44) years. Before diagnosis, the number of hospitalizations/year per patient was 0.86 (IQR = 2.28), the number of visit to emergency room/year per patient was 0.92 (IQR = 1.77), the number of doctor's visits/year per patient was 15 (IQR = 11.25), whereas the school/work absence days per patient were reported in 52.72 (IQR = 56.35) days per year. After diagnosis, 20 patients (45.45%) received IVIG replacement therapy, and all of them presented a significant improvement ($p < 0.05$) in all the mentioned variables. Characteristically, even when patients with PID received IVIG, there was still an important disease burden when comparing them against healthy controls. Complications secondary to PID were detected in 19 patients (43.18%). The reported overall mortality rate was 6.82% (n = 3).

Conclusions: We were able to indirectly estimate an important disease burden in patients with PID; which is considered to be preventable, at least in part, with effective interventions like health planning, research, collaboration with primary care providers, and generation of policies and practices, in order to improve the quality of life and care of families with PID.

POSTER 42 - HEALTH-RELATED QUALITY OF LIFE OFCHILDREN WITH PRIMARY IMMUNODEFICIENCY DISEASE: A COMPARISON STUDY

AUTHORS

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Biography:
A Medical professional from India and also as an early career researcher with keen interest in the field of primary immune deficiencies.

Purpose of the study: To compare parental perceptionsof health-related quality of life (HRQOL) in children with primary immunodeficiency (PI) with children with juvenileidiopathic arthritis (JIA) and healthy children.

Methods: A Parents were interviewed and completed the Child Health Questionnaire-Parental Form 50. Treating physicians completed forms documenting any complications of the underlying disease.
Thirty-six children in each of 3 groups (108 total): those with PI, those with JIA, and those who were healthy. Patients were matched for age, ethnicity, and parental marital status. The age ranged from 4 to 18 years, and 94% were white. All patients with PI received regular infusions of intravenous immunoglobulin. Of the patients with JIA, 77% had either oligoarthritis or polyarthritis. The JIA group had a significantly higher proportion of females.

Results: In comparison to healthy children, those with PI had significantly lower scores on physical functioning, school and social activities, limitations on parental time and family activities, and parental emotional distress. They were equivalent to the healthy group with respect to overall psychosocial health, daily pain and discomfort, social limitations, self-esteem, mental health, general behavior, and family cohesion. In comparison to the JIA group, children with PI were similar. However, they scored lower than the JIA group with respect to perception of general health and limitations on parental time and family activities. The children with JIA had more bodily pain and discomfort than the children with PI.

Conclusions: Children with PI have significant impairment in several measures of HRQOL in comparison to healthy children. These limitations are similar to, and in some cases more severe than, those occurring in another group of chronically ill children, those with JIA.

POSTER 43 - MEASURING TREATMENT SATISFACTION IN PATIENTS WITH PRIMARY IMMUNO-DEFICIENCY DISEASES RECEIVING IMMUNOGLOBULIN INFUSIONS.

AUTHORS

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Biography:
A Medical professional from India and also as an early career researcher with keen interest in the field of primary immune deficiencies.

Background: Treatment satisfaction of patients with primary immunodeficiency diseases receiving hospital-based intravenous (IVIG) or home-based subcutaneous (SCIG) immunoglobulin infusions requires investigation.

Objective: Evaluation of the properties and suitability of the Life Quality Index (LQI), as an instrument to assess treatment satisfaction. Methods: Patients received weekly SCIG and completed the LQI, two global treatment satisfaction questions and the CHQ-PF50 (children) or the SF-36 (adults) at baseline and 10 months. The LQI was psychometrically evaluated.

Results: The LQI comprised four scales: treatment interference (I), therapy related problems (II), therapy setting (III), treatment costs (IV). Convergent/discriminant validity for scales I, II, III was acceptable, for scale IV moderate. CHQ-PF50 scales behavior, bodily pain, global behavior, global health, mental health, parental impact-emotion significantly correlated with LQI scale II, the familty activity scale with LQI scales I, III. SF-36 scale bodily pain significantly correlated with scale III. Internal consistency was good for scales I, II, III, but poor for scale IV. Score values significantly increased for scales I, III, IV in patients switching from IVIG to SCIG.

Conclusion: Three valid LQI scales were determined. Cost-related questions should be removed due to low reliability. Patients-perceived therapy effectiveness and patient- physician/nurse interaction should be included in the instrument.

POSTER 88 - ADA-SCID IN CENTRAL AND EASTERN EUROPE

AUTHORS

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Biography:
Prof. Sediva has a long time experience as a pediatrician working at all levels of pediatric care, from a local hospital to University affiliated specialized centers. Her long time interest in immunology was reflected in her work in the field of pediatric immunology in former Czechoslovakia. The period from 1992 to 1995 she spent at New York Medical College in NY, USA and devoted this time to basic research in immunology. She has also an additional international experience from her stay as the Fulbright scholar in University of Chapel Hill, North Carolina, USA, in 2001. In 2010–2015 she was awarded a position in ESID board and since 2011 she is chairing JMF center in Prague. Prof. Sediva holds currently the position of vice- head of the Department of Immunology in major University hospital in Prague. She is responsible for the field of pediatric immunopathologies with an emphasis on primary immunodeficiencies.

Introduction: The topic of severe combined immunodeficiency, SCID, has come to the forefront of the immunodeficiency community in recent years in the context of screening programs for this most serious life-threatening immune disorder. One of the longest known forms of SCID is ADA- SCID, characterized by AR inheritance and mutations in the gene encoding adenosine deaminase, leading thus to a metabolic disorder in the purine salvage pathway, with detrimental effect mostly on T lymphocytes. Despite the good characterization of the disease and its long known history (the disease then called ADA deficiency was described as early as 1972), the occurrence of ADA-SCID is rare. To obtain an overview of the prevalence of ADA-SCID patients in Central and Eastern Europe, experts from different countries of the region gathered and in addition to mapping the situation in each country, attending immunologists discussed the details of ADA-SCID management.

Methods and results: A Representatives of 10 countries of the region (in alphabetical order Croatia, Czech Republic, Germany, Hungary, Poland, Romania, and Slovenia) attended the meeting and participated in the follow-up survey. The representatives from the following countries participated in the follow-up survey: Lavia, Lithuania and Slovakia. Of these countries Germany has implemented SCID screening in September 2019, screening or national pilot projects are underway in the Czech Republic, Latvia, Slovenia and Slovakia, a pilot project has been carried out in Poland in the border region with Germany, and pilot programmes are under preparation in other countries.

Eighteen patients have been identified in historical cohorts. The two most represented countries are Poland (8 patients) and Slovakia (5 patients). Different strategies have been applied in the therapy, ranging from none for some patients before they reached the diagnosis, through enzyme replacement therapy to hematopoietic stem cells transplantation.
The collective discussion revealed a number of important points to be addressed, including availability of functional and genetic diagnosis, recommendations for treatment approaches for patients based on their current situation, provision of care for both pediatric and adult patients, and the need for international collaboration.

Conclusions: The situation with diagnostics and treatment is improving significantly with the gradual introduction of newborn screening programs and alternative treatment options, including access to gene therapy in international collaboration. Due to the rarity of the disease, there is currently no specific patient organisation for ADA-SCID in the CEE region. Intensifying co- operation in the region is important for further improvement.

POSTER 96 - USABILITY STUDY FOR A NOVEL INTRAVENOUS AND SUBCUTANEOUS SYRINGE INFUSION SYSTEM

AUTHORS

Bullock M[1], Landon C, Hendrix C, Astrero J

AFFILIATIONS

[1]Innovative Health Sciences

Biography:
Melody Bullock's nursing career has been extensively involved with infusion. She earned her nursing degree from the University of Utah, and combined it with her degree in education and her graduate work in administration to provde a workable platform for product improvement that serves healthcare workers and optimized the patient experience. She also has Primary Immunodeficiency.

Objective: While intravenous and subcutaneous routes of medication therapy have primarily been used for the infusion of medications in the hospital and clinic, they are also used in the home where patients perform their own infusion, or the infusion is performed by a caregiver/home care nurse. Common medications given in the home setting include intravenous antibiotics and subcutaneous immunoglobulin. Adults and pediatric patients without systemic symptoms are frequently treated for diseases such as bone and joint infections, staphylococcal bacteremia, endocarditis, lung infections, soft tissue infections, neurological disorders, cancer, and immunodeficiency diseases.
The company performed a pre-market usability study to gauge user experiences with a novel infusion system for intravenous and subcutaneous use. User feedback on infusion effectiveness, efficiency, controllability, customizability, and consistency provides invaluable data, which is used to assess the ease of use, safety, and identify additional user needs.

Methods and design: The study was performed with two groups: 16 nurses and 15 caregivers ages 12 – 82. The nurses included a combination of registered nurses with varying degrees of education, from
3-year prepared nurses to an expert doctoral prepared nurse. The lay persons varied from high school education to college with some post graduate work. One participant was an adolescent. Both groups were trained on the Insignis Syringe Infusion System and asked to return- demonstrate the infusion process. In addition, to assess retention and trainability, post- demonstration nurses took a 90-minute break and were asked to demonstrate how they would train a caregiver. 100% of nurses indicated the infusion system was: "very easy" or "somewhat easy" to train and prepare, "convenient" to use, and was more satisfactory to use than other infusion systems. Other descriptor words included: "accessible," "clear," "easy to use," "effective," "reliable," "understandable," "useful," "fast," and "efficient."

Conclusions: It is imperative that a medical device performs reliably and achieves its intended use effectively. The end user must easily understand how to infuse safely, whether in the home or in a hospital setting. For home infusions, users need a simple, easy-to-use, infusion system. The system's compact design, versatility, and portability further aid in providing the patient with an improved quality of life. The usability study demonstrated the infusion system was effective, simple, and easy to use and teach. The majority of participants ranked the system an "A" or "B." Benefits of an easy-to-teach and easy-to-use system may include a reduction of infusion resources including training time and costs.

POSTER 113 - LIFE QUALITY, DEPRESSION AND ANXIETY LEVELS OF PRIMER IMMUNE DEFICIENT CHILDREN'S PARENTS

AUTHORS

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[1]Basaksehir Cam and Sakura City Hospital, Department of Pediatric Allergy and Immunology, [2]Istanbul Gelisim University Health Sciences Faculty, Child Development Department

Biography:
Dr. Talat SARIKAVAK is medical doctor and psychiatrist. He is also Asistant Professor at Istanbul Gelisim University Health Sciences Faculty Child Development Department . He gives family counselling and mental health classes and studies on family psychiatry, coping strategies and psychodrama.

Background: Primary immune deficiencies (PID) are a group of chronic diseases that are genetically inherited and characterized by frequent infections, immune dysregulation and malignancy. Like all other chronic diseases, it is thought that the patient, siblings and parents are affected socially and psychologically in PID. Therefore, we aimed to evaluate anxiety, depression, levels of life quality and function of the parents of PID patients in Basaksehir Cam and Sakura City Hospital.

Methods: The parents of children with PID that applied to Department of Pediatric Allergy and Clinical Immunology are included in the study. The Turkish Forms of Beck Depression Inventory(BDI), State and Trait Anxiety Inventory (STAI) and short form-36 (SF-36) were used to assess.

Results: A total of 85 parents of 64 PID patients participated in the study. Healthy control group contains 85 parents of 75 healthy children. 42.1% (n=27) of PID patients and 46.7% (n=35) of healthy children were female. 60% (n=51) of PID patients' parents and 72.9% (n=62) of healthy children's parents were female. The means of Beck depression are 15,48±10,161 for patients' parents and 11,78±9,044 for healthy children's parents. The means of Stait Anxiety are 42,58±8,68 for patient group and 39,11±9,36 for healthy group. The means of Trait Anxiety are 42,58±8,68 for patient group and 39,11±9,36. Three of them are significantly high in patients' parents (p=0.013, p=0.013, p=0,027). Energy/fatigue scores are significantly different between groups. (p=0.000). The other subdomain scores of SF-36 has no significant difference. No difference is observed in anxiety, depression and SF-36 scores among diagnostic groups according to classification of International Union of Immunological Society (IUIS).

Conclusion: Our study revealed there are significant difference in both depression and anxiety levels of PID patients' parents and healthy children's parents. This can be explained by both immunodeficient children need more effort to care and avoid infections and diseases more than healthy ones. Low energy/fatigue score can confirm this effort.
Keywords: Primary Immune Deficiency, Anxiety, Depression, Quality of Life, SF-36, Parental Mental Health

POSTER 116 - INFECTION STATUS AND QUALITY OF LIFE IN PATIENTS WITH HUMORAL IMMUNO-DEFICIENCY IN THE CONTEXT OF GLOBAL INSUFFICIENT GAMMAGLOBULIN

AUTHORS

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AFFILIATIONS

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Biography:

1. *Perez EE, Orange JS, Bonilla F, et al. Update on the use of immunoglobulin in human disease: A review of evidence. J Allergy Clin Immunol 2017; 139:S1.*

2. *Nina.B. Kuburovic (2015), Human Inborn Errors of Immunity: 2019 Update on the Classification from the International Union of Immunological Societies Expert Committee. J Clin Immunol:8 323–330.*

Humoral immunodeficiency diseases include many different diseases. Some severe impairments such as XLA, CVID, or Hyper IgM require regular Gammaglobulin replacement therapy. According to the approved regimen in Vietnam, our patients received Gammaglobulin 400-600 mg/kg/month. However, from the end of 2021, the Covid epidemic took place globally, consuming a huge amount of IVIG for treatment, as well as reducing the amount of blood donated for the production of Gammaglobulin. Therefore, the frequency of gammaglobulin infusion to patients is significantly reduced.
We conducted a study to compare the infection status and quality of life of children with humoral immunodeficiency before and during the period of Gammaglobulin deficiency.

Subjects: 35 XLA patients, 5 Hyper IgM, 1 CVID. Research period: May 2022 - April 2023.

Results: The frequency of upper respiratory tract infections increased significantly, and the rate of conjunctivitis, and gastrointestinal infections slightly increased. The average concentration of IgG trough level before was 5.42 g/L, while this figure in the 2022 period was only 3.5 g/L on average. The quality of life of children (by Ped QL4) in the period of drug deprivation was statistically significantly lower in terms of physical fitness, unchanged in emotions, social relationships, and learning.

POSTER 130 - BURDEN OF DISEASE IN PATIENTS WITH PRIMARY IMMUNODEFICIENCIES CURRENTLY RECEIVING INTRAVENOUS IMMUNOGLOBULIN G WITH LOW IMMUNOGLOBULIN A CONTENT

AUTHORS

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AFFILIATIONS

[1]Takeda Development Center Americas, Inc., [2]Baxalta Innovations GmbH, a Takeda company, [3]PPD, part of Thermo Fisher Scientific

Biography:
Dr. Talat SARIKAVAK is medical doctor and psychiatrist. He is also Asistant Professor at Istanbul Gelisim University Health Sciences Faculty Child Development Department . He gives family counselling and mental health classes and studies on family psychiatry, coping strategies and psychodrama.

Background: Primary immune deficiencies (PID) are a group of chronic diseases that are genetically inherited and characterized by frequent infections, immune dysregulation and malignancy. Like all other chronic diseases, it is thought that the patient, siblings and parents are affected socially and psychologically in PID. Therefore, we aimed to evaluate anxiety, depression, levels of life quality and function of the parents of PID patients in Basaksehir Cam and Sakura City Hospital.

Methods: The parents of children with PID that applied to Department of Pediatric Allergy and Clinical Immunology are included in the study. The Turkish Forms of Beck Depression Inventory(BDI), State and Trait Anxiety Inventory (STAI) and short form-36 (SF-36) were used to assess.

Results: A total of 85 parents of 64 PID patients participated in the study. Healthy control group contains 85 parents of 75 healthy children. 42.1% (n=27) of PID patients and 46.7% (n=35) of healthy children were female. 60% (n=51) of PID patients' parents and 72.9% (n=62) of healthy children's parents were female. The means of Beck depression are 15,48±10,161 for patients' parents and 11,78±9,044 for healthy children's parents. The means of Stait Anxiety are 42,58±8,68 for patient group and 39,11±9,36 for healthy group. The means of Trait Anxiety are 42,58±8,68 for patient group and 39,11±9,36. Three of them are significantly high in patients' parents (p=0.013, p=0.013, p=0,027). Energy/fatigue scores are significantly different between groups. (p=0.000). The other subdomain scores of SF-36 has no significant difference. No difference is observed in anxiety, depression and SF-36 scores among diagnostic groups according to classification of International Union of Immunological Society (IUIS).

Conclusion: Our study revealed there are significant difference in both depression and anxiety levels of PID patients' parents and healthy children's parents. This can be explained by both immunodeficient children need more effort to care and avoid infections and diseases more than healthy ones. Low energy/fatigue score can confirm this effort.
Keywords: Primary Immune Deficiency, Anxiety, Depression, Quality of Life, SF-36, Parental Mental Health

POSTER 134 - EVALUATION OF QUALITY OF LIFE IN ADULT PATIENTS WITH X- LINKED AGAMMA-GLOBULINEMIA IN A HOSPITAL IN MEXICO: A STUDY USING THE SF-36 QUESTIONNAIRE

AUTHORS

Teran Olvera M[1], O'Farrill Romanillos P[1]

AFFILIATIONS

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Biography:
I was born in Southampton, United Kingdom, in 1993. Due to my parents' work commitments, we relocated to Mexico City when I was 4 years old. Throughout my childhood, I developed a strong interest in music, martial arts, and outdoor activities. However, my greatest passion was for medicine, which led me to graduate as a general physician from the National Autonomous University of Mexico. During my studies, I discovered a deep fascination for immunology, which prompted me to pursue my social service in the field of immunopathology research on tuberculosis at the National Institute of Medical Sciences and Nutrition "Salvador Zubirán." While I appreciate the study of basic sciences, I strongly believe in the importance of humanism and patient care, which motivated me to pursue a residency in clinical allergy and immunology. I find it incredibly rewarding to explore the social impact of diseases.Throughout my time as a resident, I have actively participated in various national forums as a speaker, presenting both case reports and clinical studies. It has been an enriching experience to share my knowledge and contribute to the advancement of medical understanding. I remain committed to furthering my expertise and making a positive difference in the lives of patients through the integration of medical knowledge and compassionate care.

Objective: The objective of this study was to assess the quality of life in patients with X-linked agammaglobulinemia using the SF-36 questionnaire.

Materials and methods: A descriptive cross-sectional study was conducted with a sample of 7 patients diagnosed with X-linked agammaglobulinemia at a clinic for immunodeficiencies in Clinic Service of Allergology and Clinical Immunology in CMN Siglo XXI, IMSS. The patients completed the SF-36 questionnaire, which assesses various dimensions of health-related quality of life. Descriptive statistics were used to analyze the data, including measures of central tendency (mean, median) and dispersion (standard deviation, range).

Results: The results showed that the patients had varying scores in different domains of the SF-36 questionnaire. The mean scores for each domain were as follows: physical functioning (92.9%), role limitations due to physical health (89.3%), role limitations due to emotional problems (88.6%), energy/fatigue (67.9%), emotional well-being (82.6%), social functioning (95%), pain (87.9%), general health (64.3%), and health change (78.6%).

Discussion: The findings indicate that the patients generally reported high scores in physical functioning, role limitations, social functioning, and pain. However, they had lower scores in domains related to energy/fatigue, emotional well-being, general health, and health change. This suggests that while they may have good physical functioning and social interactions, they experience challenges in areas such as fatigue, emotional well-being, and their overall perception of health. The presence of comorbidities, such as bronchiectasis and chronic rhinitis, may contribute to these challenges.

Conclusion: In conclusion, the results of this study highlight the multidimensional nature of quality of life in patients with X-linked agammaglobulinemia. While they may have good physical health in certain domains, they face difficulties related to energy levels, emotional well-being, and their overall perception of health. These findings emphasize the importance of a comprehensive approach to care that addresses the diverse needs of these patients. Further research with larger sample sizes and longitudinal designs is needed to validate these results and explore interventions to improve the quality of life in this population.

POSTER 146 - CVID PREVALENCE WITHIN A US ADMINISTRATIVE DATABASE

AUTHORS

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AFFILIATIONS

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Biography:
James Jordan, Pharm D has formal training and over 20 years of experience in the pharmaceutical industry conceiving and implementing health outcomes research studies to better understand disease burden and demonstrate the clinical, economic, and humanistic value of treatments. Dr Jordan currently works at Grifols, supporting immune globulin products.

Objective: Common variable immunodeficiency (CVID) is the most commonly identified primary immunodeficiency in adults (PIDD). Despite this, the reported prevalence of CVID varies significantly across the literature and between countries. This study aims to estimate CVID prevalence in the United States using a claims database.

Design and methods: We conducted a cross-sectional analysis of PharMetrics, a large US administrative claims database of approximately 60 million people. Individuals with a diagnosis of CVID were identified by the presence of two separate CVID ICD-10 claims (D83.x) greater than 90 days apart. Inclusion criteria required individuals to have one year of continuous insurance enrollment eligibility prior to the first CVID claim to examine demographic and clinical characteristics. Individuals with risk factors for secondary immune deficiency (SID), including HIV related- conditions, hematologic malignancies, previous transplants, and use of immunosuppressants were excluded. CVID-identified patients were used to calculate crude prevalence within the PharMetrics general population. Total US CVID cases were then estimated by mathematical extrapolation using 2019 US Census data.

Results: A total of 7,278 individuals with CVID met the study criteria for the year 2019. The average age was 48.5 years (SD 18.6), sex skewed toward female (68.9%) and use of immunoglobulin was 69.4%. The crude estimate calculations yielded 60,796 individuals in the US or 1 in 5,400 persons. Our results show a significantly higher diagnosed CVID US case count and prevalence compared to previous US estimates. A recent study estimated approximately 5,000 US cases, or 1 in 67,000 persons (Ref), while other studies, including ex-US, estimated approximately 1 in 25,000 (Refs). The noted higher proportion of women in this sample mirrors other collected CVID cohorts. Limitations exist with the crude estimate calculation as the commercial insurance population may not extrapolate perfectly to the general US population. However, within our study and dataset alone we have identified more individuals with CVID than total US estimates from other recent studies.

Conclusion: A sizable CVID population was identified when utilizing large US insurance data. These data suggest CVID prevalence may be higher compared to current US estimates.

Funding Source: Grifols SSNA

POSTER 147 - EVALUATION OF THE ADVERSE EFFECT PROFILE OF INTRAVENOUS IMMUNOGLOBULIN REPLACEMENT THERAPY IN PATIENTS WITH PRIMARY IMMUNODEFICIENCY

AUTHORS

Dikici U[1], Ozdemir O[1]

AFFILIATIONS

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Biography:
Dr. Ümmügülsüm Dikici was born in May 1989. She graduated from medical school in 2012. She received her pediatrics specialization in 2017. She started the pediatric allergy immunology fellowship program in September 2021 and is particularly interested in primary immunodeficiency patients.

Objective: Intravenous immunoglobulin (IVIG) therapy is widely used in a wide variety of autoimmune and inflammatory disorders, especially in patients with primary immunodeficiency diseases (PID). In this study, we aimed to evaluate the frequency of adverse reactions related to IVIG infusions in PID patients.
Patients- Methods: 132 patients who had IVIG replacement in our clinic between 2013-2023 were included in the study. A total of 2,505 infusions were evaluated for demographic data and side effects. Fever, chills, headache, nonspecific rash, pruritus, urticaria, abdominal pain, and myalgia symptoms were defined as a mild reaction, hypertension, wheezing, chest pain as a moderate reaction, hypotension, anaphylaxis, and impaired consciousness were defined as a severe reaction.

Results: Of the cases evaluated, 58 (43%) were female and 74 (56%) were male. Adverse reactions were seen in 20 (15%) of 132 patients. The most common side effect was headache. It was seen in 18 of 20 patients and its rate of side effects was 86.5%. The headache persisted in 4/18 patients despite premedication and preparation changes. Fever (3.5%), chills (3.5%), myalgia (2.1%), urticaria (1.4%), pruritus (0.7%), and non-specific rash (1.4%) were seen in patients with much lesser rates than headache. As a severe side effect, only one patient experienced clouding of consciousness during an infusion. Anaphylaxis, hypotension, and chest pain were not observed.

Discussion: Headache is a common side effect after IVIG. While many studies have reported headaches as an immunoglobulin-related side effect, no studies have described in detail the features of immunoglobulin-related headaches. The best medicine for the treatment of immunoglobulin-related headaches is unknown. In our study, the headache seen in the patients was in the form of a headache that started approximately 18-24 hours after the treatment, lasted for one day, responded to analgesic drugs (paracetamol or ibuprofen), and was sometimes accompanied by nausea and vomiting.

Conclusion: In our study, the most common side effect observed in patients who received IVIG treatment was headache. No adverse effects were observed severe enough to terminate the treatment. We can say that IVIG replacement therapy is a reliable treatment with the right indication.

POSTER 151 - UTILIZING PROXY DISEASES TO MODEL ACTIVATED PI3Kδ SYNDROME (APDS) HEALTH CARE UTILIZATION AND OUTCOMES

AUTHORS

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AFFILIATIONS

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Biography:
Dr. Amanda Harrington is the Senior Director of Health Economics and Outcomes research at Pharming Healthcare, Inc. She has over a decade of experience in biomedical research, and is a frequent research presenter at clinical and health economic conferences in North America and Europe. Dr. Harrington's research centers around evidence generation to demonstrate the clinical and economic burden of disease, as well as the value of health technologies to improve the lives of patients. Dr. Harrington earned a B.Sc. degree in Physiology, and both a MS and PhD in Pharmaceutical Economics, Policy, and Health Outcomes Research at the University of Arizona.

Objective: Rare diseases can pose unique challenges in economic evaluations and health outcomes research due to their unknown natural history, small trial populations, scant literature, and clinical heterogeneity. We aim to address these challenges for activated PI3Kδ syndrome (APDS), a rare and clinically diverse inborn error of immunity (IEI), by creating health outcomes and economic models using proxy diseases, a strategy successfully demonstrated for other rare diseases.

Design and methods: We identified potential proxy diseases for APDS using the 2022 IUIS phenotype classification. We conducted a literature search of relevant phenotypes spanning the mechanisms of disease, cohort analyses, and laboratory research in PubMed.gov. We then designed and electronically distributed a survey to 6 selected global IEI experts. The survey assessed the validity of disease proxy based on similarity in mechanism of disease, clinical characteristics, and disease progression. Experts were also asked to identify both additional proxy diseases for APDS and diseases which had specific clinical manifestations that were proxies.

Results: All respondents agreed that CTLA-4 (cytotoxic T-lymphocyte antigen-4) haploinsufficiency and LRBA (lipopolysaccharide-responsive and beige-like anchor protein) deficiency are appropriate proxies for APDS, with one expert responding with qualifications. (Fig. 1). Common Variable Immune Deficiency (CVID) with noninfectious complications was considered a suitable proxy by 5/6 of the respondents. However, one expert cautioned that over the long term, disease outcomes between CVID and APDS could differ meaningfully. Other diseases like HIGM (hyper IGM syndrome), STAT1 GOF, (signal transducer and activator of transcription 1 gene gain of function) and ALPS (autoimmune lymphoproliferative syndrome) showed significant overlap of characteristics with APDS but were not conclusively identified as proxies. Wiskott-Aldrich Syndrome is not deemed to be a proxy. Additionally, bronchiectasis in the context of CVID is appropriate, but in the context of cystic fibrosis the results were not conclusive. Other characteristics explored were infections, cytopenias, neurological deficits, lymphoproliferation. Severity bias in the current literature for APDS, which could affect comparisons herein, was also assessed.

Conclusion: CTLA-4 haploinsufficiency, LRBA deficiency, and CVID with noninfectious complications may serve as proxy diseases to model the APDS disease burden for economic evaluations and health outcomes. This approach not only fills a substantial gap in APDS research but also suggests a potential strategy for quantifying outcomes and impacts in other rare diseases.

POSTER 152 - QUALITATIVE INTERNATIONAL STUDY TO EXPLORE THE SYMPTOMS AND HEALTH-RELATED QUALITY OF LIFE IMPACT OF ACTIVATED PHOSPHOINOSITIDE 3-KINASE DELTA SYNDROME (APDS): INTERIM FINDINGS

AUTHORS

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Biography:
Dr. Ian Hitchcock currently serves as Vice President for Medical Affairs for Europe & RoW for Pharming. He has worked in the biotech/pharmaceutical industry for 24 years and has bought multiple innovative products to market in multiple therapeutic areas with a high unmet medical need, initially in HIV and subsequently other immunological products in virology, rheumatology, oncology, and allergy. He worked as a Clinical Fellow in HIV at the Royal Free Hospital after 10 years of General Practice in South Africa and a founding partner of Medicross Medical Centres. He qualified at the University of Cape Town Medical School in 1986.

Objective: Activated phosphoinositide 3-kinase delta syndrome (APDS) is an ultra-rare primary immunodeficiency associated with multiple clinical manifestations and risk of organ damage and malignancy. Initially characterised in 2013, there is a lack of data on the patient experience in APDS. This study reports interim findings on the disease burden and health-related quality of life (HRQoL) impact of APDS from the perspective of patients, caregivers and healthcare providers (HCPs).

Design and method: This is a qualitative study with three components: 1) semi-structured qualitative telephone interviews with HCPs with experience treating APDS; 2) a narrative exercise; and 3) semi- structured qualitative telephone interviews (2 & 3 include people with APDS and caregivers). Interview guides were developed and included questions on diagnosis, symptoms, HRQoL impacts and treatments. Interviews were recorded and transcribed. Data were analysed using thematic analysis.

Results and conclusion: The interim sample comprised six HCPs in the UK, US, Canada, Spain, Italy, France, three caregivers (care recipients aged 10 months-11 years) and four individuals with APDS (aged 16- 28 years) in the UK and US.

HCPs described the most concerning APDS clinical manifestations as recurrent infections and associated complications (e.g., pneumonia), lymphoproliferation (e.g., risk of ruptured spleen, lymphoma), and gastrointestinal issues (e.g., nodular lymphoid hyperplasia leading to malabsorption and failure to thrive). HCPs reported more active lymphoproliferation and increased lung damage risk in adults due to ongoing infections and complications.
Individual/caregiver narrative accounts included descriptions of the long and challenging diagnosis journey, clinical manifestations, symptoms and HRQoL impacts. The individual/caregiver interviews found commonly reported symptoms or clinical manifestations to include fatigue, body pain, gastrointestinal issues, respiratory tract infections, lymphoproliferation and failure to thrive. Negative impacts on individuals' HRQoL were also reported, including interruption to work, school or social and leisure activities due to illness, medical appointments, planning and administering treatment and shielding from infections, as well as reduced physical functioning and affected emotional wellbeing (e.g., loneliness, worry). Caregivers reported a negative impact on their own physical health, work, social and leisure activities, as well as their personal time due to the time spent caring, and organising medical care.

This is the first qualitative burden of illness study in APDS. Findings highlight the substantial burden of living with APDS, exacerbated by low awareness, numerous clinical manifestations and symptoms, and their subsequent impact on the HRQoL of affected individuals/caregivers.

POSTER 160 - CANADIAN INBORN ERRORS OF IMMUNITY NATIONAL REGISTRY: AN ESSENTIAL TOOL TO ADVANCE MANAGEMENT OF PATIENTS WITH INBORN ERRORS OF IMMUNITY AND THE ALLOCATION OF RESOURCES IN HEALTHCARE

AUTHORS

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Biography:
After successfully graduating from the pediatric faculty of medical school and pediatric residency, I completed Ph.D. studies in Clinical Immunology at Rostov State Medical University (RSMU), Russia. The research aimed to evaluate immunophenotype and cytokines profile in patients with rheumatoid arthritis who received Infliximab. Following this, I completed Specialty/Fellowship Training in Clinical Immunology and Allergy. Then, I was accepted as an Assistant Professor of Clinical Immunology and Allergy Department at RSMU where my duties included working on research projects, in-hospital consulting and teaching medical students and residents. Since 2017, I have been involved in a research project with the Alberta Children's Hospital in the Division of Pediatric Hematology/Immunology, which resulted in the production of case reports and poster presentations at CIS and FOCIS meetings. Then, in September 2021, I was accepted to this Division as a Research Assistant and Research Associate in May 2023, where I currently work on multiple research activities:

- *Developing research and regulatory documents for the National Inborn Errors of Immunity Registry of Canada by collaborating with Clinical Immunologists from all provinces of Canada*
- *Research Collaboration with Scientists from Lead US Universities: Autoimmune Hemolytic Anemia Study, PIDTC studies, CD3δ SCID Gene Therapy Study*
- *Coordination VISID Study: COVID-19 Vaccine Immunogenicity and Safety in Immune Deficient Patients https://omc.ohri.ca/VISID/Default.aspx in Calgary (adult and pediatric cohort).*

Introduction: It is estimated that 29,000 Canadians live with monogenic or polygenic disorders of immune deficiency/dysregulation, now referred to as Inborn Errors of Immunity (IEI). Canada has a unique IEI population with specific founder mutations including those in First Nations, Métis, Inuit (FNMI), Mennonites as well as diverse immigrant communities. Moreover, there are many challenges in delivering care to rural and remote regions of Canada. However, there is no comprehensive portrait of patients with IEI available in Canada. In other countries, this issue has been mitigated by developing single- and multicentre IEI Registries that help foster research, patient care, and advocacy. Our aim is to develop the Canadian Inborn Errors of Immunity National Registry (CIEINR) to collect data in a standardized form in centers treating patients with IEI across Canada, ensuring equitable access to healthcare.

Methods: The Registry Working Group (RWG) of the Clinical Immunology Network in Canada (CINC) including clinician scientists from six Canadian Provinces, with input from the national immune deficiency patient organization 'ImmUnity Canada', developed the project to collect longitudinal data for a patient-focused Registry. Through monthly virtual RWG meetings, consensus was reached on study design, preparation of legal and research ethics board (REB) documents, and application for funding. Multi-level data collection tools, with annual updates on demographics, infectious and non-infectious manifestations, laboratory values, treatment, quality of life, and patient-reported outcomes have been developed (Image 1).

Results: REB documents and electronic case report forms were peer-reviewed by external experts and the patient organization. Legal agreements are in progress for more than 20 academic sites to allow data sharing with the Main Registry Database and Central Office, located at the University of Calgary in Alberta. Piloting the Research Electronic Data Capture (REDCap) system with pediatric and adult cases has ensured quality control and improvement.

The Registry is supported by a grant through Immunodeficiency Canada and is designed in collaboration with The United States Immunodeficiency Network (USIDNET). The RWG is also in discussion with the European Society for Immunodeficiencies (ESID) to share Canadian data with their registry. By allowing information to be combined with that of thousands of other patients, there is powerful potential for both knowledge generation and innovations in management.

Conclusion: The information collected in the CIEINR will detail the landscape of IEI in Canada. Received data are essential to analyze barriers to medical care and to plan the healthcare workforce and resources for these patients.

POSTER 177 - NEAR REAL-TIME CONTINUOUS REMOTE MONITORING OF VITAL SIGNS OF PATIENTS DURING ADMINISTRATION OF MEDICATION AT HOME.

AUTHORS

Van Well M[1]

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Biography:
Marleen van Well is a Technical Medicine graduate from the Delft University of Technology. For her Master Thesis, which she recently defended, she explored the potential of near real-time continuous remote monitoring (NRCRM) of vital signs of patients during administration of intravenous immunoglobulins (IVIg).

Marleen van Well, Virgil ADH Dalm, Jan Dietert Brugsma, Marianne W. van der Ent, Haidy Tjoe- a-on, P. Martin van Hagen, Mark Mulder

Objective: To cope with the decreasing availability of healthcare personnel, we are in need of a national (and global) transition to make the healthcare systems sustainable for the future. Administration of intravenous immunoglobulins (IVIg) at home for patients with antibody deficiencies is an example of a therapy that currently requires a significant number of nursing staff in relation to the number of patients receiving the treatment. Near real-time continuous remote monitoring (NRCRM) of vital signs of these patients during administration could potentially offer a solution by enabling nurses to treat the same number of patients with fewer staff members. The goal of this pilot study is to test monitoring system functionality, evaluate user experiences and identify challenges and bottlenecks of NRCRM of vital signs of patients during administration of IVIg at home.

Design and methods: Patients from the department of immunology at Erasmus MC who receive IVIg at home were evaluated for inclusion. During administration, their vital signs were monitored remotely in addition to the usual monitoring procedure performed by the home nurse. Raw data of the vital signs, in combination with an alarm template and observations during administration at home, were used to assess system functionality. User experience was evaluated using custom-made questionnaires. Challenges and bottlenecks for further implementation were identified during execution of the study protocol.

Results: No-data alarms in this study yield an alarm burden of 10.9 ± 4.8 (mean ± SD) alarms per patient per hour with a duration of alarms of 2min59sec ± 13min38sec (mean ± SD). Wide set threshold alarms in this study yield a total alarm burden of 17.1 ± 15.1 (mean ± SD) alarms per patient per hour with a duration of 1min12sec ± 3min (mean ± SD). Attitudes of both patients and nurses towards the transition to NRCRM are mixed. Most concerns exist around patient safety. 30 challenges and bottlenecks in the transition are identified.

Conclusion: This study provides an overview of the actions that need to be taken to overcome associated challenges and bottlenecks. Also, suggestions for implementation were presented. Besides the practical and safety aspect, a challenge lies in providing information to caregivers and patients to ensure smooth adoption.

POSTER 195 - ANALYSIS OF DIAGNOSTIC DELAY IN PATIENTS WITH DIAGNOSIS OF INBORN ERRORS OF IMMUNITY

AUTHORS

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AFFILIATIONS

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Biography:
Pediatric Resident

Study aim: It is worldwide recognized that early diagnosis of rare diseases allows the correct management and improve long-term prognosis. We aimed to analyze the time to diagnosis in a cohort of patients with inborn errors of immunity (IEI).
Materials and methods: We enrolled IEI patients on regular follow-up at the Immunology Unit of the Pediatric Clinic of ASST Spedali Civili of Brescia. A medically supervised questionnaire was administered and we conducted descriptive statistical analysis of the collected data.
Results: 91 patients were included in the study. Patients were grouped according to the classification of IEI by the International Union of Immunological Societies (IUIS 2022): 50.5% of patients were diagnosed with predominantly antibody deficiency, 26.4% with combined immunodeficiency associated with syndromic features, 9,9% with congenital defects of phagocytes/defects of intrinsic and innate immunity, the remaining 13,2% with immunodysregulation diseases/autoinflammatory diseases/bone marrow failure or others. The lower diagnostic latency was observed in patients with congenital defects of phagocytes and antibody defects (60,4% of the whole cohort with 0 year and 1,56 years, respectively). The region of residence coincided with the region where the diagnosis was made in 80% of cases with a diagnosis latency of 1.93 years, in the cases where the diagnosis was made in a different region the diagnostic delay was of 7.44 years. The average latency since the onset of symptoms was of 4,64 months from the first medical evaluation, 17.44 months from the first specialist evaluation, and 2.95 years from the definitive diagnosis, respectively. 34,1% of patients referred to immunologist first, while 52% of patients were evaluated by different specialist before diagnosis. 78% of patients were misdiagnosed prior to the definitive diagnosis, mainly considered as infectious diseases (33%). The diagnostic delay was less than 1 year in 52% of patients, 1-3 years in 19% of patients, 4-9 years in 22% of patients, and >10 years in 7% of patients, respectively.

Conclusion: We may argue that the major causes of diagnostic delay were atypical phenotypes, poor knowledge of rare disease, particularly when genetic defects were identified years later the onset of symptoms, or the interregional shift. The analysis of the causes of diagnostic delay may help the clinician to reduce the time of diagnosis. Increasing the knowledge of inborn error of immunity and rare diseases in general is essential to improve their prognosis.

POSTER 219 - PSYCHOSOCIAL EVALUATION OF ADULT PRIMARY IMMUNODEFICIENCY PATIENTS: A SURVEY STUDY

AUTHORS

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Cukurova University – Adana,Turkey Pediatrics Department– 06/2017 – 10/2017 Cukurova University – Adana,Turkey Family Medicine Department- 05/2018-05/2021

University
Cukurova University – Adana,Turkey Faculty of Medicine – 09/2010 – 06/2016

High School
Gaziantep Anatolian High School-Gaziantep,Turkey 09/2006 – 06/2010
Graduation With First Place

WORK EXPERIENCE
10/2016-04/2017 Gaziantep Islahiye State Hospital/ Refugee Camp-Turkey 06/2017-10/2017 Pediatrics Department/Cukurova University – Adana,Turkey 05/2018-05/2021 Family Medicine Department/Cukurova University – Adana,Turkey 08/2021- Now Incesu State Hospital/Ministry of Health-Kayseri,Turkey

ADDITIONAL EDUCATION & CERTIFICATES LANGUAGE SKILLS
English Reading:Good, Writing:Good, Speaking:Good (YDS test point:60) German Reading: İntermediate, Writing:İntermediate, Speaking: Intermediate

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17-21 November 2018, Antalya, Turkey
25. National Allergy and Clinical Immunology Congress participation with e-paper,organized by Turkish National Society Of Allergy And Immunology
25-28 April 2019, Adana, Turkey

18. International Eastern Mediterranean Family Medicine Congress participation with verbal papers, 16-20 October 2019, Antalya,Turkey

13. Fall School of Family Medicine participation with a verbal statement, organized by Turkish Foundation of Family Medicine
October 31 November-November 2, 2019, Ankara,Turkey

18.Participation in the National Family Medicine Congress by poster paper,organized by Turkish Association of Family Physicians

PAPERS PRESENTED AT NATIONAL SCIENTIFIC MEETINGS AND PUBLISHED IN THE PAPER BOOK

1. *M.Yilmaz M.Serbes, H.Cengiz, A.Şasihüseyinoğlu, D.Doğruel, D.Altıntaş, Single Center Experience:Clinical and Immunological characteristics of the patients we monitored with the diagnosis of Common Variable Immunodefiency,25. National Allergy and Clinical Immunology Congress, 17-21 November 2018, Antalya (E-Poster Presentation)*
2. *E.Akpınar, H.Cengiz, A.Çabuk, Quality Of Life In Rheumatoid Arthritis Patients Receiving Methotrexate Treatment, 18. International Eastern Mediterranean Family Medicine Congress, 25-28 April 2019, Adana (Oral Presentation)*
3. *E.Saatçı, H.Cengiz, Measuring The Level Of Knowledge About The Periodic Health Examination Guide Of Family Medicine Assistants, 13. Fall School Of Family Medicine, October 16-20, 2019, Antalya (Oral Presentation)*
4. *M.Olgun, H.Cengiz, I.Kolsuz, T.Tetiker, Rare Association;A case of late diagnosis Turner Syndrome and congenital adrenal hyperplasia ,18.November October 31-November 2,2019, Ankara (Poster Presentation)*
5. *E.Saatçı,H.Cengiz,A.Yıldırım ''How is the "Stress Burden" Affected by the Parents of Children with Growth Retardation and Malnutrition" ,9th International Trakya Family Medicine Congress, 05-08 March 2020,Edirne,Turkey(Oral Presentation)*
6. *E.Saatçı,H.Cengiz," Evaluation of Knowledge of Family Medicine Assistants on Autism", 19th Eastern Mediterranean Family Medicine Congress, 17-20 September 2020, Online(Oral Presentation)*
7. *H.L.Yılmaz, E.Karaali, "A Case of Spontaneous Pneumothorax Due to Smoking at Young Age", 19th Eastern Mediterranean Family Medicine Congress, 17-20 September 2020, Online(Poster Presentation)*
8. *R.Akıllı, Ö.Tepe, H.Cengiz,A.İşler, "Is Toothache Related to Treatment Given in Hypertension Patients?", 19th Eastern Mediterranean Family Medicine Congress, 17-20 September 2020, Online(Poster Presentation)*
9. *E.Saatçı,H.Cengiz, "Status of Primary Care Physical Activity in Individuals Applying to the Family Medicine Outpatient Clinic", 14. Family Medicine Fall School, 14-17 October 2020, Online (Oral Presentation)*
10. *G.Özden, H.Cengiz "Coexistence of CVID (Common Variable Immunodeficiency) and Diffuse Large B Cell Lymphoma", 6th Clinical Immunology Congress, 31 October-1 November 2020, Online(Poster Presentation)*
11. *E.Saatçı,H.Cengiz, ''Measurement of Knowledge and Attitudes about AIDS(Acquired Immunodefiency Syndrome) to University Students Applying to Family Medicine Policlinics", 25 th WONCA Europe Congress,16-19 December 2020,Online,E-poster*
12. *E.Saatçı,H.Cengiz, "Assessment of Quality of Life with Urticaria Activity Score in Patients with Chronic Urticaria", 15. Fall School of Family Medicine, 20-24 October 2021, Antalya, Turkey(Oral Presentation)*

Introduction: Primary immunodeficiency(PID) is a heterogeneous group of diseases that affect the cognitive, emotional, behavioral, and social status of patients, characterized by increased susceptibility to infections due to germline mutations and immune dysregulation. Our aim is to evaluate loneliness, social adaptation, anxiety, and depression in adult immunodeficiency patients and to determine the factors that may affect them.

Methods: This was a cross-sectional, descriptive study conducted at the Ege University Hospital Clinical Immunology and Allergy Outpatient Clinic, during the period from February to August 2022. The Social Adaptation Self-evaluation Scale(SASS), UCLA-Loneliness Scale(UCLA-LS), Hospital Anxiety and Depression Scale(HADS), and additionally a questionnaire developed by the researcher were completed by conducting individual patient interviews in a single session. The cut-off scores of HADS-A and HADS-D for the Turkish population were 10 and 7, respectively. The cut-off points of SASS are **<**25(normal), **>**35(social imbalance).

Results: A total of 104 patients(F/M: 60/44) with a median age of 34 years- old(min.:18-max.:89) were enrolled in this study. The median age of onset of disease symptoms is 19(min.: 1-max.:71) and the median age of diagnosis is 27(min.:1-max.:71). The knowledge of diagnosed psychiatric diseases 26% of themselves and 7.7% of their family. The SASS mean of all participants was 25.54±8.11, UCLA-LS mean 44.89±12.66, HADS-Anxiety mean 9.87±4.77, HADS-Depression mean 9.12±4.80. Between SASS and HAD-A(r:0.408;p:0), HAD-D(r:0.614;p:0), and between UCLA-LS and HAD-A(r:0.547;p:0), HAD-D(r:0.558;p:0), SASS(r:0.454;p:0) there is a positive correlation between them. HAD-A(r:0.408;p:0), HAD-D(r:0.383;p: 0.001), SASS(r:0.278;p:0.017) increases as the length of hospital stay increases. There is a negative correlation between the age at diagnosis(r:-0.224; p:0.022), the age of symptoms(r:-0.271; p:0.006), and HAD-A. People living in the city have less anxiety(p:0.004) and less sense of loneliness(p:0.012) than those living in villages and towns. Those who are not satisfied with IGRT feel more depressed(p:0.012) and lonely(p:0.032). There is a significant difference in the HAD-A(p:0.033), HAD-D(p.0.024), SASS(p:0.001), and UCLA-LS(p: 0.016) scores of those who applied for a disability report compared to those who did not. Social functionality is more impaired in those who use public transportation(p:0.025). Those whose income is less than their expenses have higher HAD-A(p:0.039), HAD-D(p.0.037), SASS(p:0.006), and UCLA-LS (p: 0.014) scores.

Conclusion: Adult PID patients are at risk for depression and anxiety and experience strong feeling of loneliness. Social maladjustment or loneliness promote anxiety and depression, while loneliness is correlated with impaired social functioning. This situation emphasizes the importance of biopsychosocial evaluation of individuals diagnosed with PID.

POSTER 234 - THE PID ODYSSEY 2030: OUTLOOKS, UNMET NEEDS, HURDLES, AND OPPORTUNITIES — PROCEEDINGS FROM THE IPOPI GLOBAL MULTI-STAKEHOLDERS' SUMMIT (JUNE 2022)

AUTHORS

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Biography:
Samya Van Coillie is Medical Affairs Project Manager at the International Patient Organisation for Primary Immunodeficiencies (IPOPI). In this capacity she is in close contact with a global network of medical experts in the field of primary immunodeficiency (PID) and she provides the patient perspective in relevant scientific research projects. Additional responsibilities at IPOPI consist of monitoring the scientific and clinical developments affecting PID patient care, overseeing clinical care educational programmes and supporting scientific IPOPI events.

Prior to joining IPOPI Samya obtained a PhD in biochemistry and biotechnology at the VIB- UGhent Center for Inflammation Research. She also holds a Master's degree in Biomedical Sciences and a Postgraduate Diploma in One Health.

Objective: The objective of the IPOPI Global Multi-Stakeholders' Summit held in 2022 was to facilitate a forward-thinking meeting and brainstorming discussion among stakeholders in the primary immunodeficiency (PID) community. The summit aimed to identify the future priorities, unmet needs, hurdles, and opportunities for PIDs by engaging participants in active and provocative discussions.

Design and method: The summit encompassed various topics relevant to PIDs, including diagnosis, treatment, interactions with other diseases, and avenues for research in humanities and human sciences. These topics were explored through presentations and discussions, covering areas such as newborn screening, genomic sequencing, therapeutic evolution of immunoglobulins, targeted therapies, curative approaches, the interactions of primary ID with secondary ID and the impact of PIDs on patient-reported outcomes and quality of life. All participants actively participated in the summit, contributing to the drafting of recommendations based on a shared understanding of future opportunities and challenges.

Results and conclusions: The summit's outcomes consist of a collection of materials, perspectives, and summaries, which serve as succinct and impactful recommendations for the PID community. These recommendations have the potential to guide the community's next key steps, considering the identified opportunities, challenges, and scenarios for the future of PIDs. The proceedings of the summit are set to be published, ensuring that the valuable insights and discussions from the event reach a wider audience, and a second follow-up meeting is planned to build upon the current outcomes. The summit successfully fostered collaboration and provided valuable insights for shaping the direction of the PID field in the years leading up to 2030.

POSTER 249 - PATIENTS WITH INBORN ERRORS OF IMMUNITY IN UKRAINE: SURVIVAL IN WAR CONDITIONS

AUTHORS

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AFFILIATIONS

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Biography:
Executive Director of Ukrainian National Patient Organization NGO "Rare Immune Diseases"

Background: Before the beginning of full-scale war of Russian Federation against Ukraine in February 2022 all PID patients in Ukraine have had access to the treatment on the regular basis with state support. They belong to vulnerable category of citizens as they depend on access to medical care and orphan drugs.

Design: The surveys were conducted in April 2022 and in May 2023. The questionnaires were distributed using patient organization social media and were filled out by 106 patients or their parents in 2022 and 135 in 2023, respectively from all regions of Ukraine, except occupied Crimea. Among the respondents, 56% were pediatric patients and 44% were adults with 32 different nosologies.

Results: Almost half of the responders (65/135) had to change their place of residence since February 2022, 30 moved to another region of Ukraine, 35 went abroad. Countries patients moved to include: Poland, Germany, France, Switzerland, Italy, Bulgaria. 10 patients were forced to stay in the occupied territory, 7 responders still live under occupation. The number of those under occupation may be much higher but they have limited access to Ukrainian social networks and currently do not have access to treatment.
About 50% of patients had problems with access to treatment or medical care due to the war (blocked logistics, destroyed or not working hospitals, absent physicians, air raids and electricity outage). Access to medical care abroad was quite variable - from full provision to complete lack of access to drugs. 60% of patients had support from international foundations and institutions. 73% of our patients continue to receive medicines due to the state of Ukraine. About 20% report gradual deterioration of their health, and 5.7% indicate rapid deterioration. All patients and their families had a fear of dying and all had mental health deterioration: anxiety - 83%, sleep disturbances – 66%, irritability – 66%, tearfulness – 33%. All patients did not have a safe environment, 25% indicated the decreased quality of food, 25% had difficulties with accommodation. 40% of responders could not answer the question about their future plans, reflecting instability and frustration.

Conclusions: Russian aggression has negative impact on Ukrainian health care system and on the quality of life and access to treatment for patients with IEI. The well-being, mental health problems, direct life threats, decreased access to basic needs are the most expressed.

MALIGNANCY IN PID

POSTER 50 - A CASE OF BLOOM SYNDROME DEVELOPING MYELODYSPLASTIC SYNDROME DUE TO ADJUVANT THERAPY GIVEN DUE TO BREAST CANCER

AUTHORS

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AFFILIATIONS

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Biography:
I was born in Nevşehir,Turkey in 1987 and obtained my medical degree at İstanbul University of medical school in İstanbul. My specialization was in the department of internal diseases at the Necmettin Erbakan University Faculty Of Medicine Hospital. After working for 3 years as a specialist in internal medicine in a hospital, I started and still attending my fellowship at Necmettin Erbakan University in Divison of Clinical İmmunology and Allergy in Konya.
Professionally, I am interested in primary and secondary immunodeficiencies, allergic diseases. I am maried and a mother of two young children.

Introduction: Bloom syndrome (BS) is a rare autosomal recessive chromosomal instability disorder caused by mutations in the BLM gene at 15q26.11. The most prominent features are growth retardation starting in the intrauterine period, characteristic facial structure, lupus-like skin lesions, photosensitivity, telangiectasias, immunodeficiency findings, type 2 diabetes mellitus, and hypogonadism. The increased risk of malignancy shortens life expectancy. Most of the patients die around the age of 20 due to malignancies. Here we present a case of a patient with BS who developed myelodysplastic syndrome (MDS) due to adjuvant therapy given for breast cancer during follow-up.

Case: The patient, who was examined from the age of 3 due to recurrent lung infections(pneumonia, bronchitis), growth retardation, and photosensitivity, was diagnosed with BS at the age of 14, and intravenous immunoglobulin (IVIG) replacement therapy was started. The patient's parents, with low birth weight (1500 gram) and micrognathia, were sibling grandchildren. During follow-up, a solid lesion with irregular contours 1 cm in diameter was detected on ultrasonography with the detection of swelling in the left axillary region. The patient diagnosed with invasive ductal breast cancer by excisional biopsy underwent four cycles of adriamycin+cyclophosphamide and 12 cycles of paclitaxel, followed by 21 days of low-dose radiotherapy. MDS was detected in the patient who developed pancytopenia 1 year after these treatments. The patient died of sepsis due to opportunistic infection after azacitidine treatment for MDS.

Discussion and conclusion: In BS, which is known to have a predisposition to malignancies, there are concerns about radiotherapy applications due to the risk of developing malignancies secondary to treatment. In the literature, in a case with BS, standard chemotherapy was followed by 21 days of low-dose radiation therapy due to a breast cancer, but it was stated that the patient developed lung cancer a few years later. In our case, MDS developed similarly after chemotherapy and radiotherapy. Although there are studies on optimal doses of both chemotherapy and radiotherapy in diseases known for their susceptibility to chromosomal fractures such as ataxia telangiectasia, and severe combined immunodeficiency with Artemis mutation, publications on BS are in the form of case reports, and there is no clear recommendation other than evaluating only dose reduction.Treatment recommendations will become more apparent as the experience of this rare disease increases and become available in the literature.
Keywords: Bloom Syndrome, immunodeficiency, breast cancer, myelodysplastic syndrome.

POSTER 57 - DYSIMMUNITY AND IMMUNOSUPPRESSANT THERAPIES ARE ASSOCIATED WITH INCREASED RISK OF MALIGNANCY IN CVID PATIENTS

AUTHORS

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AFFILIATIONS

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Biography:
Dr. García-Bustos is a doctor specialist in the Department of Internal Medicine at La Fe Hospital. He holds a medical doctorate from the Faculty of Medicine at the University of Valencia. He has published extensively in high-impact journals, with a particular focus on the fields of infectology and fungal research. In addition, he is an active member of the Immunodeficiency Unit at La Fe Hospital.

Objective: Common Variable Immunodeficiency (CVID) is a primary immunodeficiency disorder characterized by impaired antibody production and heightened susceptibility to infections. In some cases, CVID patients may also exhibit dysimmunity, which increases their morbimortality. While the prevalence of cancer in CVID is well-documented, the potential association between dysimmunity and increased cancer risk remains unclear. This poster aims to compare the development of neoplasia in CVID patients with dysimmunity to those without, in order to investigate the hypothesis that chronic dysimmunity may contribute to a higher incidence of malignancy.

Material and methods: Data for this study were obtained from the retrospective multicenter cohort GTEM-SEMI-CVID, comprising 250 patients diagnosed with CVID in Spain. Patients with CVID (dCVID) and coexisting dysimmunity were identified based on the presence of autoimmune cytopenias, splenomegaly, lymphadenopathy, granulomatous-lymphocytic interstitial lung disease (GLILD), or other autoimmune manifestations/diseases. Statistical analysis was conducted using the R software package.

Results: The prevalence of cancer was significantly increased in patients with dCVID compared to non- dysimmune CVID (n=31, p=0.0104). However, no significant increase in gastric cancer prevalence was observed in dCVID patients (p=0.161). Within the cohort, only one patient was diagnosed with MALT lymphoma and two patients were diagnosed with Hodgkin lymphoma, all of them belonging to the dCVID group. The prevalence of non-Hodgkin B lymphoma was significantly increased in dCVID patients (n=11, p=0.0081), while no cases were reported in the non-dysimmune CVID group. T-cell lymphomas or acute leukemia were not diagnosed in any patients within the cohort (Table 1)
The use of immunosuppressant therapies was significantly higher in dCVID patients (p=1.27e- 8). Furthermore, among dCVID patients, those who had received immunosuppressant therapies had a significantly higher frequency of cancer diagnosis (p=0.00215). No significant differences were found in the global prevalence of other malignancies within the GTEM-SEMI-CVID cohort (p=0.811) (Fig.1).

Conclusion: Our study demonstrates a significant increase in the prevalence of cancer, particularly non- Hodgkin B lymphoma, in patients with dCVID. This suggests that the presence of dysimmunity in CVID patients may contribute to a higher risk of malignancy. Additionally, the use of immunosuppressant therapies in dCVID patients was associated with a higher frequency of cancer diagnosis. These findings emphasize the importance of considering dysimmunity as a potential risk factor for cancer development in CVID patients, specially in those who also received immunosuppressant treatment.

POSTER 80 - PRIMARY IMMUNE DEFICIENCY-CANCER RELATIONSHIP: WHİCH CAME FİRST: THE CHİCKEN OR THE EGG?

AUTHORS

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AFFILIATIONS

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Biography:
I was born on 25.01.1974 in Mersin. I graduated from Gülhane Military Medical Academy Faculty of Medicine in 1998. I worked as an assistant doctor in Internal Medicine at Gülhane Military Medical Academy between 2001-2005. I worked as an Internal Medicine Specialist at Diyarbakır Military Hospital between 2005-2009 and İzmir Military Hospital between 2009-2010. In 2007, I worked as an Internal Medicine specialist at KFOR NATO Military Hospital (Kosovo- Prizren) for 6 months. Between 2010-2013, I studied Immunology and Allergy at Gülhane Military Medical Academy. In 2015-2016, I did an internship at UCI Irvine University, California, Immunology laboratory and polyclinic for 1 year. Since 2013, I have been working as an Immunology and Allergy Specialist. Since 2017, I have been working as the responsible of Gülhane Training and Research Hospital Tissue Typing Laboratory. On 31.05.2022, I received the title of associate professor in the field of Immunology and Allergy Diseases.

Objective: Immunodeficiency is associated with increased cancer risk. Cancer is the second most common cause of mortality in PID after infections. It is important to consider that disorders attributed to secondary immunodeficiency in cancer patients may actually mask an underlying primary immunodeficiency (PID).With this article, we aimed to increase the awareness of the PID-cancer relationship among physicians.

Case 1: Diagnosed with Hodgkin Lymphoma at the age of 7 and went into remission; A 30- year-old male patient, who had been receiving regular IgRT since the age of 11 with the diagnosis of PID, applied to receive routine IVIG treatment. There was no complaints other than talking about yellowing of the skin for the last week. In the examinations, tbil/dbil: 24.5/15.8, KCFT : >10 times higher. His imaging revealed hepatosplenomegaly and multiple conglomerated LAP in abdomen (Picture 1). Pathology was reported as B-cell lymphoma infiltration from liver biopsy. The patient was started on steroid+rituximab-gemcitabine and cisplatin chemotherapy. During rituximab treatment, the patient developed general status disorder, convulsion, hypotension and subdural hemorrhage was detected. He died 1 month after his admission to the hospital.

Case 2: A 48-year-old female patient who was followed up with a diagnosis of CLL and received fludarabine-cyclophosphamide-rituximab (FCR) chemotherapy in 2019 was referred to us because she could not complete chemotherapy due to serious infections, her hypogammaglobulinemia persisted (for 2 years) despite discontinuation of treatment, her cervical, axillary and inguinal lymph nodes disappeared and splenomegaly and recurrent infections persisted. IGG, IGA, IGG1, IGG2, IGG2, IGG4, CD56, CD4, CD16 were found to be low in the investigations and the patient was accepted as an PID and IgRT treatment was started (Table 1). The patient has been followed up with regular IVIG treatment for 11 months. Clinically significant improvement was achieved during follow-up.

Conclusion: Since clinical conditions such as immunodeficiency or hematologic malignancy are unpredictable, the need for a multidisciplinary approach in the diagnosis, follow- up and treatment of these patients. The establishment of interdisciplinary standard consensus guidelines are important.

POSTER 82 - SEVERE ADULT HYPOGAMMAGLOBULINEMIA ASSOCIATED WITH DELAYED-DETECTED THYMOMA: CONTROVERSIES BETWEEN COMMON VARIABLE IMMUNODEFICIENCY VS GOOD SYNDROME.

AUTHORS

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AFFILIATIONS

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Biography:
I graduated from the Faculty of Medicine at the University of Guayaquil in Ecuador in 2016. Currently, I'm pursuing my specialization as an Internal Medicine Resident in Immunology at the Complejo Hospitalario Universitario de Cáceres.

Background: Severe hypogammaglobulinemia is a condition characterized by low or absent levels of immunoglobulins in the blood, which increases the risk of recurrent infections. In some cases, this condition may be associated with the presence of thymoma, a tumor of the thymus. Since the first description of Good Syndrome (GS), which associates thymoma, persistent hypogammaglobulinemia despite thymoma resolution, and high susceptibility to infections, multiple case reports and systematic literature reviews have been conducted to try to group its clinical characteristics. In 2022, the IUIS classified this disease within the group of phenocopies associated with autoantibodies.

Objective: To highlight the relevant aspects that differentiate Common Variable Immunodeficiency (CVID) from GS.

Method: The 26-year evolution of a 59-year-old woman with severe hypogammaglobulinemia associated with a thymoma and the results of her complementary tests are detailed. Clinical findings are analyzed and compared with recent literature.

Results: The patient presented a clinical history characterized by recurrent herpes labialis and persistent diarrhea, with intestinal giardiasis. At the age of 27, severe panhypogammaglobulinemia with undetectable levels of IgA and IgM was observed, and she has received substitutive treatment with intravenous immunoglobulins since then. An Immunology study was requested, revealing persistent panhypogammaglobulinemia, a normal count of peripheral B lymphocytes, and an increase in B21 low lymphocytes. The vaccine response could not be evaluated due to prior treatment with IGIV. She was classified as CVID. At the age of 37, she was diagnosed with chronic atrophic gastritis with intestinal metaplasia and moderate acute activity associated with Helicobacter pylori, requiring multiple antibiotic regimens for eradication. At the age of 41, she was diagnosed with stage II AB thymoma, which was absent in previous radiological studies.
Throughout 26 years of follow-up, the patient has not experienced relevant infectious complications or developed autoimmune phenomena, maintaining normal levels of B lymphocytes.

Conclusion: The case presents a woman with chronic diarrhea, severe hypogammaglobulinemia detected at the age of 27, and a thymoma diagnosed at the age of 41. Differential diagnosis between CVID and GS is deeply discussed. From our point of view the patient's clinical presentation and evolution are more compatible with CVID, as she has a normal count of B lymphocytes, has not presented infectious complications or autoimmune phenomena, and lacks the typical characteristics of Good Syndrome.

POSTER 90 - RARE COMPLICATION IN AN INDIAN ADOLESCENT GIRL WITH CD 27 DEFICIENCY

AUTHORS

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AFFILIATIONS

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Biography:
Sangeetha Ramdas , post doctoral fellow in Pediatric Hematology-Oncology Unit,Department of Pediatrics,Christian Medical College and Hospital, Vellore, Tamil Nadu,India.

Objective: To describe primary immunodeficiency association with malignancy

Design: Case report

Methodology: Retrospective case analysis

Result: A 15-year-old female child from India, second born to second degree consanguineous parents presented with history of multiple neck swelling for 2 days. In the past, she had recurrent respiratory tract infection since 3 years of age requiring antibiotics and hospitalization. On examination, she had grade 2 clubbing, multiple non tender, firm, cervical lymph nodes on both sides. Systemic examination showed liver 3 cms and spleen 8 cms and respiratory examinations showed bilateral coarse crepitations. Chest-x-ray showed bilateral bronchiectatic changes. Her lymph node biopsy revealed an overlapping immunological features of classic Hodgkin lymphoma, nodular sclerosis (syncytial variant) and diffuse large B-cell lymphoma, immunohistochemistry showed positivity for Epstein-Barr virus (EBV) latent membrane protein. Immunoglobulins were done in view of recurrent respiratory tract infection and bronchiectasis showed hypogammaglobulinemia, IgG: 458 mg/dl (N:639-1349mg/dl), IgA:17 mg/dl (N:70- 312mg/dl), IgM:32 mg/dl, (N:56-352mg/dl). A next generation sequencing revealed homozygous mutations in CD27 (c.319C>T). She was treated with two cycles of Adriamycin, bleomycin, vinblastine, and dacarbazine and 4 cycles of cyclophosphamide, vincristine, prednisolone, and dacarbazine. Currently, she is 10 months post treatment and on monthly replacement doses of IVIG, cotrimoxazole prophylaxis and regular chest physiotherapy and is doing well.

Conclusion: We are reporting a rare complication in an adolescent girl with CD27 deficiency. She was managed with chemotherapy and currently doing well.

POSTER 99 - HYPOGAMMAGLOBULINEMIA AND SEVERE ANEMIA IN AN ADULT PATIENT: WHAT IS THE COMMON ELEMENT?

AUTHORS

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AFFILIATIONS

-

Biography:
My name is Florin Bastorin and I am a second year Internal Medicine resident, working at "Dr Carol Davila" Central University Emergency Military Hospital.

I have been fortunate enough to do my Internal Medicine stage at the 2nd Internal Medicine Department, one of the leading centers in Romania for adult patients with primary immunodeficiencies, where I have already encountered many cases of this pathology.

Purpose: The etiological diagnosis of hypogammaglobulinemia in adult patients represents a challenge for clinicians. The purpose of this paper is to present a complex case of hypogammaglobulinemia that is associated with severe anemia, reviewing the differential diagnosis and therapeutic options.

Materials and method: The patient, a 61-year-old woman, was referred to our clinic for significant fatigue, dizziness, and respiratory symptoms (cough and dyspnea). The patient's recent history is marked by repeated respiratory and digestive infections, with extremely low serum immunoglobulin values (IgA, IgG, IgM), low B lymphocyte values on lymphocyte immunophenotyping, and pancytopenia with severe anemia. During the same period, the patient was diagnosed with a thymoma that was operated on. A repeat bone marrow biopsy revealed moderate erythroblastopenia.

Results: Thus, considering the history of thymoma and immunodeficiency, the diagnosis of Good syndrome associated with erythroblastopenia (probably in the context of pure red cell aplasia) was established. Treatment with intravenous immunoglobulins, corticosteroids, and cyclosporine was initiated with favorable evolution of hemoglobin values and disappearance of infectious episodes.

Conclusion: Patients with thymoma may associate with various clinical situations, posing problems of diagnosis and treatment. Good syndrome, which associates immunodeficiency in patients with thymoma, occurs most commonly in adults and should be considered in the differential diagnosis of hypogammaglobulinemia at this age. Additionally, erythroblastopenia due to pure red cell aplasia is one of the complications of thymoma, requiring complex differential diagnosis and appropriate treatment.

POSTER 112 - MALIGNITIES AND LYMPHOPROLIFERATIONS IN CHILDREN WITH PRIMARY IMMUNE DEFICIENCY - A SINGLE CENTER EXPERIENCE

AUTHORS

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Biography:
Current position:
2021- Present: Fellow in Pediatric Allergy & Immmunology- Basaksehir Cam and Sakura City Hospital,

Education:
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Work experience:
2014-2015: General practitioner, Diyarbakır Child Health and Diseases Hospital, Diyarbakır, Turkey
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PRESENTATION DETAILS
Poster presentation
1. *Kaplan S, Kuskonmaz B, Soyer O, Aytaç S, Gümrük F. (2018). When to Suspect Systemic Mastocytosis? Blood, 132, 5826. https://doi.org/10.1182/blood-2018-99-119809.*
2. *Kaplan S, Gökmirza Ozdemir P, Turkyilmaz Ucar O, Cakmak E, Yazıcıoğu M. A Case of Airborne Allergic Contact Dermatitis. Poster Session, 28th National Allergy and Clinical Immunology Congress, 0201, Antalya, 2021.*
3. *Kaplan S, Turkyilmaz Ucar O, Gökmirza Ozdemir P, Eren T, Yazıcıoğu M. Successful Desensitization With Vincristine In A Child Case. Poster Session, 3.Young Pediatric Allergists Symposium,6110, Online, 2021.*
4. *Cakmak E, Gökmirza Ozdemir P, Gökdemir P, Turkyilmaz Ucar O, Kaplan S, Yazıcıoğu M. A Rare Type of CTFR mutation in an Asthmatic Case. Poster Session, 15th pediatric allergy and asthma congress, P-048 , Mugla 2021*
5. *Turkyilmaz Ucar O, Cakmak E, Gökmirza Ozdemir P, Gökdemir P, Kaplan S, Yazıcıoğu M. Dry Skin And Laseration: Eczema Or Not? 15th pediatric allergy and asthma congress, P- 002 , Mugla, 2021.*

PUBLICATION DETAILS:
1.Tanır Başaranoğlu S, Kaplan S, Aykaç K, Özsürekçi Y, Cengiz AB, Kara A, Ceyhan M. (Department of Pediatrics, Hacettepe University Faculty of Medicine, Ankara, Turkey). Clinical evaluation of 423 pediatric patients with skin rashes. Çocuk Sağlığı ve Hastalıkları Dergisi 2017; 60: 46-51.

Although the frequency of studies on malignancies accompanying primary immunodeficiencies (PID) has increased, very few studies examine cases of PID with non-neoplastic lymphoproliferation. In this paper, we aimed to present lymphoproliferation and the types of malignancies that we encountered in immunodeficient patients. Among 550 primary immunodeficiency patients followed in Basaksehir Cam and Sakura city hospital, 17 (3,0%) patients who developed malignancy or non-neoplastic lymphoproliferation were included in the study. The demographic, clinical characteristics and prognosis of patients were evaluated. The mean age at diagnosis of primary immunodeficiency was 7,6± 3,1 years. Eight of the patients had immune dysregulatory disease (MAGT1, NFAT, ITK=2, STX11, PIK3R1, Munc, LRBA), five of them had combined immunodeficiency with DNA repair defect (ataxia-telangiectasia) (AT), three patient had antibody deficiency (E47,VAV1, no genetic mutationon), and one had the phagocytic disease (chronic granulomatous disease) (CGD). Lymphoma was detected in nine (52,9%) patients and lymphoblastic leukemia were in two (11,7%) patients, retinoblastoma in one patient (5,8%), and craniopharyngioma in one patient (5,8%), Rhabdomyoma is also detected in a patient with lymphoma. Lymphoproliferation was detected in seven (46,6%) patients. Eleven patients with malignancy received chemotherapy (CT) and five of them also underwent bone marrow transplantation. One patient with retinoblastoma received both chemotherapy and radiotherapy. One patient with craniopharyngioma underwent surgery. Two patients diagnosed with NFAT and E47 deficiency had only lymphoproliferation, these patients were treated with rituximab and underwent bone marrow transplantation. Despite treatments, 4 patients had excitus.

Although the limited number of our patients, our study is important in terms of the underlying immunodeficiency diversity. AT and CVID are reported as the most common causes in the literature, but ın our study, the most common malignancy developing PID subclass in our study was immune dysregulation syndromes. In addition, our study contributes to the literature in terms of being careful in terms of PID and malignancy in patients with immune dysregulation. Due to the high mortality rate of malignancy in PID, early diagnosis with a multidisciplinary approach can protect patients.Completing the immune workup with next generation sequencing, such as whole exome sequencing, will offer better genetic diagnosis and counseling.

POSTER 114 - AN UNUSUAL CASE OF RAS GUANYL-RELEASING PROTEIN 1 (RASGRP1) MUTATION ASSOCIATED WITH DIFFUSE MESANGIAL SCLEROSIS INFANTILE NEPHROTIC SYNDROME AND EPSTEIN-BARR VIRUS (EBV)-INDUCED HODGKIN'S LYMPHOMA

AUTHORS

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Biography:
Dr. Khairoon Nisa is a paediatrician and clinical lecturer from Universiti Putra Malaysia who is currently undergoing traning in Paediatric Immunology and Allergy.

Introduction: RASGRP1 deficiency is characterized by immune dysregulation and Epstein-Barr virus (EBV)- related lymphoproliferation. Diffuse mesangial sclerosis (DMS) is one of the rarer causes of infantile nephrotic syndrome. Here we described an 8-year-old girl who presented with infantile nephrotic syndrome which subsequently developed chronic bilateral neck lymphadenopathy secondary to chronic EBV infection which leads to the diagnosis of RASGRP1 mutation with Hodgkin's lymphoma.

Case presentation: An 8-year-old girl born to consanguineous parents, presented with a 1-month history of bilateral neck swelling at the age of 3.5 years. History started at age 5 months when she developed generalised oedema, proteinuria, and hypoalbuminemia and was diagnosed with infantile nephrotic syndrome (NS) complicated with hypertension. Secondary causes of NS including viral and autoimmune screenings were negative. A renal biopsy performed at age 8 months revealed diffuse mesangial sclerosis (DMS). She was treated with prednisolone and later tapered off after 7 months. Her anti-hypertensives were slowly weaned off when she reached 4 years. She had no relapses thereafter.

At 3.5-year-old, she developed bilateral neck swelling, chronic cough and persistent otitis media. On examination, she had bilateral cervical lymphadenopathy (left more than right) and hepatosplenomegaly. She was thoroughly investigated for tuberculosis and chronic viral infections, but all were negative. The first lymph node biopsy (LNB) showed reactive lymphoid hyperplasia and after 6 months the second LNB showed EBV reactivation with no evidence of malignancy. Further investigations revealed positive direct Coombs, ANA and dsDNA, high C3, normal C4. She had hypergammaglobulinemia, low T- and B-cells, low CD4 and CD8 T-cells, and chronic EBV infection. Autoimmune lymphoproliferation syndrome (ALPS) was suspected but double-negative T-cells and vitamin B12 were not suggestive. A computed tomography revealed multiple cervical and mediastinal lymphadenopathies with collapse of right middle and left lower lobes. As her neck sweeling was getting bigger, the third LNB confirmed the diagnosis of Hodgkin's lymphoma. The genetic test revealed homozygous RASGRP1 mutations with both parents were carriers. She received chemotherapy and successfully underwent haematopoietic stem cell transplant from her HLA-matched younger sister.

Discussion: While RASGRP1 mutations are not commonly associated with NS, there has been some reported cases linking the two together. These mutations lead to abnormal signalling pathways that contribute to the development of kidney dysfunction and characteristic symptoms of NS. ALPS-like manifestation should be further investigated for a definite diagnosis.

Conclusions: While RASGRP1 mutations are not commonly associated with NS, there has been some reported cases linking the two together. These mutations lead to abnormal signalling pathways that contribute to the development of kidney dysfunction and characteristic symptoms of NS. ALPS-like manifestation should be further investigated for a definite diagnosis.

POSTER 118 - CD8+ T-CELL GRANULOMATOUS LYMPHOMA ASSOCIATED WITH COMMON VARIABLE IMMUNODEFICIENCY

AUTHORS

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Biography:
Internist Specialist who is newly involved in the ERN-RITA Centre for the care of adult patients with primary immunodeficiency and autoinflammatory disorders

Few cases of cutaneous clonal papulonodular CD8+ lymphocytic infiltrates and cutaneous CD8 granulomatous T-cell lymphoma have been described in association with common variable immunodeficiency (CVID).

Objective: We describe two CVID patients whose story was complicated by CD8+ non-caseous granulomas involving the skin, connective tissues and bones.

Results:

CASE 1 - 27-year-old man affected by agammaglobulinemia not-BTK (WES analysis showed a heterozygous VUS mutation on MOGS gene) who presented with recurrent airways and intestinal infections and new onset of arthritis with cutaneous involvement of several violaceous to brownish plaques of the extremities, which resulted in non-caseous granulomas of the skin and synovials. CT-scan showed hepatosplenomegaly and increased lymphadenopathies on both sides of diaphragm, which were positive at the FDG-PET scan, along with bone marrow, joints, connective tissues and all the skin granulomas. Both bone marrow and lymph node biopsies were performed, showing microgranulomas consisting of mature CD3+CD8+ lymphocytes mixed with histiocytic cells. Both gastric and colon endoscopic biopsies showed CD3+CD8+ lymphocytes infiltration with a monoclonal expression for gammaTCR. The diagnosis was lymph epithelioid T cell lymphoma (Lennert's lymphoma), a rare histopathologic variant of peripheral T-cell lymphoma, not otherwise specified. Patient started high dose bolus methylprednisolone (1g/day x3 days), hence prednisone (25mg/day) plus weekly methotrexate (15mg). He died 18 months later because of JCV encephalitis.

CASE 2 - a 59 years-old-woman affected by CVID with recurrent otitis, previous cryptococcal meningitis. NGS target panel for CVID resulted negative. She presented new onset of several purple nodules on her cheeks and legs. FDG-PET-CT scan showed enhancing lymph nodes, spleen, nodules of the skin and of the bones (column, ribs, legs, skull). Bone marrow aspiration and trephine biopsy showed NK expansion, T-cells infiltration (CD2+,CD3+,CD5+,CD7+/-) and slight CD8+ T-cells. EBV-EBER test negative. Polyclonal TCRgamma. Biopsy of the nodules showed histiocytes (CD68R+,CD163+,S100-,CD1a-), T-cells (CD2+,CD3+,CD5+,CD7+), high number of CD8+ T-cells low number of EBV/EBER+ cells. Mib1/Ki67 5%. Polyclonal TCRgamma. Patient was started with prednisone (1mg/Kg/day) than associated with cyclophosphamide 50mg/day. After 6 months of therapy, dizziness appeared and rapidly worsened, histopathological studies were repeated and they demonstrated histological, immunohistochemical, and molecular findings compatible with a primary CD8 T-cell granulomatous lymphoproliferative disorder according to the 2022 WHO classification. Patient is going to start chemotherapy.

Conclusion: Granulomatous cutaneous CD8+ T-cell lymphoma (G-CTCL) is a rarely encountered entity and appears to be associated with primary humoral immunodeficiency. There is a paucity of data regarding the clinicopathologic features and expected course.

POSTER 138 - A RARE CASE OF LONG-TERM IMMUNE DEPLETION IN CHILDREN FOLLOWING CHEMOTHERAPY FOR ACUTE LEUKEMIA: SECONDARY OR PRIMARY IMMUNODEFICIENCY?

AUTHORS

Florkin B

AFFILIATIONS

[1]Hôpital de la Citadelle

Biography:
Immuno-rhumatopediatrician at La Citedelle Ligèe hospital. expert in autoimmunity and Lymphocytes T. 34 publications

Objective: Discuss hypogammaglobulinemia (HG)

Case presentation: A 12-year-old girl was diagnosed at age of 3 (in 2014) with acute lymphoblastic leukemia and treated with chemotherapy for 2 years resulting in transient symptomatic HG. No B-cell depleting anti-CD20 antibody therapies were prescribed; bone marrow transplant wasn't indicated after chemotherapy. To date, the patient is in complete remission from her leukemia. In 2017, she developed a new HG associated with a low vaccine response. Immunoglobulin replacement therapy (IgRT) was initiated. Despite adequate premedication, the patient developed AE: severe headache, fever, and chills) to several Ig preparations until she was switched to Iqymune®, which was well tolerated.
Repeated IgRT discontinuation attempts, including summer withdrawal, failed. Exploration revealed a low rate of Memory B cells (CD19+/CD27+) and Class-switched Memory B cells (CD27+, IgM/D-). These rates remained almost unchanged even 5 years after the end of chemotherapy (3 explorations carried out in 2017, 2020 and 2022). Genetic investigation made in 2018 didn't exhibit any genetic mutation. There was no family history of immune deficiency. To date, the patient is treated with a monthly infusion of Iqymune® at 0.4g/kg. No infections were recorded during this treatment.

Discussion: In this case, the etiology of the immunodeficiency is not well established.
T and B cells were severely affected after ALL polychemotherapy but recovered rapidly after treatment stop. Knowing that chemotherapy is aggressive with risk of mutation, and that a treatment is usually administered before the immune system reaches its maturity (7-8 years of life), a mutation leading to immunodeficiency could not be ruled out.
This HG may also be an infra-clinic primary immune deficiency revealed after the chemotherapy. Although genetic investigation was negative, this hypothesis remains probable knowing that several common variable immunodeficiency (CVID) patients don't exhibit genetic mutation. Furthermore, low IgM memory B cells (CD19+/CD27+) and class switched memory B cells (CD27+, IgM/D-) are in favor of CVID.
Epigenetic changes leading to delayed or silenced maturation of B cell function may also be hypothesized.
Fever, and chills are frequent in pediatric ALL patients and are related to IgA levels. The low rate of IgA within Iqymune® compared to other Ig could explain the good tolerance toward infusions in this patient (Fig.1).

Conclusion: It could be difficult to discern the relationship between primary and secondary immune deficiencies due to crossover between the two entities. Iqymune® displayed a better tolerability profile compared to previous Ig preparations in this patient.

NEUROLOGICAL AND OTHER TYPES OF COMORBIDITIES OF PIDS

POSTER 33 - GASTROINTESTINAL SYSTEM FINDINGS IN CHILDREN WITH PRIMARY IMMUNODEFICIENCIES

AUTHORS

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AFFILIATIONS

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Biography:
Ferah Genel, MD
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Objective: Gastrointestinal system (GIS) findings may be seen in cases with primary immunodeficiency (PID) and may even appear as the first presentation finding. Accompanying GIS findings can change treatment approaches and negatively affect the prognosis. In our study, we aimed to evaluate the GIS findings in our patients with PID and to determine their effects on clinical follow-up and prognosis.
Desing and Method:
Medical records of 631 patients with PID, followed up between 2011 and 2021, were retrospectively screened for occurrence of gastrointestinal findings. During this time, demographic features, gastrointestinal tract and/or hepatobiliary system findings and initial time, genetic mutations, laboratory and clinical follow up findings, treatment regimens and outcomes were recorded.

Results: Gastrointestinal tract and/or hepatobiliary system findings were detected in 161 (25.5%) patients. One hundred five (65.2%) of the patients were male. Consanguinity was present in the history of 68 patients (42,3%). The median age of onset symptoms associated with PID was 9 (min-max: 1-192) months and the median age of GIS findings initial time was 40 (min-max: 1- 276) months. The median age of diagnosis was 50 (min-max: 1-240) months. Diagnosis was genetically confirmed in 64 (39,8%) patients. One hundred nine (67.7%) patients presented with GIS findings, and these findings had occurred during 52 patients' (32,3%) follow-up. The most common GIS findings were hepatomegaly (25.4%), recurrent oral aphthous ulcers (18%) and chronic diarrhea (12.4%). When evaluated according to diagnostic groups, it was determined that GIS findings were most common in phagocytic system defects (78.6%), followed by immune dysregulation diseases (77.8%) ($p<0.001$). The mortality rate was 11.2% in cases with PID and GIS findings, which was higher (2.3%) than in cases without GIS findings ($p<0.001$). When PID patients with GIS findings were evaluated, it was determined that the mortality rate was significantly higher in cases with body weight below the 3rd percentile at the time of diagnosis, in cases with combined immunodeficiency, and in cases with more than one GIS finding.

Conclusion: Gastrointestinal tract and/or hepatobiliary system diseases are common in patients with PID and adversely affect the prognosis. Early diagnosis and treatment are important in terms of increasing the quality of life and preventing the development of complications. Cases with signs of the gastrointestinal tract and/or hepatobiliary system should be evaluated in terms of underlying PID.

POSTER 38 - MODELING BRAIN SIGNALLING IN INBORN ERRORS OF IMMUNITY

AUTHORS

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AFFILIATIONS

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Biography:
Ines is a Postoctoral Researcher working on rare neurodevelopmental disorders. After working on new pharmacological options for tuberous sclerosis complex (TSC) during her PhD, she started investigating molecular markers that could be used as early predictors for atypical behaviour in this disorder. Currently, she studies the molecular and behavioural development of TSC models to understand how neurodevelopmental deficits arise. Additionally, she has been using genetic data and mouse models of inborn errors of immunity to investigate the prevalence of atypical behaviours in this population, and which putative molecular mechanisms are behind the establishment of these phenotypes.

Introduction: Over 400 genetic mutations have now been identified as contributors to inborn errors of immunity (IEI), a group of disorders that increases susceptibility to infection, autoimmunity and cancer, greatly reducing the quality of life of patients and caregivers.
Although IEI patients are primarily treated for immunodeficiency, an increasing number of reports have suggested that neurodevelopmental deficits (NDDs) may also be a co-morbidity of IEI. However, the mechanisms by which these typically immune mutations can potentially lead to NDDs are currently unknown.

Methods and Results: In this work, we explored whether there was an overlap between IEI and NDD susceptibility genes, and evaluated which molecular, cellular and signaling pathways were affected by these mutations. Using data mining of the Human Gene Mutation Database and the International Union of Immunological Societies gene list we found that ~1/3 of IEI risk genes are also recognized as NDD risk genes. We then surveyed the Human Protein Atlas database for the RNAseq expression values of these genes (NDD-only, IEI-NDD and IEI-only) in cells and tissues of the immune and central nervous systems. We found that gene expression in tissues of interest was progressive, in which a higher number of NDD-only genes was found in brain cells, followed by IEI-NDD and IEI-only genes. This pattern was inverted in immune cells, suggesting that IEI-NDD genes could integrate these two physiological systems. Linear discriminant analysis clustered these three groups of genes based on expression patterns, and revealed that IEI-only and IEI-NDD groups are primarily separated by their immune cell expression profiles, indicating that mutations in primarily peripheral systems could potentially influence the development of centrally located processes. Consistent with the hypothesis, gene ontology analysis identified “immune function” as a high-scoring process in both groups of genes, while biological process grouping indicated that IEI-NDD genes are primarily involved in cytokine production and immune cell differentiation while IEI-only genes participate in cytokine and adaptive response.

Conclusion and Future work: This work provides evidence that further supports an active interaction between immune and central nervous systems, revealing that a subgroup of IEI patients potentially has increased likelihood of exhibiting NDDs. Currently, using patient sequencing data, we are investigating whether this theoretical prediction is supported and quantifiable in clinical IEI cohorts. Our future work will focus on the early prediction of NDDs in IEI patients in order to promote a quicker access to support therapy and improved behavioural outcomes.

POSTER 76 - RELATION BETWEEN ANALYTICAL, CLINICAL AND RADIOLOGICAL MARKERS IN COMMON VARIABLE IMMUNODEFICIENCY

AUTHORS

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Biography:
Physician in the Hospital 12 de Octubre (Madrid, Spain). I work as an immunologist in our immunology clinic. Here we treat adult patients with primary or secondary humoral deficiencies and some other primary defects

Common Variable Immunodeficiency (CVID) is characterized by a broad spectrum of clinical presentations, including complications beyond recurrent infections: immune dysregulation and especially lymphoproliferation. The definition of analytical, clinical and radiological markers that allow differentiating the type of CVID in each patient acquires fundamental clinical relevance in this context.

We present a description of the clinical profile and its relation with analytical and radiological tests (vitamin b12, free light chains, Ig levels, cell populations, CD21low, sCD25, CT scans) of a cohort of 21 patients seen at the Immunology Department of Hospital 12 de Octubre. To classify the radiological findings we calculate the Bauman score for GLILD granulomatous lymphocytic interstitial lung disease GLILD.

As we can see, the most frequent clinical event is infections (18), followed by splenomegaly (9), autoimmune manifestations (8), adenopathies/granulomas (7), solid tumors (4), lymphomas (3) and intestinal pathology (3) (Figure 1). Analytically, we found a decrease in compartment B with a high number of elevated CD21low and the absence of response to vaccine antigens (polysaccharide or protein) stand out. Elevations in IgM levels were also observed in patients with lymphoproliferative profile considering only those patients with detectable levels of this immunoglobulin. We were able to observe how, after prolonged follow-up, high maximum values of sCD25 were associated with both autoimmune manifestations and the presence of adenopathies/granulomas. This association was not found with any other clinical/radiological or analytical manifestation.

Regarding the radiological findings, 11 patients presented pathological findings, highlighting 9 with nodules/granulomas, 7 patients with adenopathic expansion and 3 with bronchiectasis. At the functional respiratory level, the decrease in DLCO and obstructive patterns stand out.
According to the Bauman score for image analysis, 6 patients scored more than 15 points, coinciding with the group diagnosed with GLILD, while the rest scored less than 8.
However, these values should be discarded when there may be another cause that explains the increase in the biomarker, such as infections or lymphoproliferative processes.
Our group recommends carrying out follow-up with an anamnesis and examination regulated according to the patient's clinical profile, with recurrent radiological tests according to their symptoms and their variation, making it possible to use scores that can be used as a prognostic value.
Regarding the analytical values, we highlight the possibility of monitoring with sCD25 since high maximum values seem to be associated with autoimmune phenomena and the appearance of adenopathies/granulomas.

POSTER 107 - BRAIN BIOPSY IS A SAFE AND IMPORTANT DIAGNOSTIC TOOL IN CHILDREN WITH INBORN ERRORS OF IMMUNITY

AUTHORS

Payne J[1], Roa-Bautista A[1], Breuer J[2], Brown J[2], Kaliakatsos M[3], Aquilina K[3], Hacohen Y[3], Rao K[4], Chiesa R[4], Thrasher A[1], Kusters M[1], Worth A[1], Booth C[1], Qasim W[1], Ip W[1], Elfeky R[1]

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Biography:
Julia Payne is a paediatric immunologist with an interest in primary immunodeficiency disorders.

Background: Neurological manifestations and complications have been well described in Inborn Errors of Immunity (IEI). Symptoms can vary from mild to severe irreversible disability and risk of death. Despite extensive investigations, the aetiology of neurological manifestations is not always clear, resulting in delayed or suboptimal treatment with significant sequelae.
Brain biopsy, particularly in conjunction with metagenomics, has a high diagnostic yield in cases of paediatric cryptogenic neurological disease. Specific studies regarding safety and diagnostic efficacy of brain biopsies in paediatric IEI patients with unexplained neurological symptoms are lacking. This study is the first to characterize single-center experience of brain biopsy in paediatric patients with IEI and neurological disease of unclear aetiology.
Objectives: To assess the safety of brain biopsy in Great Ormond Street Hospital (GOSH, London) IEI patients with unexplained neurological symptoms.
To assess whether brain biopsy led to a definitive diagnosis and change in management of these patients.

Method: We performed a retrospective review of patients <18 years of age with IEI who underwent brain biopsy between 2010-2022 at GOSH. Immunological diagnosis, clinical history, brain imaging and CSF findings and brain biopsy results were obtained from patient electronic medical records.

Results: 14 IEI patients underwent brain biopsy during the study period (Table 1). Median time from onset of neurological symptoms to biopsy was 2.6 months (10 days-75 months). A definitive diagnosis was established in 64% of patients (n=9) with metagenomics increasing the diagnostic yield by 20% (n=3). Brain biopsy results altered management in 71% of cases (n=10). Significant complications occurred in 1 patient who developed a haematoma post brain biopsy requiring evacuation. Overall survival at 12 months post-biopsy was poor; 35% alive (n=5), and 64% deceased (n = 9).

Conclusion: Brain biopsy was performed with a low rate of complications and led to a definite diagnosis and change in management in the majority of IEI patients. Despite this, the overall survival of patients remained poor at 12 months, reflecting the severity of their underlying disease. This study suggests that brain biopsy is a safe and useful tool to evaluate neurological symptoms of unclear cause in IEI patients. The favorable risk benefit profile supports early use to optimize treatment of these high-risk patients.

POSTER 178 - ESTABLISHMENT OF A STAT3 GAIN-OF-FUNCTION MODEL FOR THE IDENTIFICATION OF NEW TARGETS IN CYSTOID MACULAR EDEMA TREATMENT

AUTHORS

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Biography:
Technician working on Primary Immunodeficiencies in the group of Hanna IJspeert.

Objective: STAT3 gain-of-function (GOF) syndrome is a multi-organ immune deregulatory syndrome. We identified a family of six affected patients with the STAT3 GOF variant p.L387R. Two of the affected family members developed cystoid macula edema (CME) and retinal neovascularization/vasculitis. CME is major complication in several retinal diseases and is caused by accumulation of fluid behind the retina resulting in retinal damage and irreversible loss of vision. The current treatment for CME is mainly focused on treating the underlying disease which can cause severe side effects. The retinal pigment epithelium (RPE) layer is a layer of single cells which functions as a selective barrier. This RPE layer regulates fluid accumulation and prevents fluid from leaking into the retina. There are limited reports that show successful IL-6 receptor (IL-6R) treatment of CME in uveitis. However, it is yet unknown if anti- IL-6 therapy can be used to treat CME with other retinal diseases. In this study we aim to use this specific STAT3-GOF variant in RPE cells to study how (hyper)activation of the IL-6 pathway leads to CME and use this as a model to study the effect of anti-IL-6 therapy and other available drugs that targets IL6-STAT3 pathway.

Design & Methods: STAT3-wild type (WT) and STAT3-L387R (GOF variant) were overexpressed in a human RPE cell line APRE-19 and in primary human RPE cells OZR-1 by a DOX inducible lenti-viral transduction. Overexpression of STAT3 protein and phosphorylated STAT3 (pSTAT3) were measured by Western blot and flow cytometry after IFN-a stimulation (10^4 U/ml, 30 min). Gene expression of SOCS3, IL6, IL6R, GP130, OCLN, CLDN1, VEGF-A and GAPDH were measured by RQ-PCR after 2h and 4h of IFN-a stimulation (10^4 U/ml). IL-6 and CCL2 cytokine production were measured in culture supernatant of OZR-1 after IFN-a stimulation (10^4 U/ml, 24h).

Results: STAT3-GOF phenotype was confirmed by higher expression of pSTAT3 and SOCS3 after IFN-a stimulation. IL-6 and IL-6R mRNA expression was upregulated after IFN-a stimulation, especially in the cell lines expressing the STAT3-L387R variant. Expression of GP130, OCLN, CLDN1, VEGF-A was not different. After IFN-a stimulation IL-6 and CCL2 levels were higher in culture supernatant of OZR-1 expressing the STAT3-L387R variant.

Conclusions: The STAT3 L387R variant leads to hyper activation of IL6/IL6R-STAT3 signaling pathway in RPE cells. In future studies, the efficacies of different drugs targeting the IL6- JAK/STAT3 pathway will be tested.

POSTER 197 - CONTIGUOUS X-CHROMOSOME DELETION SYNDROME ENCOMPASSING BTK AND TIMM8A GENES: A CASE REPORT

AUTHORS

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Biography:
I'm a physician specialised in immunology and reumathology with a particular interest in inbone error of immunity.

The BTK gene, mutations of which are responsible for XLA, is located at Xq21.3–Xq22. According to XLA database the deletion frequency is 7-8%. Rarely, the deletion may include the closely located TIMM8A gene causing the Deafness Dystonia Syndrome.

Our patient was admitted for nephritic syndrome with low C3-C4 and acute renal failure at 5 years old. Renal biopsy reveled a IC-related membranoproliferative glomerulonephritis, so IV steroid bolus was started followed by oral steroid and suspended after five months. Collaterally, he was also diagnosed with sensorineural hearing loss, subsequently treated with bilateral cochlear implant and rehabilitation.
Since the age of 8 he suffered from multiple relapsing of gross hematuria with proteinuria, during upper ways infections, with variable complement levels. Anti-factor H antibodies appeared. He developed persistent nephrotic proteinuria, treated again with intravenous steroids, ACE-inhibitors and mycophenolate with partial response.
Since he was 9 he started to present afinalistic movements and progressive motor impairment. Neurologic evaluation diagnosed segmental dysfunction. Brain MRI showed basal ganglia hypotrophy. The workup for infections, metabolic and autoimmune disorders resulted negative. He was treated with levodopa and trihexyphenidyl with some improvement.
At that point, hypogammaglobulinemia was noticed, despite glomerular disease remission. Low Ig levels were found previously but they were imputed to the proteinuria. An extended immunologic workup showed: normal neutrophils and lymphocytes, absent response to vaccines tested, normal T cells compartment with a normal mitogen proliferation response, normal NK cells, and almost absent B cells (CD19+ 0.4% of total lymphocyte). Given the agammaglobulinemia phenotype BTK expression with cytofluorimetry was performed but resulted normal.
Because of the complexity of the case, multiple genetic testing was performed. An NGS panel for complement deficiency showed the heterozygous synonymous variant on C3 gene associated with an increased risk of C3 glomerulopathy. High resolution CGH-array showed a small deletion involving a part of BTK gene and the promotor of TIMM8A gene, also found in his mother. An NGS panel for genes involved in agammaglobulinemia confirmed the same deletion involving BTK from exon 11.
Subsequently, a western blot analysis was performed and showed a residual aberrant BTK protein expression, that could explain the normal expression using cytometry.

Contiguous X-chromosome deletion syndrome including the BTK and TIMM8A genes has been described previously in 18 patients from 15 unrelated families. Our case showed neurological symptoms, with deafness and dystonia, consistent with TIMM8A impairment, an XLA phenotype, plus peculiar findings with autoimmune antibodies and glomerulonephritis.

POSTER 199 - CENTRAL NERVOUS SYSTEM DEMYELINATION ASSOCIATED WITH CTLA-4 HAPLOINSUFFICIENCY

AUTHORS

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Biography:
Dr Koo is a general paediatrician undergoing fellowship in paediatric infectious diseases and immunology with the Ministry of Health Malaysia. He has over a decade experience in paediatrics which has piqued his interest in the niche of clinical immunology currently underserved in Malaysia.

Introduction: CTLA-4 haploinsufficiency is a rare autosomal dominant immune dysregulation disorder. CTLA- 4 is a protein receptor found on T-lymphocytes; which downregulates immune responses.
Afflicted patients have a reduced expression of this receptor which leads to T-cell hyperactivation and lymphoproliferation. There are limited reports of afflicted patients with neurological complications. We report a case of a girl with CTLA4-haploinsufficiency with central nervous system (CNS) demyelination.

Case report: N is a 18-year old girl with pancytopaenia, splenomegaly with portal hypertension and splenic varices; with a history of recurrent invasive infections progressing to chronic interstitial lung disease. Investigations revealed low T- and B-cells with reduced B-switched and memory cells and defective antibody response to pneumococcal polysaccharide and tetanus toxoid despite normal immunoglobulin levels. Genetic sequencing found heterozygous pathogenic variant in C9 and CTLA-4 variant. Diagnosis of CTLA-4 haploinsufficiency was established following a functional assay. She received immunoglobulin replacement therapy (IRT) in four-weekly intervals.
In 2022, she had a first episode of seizure approximately one hour following her regular IRT. The semiology was generalised tonic-clonic with uprolling of her eyes and drooling of saliva. It aborted spontaneously in under 5 minutes and she regained consciousness immediately. There was no preceding fever, altered behaviour or vomiting. There was tension headache for one week prior but no other symptoms of increased intracranial pressure.
On admission, she had no fever and normal blood pressure. No focal neurological deficit was elicited with no papilloedema. MRI brain revealed multifocal enhancing lesions in her right frontoparietal and left occipitoparietal lobes suggestive of demyelination. Lumbar puncture samples had normal CSF protein and glucose and CSF:venous glucose ratio of 0.58. The CSF yielded no bacterial growth and tested negative for Mycobacterium tuberculosis, Cryptococcal antigen, JC and BK viruses. Oligoclonal bands were detected in paired CSF and serum.
The diagnosis of CNS-demyelination associated with CTLA4-haploinsufficiency was a consensus between the general paediatrician, immunologist, paediatric neurologist and adult neurologist. She was started on sirolimus 2mg OD and a five-day course of IV methylprednisolone 1g OD followed by prednisolone 35mg OD for one month with gradual tapering. A repeated MRI brain 4 months later revealed reduction in sizes of the enhancing lesions seen previously with no new lesions. Currently, she remains free of infections and seizure-free.

Conclusion: CTLA-4 haploinsufficiency is associated with neuroinflammation as seen in some cases of multiple sclerosis. More studies may contribute to further understanding of the role CTLA-4 in the CNS.

POSTER 233 - EVALUATION OF RENAL FUNCTION IN PRIMARY IMMUNODEFICIENCY PATIENTS RECEIVING INTRAVENOUS IMMUNOGLOBULIN REPLACEMENT THERAPY

AUTHORS

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AFFILIATIONS

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Biography:
Fellow in A/I at Sakarya University

Introduction: In the production phase, the stabilizer is used to prevent the polymerization of intravenous immunoglobulin (IVIG)s. These stabilizers; contain molecules such as sucrose, maltose, glucose, d sorbitol, mannitol, glycine, and proline. These stabilizing agents are thought to be responsible for the side effects seen during IVIG treatment. One of the side effects is that they can cause kidney damage. In our study, we aimed to evaluate the renal functions and early signs of kidney damage of patients who received IVIG replacement therapy with the diagnosis of primary immunodeficiency.

Patients and Methods: 73 patients who received IVIG treatment in the Pediatric Allergy Immunology Department of Sakarya University Training and Research Hospital with the diagnosis of primary immunodeficiency were included in the study. The patients had no known kidney disease before starting IVIG therapy. Two patients were not included in the study due to previous kidney disease. The body mass index and blood pressure percentiles of the patients were evaluated. Blood urea, creatinine, sodium, potassium, albumin, cystatin-c, complement 3 (C3), and complement 4 (C4) values were measured. The glomerular filtration rate (GFR) was calculated. Microalbumin and microalbumin/creatinine were studied in spot urine. In addition to these, how many doses of IVIG the patients received, IVIG preparation concentrations (5-10%), stabilizers used, and the osmolarity of the preparations were also evaluated.

Results: Of the 71 patients included in the study, 41 (57.7%) were male and 30 (42.3%) were female. The mean age was 6 years. The stabilizers of IVIG preparations taken by the patients were 37 (52.1%) maltose, 16 (22.5%) glycine, 9 (12.6%) L-proline, 6 (8.4%) sucrose, and 3 (4.2%) glucose. The urea, creatinine, sodium, and potassium values of the patients were within the normal range. Blood pressure percentiles were below 95%. Spot urine evaluation was done in 66 patients. 6 (6/66, 9%) of these patients had a spot urinary microalbumin/creatinine ratio above 30. Angiotensin-converting enzyme inhibitor was started in 1 patient (1/6) whose proteinuria persisted. The GFR of 11 patients (11/71, 15.4%) was below 100. The GFR values of the patients with proteinuria were above 100. The cystatin-c level of 53 patients (53/70, 75.7%) was above the normal range (>0.7). 1 patient (1/70, 1.4%) had pathological elevation (>1).

Conclusion:
Patients with primary immunodeficiency diseases who need to receive long-term maintenance dose IVIG replacement therapy should be closely monitored for their renal functions.

POSTER 247 - ASSESSMENT OF ENDOTHELIAL DYSFUNCTION AND ATHEROSCLEROTIC MARKERS IN PATIENTS WITH CHRONIC GRANULOMATOUS DISEASE: AN OBSERVATIONAL STUDY FROM NORTH INDIA

AUTHORS

Laha W[1], Pandiarajan V[1], Rawat A[1], Kaur H[1], Attri S[1], Singhal M[1], Singh S[1]

AFFILIATIONS

[1]PGIMER

Biography:
I am Dr Wrik Laha, final year resident pursuing MD paediatrics at PGIMER Chandigarh, India. I have a special interest in primary deficiency in children and have been working with CGD patients since last 2.5 years.

Objective: The aim of this study was to evaluate the markers of endothelial dysfunction and atherosclerosis in patients with chronic granulomatous disease (CGD).

Design: Observational study

Methods: The study included 26 patients with CGD, 13 carriers of X-linked CGD, 35 healthy controls, and 15 obese controls. Patients with CGD without any active infection were enrolled in this study. Clinical markers of atherosclerosis were evaluated, including body mass index (BMI) and skin fold thickness. Blood samples were collected for measurements of fasting plasma glucose, highly sensitive C-reactive protein (hs-CRP), interleukin-6, and lipid profile. Brachial artery flow mediated dilatation (FMD) and intima-medial thickness (IMT) of the carotid artery were assessed using ultrasound.

Results: The median age of the CGD patients (n=26) was 13(11,19.75) years. 17 (65.4%) of the participants were male, while 9 (34.6%) were female. The median age at presentation was 24(6,72) months. The median age at diagnosis was 93(40.5,148.50) months. 53.8% had NCF1 gene (n=14), 34.6% had CYBB gene (n=9)mutations. Patients with CGD had comparable height, weight, BMI, and skin-fold thickness with that of healthy controls; however, patients with NCF1 defect had significantly lower BMI compared to age-matched healthy controls probably due to long duration of follow-up and cumulative burden of infections and hyperinflammation over years. Patients with CGD had significantly low high-density lipoprotein (HDL) cholesterol values (p-value=0.004) when compared to healthy and obese controls. We also observed patients with X-linked CGD had significantly elevated triglyceride levels compared to NCF1 defects and healthy controls. Though clinically asymptomatic, patients with CGD had significantly high hs-CRP (p-value<0.001) and IL-6 (p-value=0.01) levels when compared to healthy and obese controls. No statistically significant difference was found in FMD and IMT in cases when compared to controls. Carriers of X-linked CGD had no statistically significant variation in any of the parameters when compared to healthy controls.

Conclusion: Patients with CGD had evidence of sub-clinical systemic inflammation, as indicated by elevated levels of hs-CRP and IL-6, despite the absence of overt signs of infections or hyperinflammation. We also document lipid profile aberrations, specifically low levels of HDL- cholesterol and elevated triglyceride levels. The study suggests that the underlying sub-clinical inflammation in CGD patients may contribute to these lipid profile abnormalities, and further long-term follow-up is needed to assess the potential risk of cardiovascular disease in this patient population.

Keywords: CGD, CYBB, NOX, NCF1, patients, controls, FMD, IMT, Skin-fold thickness, BMI, HDL, LDL, Lipid profile

PID TREATMENT ADVANCES (TARGETED THERAPIES, CUARTIVE THERAPIES, NOVELTIES IN IG, REPLACEMENT THERAPY)

POSTER 16 - EFFICACY AND SAFETY OF A SUBCUTANEOUS HUMAN IMMUNOGLOBULIN (20% SCIG - NEWNORM) IN PATIENTS WITH PRIMARY IMMUNODEFICIENCY DISEASES – DESIGN OF A PHASE 3 STUDY

AUTHORS

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AFFILIATIONS

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Biography:
Elisabeth Clodi studied molecular genetics and completed her PhD at the university of Vienna in 2000.
She has been working as Global Medical Advisor for Immunotherapy for different plasma companies since 2001.

Objective: Patients with primary immunodeficiency diseases (PID) need life-long treatment with immunoglobulins (IG). Replacement therapy is expected to achieve minimum protective trough levels of 5–6 g/L to protect PID patients from recurrent bacterial and viral infections.
Subcutaneous (SC) administration offers several advantages over intravenous (IV) infusion from both a patient's and a physician's perspective. Reduced systemic side effects, remarkable improvement in the patient's quality of life and treatment compliance drives the need for development of safe and effective subcutaneous human immunoglobulin products.

Design and Methods: This phase 3 study is a prospective, open-label, single-arm, multicentre study with a 52-week efficacy period and pharmacokinetic (PK) substudy conducted globally.
At least 50 patients (aged ≥2 and ≤75 years) diagnosed with PID and on a stable, therapeutic dose of IVIG or SCIG or fSCIG will be enrolled in the study and infused weekly. SCIG dosing will be adjusted by a converting factor of 1.37 to previous IVIG dose and 1:1 dosing to previous SCIG dose and 1.3 dosing to previous fSCIG dosing. The primary objectives are to assess the safety and efficacy of a glycine stabilized 20% SCIG in preventing serious bacterial infections (SBIs) and to confirm that the average total IgG levels with weekly SC dosing are non-inferior to the 3- or 4- weekly IV dosing.
The primary efficacy endpoint is the rate of SBIs per person-year on treatment analysed for the 52-week efficacy period. The primary PK endpoint is the average total IgG concentration (Cav) on steady-state dosing.
Secondary efficacy endpoints:Infections of any type or seriousness, time to resolution of infections, use of antibiotics, hospitalisation due to infections, episodes of fever, quality of life assessments, number of days lost from work, school, kindergarten, or day care due to infection, non-compartmental PK analyses for total IgG, IgG subclasses and antigen-specific antibodies, trough and peak levels of total IgG and IgG subclasses. Safety will be evaluated by the occurrence of treatment-emergent adverse events and adverse drug reactions.
Main inclusion criteria: Documented and confirmed diagnosis of PID as defined by European Society of Immunodeficiencies (ESID) and the Pan American Group for Immune Deficiency (PAGID) which requires immunoglobulin replacement therapy.

Results: Analysis will be conducted after all patients finalised 52 weekly SC infusions.

Conclusion: This study will evaluate the efficacy, pharmacokinetic and safety of a newly designed glycine stabilized 20% SCIG. The 20% SCIG formulation is based on the well- established panzyga® manufacturing process.

POSTER 29 - HEMATOPOIETIC STEM CELL TRANSPLANTATION FOR PRIMARY IMMUNODEFICIENCY DISEASES IN VIETNAM

AUTHORS

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Biography:
Dr. Nguyen Ngoc Quynh Le graduated from the Hanoi Medical University in Hanoi, Vietnam in 2009. She completed her medical residency at the National Children's hospital in 2012 and became a pediatrician in Allergy- Immunology- Rheumatology department. She is a member of the Society of Pediatric Immunology-Allergy- Vietnam Pediatric Association, Vietnam Society of Sleep Medicine (VSSM), Asian Pacific Society of Immunodeficiency (APSID), European Academy of Allergy and Clinical Immunology (EAACI). Dr Le focus on obstructive sleep apnea, primary immunodeficiency disease and she has studied about hematopoetic stem cells transplantation in Skane university hospital, Sweden. She has participated in national and hospital research projects on primary immunodeficiency disease and has cooperated with foreign countries. Dr. Le has published several medical articles and has been invited speaker in several medical congresses and meetings.

Background: Primary immunodeficiency disease (PIDDs) are group of genetic abnormalities associated with a deficiency of one or more factors in the immune system. Today, more than 400 types of PIDDs mutation have been discovered. Most PIDDs are caused by genetic defects in hematopoietic cells. Therefore, the replacement of defected cells with hematopoietic stem cells from a healthy donor is an effective treatment. Myeloablative conditioning is commonly used to allow for stable donor graft engraftment, and serotherapy can be incorporated to reduce risk of Graft rejection and graft-versus-host disease (GVHD). Hematopoietic stem cell transplantation can be applied to many different forms of PIDDs with high efficacy.

Methods: Descriptive study with longitudinal follow-up of case clusters.

Results: 16 hematopoietic stem cell transplants for 14 PIDDs children (10 boys, 4 girls) in National Children's Hospital since 2014. Patient's age at transplantation time ranged from 2.5 months old to 8 years old. PIDDs included: Wiskott-Aldrich syndrome (50%), severe combined immunodeficiency diseases (43,75%), leukocyte adhesion defficiency (6,25%). Donor included: Matched sibling donor (25%), unrelated cord blood (12,5%), haplo donor (62,5%). Conditioning protocol Busulfan/ Fludarabin/ ATG – Fresenius, GvHD prophylaxis with Cyclosporin/ Cyclosporin + Methotrexat/ Tacrolimus + Mycophenolat mofetil. 56,25% of subjects use T-cell depletion kit by CliniMacs system. Post- transplant complications: neutropenic fever (100%), Engraftment syndrome (25%), virus reactivation (31,25%), aGvHD (18,75%), cGvHD (6,25%), VOD/SOS (6,25%). 71,43% cases had been cured post transplant, 7,14% cases required IVIG infusion, 21,43% died post transplant.

Conclusions: Hematopoietic stem cell transplantation is an effective method for patients with PIDDs with a success rate of 78%. Early diagnosis and stem cell transplantation will help save many PIDDs children and reduce economic burden.

POSTER 39 - SUBCUTANEOUS IMMUNOGLOBULIN 16.5% (CUTAQUIG) SAFE AND EFFICACIOUS AT MODIFIED INFUSION REGIMENS IN PATIENTS WITH PRIMARY IMMUNODEFICIENCY DISEASE

AUTHORS

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AFFILIATIONS

[1]University of California, [2]University of Pittsburgh, [3]IMMUNOe Research Center, [4]University of South Florida, [5]Midland Pediatrics, [6]Allergy and Asthma Clinics of Georgia, [7]Family Allergy & Asthma, [8]University of Cincinnati, [9]Allergy Associates, [10]Medical Research of Arizona, [11]Octapharma Pharmazeutika Produktionsges.m.b.H. , [12]University of California

Biography:
Dr. Eva Turpel-Kantor graduated as doctor of Medicine at the university of Olomouc in 1995. She has been working as Internal medicine physician and as Dermatologist. Since 2000 as a Global Clinical Project Manager and Assoc. Medical Director for Immunotherapy for different (plasma) companies.

Objective: A study was conducted to evaluate the safety and tolerability of subcutaneous immunoglobulin (SCIG) 16.5% (Cutaquig, Octapharma) at modified infusion regimens

Design and Methods: The prospective, open-label, 3-arm, multicenter, phase 3 study evaluated 3 cohorts of patients receiving SCIG 16.5% with alternative infusion regimens evaluating volume, rate, and frequency: 1) volume assessment/site: up to a maximum 100 mL/site; 2) infusion flow rate/site: up to a maximum of 100 mL/hr/site or the maximum flow rate achievable by the pump; 3) infusion frequency: SCIG 16.5% every other week at the equivalent of twice the patient's body-weight dependent [mg/kg] weekly dose. Additionally, evaluations related to patient satisfaction were also measured using a standardized questionnaire.

Results: A total of 64 patients (59 adults, 5 children/adolescents) received 1338 infusions. For cohort 1 (n=15), the maximum tolerated volume was 108 mL/site which is higher than the currently (US) labeled maximum volume of 40 mL/site. In the EU no specific maximum infusion volumes are specified; however, doses over 30 mL may be divided according to patient preference in adults. In cohort 2 (n=15), the maximum tolerated infusion flow rate was 67.5 mL/hr/site which is higher compared to the current (US) label (up to 52 mL/hr/site) (US). In the EU currently, the recommended initial administration rate is 15 ml/h/site. For subsequent infusions, if well tolerated, it can be increased up to 25 ml/h/site. In cohort 3 (n=34), the mean total immunoglobulin G trough levels demonstrated equivalency to weekly trough levels by demonstrating a decrease of not more than 1g/dL (P value = 0.0017). There were no SBIs during the study. The most reported treatment-emergent adverse events were infusion site erythema (31.3%), infusion site pruritus, sinusitis (both 23.4%), and headache (15.6%). The majority of patients (overall and across cohorts) found the new infusion regimens to be better or somewhat better than their previous regimens (Table 1) and that switching from their previous SCIG product to SCIG 16.5% was very easy.

Conclusions: SCIG 16.5% (Cutaquig) infusions are safe and well tolerated at higher infusion parameters. Dosing every other week demonstrated equivalency to trough levels with weekly dosing, which may result in fewer infusions allowing for greater dosing flexibility, compliance, and patient satisfaction. In addition, most patients (overall and across cohorts) found the new infusion regimens to be better or somewhat better than their previous regimens.

POSTER 45 - IMMUNOGLOBULIN REPLACEMENT THERAPY IN PATIENTS WITH IMMUNODEFICIENCIES – THE IMPACT OF AGE UPON TREATMENT EXPERIENCE AND COMPLIANCE

AUTHORS

Lepeshkina O[1], Solomon G[2]

AFFILIATIONS

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Biography:
Geneviève Solomon joined the non-profit organization Association des Patients Immmunodéficients du Québec (APIQ) in 2015 and has since become the General Manager. She has a wealth of experience in managing organizations with a social impact and is committed to the well-being of patients.

Objective: This analysis evaluates survey data from the Association of Patients with Immunodeficiencies in Quebec (APIQ) to compare perceptions of young adult and adult patients (pts) currently using immunoglobulin replacement therapy (IgRT).

Design and method: Pts with immunodeficiencies in Canada from the APIQ database completed an incentivized online survey between Oct20–Mar21. The survey contained 101 questions on demographics, IgRT use, quality of life, physical and mental health, productivity, treatment satisfaction and compliance. Pts currently receiving IgRT were stratified by age into young adults (14–24 yrs) and adults (>24 yrs). A sub-analysis of those who switched IgRT from intravenous (IVIg) to subcutaneous (SCIg) immunoglobulin was performed. Variables were compared using a Mann Whitney, chi squared or Fisher's exact test.

Results and conclusions: Responses of 347 pts were eligible for analysis. At the time of the survey, 41 (12%) were young adults and 306 (88%) were adults. Regardless of age, the majority of IgRT patients were using SCIg (68%, n=28 and 75%, n=228 of young adults and adults, respectively) compared with IVIg (32%, n=13 and 26%, n=78 of young adults and adults, respectively). Characteristics are shown in Table 1. IgRT discontinuation rates were higher in young adults than adults (17%, n=9 and 3%, n=10, respectively; $p<0.005$). Overall, significantly more young adults (24%, n=10) perceived work/school to be affected by IgRT than adults (11%, n=34; $p<0.01$; Table 1). When asked what they valued in an IgRT method, young adults prioritized fewer adverse events ($p<0.001$), while adults prioritized independently injecting/infusing treatment ($p<0.01$) (Figure 1).
Of pts currently using SCIg, 43% (n=12) of young adults and 59% (n=134) of adults had switched from IVIg to SCIg. Overall, the majority of pts following the switch perceived their quality of life, productivity and satisfaction with treatment to have 'improved' or 'substantially improved', regardless of age (Figure 2). More young adults who switched perceived their physical health and treatment compliance to have 'substantially improved' ($p=0.06$ and $p<0.05$, respectively) versus adults, who mostly rated these as 'improved' or 'stayed the same' (Figure 2).

In conclusion, we recommend discussing both IgRT options with patients of all ages, but highlighting SCIg, as it resulted in increased treatment experience and compliance potentially due to perceived increases in quality of life, productivity and treatment satisfaction in comparison with IVIg.

POSTER 54 - THE RELATIONSHIP BETWEEN BRONCHIECTASIS AND REACHING TIME OF THE TARGET THROUGH LEVEL IGG IN PATIENTS WITH COMMON VARIABLE IMMUNE DEFICIENCY

AUTHORS

Önalan T[1], Çölkesen F[1], Kılınç M[1], Sadi Aykan F[1], Evcen R[1], Akkuş F[1], Yılmaz Ergün G[1], Kahraman S[1], Gerek M[1], Arslan Ş[1]

AFFILIATIONS

[1]Medical Faculty Of Necmettin Erbakan University, Division of Clinical Immunology and Allergy, Department of Internal Medicine

Biography:
I was born in Kütahya,Turkey in 1984 and obtained my medical degree at Ege University in İzmir. My specialization was in the Department of Chest Diseases at the same university. After working for 7 years as a specialist in pulmonology, tuberculosis and intensive care departments in various hospitals, I started and still attending my fellowship at Necmettin Erbakan University in Divison of Clinical İmmunology and Allergy in Konya. Professionally, I am interested in primary and secondary immunodeficiencies, interstitial lung diseases and severe asthma. I am maried and a mother of two young children.

Introduction: Bronchiectasis is a significant cause of morbidity and mortality in patients with common variable immunodeficiency (CVID), even in patients receiving regular immunoglobulin replacement therapy (IGRT). There is no consensus regarding the optimal IGRT dose in CVID patients with bronchiectasis.

Objectives: The aim of this study was to compare the time to reach a target trough level of IgG between two groups, with and without bronchiectasis in CVID patients at diagnosis.
Methods: In this retrospective cohort and single-centre study 61 adult patients with CVID were recruited.The patients were divided into two groups according to whether they had bronchiectasis or not, at the time of diagnosis. Baseline and trough level IgG levels, the time required for IgG to reach the desired limit (700 mg/dl), and the number of infective episodes during this period were recorded.
Results: The mean age of the patients was 39 (27-51) years and 29 were female (47.5%).The number of CVID patients with bronchiectasis was 21 (34.4%). There was no difference between the two groups in terms of age, age at diagnosis, gender, delay in diagnosis, type of IGRT (subcutaneous, intravenous) and baseline immunoglobulin levels. Trough level (1st and 2nd year IgG averages) ($p<0.001$), the time required for IgG to reach the desired limit ($p<0.001$) and efficacy level (through level - basal IgG) ($p=0.016$) were significantly lower in the CVID patients with bronchiectasis group (Table 1). The time required to reach the desired IgG levels and infective episodes were significantly correlated independent of bronchiectasis ($p<0.001$, Figure 1).

Conclusions: In the present study,we reported that IGRT doses initiated within the standard limits were insufficient to reach the targeted values of serum IgG levels in CVID patients withbronchiectasis. Although the main cause is unknown yet, previous studies have suggested that neonatal Fc receptors (FcRN) are essential in the IgG salvage pathway. FcRN performs this function both by preventing the degradation of IgG phagocytosed by the cells of the phagocytic system, and by allowing the reuptake of large amounts of IgG secreted into the lumen of the lung and small intestine. FcRN expression and IgG concentrations in lung tissue were found significantly higher in the lower respiratory tract lumen than on other mucosal surfaces. Further studies are needed to determine the optimal IGRT doses to protect CVID patients with bronchiectasis from progression and exacerbations.

POSTER 56 - CHOOSING THE BEST ROUTE OF IMMUNOGLOBULIN REPLACEMENT THERAPY FOR CVID: INSIGHTS FROM A MULTICENTRIC SPANISH PATIENT COHORT

AUTHORS

Moral Moral P[1], Cabañero Navalón M[1], López-León P[1], Authors of GTEM-SEMI-CVID R[2], Garcia-Bustos V[1]

AFFILIATIONS

[1]University And Polytechnic Hospital La Fe, [2]GTEM-SEMI-CVID

Biography:
Dr. Moral is an internist at La Fe Hospital and an expert in primary immunodeficiencies. He leads the Primary Immunodeficiency Clinic and is responsible for the Primary Immunodeficiency Unit at La Fe Hospital. With extensive knowledge in the field, Dr. Moral plays a pivotal role in diagnosing and treating patients with primary immunodeficiencies. His expertise and leadership contribute to the advancement of care for individuals with these conditions, ensuring they receive specialized and comprehensive treatment at La Fe Hospital. Additionally, Dr. Moral has published in reputable journals such as Frontiers in Immunology, further demonstrating his commitment to research and expanding knowledge in the field.

Objective: Common Variable Immunodeficiency (CVID) is a PID characterized by decrease immunoglobulin production. Its main treatment involves immunoglobulin replacement therapy (IgRT). This study provides a comparison of clinical characteristics between patients with CVID undergoing subcutaneous immunoglobulin therapy (ScIg) versus those receiving intravenous immunoglobulin therapy (IvIg), providing an overview of the utilization of IgRT in Spain.

Design and Methods: Two hundred and fifty patients diagnosed with CVID were included in the Spanish registry of CVID developed by the Minority Disease Working Group of the Spanish Society of Internal Medicine (GTEM SEMI). The prevalence of infectious comorbidity, autoimmune diseases, presence of dysimmunity, malignancy, and cardiovascular pathology was compared between CVID patients according to the route of administration of IgRT.

Results: There were 124 patients in treatment with IVIg, and 88 patients in treatment with ScIg. Patients receiving ScIg were younger (p=0.016) and had higher IgG trough levels (p=0.008) compared to those receiving IvIg (Table 1). There were no significant differences in the number of major bacterial or opportunistic infections between patients receiving ScIg or IvIg. There were also no significant differences in the presence of non-infectious comorbidity between the two groups, including autoimmune cytopenias, lymphadenopathy, splenomegaly, non-infectious pulmonary pathology, GLILD, gastrointestinal involvement, autoinmmune systemic diseases, dysimmune neurological involvement, or presence of malignancy. Regarding cardiovascular risk factors, while there were no differences in the prevalence of hypertension or type 2 DM, patients receiving IvIg showed a higher prevalence of dyslipidemia (p=0.04) (Fig.1), probably due to an increased mean age in this subpopulation. Patients receiving IvIg had a higher frequency of hospital-based administration of the treatment compared to patients receiving Sc Ig (p=1.03x10- 41). Mortality rate was similar among both groups.

Conclusion: This study compares clinical characteristics of patients with CVID receiving ScIg versus IvIg in Spain. Noteworthily, the majority of CVID patients were under IVIg treatment, despite the benefits of ScIg administration route being equally effective. Nevertheless, the fact that patients receiving ScIg therapy had higher IgG trough levels suggests a better control of IgG levels in these patients, which could potentially lead to improved clinical outcomes. Furthermore, the hospital-based administration of IvIg could worsen their quality of life. Further studies are necessary to confirm whether IvIg therapy promotes dyslipidemia, or if it is a consequence of the treatment. This study provides valuable insights for clinicians to make decisions regarding the optimal route for IgRT.

POSTER 81 - A PHASE 2/3 STUDY EVALUATING POZELIMAB IN PATIENTS WITH CD55 DEFICIENCY WITH HYPERACTIVATION OF COMPLEMENT, ANGIOPATHIC THROMBOSIS, AND PROTEIN-LOSING ENTEROPATHY (CHAPLE DISEASE)

AUTHORS

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Biography:
Ahmet Özen, M.D., holds the position of professor at Marmara University located in Istanbul, Turkey. He obtained his medical degree from Marmara University School of Medicine and pursued further specialization in Pediatrics at the same institution. He subsequently completed a residency program in Allergy and Immunology at Yeditepe University in Istanbul. Dr. Özen furthered his research pursuits as a postdoctoral fellow at the Laboratory of Immunology, NIAID, within the NIH.

Dr. Özen primarily focuses his research on the genomic investigation of inborn errors of immunity, specifically emphasizing monogenic inflammatory bowel disease and immune dysregulation. He has made significant contributions to the identification of various human disorders known as inborn errors of immunity, including the notable CHAPLE disease. His clinical studies have revolved around exploring innovative treatment approaches for life- threatening immunodysregulatory disorders.

Due to his remarkable research endeavors, Dr. Özen has received prestigious national and international awards. Additionally, he is the founder of the "Marmara University Işıl Berat Barlan Center for Translational Medicine." Currently, Dr. Özen serves as the Division Chief of the Pediatric Allergy and Immunology Program at Marmara University. He is also actively involved in the NIAID-MENAT Strategy for Enhanced Research Engagement Program as a member.

Objectives: CD55 deficiency with hyperactivation of complement, angiopathic thrombosis, and protein-losing enteropathy (CHAPLE) disease is an ultra-rare autosomal recessive disorder caused by loss-of-function variants of the CD55 gene, leading to overactivation of the terminal complement system. Clinical and laboratory features of CHAPLE disease include hypoalbuminemia and edema; hypogammaglobulinemia; and gastrointestinal symptoms such as abdominal pain, loss of appetite, vomiting, and diarrhea. Patients also present with micronutrient deficiency, anemia, and growth retardation (Ozen et al. N Engl J Med 2017;377:52–61). Currently, there is no approved treatment for CHAPLE disease. We assessed the efficacy and safety of pozelimab, an investigational anti-C5 antibody, in patients with CHAPLE disease.

Design and methods: This is an interim report of an open-label, single-arm, historically- controlled study in patients with CHAPLE disease (ClinicalTrials.gov, NCT04209634). Patients received intravenous pozelimab 30 mg/kg followed by subcutaneous, weight-based dosing once weekly. The primary endpoint was the proportion of patients who achieved normalization of serum albumin and demonstrated improvement or no worsening in clinical outcomes (abdominal pain, bowel movement frequency, facial edema, and peripheral edema) at week 24.
Secondary/exploratory efficacy endpoints and safety are also reported.

Results: Ten patients were enrolled in the study, and had ≥48 weeks of efficacy measurements as of the cut-off date for this analysis. All 10 patients (100%) experienced serum albumin normalization and improvement/no worsening in clinical outcomes. Over the 48-week treatment period, most patients experienced remarkable catch-up growth. Following treatment with pozelimab, patients had reduced all-cause hospitalization days; the mean number of hospitalization days across all 10 patients decreased from 26.8 days in the 48 weeks prior to treatment to 0 days by week 48. Four patients (40%) started the treatment period on corticosteroids and all were withdrawn as of the cut-off date for this analysis. Complete inhibition of complement activity (CH50) was achieved. Seven patients (70%) experienced adverse events; none were severe, and only one patient experienced adverse events that were considered related to study drug.

Conclusion: Pozelimab inhibits complement overactivation and resolves the clinical and pathophysiological manifestations of CHAPLE disease.

POSTER 83 - OUTCOMES OF SUBCUTANEOUS IMMUNOGLOBULIN DOSE REDUCTION STRATEGY IN PRIMARY IMMUNE DEFICIENCIES AMID GLOBAL SHORTAGE

AUTHORS

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AFFILIATIONS

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Biography:
Dr. López-Leon is a third year medical resident of the Department of Internal Medicine at University and Polytechnic Hospital La Fe, Valencia. In addition, she has founded Rafiki NGO, with several projects in Africa. She has also participated in several National and International Congresses of Internal Medicine and collaborates in the Unit of Primary Immunodeficiencies at University and Polytechnic Hospital La Fe.

Objectives: This work aimed to investigate the clinical and analytical impacts of a standardized subcutaneous immunoglobulin (SCIg) dose reduction regimen in patients with humoral primary immune deficiencies (PID). This investigation was prompted by the global immunoglobulin shortage during the COVID-19 pandemic, which necessitated dosage adjustments in hospitals across Spain.

Material and methods: In our institution, patients with PID under SCIg for ≥6 months, with IgG trough levels ≥ 700 mg/dl, and no significant infections in the last 6 months were homogeneously dose-adjusted by 15 mg/Kg/week for each 150 mg/dl their trough levels were above 700 mg/dl, or 900 mg/dl in cases with enteropathy, bronchiectasis, GLILD, or immunosuppressants. Clinical and analytical parameters were retrospectively recorded and analyzed at baseline, and at 6 and 12-month follow-up, focusing on changes in the rates of severe or recurrent infections and alterations in pre-dose IgG trough levels.

Results: The study included 31 patients (15 men and 26 women). The most common diagnosis was common variable immunodeficiency (CVID) (n=17) followed other non-defined PID (11) and selective IgG subtype deficit (3). Nineteen patients received conventional SCIg formulation and 12 received hyaluronidase facilitated SCIg. Mean IgG-through levels were significantly reduced approximately 4% at 6 months and up to 17% at 12 months after dose-adjustment but the mean in all periods was over 900 mg/dL ($p<0.01$). There were no differences in the incidence of severe infections such as pneumonia and other lower respiratory tract infections, major bacterial infections, opportunistic infections, skin and soft tissue infections or severe gastrointestinal infections. Furthermore, no recurrent infections (≥3/6 months) were observed after adjustment.

Conclusion: The dose adjustment led to a significant decrease in IgG levels over supratherapeutic values without an increase in severe infections or recurrent infection.

POSTER 95 - DEVELOPING A SUBCUTANEOUS INFUSION SITE REACTION GRADESCALE (SiRG): PHASE THREE

AUTHORS

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Biography:
Melody Bullock's nursing career has been extensively involved with infusion. She earned her nursing degree from the University of Utah, and combined it with her degree in education and her graduate work in administration to provde a workable platform for product improvement that serves healthcare workers and optimized the patient experience. She also has Primary Immunodeficiency.

Objective: Site reactions have been the bane of subcutaneous infusion since the inception of its use for immunoglobulin. Various attempts have been made to improve the patient experience without success. Changing needle size, flow rate, or volume per site is helpful, and requires that the patient, the nurse, the pharmacist, and the physician all be on the same page. What is considered a "bad reaction" by a patient, may be "common and expected" by the physician.
Guidelines for site reactions will make an objective assessment possible and assist with more appropriate treatment. Gradescales have been developed for pain, wounds, headache, skin tones, and many other different disease processes and symptoms. As the use of subcutaneous infusion increases for other medications such as monoclonal antibodies, pain medications, and antibiotics, it becomes imperative that site reactions are better diagnosed and managed, which necessitates a accurate, validated site reaction gradescale.

Design and Method: Using three phases (nine steps) of the scale development primer published by Frontiers in Public Health, a gradescale for subcutaneous site reactions has been developed. The validation process is currently underway.
Phase One- Item Development involved exploration of the already approved and validated gradescales available. To date, the only scale for site reactions with subcutaneous medications is for a specific medication for AIDS. A team of nurses created a list of descriptive terms and collated 80 pictures of site reactions to match the descriptions. Based on other gradescales, including the Infiltration Gradescale, it was determined that the levels would be 0- No Reaction, 1- Mild Reaction, 2- Moderate Reaction, and 3- Severe Reaction.
Phase Two- Scale Development comprised of surveys involving nurses, physicians, and pharmacists whose objective was to revise and eliminate components of the gradescale that were repetitive, inconclusive, or non-applicable. An expert nurse discussion table isolated four specific pictures to match each level of site reaction. A separate expert nurse discussion reviewed all 80 pictures and categorized each into a site reaction level. A comparison of the independent results reflected a greater than 95% agreement. The scale is now in Phase Three- Scale Evaluation.
Next steps will be ensuring the scale is parsimonious, factor analysis, and reliability testing.

Conclusions: Nurses, pharmacists, and physicians agree that a SiRG could improve the infusion experience for patients. The goal of the SiRG, in the final phase of validation, is to provide subcutaneous infusions with fewer severe reactions, with quick assessment and action.

POSTER 126 - LONG-TERM SAFETY OF FACILITATED SUBCUTANEOUS IMMUNOGLOBULIN 10% TREATMENT IN PATIENTS WITH PRIMARY IMMUNODEFICIENCY DISEASES: FINAL ANALYSIS FROM A POST- AUTHORIZATION SAFETY STUDY CONDUCTED IN THE USA

AUTHORS

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Biography:
Paz Carrasco is Sr. Clinical Scientist in the Global Clinical Sciences team of the Plasma Derived Therapy Business Unit of Takeda. She has Masters' degree in Pharmacy (MPharm) and in Biotechnology, 15+ years of Clinical Research experience in Pharmaceutical Industry (in Europe and the USA), most recently in the use of Immunoglobulin products for the treatment of Primary Immune Deficiency/Inborn Errors of Immunity.

Objectives: Facilitated subcutaneous immunoglobulin (fSCIG) 10% is an immunoglobulin replacement therapy that utilizes recombinant human hyaluronidase (rHuPH20) to enhance immunoglobulin dispersion and absorption. fSCIG 10% is approved in the EU for adults, children and adolescents (aged 0–18 years) with primary immunodeficiency diseases (PIDs) and in the USA for adults and children aged 2 years and over with PIDs. This study aimed to assess the long- term safety of fSCIG 10% in routine clinical practice.

Design and methods: This prospective, non-interventional, open-label, multicenter, post-authorization safety study (NCT02593188) was conducted in the USA from Nov-2015 to Aug-2022. Patients with PID, aged ≥ 16 years, prescribed or receiving fSCIG 10% were enrolled. Treatment regimens were planned by the attending physician in accordance with routine clinical practice. Adverse event (AE) data were collected from enrollment to study completion or discontinuation and the presence of anti-rHuPH20 antibodies was evaluated on a voluntary basis.

Results: In total, 253 patients were enrolled and included in the full analysis set (mean age [standard deviation] 54.3 years [15.6]; 79.1% female). The most common PID diagnosis was common variable immunodeficiency (71.9%). Patients received fSCIG 10% treatment for a median (interquartile range) duration of 10.0 (3.7–11.8) months, with most infusions administered every 4 weeks (54.4% [1197 of 2201 infusions]) at home (62.6% [1395 of 2230 infusions]). Overall, 98.5% of infusions were administered without a rate reduction, interruption, or discontinuation due to AEs. Treatment-related, non-serious AEs were experienced by 52 patients (20.6%, 284 events). Two patients (0.8%) each experienced one treatment-related serious AE (aseptic meningitis and deep vein thrombosis). Two fatal AEs (0.8%) were reported; neither were treatment-related. Of 196 patients tested, 14 (7.1%) were positive for treatment-emergent binding anti-rHuPH20 antibodies (titer ≥ 1:160; maximum titer 1: 10, 240); no neutralizing antibodies were detected. There was no relationship between anti-rHuPH20 antibody positivity and the occurrence of treatment-related serious or non-serious AEs.

Conclusions: Long-term, repeated, self-administration of fSCIG 10% is well-tolerated in US clinical practice by patients with PID. Development of non-neutralizing antibodies against rHuPH20 was uncommon and did not correlate with treatment-related AEs.

This abstract was previously presented at the Clinical Immunology Society (CIS) 2023 Annual Meeting. Baxalta US Inc., a Takeda company, funded this study. Takeda Pharmaceuticals International AG funded writing support.

POSTER 128 - COMPARISON OF TOLERABILITY AND SAFETY OF HYALURONIDASE- FACILITATED SUBCUTANEOUS IMMUNOGLOBULIN 10% AND 20% THERAPIES AFTER SINGLE SUBCUTANEOUS ADMINISTRATION IN HEALTHY ADULTS

AUTHORS

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Biography:
Dr. Li is currently the Head of Global Clinical Pharmacology & Early Clinical Development in PDT Business Unit at Takeda Pharmaceuticals. Her research focuses on clinical development of plasma-derived therapies for various diseases including neuro-autoimmune diseases.

Objective: Hyaluronidase-facilitated subcutaneous immunoglobulin (fSCIG) 20% (immunoglobulin G [IgG] 20% with recombinant human hyaluronidase) is under investigation for the treatment of primary immunodeficiency disease, and offers potentially beneficial reductions in infusion times and volumes versus fSCIG 10%. This current analysis aimed to compare the tolerability and safety of fSCIG 10% and 20% following single-dose subcutaneous administration.

Design and Method: Data from two Phase 1 open-label studies of fSCIG 10% (Study 1 [NCT04578535]) and 20% (Study 2 [NCT05059977]) in healthy adults aged 19–50 years were analyzed. Participants received single doses of fSCIG 10% (Study 1; 0.4 g/kg [n = 8] or 1.0 g/kg [n = 10]; ≤ 25 ± 1- week follow-up) or fSCIG 20% (Study 2; three treatment arms [0.4 g/kg or 1.0 g/kg with in-line warming, or 1.0 g/kg unwarmed; n = 8 per arm]; ≤ 12 ± 1-week follow-up).

Results: Mean total IgG doses given were similar between fSCIG 20% and 10% at the same dose strength, while mean total IgG volumes were lower with fSCIG 20% than 10% for both dose strengths (e.g. unwarmed fSCIG 20% vs fSCIG 10% 1.0 g/kg: 355.0 mL vs 667.0 mL). Mean time to deliver total IgG volume was shorter with fSCIG 20% than 10% at both dose strengths. In both studies, all infusions were tolerated and all participants experienced treatment-emergent adverse events (TEAEs). All TEAEs were mild in severity; the majority were infusion site reactions. No serious TEAEs were reported.

Conclusions: The single-dose tolerability and safety profiles of fSCIG 20% and 10% are comparable, supporting further investigation of fSCIG 20% in target patient populations.
This abstract was previously presented at the American Association of Neuromuscular and Electrodiagnostic Medicine 2023 Annual Meeting. Takeda Development Center Americas, Inc. funded this study. Takeda Pharmaceuticals International AG funded writing support.

POSTER 129 - PHARMACOKINETICS, SAFETY AND EFFICACY OF 20% SUBCUTANEOUS IMMUNOGLOBULIN ADMINISTERED WEEKLY OR EVERY 2 WEEKS IN JAPANESE PATIENTS WITH PRIMARY IMMUNODEFICIENCY DISEASES: A PHASE 3, OPEN-LABEL STUDY

AUTHORS

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Biography:
Dr. Hirokazu Kanegane graduated from Kanazawa University in 1986 and worked at the U.S. Food and Drug Administration and University of Toyama. He is now a professor of the Department of Child Health and Development, Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental University (TMDU), Tokyo, Japan since 2018. His major interests are inborn errors of immunity (IEI), especially primary antibody deficiencies and IEI susceptible to Epstein-Barr virus.

Objectives: To evaluate the pharmacokinetics, safety, tolerability, and efficacy of the subcutaneous immunoglobulin G (IgG) 20% solution (Ig20Gly; Cuvitru) administered weekly and every 2 weeks (Q2W) to Japanese patients with primary immunodeficiency diseases (PIDs; also referred to as inborn errors of immunity).

Design and method:
This phase 3, open-label, multidose study was conducted at 8 sites in Japan (NCT04346108). Enrolled patients were aged ≥2 years and had PID treated using a stable intravenous immunoglobulin (IVIG) dose for ≥3 months prior to the study. In Epoch 1, patients received IVIG every 3 or 4 weeks at the pre-study dose (200–600 mg/kg) for 13 weeks. In Epoch 2, patients switched to subcutaneous Ig20Gly (50–200 mg/kg) once weekly for 24 weeks. A subset of 7 patients were to continue in Epoch 3, with Ig20Gly (100–400 mg/L) Q2W for 12 weeks. The primary endpoint was serum total IgG trough levels during Epochs 2 and 3. Statistical analysis was descriptive.

Results: Overall, 17 patients were enrolled (median [range] age: 24 [5–69] years; 59% male) and participated in Epochs 1 and 2, of whom 7 entered Epoch 3. A stable serum total IgG trough was maintained at ≥5 g/L (protective threshold): geometric means (95% confidence intervals [CIs]) at the end of Epochs 2 and 3 were 8.56 (8.03–9.12) g/L and 8.39 (7.89–8.91) g/L,
respectively. Annual rates (95% CIs) of all infections were 1.65 (0.73–3.15; 7 events) and 2.48 (1.34–4.13; 19 events) in Epochs 1 and 2, respectively. No infections were observed in Epoch
3. One validated acute serious bacterial infection (pneumonia) was observed in one patient in Epoch 2 (annual rate: 0.13) and resolved without hospitalization. There were no hospitalizations due to infection. Related treatment-emergent adverse events (TEAEs) were all mild in severity. In Epochs 2 and 3 the most common related TEAEs, excluding infections, were injection site swelling (24%) and injection site erythema (18%). At the end of the study, most patients (14/17) expressed a preference for continuing Ig20Gly.

Conclusions: Ig20Gly given weekly or Q2W maintained serum total IgG trough levels and was efficacious in Japanese patients with PID, consistent with pivotal phase 2/3 trial results in North America and Europe. Serum total IgG trough levels were consistent with low annual rates of infections. No new or unexpected safety signals were identified. Overall treatment preference favored Ig20Gly over IVIG.

Study/writing support funding: Baxalta US Inc. and Baxalta Innovations GmbH, both Takeda companies/Takeda Pharmaceuticals International AG.

POSTER 133 - GASTROINTESTINAL MANIFESTATIONS IN PATIENTS WITH ACTIVATED PI3Kδ SYNDROME (APDS) TREATED WITH LENIOLISIB

AUTHORS

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Biography:
Dr Rao received his undergraduate and pediatric post-graduate medical education at SCB Medical College (Cuttack, Odisha, India) followed by Hematology training at the CMC Hospital (Vellore, India) and the Tata Memorial Hospital (Mumbai, India). Dr Rao then undertook specialized training through a Hematology fellowship in Australia at Westmead and Sydney Children's Hospital, followed by a pediatric hematology oncology fellowship at the National Cancer Institute in Bethesda, Maryland, USA in 1995. Dr Rao qualified as a Fellow of the Royal College of Pathologists of Australasia (FRCPA). Since 2003, Dr Rao has been a staff physician in National Institute of Allergy and Infectious Diseases (NIAID) conducting clinical research and providing care for patients with ALPS and related disorders.

Objective: Enteropathy is reported in ≤51% of patients with activated PI3Kδ syndrome (APDS). Patient burden includes polypharmacy, hospitalization, endoscopies, and surgeries. We examined the effect of PI3Kδ inhibitor leniolisib on enteropathy in 3 patients who received leniolisib for 2-3.5 years in clinical trials.

Design and Methods: Thirty-one patients with APDS completed a 12-week, placebo-controlled, phase 3 trial (RCT) of 70-mg leniolisib twice daily. Twenty-nine enrolled in an ongoing open- label extension (OLE) study with other patients with APDS. Across the trials, 24/38 patients (63%) had gastrointestinal (GI) manifestations. Changes in enteropathy were not end points in either trial but were examined through chart review.

Results: Patient 1 is a 21-year-old Black male with a PIK3CD variant. Endo/colonoscopy revealed gut lymphoid hyperplasia at age 2, followed by recurrent ascites (age 9) and duodenal varices (age 16). He takes valganciclovir since age 12 for chronic CMV colitis. Seven months before the RCT (placebo group, age 18), he experienced recurrent C. difficile infection ultimately treated with fecal transplant 10.5 months into the OLE. Anal fissures appeared after 7 months and a benign rectal adenoma was resected 8.75 months into the OLE. Rectal fistulas and proctocolitis were noted but remain stable. Patient 2 is a 23-year-old White/Asian male with a PIK3R1 variant. He experienced chronic constipation from age 4. At age 5 he had rectal polyps and recurrent hematochezia with iron-deficiency anemia responsive to IV iron. Failure to thrive was noted at age 9. He had EoE, atypical gut lymphocytic infiltration, and hematochezia requiring PRBCs and steroid pulses before the RCT. During the RCT (leniolisib, age 21) and OLE, we saw no GI adverse events. Gut disease stabilized: constipation improved, anemia resolved, he ceased symptomatic medication, and gained weight. Repeat endo/colonoscopy were not indicated. Patient 3 is a 20-year-old White male with a PIK3CD variant. At age 15, his bowel was resected due to lymphoid hyperplasia. Chronic constipation and enlarged abdominal lymph nodes persisted through trial start (placebo group, age 16) but resolved in the OLE. All patients continue leniolisib.

Conclusions: These patients with enteropathy had different time courses of response to leniolisib. The first had significant end-organ damage and recovery is tardy. The others are symptom-free and have discontinued previous medication used to treat their GI symptoms. Theses responses suggest that gut-associated lymphoproliferative disorder responds more readily to leniolisib, while infectious complications due to end-organ damage may require more time for immune system recovery.

POSTER 136 - EFFICACY AND SAFETY OF HYALURONIDASE-FACILITATED SUBCUTANEOUS IMMUNOGLOBULIN 10% IN US PEDIATRIC PATIENTS WITH PRIMARY IMMUNODEFICIENCY DISEASE

AUTHORS

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Biography:
Dr. Russo Schwarzbaum is an Associate Director in the Global Clinical Sciences team of the Plasma Derived Therapy Business Unit of Takeda. She has a Ph.D degree in the field of Mental Health and Behavioral Medicine (Medical University Vienna) and MSc in Biology (NY university). She has over 17 years of multifaceted experience in the pharma industry, both in Israel and in Vienna, currently focusing on the use of immunoglobulin products for the treatment of primary immune deficiency/inborn errors of immunity.

Objectives: This study assessed the efficacy and safety of facilitated subcutaneous immunoglobulin (fSCIG; immunoglobulin G [IgG] 10% and recombinant human hyaluronidase [rHuPH20]) in US pediatric patients with primary immunodeficiency disease (PID; also referred to as inborn errors of immunity).

Design and method: This phase 3, open-label, prospective study (NCT03277313) was conducted at 17 centers in the USA. Patients were eligible for enrollment if they were aged 2 to < 16 years, diagnosed with PID requiring immunoglobulin replacement therapy and had received a consistent IgG dose for ≥ 3 months prior to screening. Patients received fSCIG 10% using a dose ramp-up over ≤ 6 weeks (Epoch 1) followed by fSCIG 10% treatment every 3 or 4 weeks for ≤ 3 years (Epoch 2). The primary endpoint, rate of acute serious bacterial infections (ASBIs), was compared with the regulatory-defined threshold (< 1.0 ASBIs per patient-year).

Results: Final data were provided by 44 patients for Epoch 1 (mean age [range] 9.0 [3–15] years, 59.1% male) and 43 patients for Epoch 2; 34 patients completed the study. Two ASBIs (both bacterial pneumonia) were reported in one patient with specific antibody deficiency. The mean rate of ASBIs (0.04 events/patient-year [99% upper confidence interval: 0.20]) was significantly lower than the regulatory-defined threshold. The mean rate of all infections was 3.12 events/patient-year. Stable mean serum trough IgG levels were maintained during Epoch 2 (10.4, 9.2, and 9.2 g/L at Months 0, 6 and 12, respectively). Excluding infections, 336 fSCIG-related treatment- emergent adverse events (TEAEs) were reported in 34 patients (Epochs 1 and 2 combined); most were mild (247 events in 32 patients) and two TEAEs in two patients were severe (worsening of pre-existing celiac disease and headache). One serious TEAE (excluding infections) of tonsillar hypertrophy was reported and considered unrelated to fSCIG 10%; there were no related serious TEAEs. One patient with specific antibody deficiency developed anti- rHuPH20 binding antibodies (titer ≥ 1:160) without neutralizing anti-rHuPH20 antibodies. At end of Epoch 2, the majority of patients stated that they would choose to continue fSCIG 10%.

Conclusions: fSCIG 10% effectively prevented ASBIs in US pediatric patients with PID with a safety profile consistent with previous clinical studies.

This abstract was previously presented at the Clinical Immunology Society (CIS) 2023 Annual Meeting. Takeda Development Center Americas, Inc. and Baxalta funded this study. Takeda Pharmaceuticals International AG funded writing support.

POSTER 141 - STUDY DESIGN AND BASELINE CHARACTERISTICS OF A SINGLE ARM, OPEN-LABEL, MULTICENTER, US REGISTRY STUDY OF ELAPEGADEMASE TREATMENT IN PATIENTS WITH SEVERE COMBINED IMMUNODEFICIENCY

AUTHORS

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Biography:
Roberta is a Pharmacist by background, with 15 years of professional experience in different roles and in different countries. Roberta joined the Pharmaceutical Industry after 7 years of working as a Pharmacist in the UK and where she developed experience predominantly in Medical Affairs at both local and global level including senior roles. Roberta Luzzi holds a Master's Degree in 'Medical Chemistry and Pharmaceutical Technologies' and a Master of Science (MSc) in 'Economic Evaluation in Health Care' from City, University of London.

Objective: Severe combined immunodeficiency due to adenosine deaminase deficiency (ADA-SCID) is a metabolic condition that is usually fatal if left untreated. Elapegademase, a PEGylated recombinant bovine ADA-replacement therapy, is the first-line treatment for metabolic detoxification and immune recovery in patients with ADA-SCID. Owing to the ultra-rare nature of ADA-SCID, real-world clinical experience with elapegademase is limited. Here, we present registry design and baseline characteristics of patients with ADA-SCID from the elapegademase registry (NCT03878069).

Design and Method: US patients with ADA-SCID receiving elapegademase (dosed and monitored per the USPI), regardless of treatment status, will be followed ≥ 2 years or until undergoing allogeneic hematopoietic stem cell transplant (HSCT). Patients are assessed for deoxyadenosine nucleotide levels, ADA activity, clinical and immunological status, quality of life, and safety. Patients undergoing HSCT will be evaluated 1 and 6 months after last elapegademase dose to assess safety and survival.

Results: As of January 2023, 32 patients were enrolled at 11 US sites. The mean age at enrollment was 16.3 years (range: 0–47 years; 17 (53.1%) ≥ 18 years); 20 (62.5%) patients self-identified as female. Seven (21.9%) patients were enrolled soon after diagnosis: 2 (6.3%) less than 12 months after birth, 6 (18.8%) 1–2 years after birth, and 3 (9.4%) 3 years after birth. Eighteen (56.3%) patients identified as White, 9 (28.1%) as Black, 3 (9.4%) as multiple races, 1 (3.1%) as Asian, and 1 (3.1%) as other.

Conclusion: The elapegademase registry is closed. Results from this registry will provide real-world data regarding ADA-SCID progression on treatment, long-term elapegademase safety, efficacy, effect of dosage adjustment based on biochemical assessments, and outcomes of HSCT.

POSTER 142 - RESULTS OF A PHASE 3 TRIAL OF AN ORAL C-X-C CHEMOKINE RECEPTOR 4 (CXCR4) ANTAGONIST, MAVORIXAFOR, FOR TREATMENT OF PATIENTS WITH WARTS, HYPOGAMMAGLOBULINEMIA, INFECTIONS, MYELOKATHEXIS (WHIM) SYNDROME

AUTHORS

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Biography:
Rafaele Badolato is a pediatric immunologist and Professor of Pediatrics at the University of Brescia with expertise in primary immunodeficiencies. He completed a doctorate in medicine at University "Federico II" in Naples, Italy and a PhD in Cellular and Molecular Diagnosis and Treatment at University of Udine, Italy. Additionally, Raffaele was a Research Associate at the National Cancer Institute- Laboratory of Molecular Immunoregulation (Frederick, MD).

Objectives: Warts, Hypogammaglobulinemia, Infections, and Myelokathexis (WHIM) syndrome is a rare, combined immunodeficiency presenting with leukopenia and infections, predominately caused by gain-of-function variants in CXCR4. Mavorixafor, an investigational oral CXCR4 antagonist, demonstrated promising efficacy and safety profiles in a phase 2 trial for participants with WHIM syndrome. Here we report results of the randomized, double-blind, multicenter, placebo-controlled period of a phase 3 study evaluating the efficacy and safety of mavorixafor in participants with WHIM syndrome (NCT03995108).

Design and Method: Participants aged ≥12 years with clinical diagnosis of WHIM syndrome, confirmed CXCR4 variant, and absolute neutrophil count (ANC) or total white blood cell (WBC) count ≤400 cells/μL at screening were eligible. Participants were randomized 1:1 to receive mavorixafor (>50 kg, 400 mg once daily [QD]; ≤50 kg, 200 mg QD) or placebo for 52 weeks.
The primary endpoint was time above threshold ANC (TAT-ANC). Figure 1 shows study design and select secondary endpoints.

Results: Overall, 31 participants were randomized (mavorixafor, n=14; placebo, n=17) and received ≥1 dose of treatment (intent-to-treat population). The primary endpoint, mean TAT- ANC, was 15.04 (mavorixafor-group) vs 2.75 hours (placebo-group; P<.0001). Additionally, mean TAT absolute lymphocyte count (TAT-ALC) was 15.80 (mavorixafor-group) vs 4.55 hours (placebo-group; P<.0001). Mean absolute WBC count, ANC, and ALC increased from baseline into normal range and sustained at each timepoint assessed over 52 weeks with mavorixafor versus placebo. Compared with placebo-group, mavorixafor-group showed 60% lower annualized infection rate (least squares [LS] mean: mavorixafor, 1.7; placebo, 4.2; nominal P=.0072), and 40% lower total infection score, a combination of infection number and severity (LS mean [95% CI]: mavorixafor, 7.41 [1.64–13.19]; placebo, 12.27 [7.24–17.30]). Greater reduction in infection duration and type and antibiotic use was observed with mavorixafor versus placebo.

No discontinuations occurred due to adverse events (AEs). No treatment-related serious AEs or treatment-limiting toxicities were observed (Table 1).

Conclusions: Primary and first key secondary endpoints were met. Mavorixafor-group showed significantly higher mean TAT-ANC and TAT-ALC and greater reduction in infection frequency, severity, and duration versus placebo-group. Mavorixafor was generally well tolerated over the 52-week treatment period. About 87% of eligible participants enrolled in the open-label extension.

POSTER 148 - ASSESSING LONG-TERM TREATMENT WITH LENIOLISIB AND ITS EFFECTS ON BRONCHIECTASIS IN PATIENTS WITH ACTIVATED PI3Kδ SYNDROME (APDS)

AUTHORS

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Biography:
Markéta Bloomfield is a clinical immunologist, allergologist and a trained paediatrician. She received her MD and PhD degrees from the 2nd Faculty of Medicine, Charles University, Prague, and currently works as a consultant in the Department of Immunology, University Hospital Motol, Prague. She splits her time between clinical, research activities, and teaching. In the clinic, she manages pediatric patients with variety of allergic and immune disorders, particularly with inborn errors of immunity. Her research focuses on various rare monogenic immunodeficiencies both from basic and translational perspectives. She is a lecturer of immunology and pediatrics for pregraduate and postgraduate MD students of Charles University. She is a member of Czech Society for Allergy and Clinical Immunology (CSAKI), Czech Immunology Society (CIS), European Society of Immunodeficiencies (ESID), European Academy of Allergy & Clinical Immunology (EAACI) and Czech Paediatric Society (CPS JEP).
She is a board member of National Advisory Committee on Immunization Expert Working Party (NIKO EPS).

Objective: Bronchiectasis is observed in up to 60% of patients with activated PI3Kδ syndrome (APDS) in the literature. The progressive end-organ damage may develop due to both recurrent infections and nodular lymphoid hyperplasia of the respiratory tract. The burden can be extensive, requiring bronchoscopy, polypharmacy, chronic supplemental oxygen, chest physiotherapy, or lobe resections, which undoubtedly negatively affect quality of life. Here, we examined the long-term effect of PI3Kδ inhibitor leniolisib on bronchiectasis in 3 patients who received leniolisib for 6 years as part of the clinical trials.

Design and Methods: Six patients were enrolled in a dose-finding trial and are currently participating in an open-label extension study (OLE; NCT02859727) examining the long-term use of 70-mg leniolisib orally twice daily in patients with APDS. Three of 6 patients developed bronchiectasis prior to trial entry and we followed progression out to year 6 of treatment. Data collected prior to year 1 of treatment were captured in the clinical trial reports, while investigators provided additional data up to December 2022 that included health-related quality of life (HRQoL) which was assessed though a clinician-reported narrative.

Results: Three patients developed bronchiectasis prior to entry into the trial; others did not develop it at any time before or during the OLE (Figure 1, left). No one with bronchiectasis has progressed or required pulmonary support, and all are stable at year 6 of treatment with leniolisib (Figure 1, right). Pulmonary function tests revealed no new conditions. As bronchiectasis development has been linked to recurrent infections and lymphoproliferation, we assessed immune subsets and lymphoproliferation and saw durable improvements. At the latest time points with available data, mean naïve B cell levels increased from 24.00% at baseline to 83.23%, mean transitional B cell levels decreased from 43.87% to 1.42%, and the CD4:CD8 T- cell ratio normalized from 0.67 to 1.19. Lymphoproliferation reduced or resolved in all 3 patients with pre-existing bronchiectasis. Most patients report reduced severity and number of respiratory infections and increased ability to exercise without shortness of breath.

Conclusions: Bronchiectasis in all 3 affected patients showed no progression through year 6 of treatment with leniolisib. We surmise that leniolisib's enduring ability to normalize immune subsets and reduce lymphoproliferation, both of which are suspected to be key players in the development of bronchiectasis, contributed to the stabilization of permanent airway damage and these results are likely associated with health-related quality-of-life improvements.

POSTER 154 - JAK INHIBITION WITH BARICITINIB FOR SEVERE CVID-RELATED ENTEROPATHY: A CASE REPORT

AUTHORS

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Biography:
Amir is a first-year MD-PhD student with a background in both medicine and molecular biology. He pursued both his master's degrees in Rotterdam. Given his background, he is dedicated to translating fundamental research into practical applications in clinical settings. His PhD focuses on unraveling the underlying mechanisms of immune dysregulation in PIDs, with a specific emphasis on CVID.

Objectives: To illustrate the challenges in managing refractory Common Variable Immunodeficiency (CVID) enteropathy and highlight the potential therapeutic benefits of a JAK1/2 inhibitor for these patients.

Design and Method: This study involved a longitudinal case analysis of a patient diagnosed with CVID at age six, who subsequently developed severe CVID enteropathy. Treatment with standard immunosuppressants were initially effective but followed by relapses. Despite undergoing an allogeneic stem cell transplantation at age 17, the patient kept experiencing immune dysregulation ultimately leading to life-threatening electrolyte disorders and malnutrition, necessitating ICU. After exhausting alternative treatment options, off-label therapy with the JAK1/2 inhibitor, baricitinib, was initiated. This decision was based on previously reported high interferon signaling in CVID enteropathy and significantly elevated interferon- associated cytokines in the patient.

Results: Baricitinib treatment gradually led to remission of inflammatory symptoms and improvement of the patient's nutritional status, marked by weight gain, normalization of albumin levels, and tapering of total parenteral nutrition and prednisone. Follow-up measurements of interferon-associated cytokines showed decreasing, but still elevated, levels. Despite increased infection susceptibility concerns with JAK inhibitors, this patient remained infection-free under vigilant monitoring. The patient has remained in remission for over a year, with daily baricitinib doses.

Conclusions: This case demonstrates the complexity of managing CVID related enteropathy and the potential efficacy of JAK inhibitors, such as baricitinib, in cases where standard treatments have failed. It underscores the need for further investigation through randomized controlled trials or prospective cohorts to confirm the clinical utility of JAK-inhibitors in treating refractory CVID related enteropathy.

POSTER 157 - DEEP REINFORCEMENT LEARNING FOR ADAPTIVE TREATMENT OPTIMIZATION IN SEVERE COMBINED IMMUNODEFICIENCY (SCID)

AUTHORS

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Biography:
Rifaldy Fajar is a doctoral student in Computational Biology and Medicine at Yogyakarta State University. His research primarily revolves around computational immunology and the integration of artificial intelligence (AI) and machine learning (ML) in medicine. With a keen interest in leveraging computational approaches to unravel the intricacies of the immune system, Rifaldy's work focuses on developing ML-based models for predicting immunological outcomes in various diseases. He has been awarded research grants by the Ministry of Research and Technology of Indonesia, recognizing his contributions to applying ML techniques to advance medical research. Rifaldy actively engages in scientific conferences and workshops, aiming to foster collaborations and contribute to cutting-edge developments in computational immunology and the application of AI in medicine.

Objective: Severe combined immunodeficiency (SCID) is a rare, life-threatening primary immunodeficiency disorder characterized by profound impairment of T cell function. Optimal treatment decisions for SCID patients, such as hematopoietic stem cell transplantation (HSCT) or gene therapy, are challenging due to the complex interplay of genetic, clinical, and immunological factors. This research presents a pioneering research approach that utilizes deep reinforcement learning (DRL) to optimize treatment selection in SCID. The aim is to develop an adaptive framework that learns from patient data and clinical outcomes to provide personalized treatment recommendations, maximizing long-term efficacy and minimizing risks.

Methods: We compiled a comprehensive dataset from a multi-center cohort of 300 SCID patients, encompassing diverse clinical records, high-resolution genetic profiles, immune cell phenotyping data, treatment modalities, and long-term outcomes. The dataset included information from leading SCID research centers and major clinical databases, ensuring its reliability and representativeness. A DRL agent was constructed using a customized deep neural network architecture, incorporating both convolutional and recurrent layers. The value network estimated long-term treatment outcomes, while the policy network determined treatment selection based on the predicted values. The DRL agent was trained using a combination of supervised learning and reinforcement learning techniques, optimizing for cumulative treatment efficacy over time. The training process involved extensive simulation of various treatment scenarios and iterative updates to the agent's policy based on rewards and penalties obtained from the simulated outcomes.

Results: Our DRL-based adaptive treatment optimization framework demonstrated exceptional results in SCID treatment selection. The trained DRL agent achieved an average success rate of 90% in selecting the most effective treatment strategy for SCID patients. By continuously learning from patient data and adapting its treatment recommendations, the framework outperformed traditional treatment guidelines, resulting in a 25% improvement in long-term treatment efficacy. Moreover, the agent showcased the ability to adapt to individual patient characteristics and dynamically adjust treatment strategies in response to evolving clinical conditions.

Conclusions: Deep reinforcement learning presents a groundbreaking approach for adaptive treatment optimization in severe combined immunodeficiency (SCID). Our research demonstrates the effectiveness of a DRL-based framework in learning from a comprehensive dataset and optimizing treatment selection for SCID patients. By integrating clinical, genetic, and immunological information from a multi-center cohort, the DRL agent provides personalized treatment recommendations, maximizing long-term efficacy while minimizing risks. This approach has the potential to revolutionize clinical decision-making in SCID and pave the way for precision medicine strategies in primary immunodeficiencies management.

POSTER 194 - TREATMENT WITH THE SELECTIVE PI3Kδ INHIBITOR LENIOLISIB IN AN ATYPICAL CASE OF ACTIVATED PI3Kδ SYNDROME (APDS)

AUTHORS

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Biography:
Giulio Tessarin, MD is a pediatrician and PhD candidate in Molecular Genetics, Biotechnologies, and Experimental Medicine in the Department of Molecular and Translational Medicine, at the University of Brescia in Italy. His main interests are inborn errors of immunity, monogenic causes of CVID, GLIAD, APDS, and targeted treatment in IEIs.

Objectives: The clinical phenotype of patients with activated PI3Kδ syndrome (APDS) is heterogenous, ranging from asymptomatic to profound immune deficiency and dysregulation. Though it is unclear if and when disease progression will occur in minimally symptomatic patients, it is vital to implement timely, appropriate treatment to correct the underlying immune defect and to avoid irreversible end-organ damage. Here, we examined the effects of PI3Kδ inhibitor leniolisib in the treatment of APDS in a patient with an unremarkable history and atypical presenting clinical phenotype.

Design and Methods: The patient received leniolisib in a 12-week, placebo-controlled, phase 3 trial and is currently participating in an open-label extension study (OLE; NCT02859727) examining the long-term use of 70-mg leniolisib orally twice daily in patients with APDS.

Results: The patient is a 15-year-old White male with a PIK3CD pathogenic variant. His medical history was unremarkable until age 12 when he presented with a macrophage activation syndrome/hemophagocytic lymphohistiocytosis phenotype, pharyngitis, skin rash, arthritis, fever, and lymphadenopathy. Lymphadenectomy excluded malignancy. At enrollment, he had no history of sinopulmonary infections nor was lymphadenopathy present on cross-sectional imaging. Key immune subsets which were outside normal range at baseline normalized while receiving leniolisib (Figure 1). At day 463 of treatment, naïve B cell levels increased from 51.3% at baseline to 66.45%, central memory CD4+ T cells increased from 20.7% to 27.05%, senescent (CD57+) CD4+ T cells decreased from 7.90% to 3.35%, and terminally differentiated effector memory CD8+ T cells decreased from 18.40% to 13.45%. Elevated IgE levels also reached normal range, decreasing from 1559.9 µg/L to 383.5 µg/L. He experienced 3 adverse events including headache, itching, and knee excoriation; all scored grade 1, not related to study drug, and resolved without intervention. Prior to treatment, he was unable to partake in sports or attend school due to fevers and overall weakness. After year 1 of treatment, he began boxing, attending school, and medications reduced from 4 to 1.

Conclusions: During treatment with leniolisib in a patient with minimal lymphoproliferation and infections at enrollment, key lymphocyte subsets that were previously out of range normalized. Three adverse events were reported and not related to treatment. As we uncover the natural history of APDS, safe and effective treatment outcomes of an atypical phenotype are illuminating and we surmise it is worth investigating what aspects of this progressive illness could be averted with timely therapeutic interventions.

POSTER 203 - EPIGENETIC ACTIVATION OF THE TUSC3 GENE AS A POTENTIAL THERAPY FOR XMEN DISEASE

AUTHORS

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Biography:
Deputy chief physicianÐDepartment of clinical immunology, Children's Hospital of Fudan University
Academic director of Fudan Pediatric Medical Association

Objective: We sought to investigate the feasibility of activating TUSC3 expression to provide a potential therapeutic strategy for XMEN disease.

Methods: The expression profiles of MAGT1 and TUSC3 were analyzed using multiple databases, real-time quantitative PCR, and Western blot. The effects of decitabine and panobinostat on the regulation of TUSC3 expression were explored in both MAGT1 knockout (KO)/patient-derived lymphocytes and MAGT1 KO hepatocytes.

Results: Although TUSC3 is widely expressed, it is undetectable specifically in the immune system and liver, consistent with the main diseased tissues in patients with XMEN disease. CRISPR/Cas9-mediated KO of MAGT1 in the NKL cell line successfully mimicked the phenotypes of XMEN patient–derived lymphocytes, and exogenous expression of TUSC3 rescued the deficiencies in KO NKL cells. Using this in vitro model, we identified 2 epigenetic drugs, decitabine and panobinostat, by screening. Combination treatment using these 2 drugs significantly upregulated TUSC3 expression and rescued the immune and liver abnormalities.

Conclusions: Epigenetic activation of TUSC3 expression constitutes an effective therapeutic strategy for XMEN disease.

POSTER 213 - A RANDOMISED, PLACEBO-CONTROLLED, PHASE III TRIAL OF LENIOLISIB IN ACTIVATED PI3Kδ SYNDROME: ADULT VERSUS ADOLESCENT SUBGROUP ANALYSIS

AUTHORS

Rao V[1], Šedivá A[2], Dalm V[3], Plebani A[4], Schuetz C[5], Shcherbina A[6], Trizzino A[7], Zharankova Y[8], Orpia A[1], Kulm E[9], Webster S[1], Körholz J[5], Lougaris V[4], Rodina Y[6], Conlon N[10], Coulter T[11], Bradt J[12], Relan A[12], Uzel G[1]

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Biography:
Dr Niall Conlon is Head of Department / Consultant Immunologist at the Department of Immunology, St. James's Hospital and Clinical Professor at the School of Medicine, Trinity College Dublin, Ireland.

Dr. Niall Conlon graduated with distinction from Queen's University Belfast in 2001. He holds a PhD in Immunology from Trinity College Dublin and a Diploma in Allergy from the University of Southampton. Dr Conlon is a Fellow of the Royal College of Pathologists (UK) and Fellow of The Royal College of Physicians of Ireland.

After completing higher specialist training in Clinical and Laboratory Immunology he was appointed as Consultant Immunologist in the Department of Immunology, St. James's Hospital Dublin where he runs a large diagnostic immunology laboratory and clinical service. His main areas of interest are adult inborn errors of immunity, ANCA associated vasculitis, chronic urticaria and diagnostic laboratory testing.

Objectives: Activated PI3K delta syndrome (APDS) is an ultra-rare inborn error of immunity. APDS arises from hyperactive signalling within the PI3Kδ pathway and is characterised by both immunodeficiency and immune dysregulation. Treatments for APDS are often limited to symptom management (e.g. immunoglobulin replacement and antimicrobials), surgical interventions (e.g. reduction of splenomegaly) and unlicensed immunomodulatory therapies (e.g. mTOR inhibitors), which can be associated with severe adverse events (AEs).
Leniolisib, is an oral, highly selective PI3Kδ inhibitor, that targets the underlying pathophysiology of APDS, partially correcting the underlying immune defect. In a randomised controlled trial (RCT) versus placebo, leniolisib was well-tolerated and met both co-primary endpoints. Here, results of a prespecified subgroup analysis investigating treatment effects in adolescents and adults are reported.

Design and Method: A Phase 3, 12-week, triple-blinded RCT (NCT02435173) investigated leniolisib 70 mg twice daily versus placebo in 31 participants with APDS aged 12–75 years. Co-primary endpoints were Change from Baseline (CfB) in size of the index lymph nodes (in patients with ≥1 lesion at Baseline) and CfB in percentage of naïve B cells/total B cells (in patients with <48% naïve B cells at Baseline).
Prespecified subgroup analyses compared co-primary endpoints at Day 85 in adolescents (12– 17 years) and adults (≥18 years). Analysis of covariance was performed with treatment as a fixed effect and Baseline value as a covariate; use of glucocorticoids and immunoglobulin replacement therapy (IRT) at Baseline were included as categorical (Yes/No) covariates. Plasma concentration of leniolisib, safety and tolerability were also assessed.

Results: In total, 12 adolescent (39%, n=8 leniolisib; n=4 placebo) and 19 adult (61%, n=13 leniolisib; n=6 placebo) participants were recruited (Table 1).
Effects of leniolisib were consistent between adolescents and adults for the two co-primary endpoints, with leniolisib performing better than placebo at reducing lymphadenopathy and increasing the proportion of naïve B cells (Figure 1). The plasma concentration of leniolisib in participants was comparable amongst both subgroups when measured 8-hours post dose (Figure 2). The safety profile of leniolisib was similar in adolescents and adults (Table 2), with similar rates of study drug-related AEs in the leniolisib arm of each subgroup.

Conclusions: The clinical benefit of leniolisib observed in both co-primary endpoints was consistent in adolescents and adults, with leniolisib well-tolerated by both subgroups. We show that leniolisib is an effective treatment for APDS in both subpopulations.

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POSTER 214 - RESULTS OF A SECOND INTERIM ANALYSIS OF AN ONGOING SINGLE-ARM OPEN-LABEL EXTENSION STUDY OF LENIOLISIB IN ACTIVATED PI3Kδ SYNDROME: LONG-TERM EFFICACY AND SAFETY THROUGH TO MARCH 2023

AUTHORS

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Biography:
Dr Virgil A. Dalm is Associate Professor and Principal Investigator at the Departments of Internal Medicine and Immunology, Erasmus Medical Center. Dr Dalm is responsible for the clinical care of patients with primary and secondary immunodeficiency disorders within the Primary Immunodeficiency Center of the Erasmus Medical Center. His clinical research is focused on the identification and determination of various non-infectious complications in inborn errors of immunity (IEI), including endocrine, psychological, neurodevelopmental and skin complications. Dr Dalm holds the position of principal investigator in the leniolisib clinical trial programme and has many years of experience treating patients with APDS.

Objectives: Activated PI3K delta syndrome (APDS) is an ultra-rare inborn error of immunity, characterised by both immunodeficiency and immune dysregulation. Leniolisib is an oral, highly selective PI3Kδ inhibitor, that targets the underlying pathophysiology of APDS to modify the underlying immune defect.
In a randomised controlled trial (RCT) in people with APDS, leniolisib was well-tolerated and met both co-primary endpoints (reducing lymphadenopathy, increasing naïve B cells) versus placebo. A single-arm open label extension (OLE) study investigating the long-term safety and efficacy of leniolisib is ongoing. Results of an interim analysis (2.0 years median leniolisib exposure) have previously been reported. Here, the results of a second interim analysis of the OLE after a further 1.0 year of follow-up, are shown.

Design and Method: OLE participants were aged ≥12 years and had completed NCT02435173 or studies of other PI3Kδ inhibitors; participants received 70mg leniolisib twice daily. The primary endpoint was long-term safety and tolerability, reported as adverse events (AEs); efficacy endpoints included infection frequency (reported as AEs; secondary), lymphoproliferation (exploratory) and immunoglobulin M (IgM) normalisation (exploratory). Extraction date was 13-Mar-2023.

Results: In total, 37 participants enrolled into the OLE (26 previously treated with leniolisib; 11 not previously treated with leniolisib), with 31 (84%) continuing the study drug at data extraction. Median leniolisib exposure was 3.0 years (range: 1.2–6.0 years).
For the primary endpoint, 34 participants (92%) had ≥1 AE (Figure 1). No new treatment-related AEs were reported since the first interim analysis (where 32/37 participants had ≥1 AE) and most AEs were Grade 1/2. New serious AEs included a Grade 3 Classical Hodgkin's lymphoma at extension day 750 in a participant previously treated with placebo in the RCT, with therapy gaps and lymphoproliferation exacerbations.
Treatment with leniolisib led to a significant reduction in overall number of infections (−0.26; p=0.003), including respiratory infections (−0.20; p=0.02) compared to the previous year; 5 participants discontinued immunoglobulin replacement. Reductions in lymphoproliferation with leniolisib seen in the RCT were sustained with a −49.5% (standard deviation [SD]: 0.4) reduction in the mean sum of product diameters of index lymph nodes; 26/30 participants (87%) achieved a ≥30% reduction. Mean spleen volume reduced by −36.3% (SD: 0.2) with 19/31 participants (61%) achieving a ≥35% reduction. Elevated IgM levels reduced with leniolisib and remained low to the last IgM assessment (Figure 2).

Conclusions: Leniolisib remains well-tolerated, with durable efficacy at a median of 3.0 years exposure in people with APDS.

MED-INT-LEN-230006 Jun2023

POSTER 218 - CLINICAL FEATURES OF PATIENTS WITH CONGENITAL ATHYMIA WHO HAVE UNDERGONE EARLY IMMUNE RECONSTITUTION FOLLOWING TREATMENT WITH ALLOGENEIC PROCESSED THYMUS TISSUE-AGDC

AUTHORS

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Biography:
Priya Patel, PharmD, BCPS, BCMAS is an Associate Director of Medical Affairs at Enzyvant Therapeutics, Inc providing support for rare diseases. She has previously worked in the pharmaceutical industry as a Medical Science Liaison, proving clinical expertise in neonatology and cystic fibrosis. During this time, Dr Patel also completed an international assignment in Global Medical Affairs. Prior to working in the pharmaceutical industry, Dr Patel worked as a clinical pharmacist in a 125-bed neonatal intensive care unit and as a consultant pharmacist focused on smart pump technology. She has presented at numerous conferences and is a past reviewer for The Journal of Pediatric Pharmacology and Therapeutics and The American Journal of Health System Pharmacy. Dr Patel earned her Doctor of Pharmacy from the University of Florida College of Pharmacy in Gainesville, FL and completed her residency at Northside Hospital in Atlanta, Georgia. She maintains board certification as a pharmacotherapy specialist.

Introduction: Congenital athymia (CA) is an ultra-rare, life-threatening disorder in which a lack of naïve T cells results in severe immunodeficiency and immune dysregulation.1 Allogeneic processed thymus tissue-agdc is the only FDA-approved treatment for immune reconstitution in pediatric patients with CA.2 In a pooled analysis of 10 clinical trials with 105 patients who underwent allogeneic processed thymus tissue-agdc implantation, naïve T-cell counts increased and infection-related adverse events (AEs) decreased over time.3 Immune reconstitution sufficient to prevent infections and support survival develops 6 to 12 months post-implantation and may take up to 2 years.3

Objective: To identify clinical features associated with early immune reconstitution after allogeneic processed thymus tissue-agdc implantation, defined as >100 naïve CD4+ cells/mm3 at 6 months (M6).

Design and Method: All patients were enrolled in prospective, single-arm, open-label studies conducted at Duke University Medical Center between 1993 and 2020, and retrospective study data were aggregated from patients who had ≤100 naïve CD4+ T cells/mm3 or >100 naïve CD4+ T cells/mm3 at M6 vs year 1 (Y1). Patients with >100 naïve CD4+ T cells at M6 were characterized by age at implantation, phenotype, genetic background, and immunosuppressant use.

Results: At baseline, all patients with available data had naïve T-cell counts ≤50 cells/mm3. At M6, 26.9% (18/67) of patients had >100 naïve CD4+ T cells/mm3 vs 70.2% (40/57) of patients at Y1. Among patients with >100 naïve CD4+ T cells/mm3 at M6 vs Y1, mean age at implantation was lower (132.1 days vs 232.4 days) and typical phenotype was more common (72.2% vs 60.0%; Table). Of the 18 patients with early immune reconstitution (Figure), 44.4% developed >100 naïve CD4+ T cells/mm3 between 120- and 180-days post-implantation. The age at implantation was similar among phenotypes (atypical 127 days; typical 134 days).
Cyclosporine use was greater in patients with the atypical phenotype (80%) vs the typical phenotype (15.4%). A variety of infection-related AEs occurred over time with no identifiable trends. No infection-related deaths were reported in patients with >100 naïve CD4+ cells/mm3 at M6 and Y1.

Conclusions: Younger age at implantation and typical phenotype may contribute to earlier immune reconstitution at M6 in some patients receiving allogeneic processed thymus tissue- agdc. Although early immune reconstitution is associated with fewer infection-related AEs compared with the overall population,2,3 patients carry a high risk for infections in the first-year post-implantation. No infection-related deaths occurred following implantation in those with early immune reconstitution.

POSTER 231 - TEN YEARS FOLLOW-UP OF THERAPEUTIC STRATEGIES OF 35 ATAXIA TELANGIECTASIA PATIENTS FROM A SINGLE CENTER

AUTHORS

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Biography:
Responsible of Pediatrics Immunology Unit, Dept. Of Pediatrics, University of Brescia, dedicated to the management of Primary Immunodeficiencies Diseases.

Background: Ataxia Telangiectasia (AT) is a multisystemic neurodegenerative disease with a poor prognosis with a life expectancy around twenty-five years. Pulmonary failure and cancer are the major causes of death, while neurological degeneration is the major contributor to early debilitating disability: patients are usually wheel-chair dependent by the age of ten. However, nowadays there is no marketed drug approved to treat or slow down the progression of AT. Anti-parkinson drugs provide limited benefit on extrapyramidal symptoms while betamethasone led to a transient improvement in ataxia. Intra-Erythrocyte Dexamethasone Sodium Phosphate (EDS-EP), reduce steroid toxicity without affecting usefulness.

Objectives: Our study evaluates the efficacy and safety profile of these drugs in AT-patients after the long-term use.
Methods. This is an 11-years retrospective study including 35 AT-patients: four treated with betamethasone, nine with EDS-EP (five for 6-months, one for 42-months and three for ten years) and eleven with antidyskinetic drugs. The progression of the neurological disease was assessed with ICARS and the safety profile on the basis of treatment-emergent adverse events (TEAEs).

Results: In our study the cumulative survival rate reached the 80 % (figure 1). Total ICARS score showed a statistically significant difference between patients treated and untreated with EDS (p=0,004), as well as comparing patients underwent short-term and long-term treatments (p=0,0349). The same results were recorded in “posture and gait” (p<0,0001; p=0,0131) while in “kinetic” subscale this required the addiction of antidyskinetic drugs (p=0,0071). Betamethasone showed the same efficacy but with toxicity. Glucocorticoids allowed a significant improvement in “speech” and “eye movements disorders”. Monotherapy with antidyskinetic didn’t reach any statistical difference.
As regard to the safety profile, no TEAEs were observed during EDS-EP long-treatment.

Conclusions: Few studies addressed the issue of therapeutic strategies in AT patients and none for such a long time. Our study provides support for long-term use of EDS-EP in AT. In patients with severe extrapyramidal movement disorders the potential efficacy of this treatment can be used in association with the dopaminergic drugs.

POSTER 264 - COMPLICATED COURSE OF ACTIVATED PI3Kδ SYNDROME-1 (APDS- 1) AMELIORATED BY LENIOLISIB: A CASE STUDY

AUTHORS

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AFFILIATIONS

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Biography:
Prof. Dr. med. Christian Klemann ist Facharzt für Kinder- und Jugendmedizin, Kinder- Pneumologe, -Allergologe, -Rheumatologe und -Immunologe und leitet seit Juli 2022 den Bereich der pädiatrische Immunologie, Kinder-Rheumatologie und -Infektiologie an der Uniklinik Leipzig (UKL).

COMPLICATED COURSE OF ACTIVATED PI3Kδ SYNDROME-1 (APDS-1) AMELIORATED BY LENIOLISIB: A CASE STUDY

Objective: Activated phosphoinositide-3-kinase-delta syndrome-1 (APDS-1, MIM 615513) is a rare inborn error of immunity (IEI) caused by heterozygous gain-of-function mutations in PIK3CD, which encodes the p110δ subunit of PI3Kδ. Patients with APDS-1 suffer from a plethora of symptoms like infections, lymphoproliferation, autoimmunity, and malignancy. Treatments ranges from symptomatic to hematopoietic stem cell transplantation (HSCT). Possibly, targeted therapy with the PI3Kδ inhibitor could significantly reduce the burden of symptoms, even in severe cases.

Case description: Here, we present the case of a male, now 20-year-old patient who had recurring respiratory infections since childhood and was diagnosed with lymphoma at the age of 10. As his father had died of lymphoma and HLH at an early age, an autosomal-dominant disease was suspected, and APDS-1 with the E1021K mutation was subsequently confirmed.
Despite treatment with IgG substitution, antibiotics, and mTOR-inhibition with Sirolimus, the patient continued to suffer from lymphoproliferation, recurrent infections, chronic viral infection, and recurrent pleural effusion. Worsening of symptoms led to HSCT (10/10 matched sibling donor, conditioning with alemtuzumab, fludarabine, treosulfa, thiotepa). Unfortunately, autologous reconstitution occurred (donor fraction at 3.2% after 68 days), and the patient suffered from a complicated clinical course with massive diarrhea, recurrent sepsis, and a septic shock with intestinal bleeding and ileus, managed by an ileostomy. At this point, the patient was cachectic with a BMI of 15 kg/m².
The patient started receiving leniolisib as part of an individualized curative trial in July 2021. Shortly afterward, he survived another sepsis, and from then on, his clinical condition improved continuously. In early 2023, his quality of life had improved significantly, his body weight had improved to a BMI of 16 kg/m2, and he is currently able to pursue work as a mechanic. He was found to have a stable, moderate-grade restrictive ventilatory dysfunction without respiratory symptoms or infection, and antibiotic prophylaxis could be discontinued at the last check-up in 01/2023.

Conclusions: In the present case, the patient's quality of life and life expectancy was expected to be significantly reduced due to the severity of the course of the disease and failed HSCT. However, a few months after the initiation of treatment with leniolisib, a significant reduction in the burden of infection without life-threatening events was reported. Thus, targeted treatment with leniolisib may be effective in APDS patients with the most severe courses.

COVID-19 AND OTHER INFECTIOUS AGENTS

POSTER 27 - COMMON ORGANISMS OF PAROTID ABSCESS IN CAMBODIAN'S CHILDREN

AUTHORS

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AFFILIATIONS

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Biography:
My Name is Prak Farrilend, MD, DCH,COP,
A male was Born on 22-02-1991
Started working in 2017 at Angkor Hospital for Children(AHC)
Currently working at the IPD department of AHC
From Kampot province of Cambodia

Introduction: The parotid gland is the largest and the most commonly affected salivary gland by inflammation. The parotid space is one of the 11 spaces in the deep neck region and adjacent to the parapharyngeal space. Since parotid abscess can potentially spread into deep neck spaces to cause systemic infections, it may result in life-threatening complications such as descending mediastinitis, Bell's palsy , septic shock.[1]

Methods: Our study is retrospective study chart review of all the children who had parotid abscess that was confirmed during surgery. The 42 patients were all under 15 years of age and lived in Cambodia. The duration of the study was 5 years, from 01-Jan-2017 to 01-Jan-2022 here.

Results: Of the 42 patients with parotid abscess, the most common pathogen found was Burkholderia Pseudomallei in 76% (32 of cases), of which 60% (19 cases) affected the right side and 40% affected the left side (13 cases) and we less commonly saw bilaterally Staphylococcus aureus was the second most common cause and found in 24% (9 cases) of which 77% (7 cases) were on left side and only 23% (2 cases) on the right side. Cheek swelling was a chief complaint in 99% of cases and fever was a presenting feature in 90% of cases. All of the parotid abscess were localized. There were no patients died.

Conclusions: The most common cause of parotid abscess in children under 15 years of age in our study was Burkholderia Pseudomallei which is Gram negative rod shape, and mostly involved the right side and was not seen in bilaterally. The other pathogen is Staphylococcus Aureus which more commonly effected the left side. The children all live in provinces surrounding the Tonle Sap River region.
For the regional of their living were from different province and place in that we found from the surrounding the Tonle Sap River, Siem reap 77% (33), Kampong Thom 9.5% (4), Phnom Penh2.3% (1), Battambang 5% (2), Banteay Meanchey 2.3% (1).

POSTER 36 - SIDE EFFECT SPECTRUM OF COVID-19 VACCINES IN INBORN ERRORS OF IMMUNITY

AUTHORS

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AFFILIATIONS

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Biography:
I started Pediatric Allergy and Immunology fellowship in 2021 in Hacettepe University Faculty of Medicine. I have been working on researchs with immunodeficiency patients.

Background: Worldwide COVID-19 immunization has been implemented with emergency-use authorisation. Together with conventional vaccines, mRNA vaccines have been used.

Objective: We had concerns/lack of information on mRNA vaccine side effects in different inborn errors of immunity (IEI) types.

Methods: We enrolled 141 IEI patients (IEI-P) and 151 healthy controls (HC) who received SARS-CoV-2 vaccine/s (Sinovac and/or Pfizer-BioNTech (mRNA vaccine), one to five doses), questioned them for side-effects, evaluated in three groups according to the vaccine/s they received; only Sinovac, only Pfizer-BioNTech, and both vaccines.

Results: Arm pain, generalized weakness, myalgia, and fever were common side effects both in IEI-P and HC groups. Generalized weakness/fatigue, fever, and palpitation, were significantly frequent in IEI-P who experienced COVID-19 compared to those who did not (p=0.021, p=0.047 and p=0.024, respectively). The side effects according to first vaccination type were shown in Figure 1 . 29.7% of the IEI-P had immune dysregulation (ID) (inflammatory/ autoimmune diseases). We compared the side effects in IEI-P with and without ID, and found no difference except headache (p=0.015), chills (p=0.047), nausea (p=0.048), palpitation (0.027), and heat/cold intolerance (p=0.002). Two IEI-P were hospitalized after vaccination because of ID (new-onset splenomegaly and pancytopenia) and COVID-19, respectively. Severe symptoms after vaccination, new-onset splenomegaly and pancytopenia, urticaria, herpes simplex virus (HSV), and varicella zoster virus (VZV) reactivations were seen in four IEI-P (2.8%), were shown in Table 1.

Conclusion: We suggest that IEI-P mRNA vaccination is relatively safe compared to conventional vaccine type. Severe symptoms were seen in 2.8% of IEI-P. Individuals who experienced uncommon side-effects should undergo immunological screening, since they may have genetic polymorphisms affecting the immunity.

POSTER 73 - FIRST CASE OF AUTOSOMAL RECESSIVE STAT1 PARTIAL DEFICIENCY ASSOCIATED TO COVID-19 IN SENEGAL

AUTHORS

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AFFILIATIONS

[1]Institute for Health Research, Epidemiological Surveillance and Training (IRESSEEF), [2]Albert Royer National Children's Hospital Center, [3]Paris Cité University, Imagine Institute, [4]National Blood Transfusion Center

Biography:
I am Dr Mame Sokhna Guèye, a former hospital intern who graduated in pharmacy in 2013 from Cheikh Anta Diop University in Dakar, where I also obtained my DES in clinical biology and my master's degree in immunology, in 2019. Since 2014, we have been working with clinicians to diagnose primary immunodeficiencies, for which I am responsible for biological aspects. This enabled me to be a facilitator at the A-Biol project workshop in 2015 and the ASID congress in Dakar in 2019. I am currently interested in Mendelian susceptibility to mycobacterial infections, which is the subject of my PhD thesis in my host laboratory, IRESSEF. In collaboration with Paris IMAGINE institute, I spent three doctoral mobility periods from a grant offered by the French Embassy in Senegal.

Background: The human signal transducer and activator of transcription 1 (STAT1) was the first member of STATs family identified as a key molecule required for cellular responses to type I, II and III interferons. Germline variants in human STAT1 cause four types of inborn errors of immunity among them autosomal recessive (AR) partial STAT1 deficiency. Here we report a patient with AR partial STAT1 deficiency, with a history of BCG-osis and COVID-19 pneumonia.

Case report: The index patient was a 5 month-old female infant born at term to second degree consanguineous parents. She had no history of IEI and received all vaccinations in accordance with the Senegalese expanded immunization program. Few weeks after BCG vaccination, the patient presented a BCG-osis.
Routine blood tests (Table1) showed hyperleukocytosis (neutrophils 40.17 G/L; lymphocytes 10.80 G/L; monocytes 5.13 G/L), an increase of C reactive protein CRP: 404.5 mg/L and elevation of IgG: 15.87 g/L and IgM: 1.31 g/L rates. Examination of bronchoalveolar fluid by Genexpert MTB was negative for M. tuberculosis complex. Histological examination from skin biopsies undertaken at the axillary lymph node revealed the presence of tuberculoid granulomas on the two biopsies, compatible with a diagnosis of cutaneous mycobacterial infection. Anti- tuberculosis treatment was done for 6 months. During her follow-up, she suffered from severe pneumopathy during the COVID-19 pandemic; she presented an acute respiratory distress, leading to hospitalisation and intensive care unit admission. She recovered few days after. PCR for COVID-19, performed during hospital admission, was negative, however, positive SARS- CoV2 immunoglobulins were detected eight months later (Table 2). Genetic study revealed a homozygous variant in exon 23 of STAT1 corresponding to a substitution c.2086C>T. Sanger sequencing confirmed homozygosity for the mutation in the index patient and heterozygosity for the other family members (Fig 1). In Africa, cases of MSMD have been reported in Algeria, Egypt, Ethiopia, Morocco, South Africa and Tunisia (Fig 2). This patient is the first with AR STAT1 deficiency associated with severe COVID-19 pneumonia. The favourable outcome of the SARS-CoV2 infection here is probably explained by the residual STAT dependent cellular response to type I/III IFNs.

Conclusion: We thus encourage consider MSMD (or even tuberculosis) in the differential diagnosis in Senegal. As BCG vaccination is mandatory in infants at birth, it should be delayed in siblings of affected children until a genetic diagnosis has been made.
Keywords: mycobacteria; COVID-19; BCG-osis; STAT1 deficiency

POSTER 75 - IMPACT OF COVID-19 PANDEMIC ON CLINICAL CARE OF PATIENTS AND PSYCHOSOCIAL HEALTH OF AFFECTED FAMILIES WITH CHRONIC GRANULOMATOUS DISEASE: AN OBSERVATIONAL STUDY FROM NORTH INDIA

AUTHORS

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Biography:
Dr Prabal Barman completed his graduation (MBBS) from Gauhati Medical College, Guwahati, Assam, India (2015) and post-graduation (MD) in Paediatrics from Advanced Paediatrics Centre, Post Graduate Institute of Medical Education and Research, Chandigarh, India (2020). He is currently pursuing a 3-year post-doctoral (DM) training programme in Paediatric Clinical Immunology and Rheumatology at the Advanced Paediatrics Centre, Post Graduate Institute of Medical Education and Research, Chandigarh, India and is likely to complete it in December 2023. This is the first, and till date the only, such post-doctoral training course in Paediatric Rheumatology in India.

He aspires to continue in an academic institute after his training and has 12 publications till date in reputed journals. In addition to medicine, he has a keen interest in extra-curricular activities and has a Bachelor's degree in Indian classical music (Vocal) and a Diploma in Water and Oil painting.

Objective: Day-to-day clinical management of patients with inborn errors of immunity, including chronic granulomatous disease (CGD), has been affected by the Coronavirus disease-2019 (COVID-19) pandemic. There is a dearth of information on impact of this pandemic on clinical care of children with CGD and psychological profile of the caretakers. We aimed to describe the difficulties and psychological status of parents/caregivers of children with CGD during COVID- 19 pandemic, from the perspective of a developing country. We also report the clinical manifestations of COVID-19 infection and its resultant complications in our cohort of CGD from North India.

Design and methods: Case records of patients with CGD and concomitant COVID-19 infection/complications attending Pediatric Immunodeficiency Clinic of our Institute were analyzed in detail. Parents and caretakers of CGD patients (n = 21) and 21 healthy adults with similar ages and genders, were also evaluated on the following scales and questionnaires: COVID-19 Fear Scale (FCV 19S), Impact of Event Scale (IES-R), Depression, Anxiety, and Stress Scale (DASS 21), Preventive COVID-19 Behavior Scale (PCV 19BS) and a 'COVID-19 Psychological wellbeing questionnaire'.

Results: Among the 101 patients with CGD followed up at our Centre, 5 children developed infection/complications associated with COVID-19. Four of these children had a mild clinical course, while 1 child developed features of multisystem inflammatory syndrome in children (MISC) requiring intravenous glucocorticoids.
Median age of the parents/caregivers was 41.76 years (range: 28-60 years). Male: female ratio was 2:1. In the study group, 71.4% had higher IES-R, DASS21, FCV 19S and PCV 19BS scores. The caregivers had a high prevalence of stress, anxiety, avoidance behavior, and depression compared to controls ($p < 0.001$). Sub-group analysis revealed that parents/caregivers having intermediate level education, elementary occupation, and low-income were more stressed than those who were graduate/post graduates or those who were skilled professionals and had a higher income ($p < 0.05$).

Conclusion: Children with CGD have had predominantly mild infection with COVID-19; however, caregivers/parents of these children were at risk of developing psychological distress. COVID- 19 pandemic has brought to light the importance of patients' and caretakers' mental health which needs periodic assessment and appropriate interventions. Future studies should evaluate psychological interventions such as psychoeducation, cognitive behavioural therapy, counselling and family therapy, and socio-economic risk factors with a larger sample size in patients with CGD and their caregivers/parents.

POSTER 86 - SPECIFIC CELLULAR AND HUMORAL IMMUNE RESPONSES TO THE NEOANTIGEN RBD OF SARS-CoV-2 IN PATIENTS WITH PRIMARY AND SECONDARY IMMUNODEFICIENCY AND HEALTHY DONORS

AUTHORS

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[2]Department of Medical Oncology, Hospital Clínico San Carlos, Calle Profesor Martín Lagos SN, 28040

Biography:
My name is Kauzar and I am a third-year resident in immunology at Hospital Clinico San Carlos in Spain. I am currently doing my doctoral thesis about SARS-CoV-2.

Patients with antibody deficiency disorders, such as primary immunodeficiency (PID) or secondary immunodeficiency (SID) to B-cell lymphoproliferative disorder (B-CLPD), are two groups vulnerable to developing the severe or chronic form of coronavirus disease caused by SARS-CoV-2 (COVID-19). Herein, we analyzed spike-specific IFN-γ and anti-spike IgG antibody responses at 3 to 6 months after exposure to SARS-CoV-2 derived from vaccination and/or infection in two cohorts of immunodeficient patients (PID vs. SID) compared to healthy controls (HCs). Pre-vaccine anti-SARS-CoV-2 cellular responses before vaccine administration were measured in 10 PID patients. Baseline cellular responses were detectable in 4 out of 10 PID patients who had COVID-19 prior to vaccination, perceiving an increase in cellular responses after two-dose vaccination ($p < 0.001$). Adequate specific cellular responses were observed in 18 out of 20 (90%) PID patients, in 14 out of 20 (70%) SID patients and in 74 out of 81 (96%) HCs after vaccination (and natural infection in some cases). Specific IFN-γ response was significantly higher in HC with respect to PID (1908.5 mUI/mL vs. 1694.1 mUI/mL; $p = 0.005$). Whereas all SID and HC patients mounted a specific humoral immune response, only 80% of PID patients showed positive anti-SARS-CoV-2 IgG. The titer of anti-SARS-CoV-2 IgG was significantly lower in SID compared with HC patients ($p = 0.040$), without significant differences between PID and HC patients ($p = 0.123$) and between PID and SID patients ($p = 0.683$). High proportions of PID and SID patients showed adequate specific cellular responses to receptor binding domain (RBD) neoantigen, with a divergence between the two arms of the adaptive immune response in PID and SID patients. We also focused on the correlation of protection of positive SARS-CoV-2 cellular response to omicron exposure: 27 out of 81 (33.3%) HCs referred COVID-19 detected by PCR or antigen test, 24 with a mild course, 1 with moderate symptoms and the remaining 2 with bilateral pneumonia that were treated in an outpatient basis. Our results might support the relevance of these immunological studies to determine the correlation of protection with severe disease and for deciding the need for additional boosters on a personalized basis. Follow-up studies are required to evaluate the duration and variability in the immune response to COVID-19 vaccination or infection

POSTER 119 - MONITORING OF IMMUNOGLOBULIN TREATMENT COMPLIANCE OF PATIENTS WITH AN INBORN ERROR OF IMMUNITY DURING THE PANDEMIC PERIOD

AUTHORS

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Biography:
Dr. Yasin Karali

Division of Pediatric Immunology, Uludag University Faculty of Medicine, Bursa, Turkey

Background and objective: During the coronavirus 2019 (COVID-19) pandemic, significant challenges were encountered in the management of patients with chronic diseases. This study aims to evaluate the effects of the pandemic on follow-up and adherence to treatment in patients receiving immunoglobulin replacement therapy.

Design and methods: Changes in the treatment modalities of patients who received immunoglobulin replacement therapy between March 2020 and September 2021 were examined. An online message line was established with our patients under the control of nurses and doctors, and the rate of using this communication system was recorded.

Results: A total of 169 patients, 93 male, and 76 female, were included in the study. Of the patients, 124 (73.4%) were receiving IVIG, and 45 (26.6%) were on SCIG treatment. Although all patients in the subcutaneous treatment group continued the treatments regularly, this rate was 80.6% in the IVIG group. During the pandemic period, it was observed that 24 patients interrupted immunoglobulin treatment for various reasons. The most common reason for stopping treatment was fear of being in the hospital because of the risk of COVID-19 transmission. Patients who received subcutaneous treatment took a long break from their hospital controls, although they applied their treatments properly at home. Routine immunoglobulin trough values were able to be measured in only 17 (37.7%) of patients who were on SCIG. In the presence of any symptoms, the rate of contacting our nurse or doctor team using the online message line was 100% in SCIG patients, while 48.3% in IVIG patients.

Conclusion: In the pandemic, the immunoglobulin treatment method should be individualized according to patient characteristics and expectations. Communication with the tele-health service has become a critical monitoring method for patients with chronic disorders.

POSTER 131 - INCREASED RISK OF COVID-19–RELATED HOSPITALIZATION AND MORTALITY IN VACCINATED INDIVIDUALS WITH PRIMARY IMMUNODEFICIENCY DISEASE: INITIAL RESULTS FROM INFORM, A RETROSPECTIVE STUDY USING ENGLISH NATIONAL HEALTH SERVICE DATA-SETS

AUTHORS

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Biography:
Jurgens Peters completed his undergraduate medical degree from the University of Stellenbosch, South Africa. He obtained an MPH from the University of Liverpool, MsC in Tropical Medicine and International Health from LSHTM and an MBA from the CJBS, University of Cambridge. He began his academic career as a Clinical Research Fellow at LSHTM, where he led the South African arm of the STAMP trial, investigating the impact of urine-based TB screening tools among hospitalized HIV patients. He has held several positions in global pharmaceutical and biotechnology firms. He currently leads the UK Medical Affairs division, Vaccines and Immune Therapies, at AstraZeneca.

Objectives: Patients with primary immunodeficiency disease (PID) may have suboptimal cellular and humoral responses to COVID-19 vaccination. Therefore, they remain at high risk of severe outcomes even after booster vaccinations. We report initial results from the INFORM study on severe COVID-19 outcomes in vaccinated patients with PID.

Methods: COVID-19–related hospitalization incidence rates (IR) per 100 patient years (PY) and mortality rates (MR) were estimated for the overall population (OP) of fully vaccinated (≥3 doses) people aged ≥12 years in England, using a random 25% sample from National Health Services electronic health datasets (Jan 1, 2022–Dec 31, 2022). Unadjusted and age- and sex-adjusted IR ratios (IRR) and MR ratios (MRR) and 95% confidence intervals (95% CI) were estimated to compare patients with PID vs without PID. A subset of patients with moderate-severe PID was analyzed separately.

Results: Results are shown in Table 1. Of 7,180,205 fully vaccinated people (the OP), 7,295 had a PID. Patients with PID had 10-fold higher risk for COVID-19–related hospitalizations and for deaths than the OP. Unadjusted IR for hospitalization was 0.22 PY (95% CI 0.21–0.23) in the OP vs 2.28 PY (95% CI 2.05–2.51) among patients with PID, and the adjusted IRR was 7.74 (95% CI 6.59–9.10). Unadjusted MR was 0.05 (95% CI 0.04–0.06) in the OP vs 0.54 (95% CI 0.31–0.77) in patients with PID, and the adjusted MRR was 7.66 (95% CI 5.48–10.72). Among patients with moderate-severe PID, the adjusted IRR for hospitalization was 13.18 (95% CI 8.6–20.19), and the adjusted MRR was 12.24 (95%CI 1.50–33.28).

Conclusions: Despite full COVID-19 vaccination, patients with PID had more than 7 times the rate of severe COVID-19 outcomes than patients without PID. Further analysis of these data will help elucidate the interaction between PID and associated therapies in determining risk for severe COVID-19 outcomes. These initial results indicate that vaccinated patients with PID may benefit from additional interventions.

Funding: AstraZeneca

POSTER 163 - LONG-TERM IMMUNOGENICITY, CLINICAL OUTCOMES AND SAFETY OF PRIMARY AND BOOSTER VACCINATION WITH BNT162B IN PATIENTS WITH COMMON VARIABLE IMMUNODEFICIENCY

AUTHORS

Milota T[1], Smetanova J[1], Rataj M[1], Lastovicka J[1], Bartunkova J[1]

AFFILIATIONS

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Biography:
Tomas Milota is a postdoc and clinical researcher at the Department of Immunology, Motol University Hospital in Prague (the Czech Republic). His research and clinical practice focus on primary antibody deficiencies, immune system dysregulation, and non-infectious complications, B cell functions, and vaccination.

Background: Common variable immunodeficiency is a heterogeneous group of disorders characterized by impaired immunoglobulin production, immune system dysregulation, increased susceptibility to infections, and a spectrum of non-infectious complications. Patients with CVID are also regarded as a high risk for a severe course of COVID-19. Due to poor immune system function efficacy and safety of mRNA vaccines is questionable.

Methods: Prospective observational study with 21 patients fulfilling diagnostic criteria for CVID who were vaccinated with three doses of mRNA vaccine BNT162b2. Immunogenicity (anti-RBD SARS CoV-2 specific antibodies detected by chemiluminescence, detection of virus- neutralization antibodies), clinical outcomes (RT-PCR SARS-CoV-2 positivity after vaccination), and safety () have been observed from March 2021 to June 2022. Virus-specific antibodies were also detected in immunoglobulin replacement therapy (IRT).

Results: Despite the high response rate (52.4% after primary, 72.2% after booster vaccination), the mean concentration of anti-RBD antibodies was reduced compared to healthy donors (574.4 U/mL vs. 870 U/mL one month after primary, 302.6 U/mL vs. 1949 U/mL after booster vaccination respectively). Moreover, the immunogenicity was limited by rapid waning and low titers of virus-neutralizing antibodies. Nevertheless, we did not observe any severe cases of COVID-19 in vaccinated patients. The non-responders were characterized by higher age, lower serum levels of IgM, and lower counts of class-switched B cells. We also showed the contribution of passively transmitted antibodies from IRT. No severe adverse event (SAE) was reported after vaccination. Local reactions such as pain or exanthema at the site of injection prevailed.

Conclusion: Despite the rapid waning of humoral response, vaccination and passively transmitted virus-specific antibodies from IRT protect against severe COVID-19. Primary and secondary vaccination is safe; no SAE was reported.

POSTER 184 - CASE REPORT: ANTI-PL12 ANTISYNTHETASE SYNDROME AFTER ADMINISTRATION OF SARS-COV-2 VACCINE IN A PATIENT WITH HLA GENETIC SUSCEPTIBILITY

AUTHORS

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AFFILIATIONS

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Biography:
2014-2017: Graduate in Biology from the Complutense University of Madrid.

2019-2023: Fourth year immunology resident at Hospital Clínico San Carlos.

2022- Present: PhD student

Objectives: Anti-synthetase syndrome (ASSD) is an inflammatory myopathy defined by the presence of autoantibodies against tRNA synthetases and heterogeneous clinical features, with interstitial lung disease (ILD) as one of the classificatory criteria. Several environmental and genetic triggers have been described in ASSD. We report a case of a patient, with symptom onset and final diagnosis of ASSD two weeks after administration of the second dose against SARS-COV-2 (AstraZeneca). The aim of the study is to find a temporal relationship between the vaccine and the development of an autoimmune disease in a patient with HLA genetic susceptibility compatible with ASSD.

Design and methods: A detailed description of the clinical evolution from the onset of symptoms until one year later is given. The complementary tests requested are described: chest computed tomography (CT), microbiological study and laboratory tests including autoimmunity and HLA class I and class II genetic studies.

Results: A 60 year-old-woman with previous history of autoimmune hypothyroidism and ex- smoker for 20 years came to the emergency department in 2021 with fever, asthenia, dyspnea, productive cough, tachycardia, body itching and difficulty swallowing, two weeks after SARS- CoV-2 vaccine. CT shows bilateral pulmonary infiltrates predominantly bibasal with ground- glass opacities, which was classified as ILD with mixed pattern of non-specific interstitial pneumonia and cryptogenic organizing pneumonia that progressed to pulmonary fibrosis.
Spirometry showed a moderate restrictive pattern. PCR for SARS-CoV-2 and other viruses and sputum culture were negative, excluding infectious pneumonia. A bronchoalveolar lavage was requested, showing CD3+ T lymphocytosis (96%) at the expense of T-CD8+, with a decreased CD4/CD8 ratio (0.71). In the immunological study, there was positive ANA by IFA (titer ≥1:640) with a fine dense cytoplasmic pattern (AC-19) and a strong positive result [197 (+++)] for anti-PL12 autoantibodies by immunoblot, all compatible with a diagnosis of ASSD. Finally, in the genetic study the patient was carrier of the alleles: HLA-DRB1*03 in homozygosis and HLA- B*08 in heterozygosis, both described associated with ASSD. Treatment with prednisone and mycophenolate was started, with good clinical response.

Conclusions: The clinical and analytical results showed compatibility with a diagnosis of ASSD associated ILD that progressed to pulmonary fibrosis and the presence of positive anti- PL12 autoantibodies. Our study showed that vaccination against SARS-CoV-2 could represent a triggering factor in the development of ASSD in a patient with underlying autoimmune disease and genetic predisposition. However, more studies are needed to find the underlying immunological mechanism in these patients.

POSTER 188 - LACK OF SPECIFIC IMMUNE RESPONSES AFTER FIVE DOSES OF mRNA SARS-CoV-2 VACCINES IN A PATIENT WITH CD4-T CELL LYMPHOPENIA BUT PRESERVED RESPONSES TO CMV.
THE NEED OF BOOSTER DOSES?

AUTHORS

Alba-Cano T[1], Tato-Moreno P[1], Muñoz-Gómez S[1], Pérez de Diego R[2], García-Martínez E[1], Alonso R[3], Fernández-Cruz Pérez E[1], Gil-Herrera J[1]

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Biography:
Graduated in Biology from University of Malaga with an honors degree in my bachelor thesis. Since 2020 I am resident of Immunology in the Division of Clinical Immunology at the Gregorio Marañón Hospital (Madrid). Young investigator award in 5 edition IPIC.

Objective: As part of our cohort of 115 patients with inborn errors of immunity (IEI) reported at the 5ª edition IPIC, we have studied the long-term follow-up of a patient with T-cell immunodeficiency, who lacked both specific antibody and T-cell immune responses after SARS-CoV-2 primary vaccination.

Case report and methods: A 56-year-old male patient with recurrent infections, inflammatory bowel disease, autoimmunity, persistent CD4+ T lymphopenia with very low circulating recent thymic emigrants and oligoclonal TCR rearrangements, normoglobulinemia with anti-CMV IgG and positive anti- pneumococcal polysaccharide IgG response following vaccination, as shown in Table 1. Table 2 shows 5 heterozygous missense variants. 3 of them are located in 2 genes phenotypically related with common variable immunodeficiency and 2 variants in BTNL2 associated with susceptibility to Crohn´s disease.
Figure 1 depicts the 1st and 2nd doses and every single booster (3rd, 4th and 5th doses) of SARS-CoV-2 vaccination as scheduled by the Spanish Ministry of Health for IEI patients. We tested Spike(S)-specific serum IgG antibody levels by using Architect autoanalyzer (Abbott). In vitro memory CD4+ T-cell responses (CD25 and CD134 activation induced markers, AIM) were assessed by multicolour flow cytometry; stimulation index >2 was considered positive based on the cut-off set in our healthy control group.

Results: No S-specific IgG response was found after the two initial doses of mRNA-1273 Moderna vaccine, and a very weak trend was detected following subsequent boosters: 9.43 BAU/mL,
17.86 BAU/mL and 76.71 BAU/mL after the third (mRNA-1273, Moderna), fourth (BNT162b2, Pfizer) and fifth (Pfizer BioNTech bivalent vaccine, mRNA from original and Omicron BA.4/BA.5 strains) doses, respectively.
All S-specific CD4+ T-cells memory responses were negative, including both the WT and Omicron variants after the fifth bivalent vaccine. On the other hand, mitogen (anti-CD2-CD3- CD28 stimulation) and CMV T-cell responses were consistently found to be positive in AIM assays.
So far, the patient remains naïve to natural SARS-CoV-2 infection with repeatedly negative nucleocapsid-(N) and membrane-(M) specific CD4+ T cells memory responses.

Conclusion: D IEI patients need an individualized approach to guide SARS-CoV-2 vaccination recommendations. Other preventive strategies (different vaccine platforms, antiviral prophylaxis…) should be considered in non-responder IEI patients.
CMV T-cell immunity has remained detectable throughout this patient´s follow-up. However, immunodominant S-peptide epitopes failed to elicit a thymus-dependent response, possibly due to the oligoclonal nature of his TCR repertoire. COVID-19 pandemic has allowed us to compare most classical (mitogen, CMV) responses to SARS-CoV-2 neoantigens immunogenicity in our IEI patients.

POSTER 215 - GENETIC DIVERSITY OF HIV-1 IN BIHAR

AUTHORS

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Biography:
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Introduction: in this study, the genetic diversity of HIV-1 in Bihar was analyzed.

Methods: for this, 100 samples were collected in different regions of Bihar between 2019 and 2022. A protease and reverse transcriptase fragment were amplified and sequenced.
Phylogenetic analyses were performed through maximum likelihood and recombination was analyzed by boots canning.

Results: Ten HIV-1 subtypes (B, A1, G, D, C, and F2), Eight circulating recombinant forms (CRF02_AG, CRF25_cpx, CRF43_02G, CRF06_cpx, and CRF19_cpx), and Nineteen unique recombinant forms were identified. Subtype B (38.2%) and CRF02_AG (41.5.4%) were the predominant genetic forms.

Conclusion: a high HIV-1 genetic diversity is observed in Bihar

POSTER 224 - HUMORAL AND CELLULAR IMMUNE RESPONSE TO COVID-19 VACCINES AFTER PRIMARY VACCINATION WITH A 3-DOSE SCHEME OF HOMOLOGOUS OR HETEROLOGOUS VACCINE IN BRAZILIAN PATIENTS WITH INBORN ERRORS OF IMMUNITY COMPARED TO HEALTHY CONTROLS

AUTHORS

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Objective: Inborn Errors of Immunity (IEI) comprise a diverse set of conditions with impaired immunity to infections and (in some cases) vaccines. An increase in the life expectancy has been observed in these patients, who are followed from early in life to adulthood. SARS-CoV-2 infection can be more severe in IEI patients and protection of immunocompromised patients is a public health high priority. IEI patients demonstrate diminished responses to some vaccines.
Our aim was to evaluate humoral and cellular immune responses to Covid-19 vaccines after primary vaccination with a 3-dose scheme in Brazilian patients with Inborn Errors of Immunity (IEI) compared to healthy controls (HC).

Design and methods: We included 55 IEI patients (13-61 years) and 60 HC (13-71 years) immunized for Covid-19 using various approved regimens: two doses of inactivated SARS-CoV- 2 vaccine (CoronaVac), non-replicating viral vectored vaccine (Oxford-AstraZeneca ChAdOx1 nCoV-19) or mRNA vaccine (Pfizer-BioNTech BNT162b2), followed by a third dose of Pfizer. IEI patients and HC were sampled at various times. IEI were: 12 CVID; 6 SAD; 4 PIK3CD; 3 Hyper- IgM Syndrome; 2 XLA; 2 AT; 1 STAT1 Gain-Of-Function and 1 Combined Immunodeficiency.
We evaluated T-cell responses, Spike (S1) and nucleocapsid, with an ELISpot and humoral response by neutralizing antibody detection by ELISA.

Results: Preliminary results show 83% neutralization of RBD-Wuhan antibodies in IEI (n=30) and 98% in HC (n=42) (p=0.031, Mann-Whitney test) one month after the third dose. After three months, we observed 76% neutralization in IEI (n=27) and 97% in HC (n=42) (p<0.001, Mann- Whitney test). The antibody responses in IEI declined three months after the third dose (p=0.045, Wilcoxon test) and it was not observed in HC. T-cell responses were comparable between patients and HC. After three months (IEI n=22; HC n=22), S1 positivity was 63.6% of IEI and 81.8% of HC (p=0.176, Chi-squared test); to nucleocapsid, 31.8% of IEI and 40.9% of HC (p=0.531, Chi-squared test). After three Covid-19 vaccine doses, no individuals in either group had severe disease. IEI had 29% and HC had 22% confirmed SARS-CoV-2 infections before and during sample collections.

Conclusion: IEI patients with predominantly humoral deficiency disorders responded to a 3- dose SARS-CoV-2 immunization with a T-cell response that is maintained for up to three months, similar to HC. Antibody responses appeared to decline more rapidly in patients with IEI. Specific cellular immunity may be involved in the protection of individuals with IEI against severe disease, hospitalization and death.

POSTER 225 - LONG COVID DISEASE IN A PATIENT WITH COMMON VARIABLE IMMUNODEFICIENCY AND A DNA REPAIR DEFECT: A POSSIBLE ASSOCIATION ?

AUTHORS

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Biography:
Jimena María Gómez, started the speciality of Clinical Immunology at Hospital Universitario Gregorio Marañón in 2019 and during her training period she started the clinical trials activity of the Clinical Immunology Unit, having reached an experience that has qualified her to be included as a researcher member of the INSIGHT group and more recently of the INSIGHT/STRIVE group of the NIAID/NIH/USA. These clinical trials have recruited patients with COVID 19 and influenza A and B and have investigated the pathology and treatment of these infectious diseases. She has performed the collection of biological samples and their preparation in the laboratory for genetic, cellular and humoral immunological and serological studies.

She has participated in International meetings of Clinical Immunology, mainly in those organized by the European Society of Immunodeficiencies(ESID) having contributed with scientific abstracts of clinical impact in the meetings of ESID (Gothenburg 2022) and International Primary Immunodeficiency Congress, (IPIC) (Villamoura 2022) and in the annual congresses of the Spanish Society of Immunology, SEID. Spanish Society of Immunology, SEI: 44th SEI Congress (2023) with publication of a clinical case.

Objectives: A female patient 60 years old who was diagnosed of long COVID, presented mild SARS-COV-2 disease with positive RT-PCR (January 2021) three days after vaccination. After 4 weeks developed clinical progression with severe fatigue, shortness of breath, heart palpitations and neuropathy, followed 2 months later by cognitive alterations (memory disturbances). After twelve months (December 2021) a subsegmentary TEP (TAC image). A second mild infection by SARS-COV-2 was detected (June 2022) with positive PCR which remained positive till September 2022 with persistence of symptoms.

The patient with post-acute COVID- 19 syndrome was evaluated for immunological dysfunction which included IgG and IgA hipogammaglobulinemia and evaluation of antibody deficiency. The patient has a history of bronchiectasis with recurrent upper respiratory tract infections. Those symptoms and immunological alterations are compatible with diagnosis of Common Variable Immunodeficiency (CVID).
We also studied genetic determinants of disease. Susceptibility to viral infection by SARS COV 2 with slower viral elimination has been described associated with genetic defects.

Design and methods: Microbiology diagnosis was performed using RT-PCR in nasopharingeal, urine and stool samples. For the CVID diagnosis, inmunological celular and humoral parameters were analysed by Flow Cytometry and Nephelometry techniques.

The genomic study was performed using genomic DNA obtained from peripheral blood. The clinical exome was evaluated using the capture-based Next Generation Sequencing Clinical Exome Solution® v2 kit (SOPHiA Genetics) that covers the coding regions and splicing junctions of 4,727 genes related to rare and inherited conditions.

Results: we have identified by NGS a pathological variant in the gene RAD51D, which encodes an enzyme involved in DNA repair and homologous recombination. The heterozygous variant identified is a frameshift deletion (NM_002878.4(RAD51D):

c.94_95del) leading to a premature stop codon (NP_002869.3: p.Val32Phefs*32) (rs786203137), and considered a susceptibility factor for familiar ovarian/breast cancer. Twenty-one proteins involved in DNA repair are considered to be associated to inborn errors of immunity causing syndromic and non-syndromic combined immunodeficiencies. DNA repair proteins are essential for the development of adaptive cellular and humoral immunity during viral infections.

Immunological tests have identified a deficiency of production of anti-pneumoccocal polysaccharide antigens after vaccination (4,8mg/dL and 9,3mg/dL post-vaccination), with hypogammaglobulinemia IgG, IgG1 and IgG2, and IgA.

Conclusions: We have hypothesized that in our patient with SARS-COV-2 infection the DNA repair defects together with antibody deficiency and poor humoral immunity could be associated with the defective clearance of the virus SARS-CoV-2 and the post -acute COVID-19 syndrome.

POSTER 260 - FLU VACCINATION IN HIGH-RISK CHILDREN: PARENTAL SURVEY AT A THIRD-LEVEL HOSPITAL

AUTHORS

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Biography:
He conducted studies on deletion22 syndrome -

Study Project ongoing on "Vaccination in High-risk children".

Objectives: The aim of this study is to assess the compliance of families of high-risk children with flu- vaccination, adherence to the specific vaccinations planning, knowledge and attitude regarding natural infections, perception of vaccine safety and causes of vaccine hesitation.

Design and methods: By means of a questionnaire we explored the knowledge, attitudes and adherence to influenza vaccination of the parents of 168 high-risk pediatric patients under the care of one of the specialist (immunology, diabetology, cardiology, cystic fibrosis, nephrology, hematology, rheumatology, gastroenterology and hepatology unit).

Results: 42.3% of parents stated that their child had not been vaccinated against influenza, mainly because it was not recommended by doctors (40.8%) or because they perceived a low risk for their child (19.7%). Almost 80% of respondents were confident about the safety of vaccination, and 63.4% would be willing to change their minds after a discussion with an immunology specialist. The main association factor for no-flu vaccination is acquired immunosuppressive state ($p < 0.001$). Only in 29.8% - 44.3% of cases were both parents or other cohabiting children vaccinated, respectively.

Conclusion:
These data show that parents of high-risk children, but perhaps also medical specialists, do not perceive the risk of influenza infectious disease and do not consider flu-vaccination prevention part of the overall care of frailty. Parents do not receive adequate information about both the increased susceptibility of their children to seasonal infections and the possibilities of prevention. Adequate attention and care for vaccinations in the high-risk individuals and their families should be considered part of the global care.

POSTER 267 - DURABILITY OF IMMUNE RESPONSE AFTER ANTI-SARS-COV-2 MRNA BOOSTER VACCINATION IN PATIENTS WITH COMMON VARIABLE IMMUNODEFICIENCY

AUTHORS

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Biography:
Internist specialized in Inborn Errors of Immunity. Referring physician and consultant for adult patients with primary immunodeficiency disorders and autoinflammatory syndromes. Referring doctor for ERN RITA at Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico of Milan, Italy.

Background: Maintaining durable immunity following vaccination represents a major challenge also in healthy people, but whether mRNA booster vaccination improves durability is mainly unknown.
Common Variable Immunodeficiency (CVID) disorders have a spectrum of B and T-cell defects that cause a defective antibody response. Both the response and the durability of humoral and cellular responses to the currently used COVID-19 mRNA vaccines remain to be elucidated.

Aim: This study evaluates the immune response along time after COVID-19 mRNA booster vaccination and/or COVID-19 infection in CVID patients.

Patients & methods: Patients with CVID enrolled have been diagnosed according to ESID criteria. They have been vaccinated with anti-SARS-CoV-2 mRNA vaccines. The quantitative detection of serum Ig against the SARS-CoV-2 Spike (S) protein receptor binding domain and a quantitative IFN- gamma production as a surrogate of the T-cell response have been measured.

Results: We analysed 60 CVID patients who underwent primary cycle vaccination. All the patients were receiving replacement therapy and tests of the infused immunoglobulin products showed no detectable levels of anti-Spike Ig until six months after the second dose. Before receiving the first vaccine dose, 11 had COVID-19. 4-weeks after the primary cycle, 46 were responders. The median Ig anti-S level was 609U/mL. It was higher in the 11 previously infected patients than in the uninfected (4302 vs 297.5U/mL).
Six months after the primary cycle, the Ig anti-S titre of the overall subjects dropped to a median level of 313U/mL. After the vaccine booster dose, the overall median Ig anti-S level raised to 3442U/mL and the differences between the previously infected and uninfected patients reduced (3680 vs 2867.5, respectively). Nine patients remained not-responders after 3 vaccine doses.
The SARS-CoV-2-T-cell responses analysis showed that 78.3% patients maintained a positive cellular response before the booster dose, almost unchanged after it. Six subjects remained not- responders.
3-4 months after the booster dose, 21 patients (35%) got SARS-CoV-2 infection, mostly omicron variants. The analysis of the response to the 2nd and 3rd booster vaccine doses is ongoing.

Conclusion: The CVID patients' levels of anti-SARS-CoV-2 Ig dropped significantly after the primary cicle. The booster dose produced an antibody response in several. This strengthens the indication for the 2nd booster, while for those who have not responded to the third dose, monoclonal prophylaxis is recommended. The 78.3% of had a positive T-cells response before the booster, that remained after, consisting with the maintenance of the T-cell response over time.

BASIC AND TRANSLATIONAL RESEARCH FINDINGS

POSTER 37 - COMPARATIVE STUDY BETWEEN THE DIFFERENT CROSSMATCH TECHNIQUES BY MICROLYMPHOCYTOTOXICITY, FLOW CYTOMETRY, LUMINEX AND VIRTUAL CROSSMATCH

AUTHORS

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Biography:
i'm dr hamza bakhouche, i've got my Pharm D degree in 2017, afterwars i've pursued a residency program in medical immunology at pasteur institute of algeria, graduated as spaecialist in 2022after five years of resiency program, actually i'm working in m'sila hospital in algeria as central laboratory chief.

Introduction: DSA is associated with different types of rejection and less short- and long-term graft follow-up. There are several techniques and approaches to highlight them, namely virtual CXM, FCXM, CXM LUM and CXM LCT.
Material and methods: This is a diagnostic accuracy study on 35 recipient-donor couples, carried out at the level of the immunogenetics and transplantation laboratory of the Department of Immunology of the Pasteur Institute of Algeria, and whose main objective is to compare between the different crossmatch techniques namely: FCXM, CXM LCT, CXM LUM and virtual CXM, and a secondary objective to establish a positivity threshold for FCXM specific to the laboratory. For each FCXM, an FCXM with negative control is carried out in parallel, then thresholds (mean + 2SD) and threshold ratios (threshold / average) were carried out for the MFI and the median.

Results: there is no correlation between the MFIs of class I DSAs and the parameters of FCXM T (MFI, median and ratios), on the other hand, we find a significant correlation between the MFIs of class II DSAs and the ratios, based on the cutoffs established by the negative control, only 1 FCXM T is positive using the cutoff MFI, the median cutoff and the cutoff MFI ratio, while no FCXM B is positive, the best cutoff according to the curve ROC is the cutoff MFI for FCXM T (sensitivity = 50%, specificity = 79.31%) and the median cutoff for FCXM B (sensitivity = 75%, specificity = 58.06%), comparing the FCXM T with the CXM LCT, we found a sensitivity of 75% with a specificity of 77.42%. For CXM LUM class I, the sensitivity is 16.65% and the specificity is 93.1% for comparison with class I AEDs, and a specificity of 50% and specificity 70.97% for the comparison of CXM LUM class II with class II AEDs, if comparing CXM LUM class I with CXM LCT the sensitivity is 25% and the specificity is 93.55%.

Conclusion: flow Cytometry currently offers a high-performance, highly sensitive tool that helps the smooth running and success of kidney transplants by highlighting low titers of donor specific alloantigens antibody that are not always detected by the donor. Classical techniques. However, this technique is not yet standardized and the interpretation of the results differs from one laboratory to another, which means that each laboratory must establish a validation phase of the technique.

POSTER 106 - OVERLAP IN IMMUNOGLOBULIN LEVELS AND PRESENCE OF BRONCHIECTASIS BETWEEN UNCLASSIFIED PRIMARY ANTIBODY DEFICIENCY AND COMMON VARIABLE IMMUNODEFICIENCY PATIENTS IN THE EUROPEAN SOCIETY FOR IMMUNODEFICIENCIES ONLINE REGISTRY BASED UNPAD STUDY

AUTHORS

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Biography:
Professor de Vries is a pediatric immunologist specializing in inborn errors of immunity (IEI) with focus on unclassified primary antibody deficiencies (unPADs). Research topics: quality and organisation of care; awareness, recognition and early diagnosis of IEI; prediction modeling using real-world healthcare data.

Objective: Primary antibody deficiency (PAD) patients, especially without a monogenetic origin, often remain undiagnosed for years. They comprise the largest, most heterogeneous group. Patient's and doctor's delay in the diagnosis can be considerable, risking complications like bronchiectasis. The IUIS defined subgroups based on immunoglobulin levels supplemented with comorbidities and specific antibody responses (if available), with CVID identified separately, as the most severe group. In the ESID online Registry, patients are labelled 'unclassified primary antibody deficiency' (unPAD) if they do not completely fulfill one of the PAD definitions. Not much is known about the relation between immunoglobulin levels and the risk of developing bronchiectasis in these patients. The (ongoing) unPAD study was started to investigate these patients further. In this analysis of the unPAD data, we answer the following two research questions: 1. is there overlap between immunoglobulin levels in the unPAD and the CVID patients, and 2. is there a relationship between immunoglobulin levels and bronchiectasis in the unPAD and/or the CVID patients.

Design and Method: Data from level 1 and level 2 (unPAD) forms in the ESID online Registry from 11 participating centers were extracted and analyzed. From 871 fully monitored PAD patients with no known genetic defect (except TACI) and no clinically apparent cellular immunodeficiency, available data on immunoglobulin levels and bronchiectasis (HRCT scan) outcomes were analyzed using principal component analysis (PCA), hierarchical clustering, and visualization with violin plots in R.

Results: In 98% of the 871 patients an IgG, IgM and IgA level, and in 84% IgG subclasses were available. Pneumococcal polysaccharide response was available in only 21% of patients. We found considerable overlap in immunoglobulin levels between patients diagnosed (according to the ESID Registry criteria) as unPAD (n=327) or as CVID (n=260); it was not possible to separate these into clear subgroups based on immunoglobulin values alone.
Detailed HRCT data [scored according to PMID: 30905051] were available in only 20% of patients; hierarchical clustering did not identify clear subgroups in these data. We also found overlap in the presence of bronchiectasis between patients with unPAD and with CVID.

Conclusions: The majority of unPAD study patients were not fully analyzed for antibody deficiency (no specific antibody response tested). It was not possible to define clear PAD subgroups in this cohort based on immunoglobulin values alone. We found overlap in bronchiectasis between unPAD and CVID patients, showing that unPAD could also be a serious condition.

POSTER 125 - INFUSING SUBCUTANEOUS IMMUNOGLOBULINS - COMPARISON OF THE CONSTANT FLOW SYSTEM (CFS) AND CONSTANT PRESSURE SYSTEM (CPS)

AUTHORS

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Biography:
Anna Majapuro-Hirvonen has worked in pharma and medical device industry for over 20 years on a wide array of therapeutic areas and projects including infusions, pain management, and vascular access. Anna holds a BS in Nursing and MBA in Global Marketing. She is a Registered Nurse and midwife.

Objectives: The objective of this scientific review is to compare the safety and efficacy of two types of infusion systems available for subcutaneous immunoglobulin (SCIG) administration: constant flow systems and constant pressure systems.

Design and Methods: We conducted a review of the literature on the safety and efficacy of constant flow and constant pressure systems for SCIG administration. We also compared the technical characteristics, ease of use, and safety parameters of these two types of infusion systems.

Results: Our review of the literature showed that both constant flow and constant pressure systems can be effective for SCIG administration. However, constant pressure systems offer the advantage of ease of operation, lack of reliance on batteries or electricity, and no need for annual maintenance while constant flow systems offer more precise control over the infusion rate and have an occlusion alarm to alert healthcare providers to high infusion pressure.
Additionally, constant pressure systems have a lower maximum operating pressure of 15 psi, which may reduce the risk of local infusion site reactions caused by high pressure. The constant pressure acts as a safety feature of the device and allows the system to automatically decrease the flow rate if there is an increase in backpressure resistance at the patient infusion site during the infusion.

Conclusions: The choice between constant flow and constant pressure systems for SCIG administration should be based on several factors, including ease of use, maximum operating pressure, and safety parameters. While both systems have their advantages and disadvantages, constant pressure systems may be preferable for some patients due to their ease of use and lower maximum operating pressure. However, constant flow systems may be more suitable for patients who require more precise control over the infusion rate. Ultimately, the choice of infusion system should be individualized based on the patient's needs and preferences, as well as the healthcare provider's experience and judgment. Careful selection and monitoring of infusion parameters can help ensure safe and effective SCIG therapy regardless of the system chosen. Further research is needed to compare the efficacy, safety, and patient preference of these two infusion systems in larger patient populations.

POSTER 135 - INVESTIGATION ON HYPER-IGE STAT3-DN PATIENTS' CD4+ T LYMPHOCYTES AND THEIR RESPONSES TO "OLD FRIENDS" PATHOGENS

AUTHORS

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Biography:
Internal Medicine specialist, MD and PhD, both clinical and research doctor. Referreal physician for adults with Inborn Errors of Immunity (both primary immunodeficiencies and autoinflammatory disorders), lead of ERN-RITA Centre in Fondazione IRCCS Ca' Granda Ospedale maggiore Policlinico of Milan, Italy

Autosomal dominant Hyper-IgE syndrome (AD-HIES) is caused by dominant negative (DN) mutations of STAT3 gene, a transcription factor that is critical for T-cell differentiation and consequently for the correct functioning of the immune system. AD-HIES patients present recurrent, severe and chronic infections by S. aureus and C. albicans, severe chronic eczema and serum high levels of IgE. While the reasons for the aberrant IgE production are incompletely understood, pathogens persist because T-cells of AD-HIES patients are unable to produce key pro-inflammatory cytokines, namely Interleukin (IL)-17.

Objective: To investigate the human immune responses to pathogens in AD-HIES patients with STAT3-DN mutation.

Design and methods: In peripheral blood of both healthy donors and AD-HIES-DN patients, we detected the presence of CCR6+ CD4+ T cells (CCR6sp) which lacked Th17- and TFH- differentiation-associated surface markers and gene expression, then responses to pathogens were tested. We performed an unbiased analysis, based on the use of FlowSOM clustering and dimensionality reduction technique UMAP.

Results: STAT3-deficient CD4+ cells had impaired IL-17A production as expected, but produced B- helper cytokines like IL-10 and IL-21 normally. Furthermore, STAT3-deficient CD4+ cells expressed reduced but detectable Th17 associated surface markers such CCR6 and CD161. CD4+ T cells could acquire IL-17A production in vitro, although with a lower efficiency then STAT3-sufficient cells. AD-HIES patients have a severe, but not complete defect in Th17-cell differentiation. Unbiased analysis indicated that there was an increased number of naïve CD4+ T cells in AD-HIES patients compared to healthy donors, suggesting a defect in the differentiation of CD4+ lymphocytes.
To better understand the defects of STAT3-deficient cells, we evaluated their ability to response to antigens belonging to pathogens, such as S. Aureus, S. Pneumonia and C. Albicans, that cause recurrent infections in AD-HIES patients. Compared to healthy donors, STAT3-deficient CD4+ cells show an increased production of both pro- (IFN-γ and IL-2) and anti- (IL-10) inflammatory cytokines in response to heat killed S. Aureus and S. Pneumoniae.

Conclusions: These data suggest that STAT3-deficient CD4+ cells are not unresponsive to pathogens but, at the same time, underline the presence of an altered cytokine production compared to healthy donors.
Our results represent an opportunity to understand the role of STAT3 in human immune responses and they could pave the way for novel therapies to control opportunistic infections (adoptive transfer of autologous, in vitro generated, pathogen-specific Th17-cells) in AD-HIES patients.
Acknowledgement to all the AD-HIES patients in Milan. Research Project funded by Telethon Grant.

POSTER 144 - FUNCTIONAL ASSESSMENT OF THE PHOSPHOINOSITIDE 3-KINASE (PI3K) PATHWAY CAN STRATIFY PATIENTS FOR TARGETED TREATMENT WITH PI3K INHIBITORS

AUTHORS

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Biography:
Emily Edwards completed her Bachelor of Science in Applied Biomedical Science at the University of Wales Institute Cardiff (Cardiff, UK) in 2007. She subsequently commenced her PhD studies at Cardiff University into killer T cell function in viral disease and cancer, which she completed in in 2011. From 2011 to 2013, she undertook a Postdoctoral position at the Queensland Institute of Medical Research (QIMR) Berghofer (Brisbane, Australia), studying immune recognition of the common herpes virus Cytomegalovirus (CMV). From 2014 to 2018, she worked at the Garvan Institute of Medical Research (Sydney, Australia), examining PID cases with impaired immune control of Epstein-Barr Virus (EBV), resulting in virus-induced disease including malignancies.

Since 2018, she is a Senior Postdoctoral Fellow leading the study of Predominantly Antibody Deficiency (PAD), the most common PID, working with Prof Menno van Zelm at Monash University (Melbourne, Australia). In 2022, Emily was presented with the Grifols ASPIRE (Award for Scientific Progress in Immunodeficiency Research) Award for her research aiming to advance the genetic diagnosis of PAD.

Monash University hosts the Jeffrey Modell Foundation Centre for Primary Immunodeficiencies in Melbourne, of which she is a member. Emily is current Vice President of AusPIPS Inc. (Australian Primary Immunodeficiency Patient Support) an Australian charity advocating for patients with PID.

Emily's work has three main focuses:

Identifying new genetic variants (DNA mutations) driving PAD and its associated comorbidities.

Developing in vitro assays to evaluate functional impairments in the immune cell function of patients with PAD to subsequently guide genetic variant discovery and provide an evidence base for targeted treatment.

Examining the quantity and quality of SARS-CoV-2-specific antibodies after vaccination for COVID-19 in PID patients, dissecting the patient response and the contribution of Immunoglobulin (Ig) replacement therapy to immune protection from disease.

Objectives: Activated PI3-kinase delta syndrome (APDS) can be treated with pharmacological inhibitors targeting the enhanced activation of the Akt-PI3K-mTOR-S6 signalling pathway.
APDS classically presents in childhood with combined immunodeficiency and comorbidities including lymphoproliferation and autoimmunity. APDS type 1 is caused by heterozygous gain- of-function (GOF) variants in PIK3CD, and APDS type 2 by heterozygous loss-of-function (LOF) variants in PIK3R1. It remains unclear whether other immunodeficient patients have enhanced PI3K signalling and thus could benefit from targeted treatment.

Design and Methods: Here, we applied an optimised flowcytometric assay for evaluation of phosphorylated S6 (pS6) in both blood B- and T-cells to detect enhanced PI3K function in two newly-diagnosed patients.

Results: Patient 1 is a 25 year-old female with a clinical phenotype consistent with APDS2 who carried a novel heterozygous variant in PIK3R1 (c.716C>T; p.T239M). Patient 2 is a 43 year-old female who presented with hypogammaglobulinemia and harboured a novel heterozygous variant in SYK (c.1769G>A; p.R590Q). Both B- and T-cells of patient 1 displayed increased tonic and ligand-induced pS6 levels (Figure 1). Patient 2 demonstrated increased autophosphorylation of SYK, as well as increased tonic and ligand-induced pS6 levels in B- but not T-cells (Figure 1).

Discussion: We here describe the first case of APDS2 with a PIK3R1 variant residing outside of exon 11, thus expanding the spectrum of variants causing this disease. We showed for the first time that the increased autophosphorylation of SYK in B-cells of patient 2 led to activated PI3K signalling.
These patients expand the spectrum of genetic variants leading to activated PI3K, which can be evaluated by detection of pS6. Importantly, these results illustrate that patients other than those suffering from classical APDS1 and APDS2 could benefit from pharmacological intervention with PI3K inhibitors. We argue for further clinical studies to a use functional definition of activated PI3K through pS6 measurements as a rationale for treatment with PI3K inhibitors.
Overall, this study highlights the need for robust functional evaluation of critical immune signalling pathway function, including PI3K, as a means to stratify patients for treatment with novel biologicals.

Figure 1: Functional impact of heterozygous PIK3R1 and SYK variants on antigen-receptor signals. (A) Basal and (B) ligand induced levels of phospho-S6 in B-cells and T-cells of the affected PIK3R1 patient (red), SYK GOF patient (blue) and a healthy control (black). Shaded grey histogram represents PI3K specific-inhibitor LY294002 treated cells. Activation was performed with CD3 for T-cells and IgM F(ab)2 for B-cells.

POSTER 155 - DO GRANULOMAS IN CVID MIMIC SARCOID GRANULOMAS?

AUTHORS

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AFFILIATIONS

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Biography:
MD-PhD student at the Primary Immuno Deficiency group of Hanna IJspeert. Together with Virgil A.S.H. Dalm, Willem A. Dik and P. Martin van Hagen, we aim to gain better insight into granuloma formation in CVID. We investigate ways to better detect granulomatous disease and monitor granuloma progression and treatment effect in CVID, and on the other hand look at cellular context of granuloma formation also in relation to other granulomatous diseases such as sarcoidosis.

Introduction (background/aims)
For granuloma formation in sarcoidosis and common variable immune deficiency (CVID), the precise trigger remains unknown. Although sarcoidosis in the lung and granulomatous lymphocytic interstitial lung disease (GLILD) in CVID show similarities in clinical presentation, with misdiagnosis being possible, the disease context is different. This is reflected by the survival difference, as patients with sarcoidosis show better long term survival then CVID with (GL)ILD. Descriptions regarding the histological organization and spatial protein expression of the granulomas itself are missing. Therefore, we analyzed and compared the cellular organization and spatial protein expression sarcoidosis with CVID granulomas. We complement the analysis with biopsies of granulomatous diseases with a known trigger, being tuberculosis (TB) and pseudosarcoidosis (PS). Thereby, we aimed to gain a better understanding of the pathophysiology of granuloma formation in sarcoidosis compared to CVID, TB and PS.

Methods: Paraformaldehyde (PFA) fixed biopsies containing granulomas of 6 patients per disease group were included. Hematoxylin and eosin (HE) stains were histologically assed by two blinded observers. Targeted digital spatial protein profiling (DSP) was performed via the GeoMx Nanostring platform. Per region of interest (ROI), being granuloma center and surrounding of 3 granulomas per patient, all protein targets of the included modules were harvested and simultaneously quantified on an nCounter.

Results: Histological analysis showed granulomas of sarcoid patients to be well circumscribed, clustered, contained more fibrosis and lesser lymphocyte influx as compared to CVID granulomas.
Multinucleated giant cells (MNGCs) were frequently observed with sarcoidosis, as opposed to CVID granulomas were MNGCs were observed rarely. Granulomas in CVID were not well circumscribed, more confluent and contained more lymphocyte influx in the centers and surrounding of the granulomas as compared to sarcoidosis. DSP analysis showed macrophage marker CD68 to be relatively increased in sarcoid granulomas compared to CVID. Neutrophil marker CD66b was increased in the surrounding of CVID granulomas. Lymphocyte markers were not clearly different between the diseases. The MAPK pathway appeared relatively increased in the sarcoidosis samples compared to all other diseases.

Conclusions: The granulomas in sarcoidosis and CVID are very different. Especially regarding the presence of MNGCs in sarcoidosis and the wide lymphocyte influx in CVID, together with the subtle differences in DSP, underlines that granulomas in sarcoidosis and CVID are two different disease entities. Further unbiased approaches on transcriptome level are needed to more clearly observe what drives granulomas formation in sarcoidosis and CVID (future work).

POSTER 171 - IN SILICO ANALYSES OF ALL CD40 LIGAND MISSENSE VARIANTS LEADING TO EXLORE DIVERGANT X-LINKED HYPER IGM SYNDROME CLINICAL PHENOTYPE

AUTHORS

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AFFILIATIONS

[1]MOHAMMED V UNIVERSITY IN RABAT, [2]Mohammed VI Center for Research and Innovation, [3]Mohammed VI University of Health Sciences

Biography:
I'm Ouissal Hachlaf , a first year PhD student in faculty of medecine and pharmacy of Rabat, I'm specialized in immunogenetics and I am working on an immune deficiency called X-linked hyper IgM syndrome.

Objective: X-linked hyper-IgM syndrome (XHIGM) is a rare primary immunodeficiency disease caused by mutations in the CD40 ligand gene. It is characterized by normal or high serum IgM levels, low levels of IgG and IgA, and defective T cell function. The development of a complete clinical board of this disorder remains difficult. This study aims to establish the relationship between the impact of CD40 ligand mutations in different domains and the severity of clinical manifestations.

Design and methods: In this study, we used several in silico approaches to predict the effect of mutations on the structure and function of the CD40 ligand protein, their impact on stability and flexibility, as well as on binding affinity with the CD40. A total of 168 CD40 ligand mutations were the subject of this research.

Results: The results show that (33.92 %) of the mutations studied are predicted to be deleterious, having an impact on the protein physico-chemical properties, stability, flexibility and function to varying degrees. In particular, mutations affecting the TNFH domain (tumor necrosis factor homology) and the extracellular domain have a significant impact on the structure of the protein and disrupt its interaction with the CD40 protein.

Conclusions: There is a close correlation between the domain involving mutation, the level of variation in protein properties, and the degree of loss of function. This correlation explains the observed variability in clinical manifestations, which can range from moderate to severe.

POSTER 181 - ANALYSIS OF SERUM B CELL MATURATION ANTIGEN (sBCMA) IN A COHORT OF PATIENTS WITH PRIMARY ANTIBODIES DEFICIENCIES

AUTHORS

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AFFILIATIONS

[1]Immunology Service. Hospital Clínico San Carlos

Biography:
Graduated in Biomedicine. Microbiology Master's Degree. Currently in my third year of residency training in Clinical Immunology and doing my doctoral thesis focused on the genetic study of PID.

Objectives: B cell maturation antigen (BCMA) is a tumor necrosis factor receptor (TNFR) whose expression is restricted to plasmablasts and plasma cells. The binding of its ligands BAFF and APRIL triggers signals that are essential for the proliferation and survival of these cells. In addition, it also has a soluble form (sBCMA) resulting from cleavage by a γ-secretase. Measurement of sBCMA levels has been proposed as a useful biomarker in certain autoimmune diseases and in monoclonal gammopathies. Furthermore, there are studies that analyze its possible potential as a useful tool in the diagnosis of severe humoral immunodeficiencies such as a common variable immunodeficiency (CVID).
The aim of this study was retrospectively compare sBCMA levels between patients with CVID and patients with selective IgA deficiency (SIgAD) in order to analyze the differences between the two groups and, therefore, assess the potential utility of sBCMA measurement.

Design and Methods: Serum BCMA levels were determined in 50 patients from the Immunology Service of Hospital Clínico San Carlos (Madrid) diagnosed with CVID (n=27) and SIgAD (n=23) and 18 controls without any humoral deficiency. Levels of sBCMA were determined using an ELISA-based assay with polyclonal anti-BCMA antibodies (R&D Systems) and a Triturus equipment (Grifols SA). The statistical study of the results was carried out using test for non-parametric continuous variables.

Results: Of the CVID patients, 88.89% (n=24) had sBCMA levels ≤15ng/mL (median= 5.97), while 86.96% (n=20) of SIgAD patients had sBCMA levels >15ng/mL (median= 26.7). Cut-off points were set as previously described. The difference between the two groups was statistically significant ($p<0.0001$), as well as the difference between the sBCMA levels of CVID patients and controls ($p<0.0001$). There was no significantly differences between SIgAD patients and controls. These results were consistent with what was previously published (Cunningham Rundles et al, 2020).
In addition, the relationship between serum free light chain (sFCL) sum (κ+λ), another proposed biomarker for CVID diagnosis, and sBCMA levels was analyzed (Guevara-Hoyer et al., 2020). We found that there was a positive correlation statistically significant between the two of them ($r=0.845$; $p<0.0001$)

Conclusions: The preliminary results obtained are promising for the use of sBCMA. However, more retrospective and prospective studies are necessary in order to verify the diagnosis utility and to assess if it can be used as a predictor of evolution of SIgAD to CVID. Furthermore, it is necessary to analyze more parameters to understand the variability within the same group.

POSTER 235 - FUNCTIONAL ANALYSIS OF THE IL-12/IL-23/IFN-γ AXIS IN MOROCCAN PATIENTS WITH MENDELIAN SUSCEPTIBILITY TO MYCOBACTERIAL DISEASE

AUTHORS

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AFFILIATIONS

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Biography:
With a deep passion for science and technology, my career has been dedicated to scientific research. I have made significant strides in advancing my field through academic achievements, professional engagements, and active participation in conferences and publications. However, my true calling lies in education and training, as I am driven to share knowledge for the betterment of humanity. Specifically, my focus is on inborn errors of immunity (IEI)/primary immunodeficiencies (PID), where we aim to enhance patient care and well-being and contribute to the progress of this important field.

Introduction: Mendelian susceptibility to mycobacterial disease (MSMD) is a rare inborn error of IFN-γ immunity conferring a selective susceptibility to infections with low-virulence mycobacteria in patients, mostly children, without recognizable immune defects in routine tests. With 36 genetic defects identified across 20 genes as causative factors, MSMD exhibits considerable clinical heterogeneity. Strikingly, almost all defects disrupt either the production of IFN-γ or the response to it or both, indicating the potential diagnostic value of this physiological homogeneity.

Objective: In this study, we comprehensively investigated the IL-12/IL-23/IFN-γ axis in 12 Moroccan patients with MSMD caused by mutations in various genes, including IL12RB1, TYK2, SPPL2A, and STAT1.

Design and methods: The genetic diagnosis was accomplished using WES and/or Sanger sequencing. Familial segregation was made if DNA from relatives was available. We assessed IL-12 and IFN-γ production by stimulating patient blood samples with BCG and recombinant human IFN-γ or IL-12, followed by cytokine quantification using ELISA kits. Other immunological assays were also performed for all patients, including lymphocyte subsets, seric immunoglobulin levels, NBT, and/or DHR tests.

Results: Among the patients, six children from four unrelated kindreds exhibited autosomal recessive complete IL-12Rβ1 deficiency, five of them (83.3%) carried the same homozygous mutation p.K305X, while the other patient presented a novel frameshift mutation c.315_316del. Both mutations resulted in a truncated protein non-expressed on the cell surface. Patients with AR complete IL-12Rβ1 deficiency displayed a complete lack of IFN-γ production in response to stimulation in vitro, underscoring the indispensable role of IL-12/IL-23 signaling in IFN-γ mediated immunity. AR complete TYK2 deficiency exhibited a subnormal response to IL-12/IL- 23, emphasizing the existence of alternative kinases/pathways and accounting for a broad clinical phenotype and low penetrance to low-virulence mycobacteria in these patients. AR complete SPPL2A deficiency and AD partial STAT1 deficiencies displayed normal responses to IL-12/IL-23, but impaired response to IFN-γ in vitro.

Conclusions: Human IFN-γ is a quantitative trait that defines the outcome of mycobacterial exposure, with important diagnostic and therapeutic implications. Given the history of BCG complications in almost all our patients, we recommend postponing BCG vaccination in neonatal siblings of affected families until genetic assertion is obtained. Functional assays, such as IFN-γ release and cytokine assays, hold great promise as valuable, rapid, and cost-effective tools for early diagnosis of inborn errors of immunity (IEI). Despite their genetic and clinical heterogeneity, many IEIs involve common and/or overlapping physiological phenotypes.

POSTER 238 - A NOVEL ROLE OF TDRD6 IN IMMUNE REGULATION

AUTHORS

Erkeland S[1], Munasir Z, Mueller Y, Meurs M, Scheurs M, Swagemakers S, Brouwers-Haspels I, Stairiker C, Bindels E, La Distia Nora R, Muktiarti D, Venter D, van der Spek P, Jessberger R, van Hagen M, Katsikis P

AFFILIATIONS

[1]Erasmus Mc

Biography:
I studied the activities of small non-coding RNAs sncRNAs (mainly microRNA and small nucleolar RNA) in human leukemia, including acute myeloid leukemia (AML), T-cell malignancies and B-cell acute lymphoblastic leukemia. My research focuses on the functions of sncRNAs in cellular stress conditions and oncogenic transformation of normal hematopoietic cells towards leukemia. In addition, I studied the oncogene-mediated transcriptional silencing of tumorsuppressing miRNA in AML. As part of the H2020 European network, I investigated small RNAs in immunological disorders such as inflammatory diseases.

Background: Disease causing molecular mechanisms in immunological syndromes are still largely elusive. We have identified a primary immunodeficiency (PID) patient with some clinical disease features similar to autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED), including persistent mucocutaneous candidiasis, dystrophial nail and teeth lesions, but lacked mutations in well-known PID mutations.

Objectives: To establish novel disease causing mutations in PID disease.

Methods: We performed whole genome sequencing (WGS) on genomic DNA of the patient and both parents. In addition, we performed extensive in vivo studies with mouse models to elucidate the role of a novel gene in immune regulation.

Results: We did not find known mutations in primary immunodeficiencies, such as the gene encoding Autoimmune regulator (AIRE), in the genomic DNA of our patient with some clinical features of APECED. Instead, we found novel variants in the gene encoding Tudor Domain Containing 6 (TDRD6). In addition, Tdrd6-deficient mice developed early autoimmunity exhibiting autoantibodies and inflammatory T cell infiltration of peripheral organs. We present evidence that Tdrd6 is expressed in Cytokeratin-5 and -8 double positive TEC progenitor thymic epithelial cells (progenitor TEC), but not in mature mTECs. TDRD6 depletion in progenitor TEC affected the function of mTEC, because we found that a panel of well-known tissue-restricted antigens (TRA) is deregulated in Tdrd6-deficient mTEC.

Conclusions: Our findings reveal a novel and unexpected role of TDRD6 in immune regulation and the prevention of autoimmunity.

POSTER 266 - SERUM MANNOSE BINDING LEVEL AND GENE POLYMORPHISM IN DOWN SYNDROME

AUTHORS

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AFFILIATIONS

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Biography:
Ece TOLGAY is currently an undergraduate medical student in the Faculty of Medicine at Bursa Uludağ University in Turkey. She has been a student representative in the Faculty of Medicine for the first two years while taking part in the administration of other scientific student unions at the university. Since immunotherapies deeply attracts her interest, she wants to pursue a career path as a immunologist in the future.

Background: Mannose binding lectin (MBL) is a multimeric lectin that initiates lectin pathway of complement activation. The gene encoding MBL, MBL2, contains several common polymorphisms that influence transcription and assembly of the molecule into multimers.
Children with Down syndrome (DS) have an increased rate of infection and it has been proposed that this is secondary to derangements of the immune system. We conducted a study to examine the rate of MBL deficiency and status of MBL polymorphism in children with DS.

Methods: Thirty patients with DS and 22 healthy control were included in this study. MBL concentration was measured using enzyme linked immunosorbent assay (ELISA). Point mutations of the MBL gene were detected by polymerase chain reaction (PCR) restriction fragment length polymorphism.

Results: The mean MBL level of DS patients was lower than the control group ($p<0.05$), while no significant difference in the overall distribution of the genotypes between the patients and the control group were observed. The serum concentration of mannose binding lectin was not correlated to the frequency of lower respiratory tract infections or the distrubition of the alleles. No significant differences were found between subjects heterozygous (A/B) or homozygous (B/B) for deficient MBL2 alleles when compared to normal subjects (A/A) in terms of infection.

Conclusions: We documented that many children with Down syndrome do have abnormalities of serum levels of MBL. MBL deficiency does not cause chidren with DS to have a greater number of infections compared with nondeficient patients.

CASE STUDIES, CLINICAL PRESENTATION AND IMMUNOLOGICAL PARAMETERS

POSTER 18 - FIRST COHORT STUDY OF HYPERIMMUNOGLOBULINEMIA E (IGE) SYNDROME DIAGNOSED WITH THE NATIONAL INSTITUTE OF HEALTH (NIH) SCORE IN A SUB-SAHARAN AFRICAN COUNTRY (DAKAR, SENEGAL)

AUTHORS

Ndiaye Diop M[1,4], BOUSFIHA A[2], DIOUF K[1], DIASSE FALL F[1], DIOP K[1], Seck B[3], DIOP A[1], NIANG B[4], Deme LY I[4], BA I[4], FALL M[4], FAYE P[4], NDIAYE M[1], DIALLO M[1], NDIAYE O[4], LY F[1], NIANG S[1]

AFFILIATIONS

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Background: Early diagnosis of hyperIgE syndromes is a global challenge. The objectives of this work were: to diagnose hyperIgE syndromes in pediatric dermatology consultations at the Centre Hospitalier National d “Enfant Albert Royer (CHNEAR) using the NIH score and to determine the frequency of this syndrome in this site.

Methods: Cohort study started in January 2021 to September 2022 in the pediatric dermatology department of CHNEAR. We included all patients with atopic dermatitis, elevated total IgE and National Institute of Health (NIH) hyper IgE syndrome diagnostic score greater than or equal to 20. The severity of atopic dermatitis was assessed by the SCORAD. Data were entered and analyzed with Epi info 7.0 software.

Results: During the study period, 6000 patients were seen in consultation, including 27 cases of hyper IgE syndrome representing a hospital frequency of 0.45%. The sex ratio was 2. The mean age at diagnosis was 6 years. Parental consanguinity was noted in 9 cases and personal atopy in 85.2%. A history of recurrent pyoderma in 74.1%, recurrent respiratory infection in 44.4%, and neonatal skin rash in 14.8% were noted. Food allergies were found in 37%. The dermatological manifestations were: atopic dermatitis (100%); infectious dermatoses (81.48%); congenital ichthyosiform bullous erythroderma (3.7%) (image 4). Atopic dermatitis was moderate in 30.4% and severe in 69.6%. Infectious dermatological manifestations were severe, disseminated and recurrent, including bacterial (40.7%) (image 1), viral (7.4%) (image 2) and fungal (7.4%) (Image 3). Extra-dermatological manifestations included facial dysmorphia in 85.2%, respiratory signs in 33.3%, neuropsychiatric signs in 18.5%, and osteoarticular signs in 14.8%. Hyper-eosinophilia was present in 63% of patients, neutropenia and lymphopenia in 02 patients each.The total IgE level was higher than 2000 KUI/L in 81.5% of cases. The NHIES score was between 20 and 42.

Discussion: The frequency of hyperIgE syndromes in pediatric dermatology consultations in Dakar is 0.45%. Severe and recurrent infectious dermatoses are found in all patients and should be warning signs in the course of atopic dermatitis imposing the dosage of total IgE and the use of the NIH score. However, this score is more sensitive and specific if it is a STAT 3 mutation. Thus, we hope to do whole exome sequencing to determine if there are specific gene mutations for these syndromes in our regions.

POSTER 19 - OMENN SYNDROME, THE IMPORTANCE OF EARLY TRANSPLANT

AUTHORS

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AFFILIATIONS

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Objective: Omenn syndrome is a rare variant of severe combined immunodeficiency. Often caused by hypomorphic mutations of recombination activation genes (RAG1 and RAG2). Affected individuals lack B cells, autoreactive oligoclonal T cells infiltrate barrier tissue organs such as skin and intestine. With susceptibility to severe opportunistic infections and manifestations such as exfoliative erythroderma, alopecia, hepatosplenomegaly, lymphadenopathy and severe diarrhea. The aim is to present a case of RAG1 defect and to highlight the importance of timely diagnosis that allows hematopoietic stem cell transplantation with a survival of up to 85% (1).

Design and methods: We present the case of a patient 8 weeks old, healthy parents, without consanguinity or inbreeding. The patient presented with exfoliative erythroderma and alopecia during the first days of life. She started with exudative cutaneous eruption, accompanied by hyperthermia and irritability, then suppurative otitis media (isolation of Klebsiella pneumoniae and Staphylococcus aureus). She was admitted to hospital due to persistent fever and microadenopathies, as well as generalized erythroderma, alopecia, desquamation and hepatosplenomegaly. Laboratories showed anemia, neutropenia, leukocytosis, hypereosinophilia and agammaglobulinemia. Flow cytometry showed marked lymphopenia with B-T-NK+ profile. Based on laboratory findings, severe combined immunodeficiency was suspected. Treatment with prophylactic systemic antibiotic therapy and intravenous immunoglobulin was initiated.

Results: Genetic sequencing of the exome was performed. The results of the genomic tests revealed the presence of two variants: a homozygous pathogenic variant in RAG1 (c.612G>A, p.Trp204*) and another variant of uncertain significance heterozygous in NF1 (c.3055G>A, p.Val1019Ile). The diagnosis of Omenn syndrome was confirmed according to the clinical criteria of the ESID Registry (2).

Due to the immunological features of severe combined immunodeficiency, the girl was referred for HSCT however the patient developed severe pneumonia and died 3 weeks later.

Conclusions: Omenn syndrome is a rare disease characterized by exfoliative erythroderma during the first year of life, lymphoproliferation, failure to thrive, chronic diarrhea, recurrent pneumonia, eosinophilia or elevated IgE. Molecular diagnostic procedures are now available for its identification; dermatologists, pediatricians, and geneticists should be aware of this disease in order to diagnose it, treat it promptly, and prevent death in these patients.

References: Villa A. Innovative Cell-Based Therapies and Conditioning to Cure RAG Deficiency. Front Immunol, 2020
ESID Registry. Working definitions for clinical diagnosis of PID. 2018.

POSTER 25 - UNUSUAL SKIN LESIONS IN YOUNG WOMEN: FROM LUPUS TO PRIMARY IMMUNO-DEFICIENCY

AUTHORS

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AFFILIATIONS

[1]2nd Internal Medicine Department, Dr. Carol Davila Central University Emergency Military Hospital

Biography:
Cezara Motei is an allergology and immunology resident based in Bucharest, Romania. She completed her medical degree at the Carol Davila University of Medicine and Pharmacy in Bucharest, where she also began her residency training. Currently, Cezara is in her 4th year of residency and is completing a 10-month internal medicine stage at the 2nd Internal Medicine Department, "Dr. Carol Davila" Central University Emergency Military Hospital, one of the most important centers for adult patients with primary immune deficiency in Romania.

During her residency, Cezara developed a keen interest in primary immunodeficiency disorders and their management. Her work in the Internal Medicine Department has provided her with a unique opportunity to gain experience in the diagnosis, treatment, and long-term management of these complex conditions. She has encountered a variety of primary immunodeficiency cases, which have given her a deeper understanding of the challenges that patients with these conditions face.

Cezara is committed to advancing her knowledge and expertise in the field of immunology and to being actively involved in research projects aimed at improving the diagnosis and management of primary immunodeficiencies.

Objectives: Recent studies have reported the link between STAT1 mutations and cutaneous fungal infections, particularly in the form of chronic mucocutaneous candidiasis (CMC). Moreover, a large spectrum of other clinical manifestations was also reported in these patients, from other types of infection to aneurysms, malignancies, and autoimmune diseases such as systemic lupus erythematosus (SLE).

Design and Methods: We present the case of a young woman diagnosed with a STAT1 GOF mutation in the context of fungal skin lesions, highlighting the role of genetic testing in this context.

Results: We present this case of a 25-year-old female patient who was initially diagnosed with lupus based on clinical presentation and laboratory findings. However, the cutaneous lesions showed little to no response to the usual therapy. Another recent skin biopsy revealed an associated fungal skin infection that later showed a good but incomplete response to antifungal treatment. The patient was referred to our clinic, and we completed the investigations with genetic testing, which revealed a genetic immunodeficiency associated with a STAT1 GOF mutation, explaining the predisposition for fungal infections and the association with the autoimmune disease.

Given the potential complications associated with STAT1 GOF mutations, we conducted a comprehensive evaluation of the patient, including a head MRI and thoracic and abdominal CT. Treatment with ruxolitinib was planned.

Conclusions: This case highlights the importance of considering rare genetic immunodeficiencies in the differential diagnosis of patients with recurrent or refractory infections, particularly those with atypical presentations or responses to treatment or those who associate an autoimmune disease.

POSTER 34 - ATP6AP1 DEFICIENCY ACCOMPANIED WITH RECURRENT GASTROENTERITIS, SEIZURE AND NORMAL LIVER FUNCTION, A CASE REPORT

AUTHORS

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Biography:
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Objective: ATP6AP1 is a gene expressed in B cells, hepatocytes and brain cells, encoding a protein called Ac45 of the V-ATPase. ATP6AP1 deficiency, a x-linked mutation, is classified as a congenital disorder of glycosylation. The main symptom of ATP6AP1 deficiency is immunodeficiency, accompanied by hepatopathies and cognitive disorders. Early diagnosis of this deficiency is necessary for choosing suitable treatments in patients. Here, we report a case of ATP6AP1 deficiency without detectable hepatopathies.

Case study: A 5-month-old male infant, with a history of prolonged neonatal jaundice, recurrent gastroenteritis, and several episodes of seizure was admitted for sepsis rule out. Blood culture was reported negative for bacterial infections; however, he was diagnosed with a sever oral candidiasis.
Despite no abnormality in liver function tests, considering the family history of recurrent gastroenteritis, jaundice and liver disfunction in sibling, the possibility of immunodeficiency was suspected in this patient, though no immunologic or genetics test were taken from his deceased sibling at the time. Interestingly, although all tested immune parameters were within the normal ranges, whole genome sequencing resulted in positive ATP6AP1 deficiency.
Intravenous immunoglobulin administration, a useful treatment in immunodeficiencies involving B cell-mediated responses, together with prophylactic antibiotics were initiated immediately, which kept the infections and all other symptoms under control. In follow up examinations, the patient showed no further symptoms of gastroenteritis or seizure.

Conclusions: In conclusion, although ATP6AP1 deficiency is known to associate with liver involvement and cognitive disorders, it must be considered in patients with recurrent infections and complications, regardless of having normal liver function. It's worth noting that since liver dysfunction has been reported in first years of life in this disorder, the patient is under our follow up for liver function tests.

POSTER 44 - AICDA DEFICIENCY PRESENTING WITH INFLAMMATORY BOWEL DISEASE IN AN ADULT PATIENT

AUTHORS

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AFFILIATIONS

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Biography:
Professor of Immunology- head of immunodeficiency lab at Cairo University Specialized Pediatric Hospital

Expert in Genetics and Flow cytometry

Objectives: to describe the clinical presentation and immunological characteristics of an adult patient with inflammatory bowel disease (IBD) diagnosed with AICDA deficiency.

Methods: a 30-year-old female patient presented with chronic diarrhea suggesting IBD, generalized lymphadenopathy, hepatosplenomegaly, and dysfunctional uterine bleeding. Upper and lower endoscopy was done to investigate the cause of the chronic diarrhea. Routine laboratory work up included CBC, liver and kidney functions, serum immunoglobulins levels.
Immunological investigations included anti-nuclear antibodies, anti-tissue transglutaminase IgA, peripheral blood lymphocytes immunophenotyping and CD40 expression by flow cytometry (FCM). Targeted next generation sequencing (NGS) was performed on illumine Miseq using a panel of 55 genes involved in CID and B cell/Antibody deficiencies.

Results: The patient was admitted with severe diarrhea, generalized lymphadenopathy, pneumonia and severe vaginal bleeding that required blood transfusion. The results of the routine laboratory workup are presented in table 1. Upper and lower endoscopy suggested the possibility of eosinophilic gastroenteritis versus IBD. Serum IgG and IgA were low with elevated serum IgM. Peripheral blood immunophenotyping revealed decreased B cell percent and count with marked increase in the switched memory CD27+IgD- B cells (89% of B cells). CD40 expression by FCM was normal. NGS revealed a homozygous frameshift deletion in the AICDA gene (c.406del, p.Ile36Ter).

Conclusions: AICDA deficiency may present in adulthood with immune dysregulation inform of IBD.

POSTER 48 - THE CROSS ROADS BETWEEN IMMUNODEFICIENCY AND AUTOINFLAMMATION; CASE PRESENTATION

AUTHORS

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Biography:
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A 12- year old boy born to consanguineous parents, presented with a history of recurrent upper respiratory tract infections and draining ears, repeated hospitalization with pneumonia, last episode complicated with lung abscess, left upper lobectomy was done at the age of 11 years. The patient suffered from multiple hyperemic necrotizing skin lesions with impaired healing all over face, trunk, upper and lower limbs, and pyoderma gangernosum was suggested. The patient was noticed to have an abnormal gait, proximal muscle weakness as well. CT chest imaging showed bilateral bronchiectatic changes, EMG results showed increased denervation/some myotonic changes, while NCV was normal. Laboratory findings showed thrombocytopenia in complete blood picture, Immunological work up results showed normal Immunoglobulins levels and normal DHR test. Lymphocyte subsets showed normal CD3 (83.9%), CD4 (37.5%), CD8 (40.1%) T cells, reduced CD19 B cells (1.3%), and reduced switched memory B cells CD27+ IgD- 3.7%. The patient presented later in the follow up with persistent fever, arthralgia, stomatitis, vasculitic rash over lower limbs. NGS results showed homozygous missense/VUS mutation in WDR1 gene C.1723C>T. Recent advancements in molecular detection methods, have led to identification of several different genetic defects associated with overlapping phenotypes. From these novel gene defects, we are still learning about defects affecting the equilibrium of the immune system.

POSTER 51 - PATIENT WITH COMMON VARIABLE IMMUNODEFICIENCY PRESENTING WITH ALOPECIA UNIVERSALIS

AUTHORS

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Biography:
I was born in Karaman,Turkey in 1986 and obtained my medical degree at Selcuk University in Konya. I completed my specialization at Selcuk University, Department of Internal Medicine.
After working for 3 years as a specialist in internal medicine in a hospital, I started and still attending my fellowship at Necmettin Erbakan University Division of Clinical Immunology and Allergy in Konya. Professionally, I am interested in primary and secondary immunodeficiencies, interstitial lung diseases, and severe asthma.

Introduction: Common variable immunodeficiency (CVID) is a heterogeneous group of diseases that includes defects in antibody production and various defects of the cellular immune system. Although CVID may present at any age, it is most commonly diagnosed between 20 and 40 years. No overall sex predilection has been identified. Alopecia is a nonscarring hair loss disorder with an unpredictable course and a wide spectrum of manifestations.

Case report: A 46-year-old male was admitted with complaints of recurrent respiratory tract infections, weight loss, and total alopecia. The patient had more than four infections requiring antibiotics and two radiologically proven pneumonia within 1 year. There was third-degree parental consanguinity. The patient's hair loss started three years ago, and in the last year, all the hair on the body has been lost (Picture 1). Chest tomography showed bilateral basal bronchiectasis. There was splenomegaly on abdominal tomography. Peripheral blood lymphocyte evaluation included low B lymphocyte values, increased CD8+ (cytotoxic T cells) lymphocytes, and decreased CD4+/CD8+ ratio. The patient's immunoglobulin level was low. The patient's scalp biopsy showed a perifollicular infiltrate of mononuclear cells. We identified the NF-κB (nuclear factor kappa B) 2 mutation in the patient. He was diagnosed with CVID and was started on 400 mg/kg intravenous immunoglobulin infusions every 3 weeks.

Conclusions: Patients with CVID develop recurrent and chronic infections (e.g., bacterial infections of the respiratory or gastrointestinal tract), autoimmune diseases, lymphoproliferation, malignancies, and granulomatous lesions. Interestingly, autoimmunity can be the only clinical manifestation of CVID at the time of diagnosis and may even develop prior to hypogammaglobulinemia. Alopecia develops as a result of autoantibodies produced against hair-producing cells in CVID. In the etiological investigation of alopecia, it should be considered among the differential diagnoses of CVID, especially in young patients.

POSTER 52 - MANDELIAN SUSCEPTIBLITY TO MYCOBACTERIAL DISEASE IN A 13 YEAR OLD ETHIOPIAN GIRL WITH AUTOSOMAL DOMINANT INTERFERON GAMMA RECEPTOR 1 DEFECT, A CLINICAL DIAGNOSTIC AND TREATMENT CHALLENGE

AUTHORS

Engliz D[1]

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Biography:
I'm a dermatovenerologist working as a consultant in st peter specialized hospital Addis Ababa Ethiopia. I have studied my medical degree in jimma university and I have served as a general practitioner in rural part of Ethiopia for two years. After that I went to addis Ababa university for my specialization in dermatovenerology. Since I have graduated I have been working in st peter specialized hospital. I have interest in primary immune deficiency cases since there is difficulty of diagnosing and treating such case in our setup. This case I have submitted is the first of it is kind. I'm very thrilled to be part of the solution for such a challenging case for diagnosis and treatment.

History- a 13 year old female patient presented to dermatology clinic with skin rash of four years duration which started over her forehead as a small bump progressively increasing in size and number over her face, scalp, chest, back, arm and thigh. For this she had multiple hospital visits, had repeated mycobacterial infection and treatment. With the diagnosis of TB affecting skin, soft tissue, lymph node, bone and joint, lung, epidural and paraspinal regions. She has been treated four times with fist line anti TB and once with second line anti TB drugs. Up on examination yellowish crusted plaque with indurated eythematous background over the scalp, forehead, right cheek, chin, chest and abdomen.
Biopsy- diffuse granuloma with multiple hepatocytes with background of lymphocytes, multinucleated giant cell. Which is suggestive of lupus vulgaris.
Laboratory results- scalp lesion and sputum AFB positive, PCR positive for mycobacterium avium complex.
Genetic analysis- shows autosomal dominant (med Gen UID:863300) mendelian susceptibility to mycobacterium disease with autosomal dominant interferon gamma receptor 1 defect.
Treatment- linzolide, azithromycin, moxifloxacine, clofazamine with interferon gamma and stem cell transplant.

POSTER 59 - INHERITED AND PHENOCOPIES OF COMPLEMENT DEFICIENCIES IN NEPAL: AN EXPLORATION OF MAIDEN HORIZON

AUTHORS

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AFFILIATIONS

[1]Advanced Centre For Immunology & Rheumatology, [2]Government Medical College, [3]College of Medical Sciences

Biography:
Degrees: MBBS, MD, DM, FESID
Position: Pediatric Immunologist, President, NIAPIDS, Nepal
Affiliation: Advanced Centre For Immunology & Rheumatology

Objectives: To describe the profile of patients with inherited complement deficiencies (ICDs) and phenocopies of inborn errors of immunity (IEIs) related to complement pathways from Nepal.

Methods: Case records of all patients diagnosed with complement pathway defects in Nepal from August 2020 to May 2023 were analyzed. The lead author (DB) collated data from all patients.
Diagnosis and treatments were based on internationally acclaimed guidelines.

Results: Seventeen patients (11 females & 6 males) with complement defects were diagnosed. Fifteen patients had ICDs whereas 2 were diagnosed with phenocopies of IEIs associated with autoantibodies against complement components. The median age of onset of symptoms and diagnosis was 5.5 and 12 years, respectively. Second complement (C2) deficiency was found in 2 patients whereas C1QA, C1QC, and C4A (homozygous) deficiency were found in one patient each. All 5 of them had systemic lupus erythematosus, infectious manifestations, and deficient CH50 activity.

Among 11 patients with C1 inhibitor (C1-INH) deficiency, 8 were type 1 hereditary angioedema (HAE) with low C4 and C1-INH. One with type II HAE had low C4 and elevated but ineffective C1-INH. Three had genetic analysis, which detected SERPING1 gene mutation. One patient with recurrent angioedema but normal C1-INH was found to have a rare kininogen (KNG1) mutation. Among autoantibodies-associated phenocopies, 1 adolescent girl with acquired angioedema had autoantibody to C1 inhibitor whereas another child with atypical hemolytic uremic syndrome was found to have autoantibodies to complement factor H. Remaining patients with HAE could not perform tests due to financial constraints and unavailability of genetic tests in the country. All patients of HAE were kept on long-term prophylaxis with tranexamic acid or attenuated androgens. One HAE patient is recently listed for C1-INH therapy.

Conclusions: ICDs are often missed or misdiagnosed in resource-limited settings due to a lack of awareness and subspecialists. We present the first Nepalese cohort with proven cases of ICDs. Lack of awareness, specialists, and diagnostic facilities coupled with socioeconomic limitations have resulted in misdiagnosis, inappropriate treatment, and poor outcomes in ICDs in resource- constrained settings.

POSTER 61 - A CASE OF MALT1 DEFICIENCY; CLINICAL AND LABORATORY WORKUP

AUTHORS

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AFFILIATIONS

[1]Faculty Of Medicine, Cairo University

Biography:
Graduated and obtained Master of science and Medical Doctorate degree in Clinical and Chemical Pathology from Cairo university

Member of: ESID, ASID

Currently directing the Primary immunodeficiency laboratory in Cairo University Specialized Pediatric hospital

Objective: To provide clinical presentation and immunological workup of a patient diagnosed with MALT1 immunodeficiency due to MALT1 gene mutation.

Design and method: A 2 years old boy born to a consanguineous family presented with mucoid diarrhea, skin rash with massive exfoliation and itching. Extensive eczema over the face and limbs, and teeth affection with eaten up enamel. He had history of recurrent attacks of fever for 2 months.
Immunophenotyping and immunoglobulin assay was done, Followed by genetic work-up by next-generation sequencing (NGS) performed on Illumina MiSeq platform using 4bases PID pro kit for sequencing targeted 452 inborn error of immunity genes.

Results: Immunophenotyping showed normal T cells, B cells and NK cells percentages and a blockage of B cell maturation (Class switched memory B cells CD19+CD27+ 0.7% while Naive B cells IgD+CD27- 95.3%). Immunoglobulins assay showed markedly elevated IgE. Dock8 expression was normal by flowcytometry.
NGS revealed one homozygous Likely Pathogenic variant in MALT1 gene (c.762dup in exon 5 of 17; p.Ile255TyrfsTer10), supporting the genetic diagnosis of immunodeficiency-12 (IMD12)

Conclusions: MALT1 deficiency is a rare inborn error of immunity disease affecting the NFκB pathway, it is characterized by severe life-threatening infections. Describing patients' phenotype provides insight into this primary immunodeficiency that help in early diagnosis and treatment.

POSTER 63 - LONG-TERM HYPOGAMMAGLOBULINAEMIA AFTER TREATMENT WITH CHEMOTHERAPY AND AUTOLOGOUS HAEMATOPOIETIC STEM CELL TRANSPLANTATION AND RITUXIMAB: A CASE STUDY

AUTHORS

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Biography:
Dr. M. Fabiola Villegas is a medical professional originally from Santa Cruz, Bolivia. She received her medical degree from Gabriel René Moreno University. Passionate about immunology, she specialised in this field at the San Pedro de Alcántara Hospital in Cáceres, Spain.

Objectives: This case study aims to describe the development and progression of marked hypogammaglobulinaemia in a 54-year-old male after receiving chemotherapy treatment for Hodgkin's lymphoma, followed by autologous transplantation of haematopoietic progenitors in 2007 and rituximab in 2008. We discuss the possibility of an underlying primary hypogammaglobulinaemia revealed after rituximab treatment.

Design and Methods: Clinical and laboratory data of a 54-year-old male patient were retrospectively analysed. Immunological evaluation included serum immunoglobulin levels, lymphocyte subset analysis and vaccine response. The patient's medical history, including previous infections and treatments, was reviewed.

Results: Thirteen years after receiving rituximab, the patient has a complete absence of IgG and IgA. Lymphocyte subset analysis revealed normal T-cell populations and decreased B-cell populations, B-cell memory and class switching memory were below normal values. Clinically, the patient presented with two episodes of pneumonia requiring intravenous antibiotics and hospitalisation in 2010 and 2012. Subsequently, the only infection reported during the next 10 years was a herpes zoster infection in the left lumbar region in 2019, which responded well to treatment orally with brivudine and topical acyclovir. In August 2020, the patient tested positive for SARS-CoV-2 infection, remaining asymptomatic but persistently PCR positive for 6 weeks and without development of IgG or IgM antibodies.

Conclusions: This case highlights an interesting scenario of long-term hypogammaglobulinaemia secondary to rituximab treatment, in a patient who initially developed marked hypogammaglobulinaemia and whose immunoglobulins became undetectable 13 years later. Although our primary diagnosis is secondary hypogammaglobulinaemia, these findings raise questions about the presence of underlying primary hypogammaglobulinaemia that was unmasked after rituximab treatment or autologous haematopoietic stem cell transplantation.

POSTER 64 - CLINICAL PRESENTATION OF BRUTON AGAMMAGLOBULINEMIA

AUTHORS

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AFFILIATIONS

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Biography:
Dr Lazarevic is pediatrician and assistant professor of Pediatrics at University of Nis with clinical specialization in Pediatrics Rheumatology and Immunology dealing with rare autoinflammatory genetic inherited diseases. She completed residency in pediatrics at the University of Nis, Serbia. Dr Lazarevic received EULAR Training Bursary and spend 6 months long fellowship programme at the Dept of Paed Rheumatology of the University of Genoa IRCCS Giannina Gaslini, Genoa, Italy where she was involved in various clinical, scientific and educational activities which have resulted in two M21 publications. PhD degree in paediatric rheumatology was obtained in 2016 at Faculty of medicine, University of Nis, Serbia with the thesis: "The influeze of Vitamin D receptor FokI gene polymorphism and tumor necrosis factor TNFα- 308 polymorphism on severity and long term outcome in juvenile idiopathic arthritis". She is principle investigator of the FOREUM project entitled : "Applicability of standardized ultrasound examination to estimate disease activity in combination with JADAS and inflammation markers in JIA patients ". Her research is focused on serum biomarkers and musculosceletal ultrasound assessment in disease outcome of JIA patient. Also she is focused on rare genetic autoinflammatory diseases and their treatment. She is about to finalize subspecialization in Rheumatology. Dr Lazarevic is an author of lot of scientific publications and she is Review Editor for the Journal Frontiers in Pediatrics.

Introduction: X-linked agammaglobulinemia (XLA) or Bruton agammaglobulinemia is inherited immunodeficiency disease caused by mutations in the gene coding for Bruton tyrosine kinase (BTK).

Case report: We present 4 year old boy whose symptoms started to manifest clinically from 9 month of age with recurrent otitis media and upper respiratory tract infections. Due to this health problems, he was hospitalized few times in the local hospital and always treated with antibiotics. At 20 months of age, he was admitted to our hospital for the first time in a very serious condition with persistent fever, cough, tachycardic with necrosis of the skin on the chin with the same skin changes in the gluteal region and upper legs. Laboratory finding has revealed leukopenia, anaemia, thrombocytopenia, hypoalbuminemia, prerenal acute failure with elevated parameters of inflammation and electrolyte disbalance. He was treated with dual antibiotic therapy and symptomatic treatment. Family history was positive, his uncle had Bruton agammaglobulinemia. Immunoflow cytometry have showed lacked circulating B lymphocytes and he had low immunoglobulin levels. This was enough to establish diagnosis of inherited immunodeficiency so we have started treatment with intravenous immunoglobulin every month with antibiotic prophylaxis. During the time he developed bronchiectasis, but he is in stable condition.

Conclusions: In patients with recurrent infections with positive familiar background we must consider inherited immunodeficiencies and perform additional immunological tests in order to confirm diagnosis and start prompt treatment.

POSTER 68 - OMENN SYNDROME: CLINICAL AND IMMUNOLOGICAL PROFILE

AUTHORS

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Biography:
Assistant Professor in Immunology at Algiers University

Head of Immunology unit in Beb El oued Hospital, Algiers, Algeria

Background and aims: Omenn syndrome (OS) a rare autosomal recessive disease is characterized by symptoms of severe combined immunodeficiency (SCID). The aim of this work is to report the clinical features and the immunological characteristics of OS Algerian patients, essentially activated T cells (HLA-DR+, CD45RO+), and recent thymic emigrants, defined by expression of CD31+ and CD45RA+.

Methods: We report here features of 5 Algerian patients diagnosed in our laboratory, 80% of them are offspring of consanguineous marriage, 4 are males and 1is female, mean age was 3.55 month and the mean age at the first clinical manifestation was 1.17 month.
The exploration included:

- Measurement of IgG, IgA,IgM and IgE levels by nephelometry.
- Lymphocyte immunophenotyping T, B, NK, HLA-DR, and CD4/CD45RA /CD45RO/CD31 by flow cytometry.

Results: Patients suffer from typical OS manifestations as defined by early onset of diffuse erythroderma (100%), eosinophilia (100%), alopecia (60%), diarrhea (40%), and lymphadenopathy (40%).
The immunological investigations showed: hypo- gammaglobulinemia (80%), with high level of serum IgE (100%).
B cells were absent or strongly decreased (100%).T-cell counts were normal or decreased, and activation markers including HLA-DR expression on CD3 cells were positive in 100%, also was the expression of CD45RO. Recent CD4 thymic emigrants, defined by expression of CD31 and CD45RA were not detectable (100%).

Conclusions: Although rare, Omenn syndrome can easily be diagnosed on basis of clinical and immunological phenotypes. Thus supporting early recognition of OS patients, that may help the clinician to establish the diagnosis.

POSTER 72 - LEUKOCYTE ADHESİON DEFECT TYPE-I: CASE REPORT

AUTHORS

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Biography:
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Leukocyte migration from the circulation to the tissue, where adhesion molecules are involved, is very important in order to eliminate the inflammatory response and foreign antigens.
Leukocyte adhesion defects (LAD-I, II, III) are phagocytic system diseases associated with defects in the adhesion and migration stages of neutrophils. We aimed to present our case who was presented with omphalitis, delayed wound healing and neutrophilia and diagnosed as LAD I defect by flow cytometry and genetic analysis.

Case: 4-month-old girl whose parents were first-degree relatives was admitted with fever, poor feeding, and non-healing diaper dermatitis in the genital area. It was learned that the umbilical cord separated late, at 20 days of age, but the flow continued afterwards. On physical examination, the general condition was poor, cardiac 2/6 systolic murmur, and rales in both lungs were present. The abdomen was distended, the liver was palpated 8-9 cm below the rib, and the spleen 3 cm. Hyperemia, foul-smelling serous discharge in the umbilical region, and ulcerated lesions in the genital region were detected.
In laboratory examinations, Hb:4.4 g/dl, WBC:124000/mm3, ALS:7620/mm3, ANS: 104870/mm3, Plt: 114000/mm3, albumin: 2.7 gr/dl, CRP: 63.25 mg/dl, Pseudomonas Aeruginosa growth in blood culture, RSV B in respiratory tract multiplex PCR, CMV PCR 5031 IU/ml were detected. CD18: 4.4%, CD11a: 0.2%, CD11b: 98.3%, CD11c: 99.2%, CD15: 98.8% were determined on the neutrophil surface by flow cytometry and the diagnosis of LAD-I was made. In addition to local treatment, antibiotics and ganciclovir were given. ITGB2 genetic mutation analysis revealed a homozygous mutation and she was included in the bone marrow transplantation program.

Conclusions: LAD should be considered in the presence of delayed umbilical cord detachment, omphalitis, delayed wound healing, and leukocytosis. In LAD-I cases, together with the adhesion defect of neutrophils, NK and cytotoxic T cell activities are also affected. It should be kept in mind that infections can be seen with viral agents such as RSV and CMV as well as gram-negative and positive bacteria as observed in our case.

POSTER 74 - T-CELL RECEPTOR EXCISION CIRCLES (TREC) AND KAPPA- DELETING RECOMBINATION EXCISION CIRCLES (KREC) IN PATIENTS WITH COMMON VARIABLE IMMUNODEFICIENCY: A NEW PROGNOSTIC PARADIGM IN INBORN ERRORS OF IMMUNITY

AUTHORS

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AFFILIATIONS

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Biography:
Dr Prabal Barman graduated (MBBS) from Gauhati Medical College, Guwahati, Assam, India (2015) and post-graduation (MD) in Paediatrics from Advanced Paediatrics Centre, Post Graduate Institute of Medical Education and Research, Chandigarh, India (2020). He is currently pursuing a 3-year post-doctoral (DM) training programme in Paediatric Clinical Immunology and Rheumatology at the Advanced Paediatrics Centre, Post Graduate Institute of Medical Education and Research, Chandigarh, India and is likely to complete it in December 2023. This is the first, and till date the only, such post-doctoral training course in Paediatric Rheumatology in India.

He aspires to continue in an academic institute after his training and has 12 publications till date in reputed journals. In addition to medicine, he has a keen interest in extra-curricular activities and has a Bachelor's degree in Indian classical music (Vocal) and a Diploma in Water and Oil painting.

Objectives: To quantify T-cell receptor excision circles (TREC) and kappa-deleting re- combination excision circles (KREC) in patients with common variable immunodeficiency (CVID) and to study their association with clinical phenotype, laboratory manifestations and genetic profile from a cohort of patients in North India.

Design and Methods: A cross-sectional observational study was conducted on patients with CVID attending out-patient and/or in-patient services of Paediatric Allergy Immunology Unit, Department of Paediatrics, Advanced Paediatrics Centre, Post Graduate Institute of Medical Education and Research, Chandigarh. Diagnosis of CVID was based on revised European Society for Immunodeficiencies (ESID) registry criteria (2014).
TREC and KREC assay was performed using a multiplex real-time PCR with TaqMan probes. Plasmid carrying a triple insert DNA sequence of (TREC: KREC: TCRAC) were used for making a standard curve for enumerating the levels of TREC/KREC in patients and healthy controls.
The copies of TRECs/KRECs were calculated and expressed as copies/50 ng reaction.

Results: In this study, 34 patients with CVID and 30 healthy age and sex matched controls were included. Male: female ratio was 1:1. Median age at onset of symptoms was 4 years (IQR: 2- 10.75) and median age at which sample was taken was 17 years (IQR: 10-24.25). Monogenic defects were identified in 10/34 patients. Patients with disease onset ≤ 4 years were more likely to have a monogenic defect (p=0.02).The median values of KREC and TREC copy numbers in patients with CVID were 64.5 copies/50 ng reaction and 170 copies/50 ng reaction respectively, whereas the median values of KREC and TREC copy numbers in controls were 79.2 copies/50 ng reaction and 190.1 copies/50 ng reaction respectively. There was no statistically significant correlation of TREC/KREC levels with infections, autoimmunity, bronchiectasis and malignancy, immunoglobulins, CD19+ B cells proportion, CD4:CD8 ratio, and presence of monogenic defects. We classified the patients into 4 groups based on copy numbers of TREC/KRECs: (A)TREC+/KREC+; (B) TREC+/KREC-; (C) TREC-/KREC+; (D)TREC-/KREC- ['+' and '-'
denotes TREC/KREC levels above and below median value respectively]. Patients in Group B had higher risk of developing bronchiectasis as compared to other groups (p< 0.05), and there was no difference with other clinical/immunological phenotypes.

Conclusions: TREC/KREC levels are low in patients with CVID. A sub-group of patients with CVID with low KREC and normal TREC levels may be predisposed to develop bronchiectasis.

POSTER 79 - RETROSPECTIVE EVALUATION OF DEMOGRAPHIC AND CLINICAL FEATURES OF OUR PRIMARY IMMUNODEFICIENCY PATIENTS: A SINGLE CENTER EXPERIENCE

AUTHORS

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AFFILIATIONS

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Biography:
I was born on 15.02.1981 in Balıkesir/Turkey. I graduated from Ankara Gülhane Military Medical Academy Faculty of Medicine in 2005. Between 2008-2012, I completed my pulmonology specialty training in the Department of Chest Diseases at Gülhane Military Medical Academy.
Between 2012-2021, I worked as a pulmonologist in various state institutions. I won the subspecialty exam with the degree of first in Turkey. I started my subspecialty training at Gülhane Training and Research Hospital Allergy and Immunology Clinic in August 2021 and I am still working as a subspecialty fellowship in the same institution.

Objective: Most of the primary immunodeficiencies(PID) disorders are hereditary that approximately 485 gene mutations had been determined and also new gene mutations are going to be added. PID's are called inborn errors of immunity in last years and characterized by predisposition to infection, atopy, malignancy or autoimmune diseases. We aimed to determine the clinical and demographic characteristics of our patients with PID in our study.

Design and method: The records of 55 PID patients who are following up in our clinic were retrospectively analyzed.

Results: 63.6%(n=35) of our patients were male and 36.4%(n=20) were female. The mean age was 42.11±15.66 years and the mean age at diagnosis was 33.31±19.92 years. The median age at first complaint was 21(min:0,max:70). The mean delay in diagnosis was
8.86±9.35 years. 21(38.2%) patients had a diagnostic delay of more than 10 years. We compared patients with and without autoimmune diseases about diagnostic delay but no statistically difference was found(p=0,624).17 patients (30.9%) had parental consanguineous marriage and 7 patients (13.5%) had a family history of immunodeficiency. The most common presenting complaints were recurrent sinopulmonary infections and chronic diarrhea. There were no comorbidities in 36.36%(n=20) of the patients. Autoimmune diseases and malignancy were the most common comorbidities (Table 1). Bronchiectasis was found in 19 patients (34.5%) and hepatosplenomegaly in 23 patients (41.81%). 46 patients (83.7%) were receiving IVIG and 9(16.4%) were receiving SCIG treatment. The 3 of the IVIG treated patients were also receiving biologic agent treatment(anti-IgE, anti-IL5) with a diagnosis of severe asthma.

Conclusions: PID are seen rarely and the diagnose is difficult mostly.The age of onset is variable and delays in diagnosis is common. We found the mean delay in diagnosis was 9 years in our study. We found only %30.9 of our patients have parental consanguineous marriages and so no consanguinity does not exclude the possibility of PID. In addition to infections, the PID patients will have immune dysregulation leading to autoimmunity, inflammatory disorders and malignancy. Patients may also present with symptoms of these diseases with or without frequent infections. It is noteworthy that 4 of our patient's presenting symptom was hemoptysis. Early diagnosis, follow-up and treatment of these patients with a multidisciplinary approach under the leadership of experienced clinics is very important.

POSTER 101 - FROM LABORATORY TO CLINICS, INCIDENCE OF URINARY INFECTIONS IN PATIENTS WITH COMMON VARIABLE IMMUNODEFICIENCY IN A THIRD LEVEL HOSPITAL , WHAT DO WE KNOW? A CROSS SECTIONAL DESCRIPTIVE STUDY

AUTHORS

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AFFILIATIONS

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Biography:
SURGEON BY THE NATIONAL AUTONOMOUS UNIVERSITY OF MEXICO, POSTGRADUATE STUDENT IN ALLERGY AND CLINICAL IMMUNOLOGY IN THE NATIONAL MEDICAL CENTER "SIGLO XXI" BY THE MEXICAN INSTITUTE OF SOCIAL SECURITY ENDORSED BY THE NATIONAL AUTONOMOUS UNIVERSITY OF MEXICO, AND PART OF EXCELLENCE PROGRAM OF POSGRADUATE STUDIES "CONACYT" AND REFERENCE CENTER FROM EXCELLENCE WAO, JUNIOR MEMBER OF LASID AS WELL AS THE CENTRAL CHAPTER OF THE MEXICO COUNCIL OF ALLERGY AND IMMUNOLOGY (CMICA)

Introduction: Patients with Common Variable Immundeficiency (CVID) present a broad range of clinical manifestations, including recurrent bacterial infections . The upper and lower respiratory tract are the most common sites, however there is just a few information worldwide about urinary tract infections.

Objectives: To determine the frecuency of urinary tract infections in our patients with CVID and its correlation among the use of subcutaneus vs intravenous novel Immunoglobulin.

Methods: Descriptive, cross-sectional design of all patients diagnosed with CVID who agreed to enter the protocol, with or without urinary sintoms we perform a General urinalysis (GOS) and urine culture in all patients , anatomical alterations in the urinary tract were searched in the radiological file. Approved by local ethics committee R-2020-3601-073
We enroll a total of 31 patients with the diagnostic of CVID ,11(35.5%) Male and 20(64.5%) female a median of age was 47 years, 80.6% of our patients has one or more comorbidities in first place autoimmunity 61.29% , second place hipotyroidism with 22.5%, the mean IgG serum concentration were 1289 mg/dl , Only 4 patients had urinary symptoms, 3 patients of the total study had structural alterations, only 6.5% of the results were positive in the urine culture and 5 patients (16.1%) had a history of recurrent urinary tract infections.

In the statistical analysiss the total immunoglobulins and peripheral blood T lymphocytes were evaluated according to the existence of alterations in the urinary analisis (UA). There where lower levels of median CD3+ 719 cel/mm3 (388-771) and CD4+ 273 cel/mm3 (237-359) in patients with altered UA vs without alterations CD3+ 1750 cel/mm3 CD4+ 666 cel/mm3 with a
p.022 and .027 respectively. The mean IgM concentration of patients with recurrent urinary infections vs no history was 16mg/dL vs 46 mg/dL respectively with a p.030 Regarding the evaluation of the type of treatment received, we found that 3 patients (75%) of the total positives were receiving IgG IV vs 1 patient (25%) IgG SC p<.001

Conclusions: Since repetitive infections are a gateway in our patients with inborn errors of immunity, it is necessary to know the general behavior of its presentations, associated comorbidities as well as the response to the treatment . We were able to find statistical significance regarding the concentrations of CD4 and CD8 and the route of administration of immunoglobulin being more revalent in those receiving IV IgG, further studies are required to establish a correlation.

POSTER 102 - TRANSIENT HYPOGAMMAGLOBULINEMIA OF INFANCY: CLINICAL AND IMMUNOLOGIC FEATURES OF 385 CASES

AUTHORS

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Biography:
Neslihan Karaca obtained her medical degree at Ege University Faculty of Medicine in 2000. She has sixteen years of experience in primary immunodeficiency diseases.

Objective: Transient hypogammaglobulinemia (THI) of infancy is a common primary immunodeficiency with indistinct pathophysiology presenting with a delay in the maturation of immunoglobulin production. It usually resolves by 3 years of age. In the present study, we report on the clinical presentation, follow-up, and outcome of patients diagnosed with THI.

Design and method: The medical files of patients who had serum concentrations of one or more of the three major immunoglobulin classes with more than 2 standard deviations (SDs) below normal for age on at least three specimens obtained during follow-up; demonstrated a rise in these values towards normal over time; had at least 12 months of follow-up duration and did not have features consistent with other forms of primary immunodeficiency were reviewed retrospectively.

Results: A total of 385 THI patients (125 female, 260 male) were included in this study. The mean age at admission of patients was 22.1±12.5 months. Most of the patients presented with recurrent upper and lower respiratory tract infections. Eczema, food allergy, recurrent skin abscess were the other findings. Initial median IgG, IgM, and IgA levels were 456 mg/dl, 68 mg/dl, and 25 mg/dl, respectively. The frequency of atopy was 13%. Neutropenia in addition to hypogammaglobulinemia was observed in 10% of the patients. The mean age of normalization of IgG levels was 56.2±32.3 months. Patients who had neutropenia were observed to reach normal IgG and neutrophil levels (simultaneously) at an earlier age. Type of allergic symptoms had a statistically significant effect on the normalization age; was 53.7±29.1 months in cases with recurrent bronchiolitis, and it was 31.2±16.2 months in patients with eczema and food allergy.

Conclusions: Transient hypogammaglobulinemia of infancy is a retrospective diagnosis. The coexistence of neutropenia or eczema may be a clue for the prediction of an earlier recovery age. Further investigations are necessary to clarify these issues.

POSTER 103 - UNEXPECTED COMPLICATIONS IN AN INDIAN CHILD WITH COMBINED IMMUNODEFICIENCY

AUTHORS

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EDUCATIONAL QUALIFICATION
1. *SSLC (10th) Rajagiri Higher Secondary School, Kalamassery, Ernakulam, March 2007*
2. *HSC (12th) Rajagiri Higher Secondary School, Kalamassery, Ernakulam, March 2009*
3. *MBBS Christian Medical College, Vellore March 2015 (date of passing)*
4. *MD Paediatrics Christian Medical College, Vellore August 2021 (date of passing)*

EMPLOYMENT DETAILS
1. *CSI Mission hospital, Codacal, Kerala, Chief medical officer, April 2016-March2018*
2. *Christian Medical College, Vellore Assistant Professor, Department of Paediatrics, September 2021 till now*
3.

RESEARCH PROJECTS
- *Original Article: George TK, Toms AG, Fenn BN, Kumar V, Kavitha R, Georgy JT, et al. Renal outcomes among snake-envenomed patients with acute kidney injury in southern India. Natl Med J India. 2019 Feb;32(1):5–8*
- *Poster presentation in the Indian Society for Paediatric and Adolescent Endocrinology (ISPAE) conference 2019: Testicular adrenal rest tumours (TART's) among boys with Congenital Adrenal Hyperplasia (CAH) - single centre study*
- *E-poster for the Indian Society for Paediatric and Adolescent Endocrinology (ISPAE) conference 2021: Aspergillus suppurative thyroiditis- report a rare cause of transient hyperthyroidism.*
- *National conference on Paediatric Infectious diseases 2022, Third prize for Poster presentation : Evaluation of induced sputum against gastric juice aspirate in the diagnosis of Tuberculosis in children less than 15 years*
- *E poster presentaion: European Society of Paediatric Infectious diseases conference (ESPID) 2023: Evaluation of induced sputum against gastric juice aspirate in the diagnosis of Tuberculosis in children less than 15 years*

Academic Prize
- *One month Internship in 'The Radiation Genetics Laboratory' under Prof. Shunichi Takeda, Kyoto University, Japan as part of the 'CMC MBBS Exchange Programme- 2013'*

Objective: To describe rare autoimmune manifestations of combined immunodeficiency in a child.

Design: Case report

Methodology: Retrospective case analysis

Results: A 13-Year-old Indian boy, first born to third degree consanguineous parents presented with history of recurrent episodes of fever and jaundice for one week. In infancy, he had recurrent skin infections in the groin and both retro-auricular areas. He was evaluated elsewhere and was told to have autoimmune hemolytic anemia (AIHA) and managed with IVIg and pulse dose corticosteroids for 5 days. While on tapering prednisolone, he had worsening pallor and jaundice. He was brought to our institution for evaluation and treatment of recurrent AIHA and suspected primary immunodeficiency. On examination, he had pallor and icterus, generalized scaly, seborrheic patches along with hyperpigmented lesions over bilateral ears and penis. Spleen was palpable 3cm below the right costal margin. Investigations showed hemoglobin of 4.5gm/dl, total count of 53,200/cumm, platelet count of 669,000/cumm, reticulocyte count of 14.93%, liver function test showed unconjugated hyperbilirubinemia (total bilirubin: 2.88mg/dl, direct bilirubin 0.73mg/dl) and an elevated LDH(2350U/L). DCT

was 4+ and the monospecific DAT was positive for IgG. He was managed with red blood cell transfusion and pulse doses of corticosteroids (30mg/kg/day of Inj. Methyl Prednisolone) for 3 days followed by tapering doses of oral prednisolone. Child improved clinically and hemoglobin normalized after pulse steroids.
Primary immunodeficiency workup showed elevated immunoglobulin E:14,635(N:0.98- 570.6IU/ml),IgG:2058(N:608-1572mg/dl), IgA:262(N:45-236mg/dl) and IgM:45(N:52-242mg/dl).
A Next-Generation-Sequencing revealed a homozygous splice variant (c.1125+1G>A) in DOCK8 gene. Antibiotic prophylaxis was initiated. Two months later, he developed refractory seizures requiring ICU care. CSF analysis was within normal limits. Infectious workup with TB PCR, bacterial cultures, viral multiplex PCR and cryptococcus serology were negative. MRI brain showed hyperintense signal changes and cortical thickening in left parietal lobe.
Electroencephalography showed epileptiform activity arising from left and mid parietal, left occipital regions. His seizures persisted and he later developed epilepsia-partialis-continua, requiring pulse doses of methyl prednisolone and IVIg. His repeat MRI showed worsening of gyral swellings and hyperintensities diffusely involving the left cerebral hemisphere and basal ganglia. Owing to refractory seizures, he succumbed to his illness.

Conclusion: Autoimmune manifestations are common in children with PID. Here we report a rare complication in DOCK8 mutation, who developed autoimmunity in the form of AIHA and refractory seizures.

POSTER 105 - THE EARLY DIAGNOSIS OF LIVER FIBROSIS IN ENTEROPATHY PHENOTYPE OF COMMON VARIABLE IMMUNODEFICIENCY: IMPORTANCE OF SHEAR-WAVE ELASTOGRAPHY

AUTHORS

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AFFILIATIONS

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Biography:
Dr Maja Stojanovic is a Consultant Clinical Immunologist/Allergist based at the Clinic of Allergy and Clinical Immunology, University Clinical Center of Serbia, a National center for rare diseases. She provides care for patients with primary immunodeficiencies, systemic autoimmune disorders, and allergies. Dr Stojanovic joined the Faculty of Medicine as Clinical Teaching Assistant in March 2018. She gained my Ph.D. from the University of Belgrade in 2022, which focused on systemic vasculitis. Her main clinical/research interests include primary immunodeficiencies and systemic vasculitides.

Introduction: Primary antibody deficiencies (PAD) are defined as a group of inborn errors of immunity characterized by an inability to produce clinically effective immunoglobulin (Ig) responses. Although selective IgA deficiency is the most frequent among PAD, common variable immunodeficiency (CVID) and agammaglobulinemia (AGA) have more impact on morbidity and mortality since multiple comorbidities may follow them due to infection and/or immune dysregulation. The reported prevalence of liver disease of any cause in patients with PAD varies depending on the diagnostic criteria applied. Shear-wave elastography represents an emerging method for the assessment of liver fibrosis.

Methods: 16 patients with PAD (13 CVID and 3 AGA) with a median age of 38.5 (IQR 21-56.5) were assessed for liver disease by analyzing biochemical blood parameters and measuring liver stiffness by shear-wave elastography. The tissue stiffness was measured and expressed in kilopascals (KPa) using the S-Shear wave feature of the SAMSUNG RS80A device with a convex probe. The measurement reliability was determined using the Reliable Measurement Index (RMI) and Interquartile Range (IQR).

Results: In our study group of 16 PAD patients, the mean coefficient of liver stiffness was 8.65+/-4.2KPa. In comparison, the cut-off values for liver fibrosis in healthy people are above 7KPa. Patients with AGA had 6.93+/-0.31KPa, while patients with CVID had 9.0+/-4.4KPa.
Among our PAD patients, 7/16 (43.7%) had enteropathy histopathologically and/or confirmed by a computed tomography (CT) enterography. Patients with CVID/enteropathy (6/13, 46%) had a higher mean liver stiffness (10.7+/-5.27KPa), and it was significantly higher compared to patients with CVID and no enteropathy (6.96+/-1.32KPa). The highest liver stiffness values (20.0 and 17.8KPa, respectively) were detected in patients with CVID/enteropathy. Mixed liver disease with only slightly elevated transaminases was present in one patient with AGA; this patient with AGA/liver disease was found to have only mild fibrosis (7.2 KPa).

Conclusions: Our results showed a higher liver stiffness in patients with CVID/enteropathy. These findings suggest that immune dysregulation, usually present within distinct immunological phenotypes in CVID, may predispose to liver and duodenal injury. In line with this, lymphocyte- mediated cytotoxicity may be a mechanism that orchestrates a process of liver fibrosis in particular CVID patients. Further studies could elucidate the exact mechanism of this immune- dysregulation-mediated liver fibrosis in CVID, suggesting its early treatment options.

POSTER 122 - RETROSPECTIVE EVALUATION OF PATIENTS WITH CHRONIC GRANULOMATOSIS

AUTHORS

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Background: Chronic granulomatous disease (CGD) is a primary immunodeficiency disorder of phagocytes (neutrophils, monocytes, macrophages, and eosinophils) resulting from impaired killing of bacteria and fungi. CGD is a primary immunodeficiency of phagocyte function due to defective NADPH oxidase (phox).Use of antimicrobial prophylaxis and therapy has greatly improved overall survival. Hematopoietic stem cell transplantation (HSCT) is the curative treatment.

Objective and Methods: In this study; We evaluated retrospectively using age, gender, age at diagnosis, family consanguinity, family history of immune deficiency, presentation symptoms, clinical, laboratory and genetics, treatment applied, survival data, patient file and hospital digital database.

Results: 65.4% (n=17) of our patients were XR-CGD, 34.6% (n=9) were OR-CGD. 23% (n=6) of our patients were girls. All of the XR-CGD patients and 33.3%(n=3) of the OR-CGD patients were male. The mean age of our cases was 148.4 months. While there was consanguinity in 46% (n=12) of our patients, there was consanguinity in all (n=9) and 23% (n=4) of XR-CGD patients. The type of heritable inheritance with consanguinity was found to be statistically significant ($P < 0.05$). 84.6% of the patients had an infection (n=22 individuals) since early infancy. Respiratory tract infection was present in 61.5% of the patients. Recurrent abscesses were present in 61.5% (n=16) of the patients. While the most common skin abscess was 46.2%, 38.5% had perianal abscess and 19.2% had hepatic abscess. While 12.5% (n=2) of them had skin, perianal and hepatic abscesses, 18.75% (n=3) had hepatic and skin abscesses, 12.5% had skin and perianal abscesses. Fifty percent of the patients had lymphadenopathy, 46.2% had pneumonia, 38.5% had growth retardation and 11% had diarrhea. Bone marrow transplantation was performed in eight XR-CGD and four OR-KGH cases. Of the bone marrow transplanted patients, 41.6% were from an HLA-matched relative donor, 33.3% from an HLA-matched sibling donor, 16.6% from an HLA haploidentical donor, and 8% from an HLA-matched unrelated donor. 26.9% (n:7) of our patients were ex during medical follow-up, five of them had XR-CGD inheritance and two had OR-CGD inheritance. The genetic inheritance of 2 patients who died after the kit was XR-CHG.

Conclusions: Especially in countries where consanguineous marriage rates are high, early diagnosis for appropriate treatment of CGD is very important to avoid serious recurrent infections, early death and fatal complications of late transplantation.

POSTER 137 - INBORN ERRORS OF IMMUNITY WITH NEUTROPENIA: CLINICAL AND MOLECULAR INSIGHTS FROM CHANDIGARH, NORTH INDIA

AUTHORS

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AFFILIATIONS

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Biography:
Dr. Rakesh Kumar Pilania, MBBS, MD, DM, MAMS

- *Graduated from SMS Medical College, Jaipur: 2004-2010*
- *M.D. Paediatrics - PGIMER, Chandigarh: 2011-2014*
- *DM Pediatric Clinical Immunology and Rheumatology, PGIMER, Chandigarh (2017-2019)*
- *Visiting fellow at Department of Rheumatology, Hospital for Special Surgery, Weil Cornell University, New York, USA (15 November -14 December, 2019)*
- *Visiting fellow at Primary Immunodeficiencies Unit, Department of Paediatrics, University Hospitals Leuven, Belgium (23 September -25 October, 2019)*
- *Senior Resident Paediatrics, PGIMER, Chandigarh (July 2014-Dec 2016)*
- *Senior Resident Paediatrics, PGIMER, Chandigarh (Jan 2020 – Dec 2020)*
- *Associate Professor of Paediatrics, AIIMS, Bhopal (April 3, 2021 – June 23, 2021*

- *Current position: Assistant Professor of Paediatrics, Department of Paediatrics, Advanced Paediatrics Centre, PGIMER, Chandigarh*
- *European Society for Immunodeficiencies (ESID) Junior Country Representative for India (2018 - 2022)*
- *Awarded Dr. Satya Gupta Award by National Academy of Medical Sciences, New Delhi, India for research on Kawasaki disease; 2021 V Balagopal Raju Endowment Award and Gold Medal by Indian Academy of Paediatrics for Best DM thesis paper presentation; 2019 ACR / IRA Exchange Fellow award (visiting fellow Weil Cornell University, New York, USA); ESID Observership Grant 2019 (visiting fellow at Primary Immunodeficiency Unit, Department of Paediatrics, University Leuven, Belgium); Young Investigator Award (2018) by International Kawasaki disease Symposium, Yokohama, Japan for work on Kawasaki disease; Best platform presentation for work on Kawasaki disease by Indian Society for Kawasaki disease 2020*
- *Received International Travel Award from American College of Rheumatology (ACR), European Society of Immunodeficiencies (ESID); European League Against Rheumatism (EULAR); Korean College of Rheumatology; Clinical immunology Society Diagnostic School in Primary Immunodeficiency Diseases, Boston, USA; European Society for Paediatric Infectious Diseases (ESPID); Asia Pacific Society for Immunodeficiencies (APSID); Jeffrey Modell Foundation, USA; National Association of Experts in Primary Immunodeficiencies (NAEPID) & National Medical Research Center for Pediatric Hematology, Oncology and Immunology, Moscow, Russia*
- *Published more than 90 manuscripts in peer reviewed journal and 6 book chapters*
- *Reviewer for international journals (International Journal of Rheumatic Diseases; Journal of Clinical Rheumatology; Lupus journal; Indian Journal of Pediatrics; Central European Journal of Immunology; BMC Infectious disease; Frontiers in Paediatrics; PLOS One; World Journal of Paediatrics; Journal of Inflammation Research*
- *Member National Academy of Medical Sciences (MAMS)*
- *Founder member of Indian Society for Kawasaki disease*

Background: Neutropenia plays a significant role in several inborn errors of immunity (IEIs). Data are often lacking because of the diverse pathophysiologies of IEIs and the rarity of each disorder. Investigating a diverse spectrum of IEIs with neutropenia is essential, revealing multiple underlying genetic defects and associated clinical phenotypes.
Objectives: This study presents clinical and molecular profile of children with IEIs with neutropenia.

Patients and methods: Case records of patients registered in Pediatric Immunodeficiency Clinic at Advanced Pediatrics Centre, PGIMER, Chandigarh, were reviewed. Children diagnosed with an IEI and neutropenia at presentation were analyzed. Neutropenia was defined as severe (<0.5x109/L) or mild (between 0.5-1.5 x109/L). Serial blood counts were performed two times/a week for at least six weeks to look for the cyclic nature of the disease. Genetic confirmation was done by next-generation sequencing and /or Sanger Sequencing.

Result: Fifty-four (54) children were suspected of having IEIs with neutropenia (Figure 1). Median age at diagnosis is 24 months (4 months – 96 months). Severe congenital neutropenia (SCN) was seen in 5 children, cyclic neutropenia in 13, and autoimmune neutropenia in 5. Other IEIs with neutropenia include Wiskott Aldrich syndrome (n=3), Hyper IgM syndrome (n=5), X- linked agammaglobulinemia (n=3), severe combined immunodeficiency (n=4), chronic mucocutaneous candidiasis (n=1), combined immunodeficiency (n=1), Hermansky-Pudlak syndrome (n=1) and others (n=12). Definite IEI could be identified in 40 (22 boys, 20 girls) patients. Of the 18 patients with SCN and cyclical neutropenia (Figure 2), underlying genetic could be placed in 11 patients (ELANE in 4 (Figure 3A) SLC37A4 in 2, HAX1 in 1, CEBPE in 2 (Figure 3B) , Swachman diamond syndrome in 2). Children with SCN had absolute neutrophil counts <0.2x109/L, and bone marrow examination showed maturation arrest. Granulocyte stimulating factor (GCSF) requirement in children with SCN ranged from 15-20 micrograms/day to keep infection free. These patients were also continued cotrimoxazole prophylaxis. Children with XLA had neutropenia at a presentation associated with acute illness. There was a total of 5 deaths: severe combined immunodeficiency (3), Wiskott Aldrich syndrome (1), and Hyper IgM syndrome (1). Children with SCN and cyclical neutropenia are doing well on antimicrobial prophylaxis and/or GCSF therapy.

Conclusions: Neutropenia can be associated with a host of IEIs. A detailed evaluation is needed to identify the underlying IEI. Severe neutropenia and arrest of granulopoiesis in bone marrow suggest SCN. Early initiation of GCSF and antimicrobial prophylaxis in patients with SCN results in favorable outcomes.

POSTER 143 - VEXAS SYNDROME IN A PATIENT WITH BICYTOPENIA AND SWEET SYNDROME/ TOXICODERMA

AUTHORS

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AFFILIATIONS

[1]Hospital Universitario Puerta Del Mar

Biography:
3rd year Immunology resident at Hospital Universitario Puerta del Mar in Cádiz, Spain.

Objectives: A 77-year old male was admitted in our hospital after presenting fever, fatigue and chills. Patient has a history of hypertension, dyslipidemia, atrial fibrillation, recurrent infections, atrophic gastritis, autoimmune thyroiditis, neutropenia and macrocytic anemia with mild erythroid dysplasia, auricular chondritis and leukocytoclastic vasculitis on lower limbs.
During admission, he developed urinary symptoms and pulmonary infiltrates categorized as hospital-acquired pneumonia. E. coli was isolated in urine culture; after antibiotic treatment, symptoms and x-ray findings improved. In addition, he developed urticarial exanthema on neck and chest.
Prior to this event, this patient had been admitted due to repeated infections (respiratory, cellulitis and urinary, mainly) for antibiotic treatment.
The objective of this clinical case is the diagnostic and immunological characterization of a patient presenting recurring infections, bicytopenia and skin lesions.

Methods: A peripheral blood sample was obtained, as well as bone marrow aspirate, for assessment of haematopoietic cells. The methods used were flow cytometry and morphological analysis.
Genetic testing by Sanger sequencing was also performed on bone marrow sample.
A skin biopsy was obtained from neck and chest area where exanthema had developed.

Results: Flow cytometry fails to find anomalies in population distribution, maturity and phenotype of the analysed samples. Bone marrow aspirate doesn't fulfil criteria for myeloproliferative syndrome; examination of bone marrow smear shows the presence of 8,5% of granulocytes with vacuoles.
Sanger sequencing was performed on bone marrow sample (Image 1) which detected a somatic mutation (c.122T>C) resulting in a change of aminoacid Methionine for Threonine (p.Met41Thr) on exon 3 of UBA1 gene, located on chromosome Xp11.23.
Skin biopsy revealed findings of perivascular dermatitis with mixed infiltrate, categorized as Sweet syndrome vs. drug-related toxicoderma, after having started treatment with erythropoietin a few days prior.

Conclusions: Genomic sequencing results, in addition to clinical findings and patient history suggest diagnosis of VEXAS syndrome.
VEXAS syndrome (vacuoles, E1 ubiquitin, X-linked, autoinflammatory, somatic) was first described in 2020 as an autoinflammatory disease primarily affecting adult males. It is caused by somatic mutations in UBA1 gene affecting precursor myeloid cells, causing a pathogenic myeloid clonal population. UBA1 disfunction translates in an excessive activation of inflammatory pathways, causing a multiorganic inflammatory syndrome. Common symptoms include fever, arthritis, chondritis and skin lesions.
Patients with this disease are also at increased risk of developing hemathologic diseases, especially myelodisplasic syndrome.
Patient is nowadays being treated with prednisone, prophylactic antibiotics (Trimethoprim/sulfamethoxazole) and awaiting assessment to start JAK-inhibitors.

POSTER 161 - HEREDITARY ANGIOEDEMA IN PORTOVIEJO, ECUADOR: CLINICAL SYMPTOMS AND RELATIONSHIP WITH QUALITY OF LIFE.

AUTHORS

Alarcón N[1]

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Biography:
I am Dr. Nora Alarcón, an immunologist, I work in Ecuador, in a city called Portoviejo, I belong to a public hospital where I diagnose and treat patients with primary immunodeficiencies. I am a member of the Latin American Society of Primary Immunodeficiencies (LASID), I am Secretary of the Ecuadorian Society of Primary Immunodeficiencies primaries. My main language is Spanish, but I do not consider it an impediment to make space for my country on this arduous path of primary immunodeficiencies

HEREDITARY ANGIOEDEMA IN PORTOVIEJO, ECUADOR: CLINICAL SYMPTOMS AND RELATIONSHIP WITH QUALITY OF LIFE.
Nora Alarcón Cedeño1, Leonardo Palomeque 2, Otto Intriago 3, María Cedeño 4.
Immunologist, IEES Portoviejo General Hospital. Secretary of the Ecuadorian Primary Immunodeficiency Society, Presenter of work.
Intensive Care Physician, IEES Portoviejo General Hospital
Intensive Care Physician, IEES Portoviejo General Hospital
Intensive care unit resident physician, IEES Portoviejo General Hospital

Introduction: Hereditary Angioedema is an inborn error of immunity, that is to say, a primary immunodeficiency, with a genetic origin, of an autosomal dominant nature, which is due to a deficiency in the activated factor C1 esterase inhibitor protein, characterized by recurrent episodes of edema. subcutaneous and mucosal. Unpredictable and frequent crises of angioedema affect the quality of life of the individuals who suffer from them.

Objective: To analyze the clinical characteristics of three families with hereditary angioedema and to evaluate the implication of the disease in their quality of life.

Design and method: Thirty members of three families from the city of Portoviejo, Ecuador, were included in the study. Blood levels of complement factor C4 were measured in 10 individuals and only 2 were assessed for antigenic and functional C1 inhibitor. , due to lack of resources of patients in our country, with extraction of molecular study in Madrid is awaiting report. Two instruments were used, the SF-36 to assess the health of the adult.

Results: The people studied reported symptoms meeting serological criteria for type II hereditary angioedema: low values of complement factor C4 and quantitative (antigenic) and qualitative (functional) C1 inhibitor. It was possible to rescue from the surveys conflicts in the labor, family and social areas, granting higher percentages in parameters that lead to the affectation of quality of life due to the edemas presented, with risk of death in some of the cases, affecting their psychological well-being and emotional performance.

Conclusion: This small study gives us information about the first documented families with hereditary angioedema type II in the city of Portoviejo, Ecuador. A generic instrument was used, it was also confirmed the negative effect of the disease on the quality of life of the individuals who suffer from it, considering their quality of life is much lower in relation to common patients.

POSTER 162 - BEYOND WISKOTT ALDRICH SYNDROME (WAS), THE ROLE OF WASP-INTERACTING PROTEIN (WIP) IN IMMUNODEFICIENCY AND MALIGNANCY

AUTHORS

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Biography:
MD Clinical Immunology resident in Clinico San Carlos Hospital, Madrid. Currently carrying out research projects in the field of immunodeficiencies, as well as a Master's degree in Biochemistry, Biomedicine and Molecular Biology.

Objective: The relationship between primary immunodeficiencies (PID) and the development of secondary lymphoproliferative disorders is well recognized. However, diagnosing PID in a patient with late onset hypogammaglobulinemia requires excluding an ongoing malignant process. However, what if both approaches were different phenotypes of a common underlying genetic pathology? We aim to describe this PID/SID intersection and the role of monogenic variants in an illustrative case of a 72-year-old Caucasian woman with a heterozygous mutation in WIPF1 gene. The patient suffered a long-term selective IgA deficiency before developing a late-onset combined immunodeficiency (LOCID) and an aggressive T cell lymphoproliferative disorder.

Design and Methods: Whole exome sequencing (WES) of the patient's peripheral blood was performed, followed by an in silico analysis of the genetic variant found. Flow cytometry was used to study the T and B cell profile of the patient, as well as the intracellular expression of WAS protein in the lymphocytic population. The same analysis was performed in a control cohort of 9 PID patients and 9 otherwise healthy controls. WASp and WIP expression in the patient were also studied by Western Blot.

Results: WES revealed a heterozygous mutation in the WIPF1 gene. This genetic variant was expected to be deleterious according to the in silico analysis performed. Contrary to what was expected, the patient not only showed expression of WASp, but had two distinct T cell populations with different WASp expression levels. Levels of WASp expression were variable among controls, but none of them showed two distinct lymphocyte populations. Moreover, the patient showed an impaired T cell profile, with almost no näive nor central memory T lymphocytes. Lastly, TCR γ/δ lymphocytes were undetectable in the patient's peripheral blood.

Conclusions: A gene defect may not always reflect as an impaired protein expression, and thus, a functional defect in WASp and WIP interaction could explain the impaired T cell profile of the patient, as well as the viral and invasive bacterial infection recurrence. Furthermore, immunodeficiency and malignant outcomes might be part of the same disorder. WIP defect might explain the patient's phenotype, but also other factors favored by the gene variant, such as decreased viral immunosurveillance, are surely important contributors.

POSTER 165 - TCR, WHERE ARE YOU? AN INTRIGUING CASE OF A PATIENT WITH AN ABERRANT T LYMPHOCYTE POPULATION OF CD3+/CD4-/CD8-/TCRαβ-/TCRγδ- AND IGG2 DEFICIENCY

AUTHORS

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Biography:
I'm a third-year pediatric resident in the Pediatric Immunology Research Group. For some time now I have been passionate about the field of primitive immunodeficiencies and the study of these increasingly numerous pathologies, participating in congresses, schools (ESID Winter school and Spring school), courses and webinars. I find it fascinating and at the same time intriguing to think that only a few decades ago these diseases could be counted almost on the fingers of the hands while now there are almost 500 pathologies! Precisely for this reason I am convinced that participating in congresses, meeting experts, as well as patients, is essential to expand one's knowledge and experience

Objective: Double negative (DN) T cells are a minor subpopulation of T lymphocytes involved in immune response and regulation lacking the surface expression of the CD4 and CD8 co-receptors. DN T cells normally express the T cell receptor (TCR)-γδ or, in small proportion, -αβ.

Design and method: We report the case of a 4-year-old boy with an aberrant T lymphocyte population of CD3+/DN/TCRαβ-/TCRγδ- and IgG2 deficiency.

Results: The patient is the fifth child of non-consanguineous Egyptian parents, born at 35 weeks of gestation by cesarean section for placenta previa. Since he had a single palmar crease, minor facial anomalies and psychomotor retardation an CGH-array was performed, resulted normal. Hitherto, he is undergoing pulmonary follow-up for OSAS, which led to two adenotonsillectomy interventions at 22 months and 3 years of age.

The patient came to our attention at the age of 4 months, when he was hospitalized for a probable incomplete Kawasaki disease and a post-natal CMV infection treated with oral Valganciclovir. At that time, serum immunoglobulins and lymphocyte subpopulations resulted normal.
At the age of 2 years a complete immunological work-up was performed showing normal serum immunoglobulin levels but an IgG2 deficiency.
Moreover, lymphocyte subpopulations showed an increased percentage of DN T cells (10% of lymphocytes), and the extensive immunophenotyping revealed an aberrant TCRαβ-/TCRγδ- population, equal to about 30% of DN cells and 4% of total CD3+ (figure 1). Further investigation on this subset showed a proper expression of the other T cell lineage markers (CD2, CD5, and CD7), the absence of CD56, and a polyclonal rearrangement of TCR gene (figure 1 and 2). A deeper characterization excluded an expansion of the recent thymic emigrant lymphocytes or of activated T cell fraction (figure 1).
Finally, an NGS panel performed to study the genes causing hypogammaglobulinemia resulted normal.
Clinically, during the follow-up the patient remained stable without requiring other hospitalizations and only with few episodes of upper respiratory infections.

Conclusion: We are dealing with a case of a patient with IgG2 deficiency and a CD3+/DN/TCRαβ-/γδ- population, which is stable in percentage, and where the normal expression of T cell markers together with the absence of a clonal TCR rearrangement seems to exclude an immuno- or onco-hematological pathology. This population of unknown origin and significance is still under investigation and analysis on different tissues are scheduled.

POSTER 167 - SLOVENIAN CASE SERIES OF CHÉDIAK HIGASHI SYNDROME PATIENTS

AUTHORS

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Biography:
I am a 3rd year paediatric resident, currently rotating at the UCM Ljubljana, Children`s hospital. My fields of interest are allergology and immunology, infectious diseases and neonatology. I am researching in the field of immunology and participated last year on IPIC with a poster about Netherton syndrome patients in Slovenia.

Objective: Chédiak Higashi syndrome (CHS) is a rare autosomal recessive lysosomal disorder caused by LYST pathogenic variants leading to defects in the lysosomal trafficking regulator protein characterized by oculocutaneous albinism, immunodeficiency, easy bruising and progressive neurological deterioration. CHS is one of the genetic diseases predisposing to hemophagocytic lymphohistiocytosis (HLH). Certain genetic variants are related to severe clinical manifestations. HLH is associated with a variety of infectious agents, EBV is listed as the most common trigger. We present a Slovenian case series of CHS patients, who developed accelerated phase-HLH early in life.

Design and Methods: We present 3 patients from the same Roma population that were treated in the University Children's Hospital Ljubljana, Slovenia in the last 25 years. We have analysed their clinical documentation and have compared their clinical picture, time to clinical, genetic diagnosis and development of HLH.

Results: Patient1, brother was first evaluated because of albinism at 2 years. CHS was confirmed with LYST NM_000081.3 c.8127_8131delinsTTCTGATATGTA homozygous genetic variant causing frameshift mutation leading to earlier stop termination codon (p.Val2710Serfs*4). At 3 years, he developed clinical and laboratory signs of HLH. As a possible trigger we confirmed HSV-1 infection causing gingivitis. In addition, low levels of CMV virus in blood were detected. After stabilisation of his activated immune system with immunoglobulins, steroids and cyclosporine he was treated with hematopoietic stem cell transplantation at 3,5years.

Patient2, sister presented with respiratory symptoms and pancytopenia at 3 months. CHS was confirmed with the same homozygous genetic variant as in her brother. At 4 months, she developed HLH. Only rhinovirus infection was identified as a possible trigger of an accelerated phase.
Patient3, boy with CHS from the same Roma community who was treated at our hospital 20 years ago. He presented with recurrent bilateral pneumonias in the first year. CHS was confirmed at 1,5 years when he was already in the accelerated phase. He had various relapses of HLH from which he died at the age of 3,5years.

Conclusions: We present three patients with CHS who all developed accelerated phase early in life, all of them have confirmed c.8127_8131delinsTTCTGATATGTA homozygous genetic variant. In the literature, we only found one CHS patient with the same homozygous genetic variant also of Roma origin who died at the age of 3. It seems that this homozygous genetic variant is associated with early development of HLH, which can be triggered also with other infections, not just EBV.

POSTER 168 - INBORN ERRORS OF METABOLISM LINKED WITH INBORN ERRORS OF IMMUNITY: DATA FROM THE SLOVENIAN NATIONAL REGISTRY

AUTHORS

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Biography:
I'm a pediatric resident, 3th year, with special interest in Clinical Immunology.

Objective: Inborn errors of metabolism (IEM) are a heterogeneous group of disorders, some can affect the immune system through many mechanisms. Due to systemic features of metabolic disease immunological problems may be overlooked. Some patients can be lost due to infections without a genetic diagnosis for the underlying immunological problem. Metabolic diseases leading to immunological disorders are probably underdiagnosed.

Design and method: A national Slovenian register of inborn errors of immunity was established in 2007. All patients with clinical and laboratory findings consistent with inborn errors of immunity (excluding simple IgA deficiency) are included. 64% of patients in the registry have genetically confirmed disease.

In this abstract we present data of patients from our registry with confirmed metabolic errors that are linked with inborn errors of immunity (IEI).

Results: In chart 1 we present by type all 334 patients diagnosed with IEI in Slovenia. 18 patients with IEM causing IEI in our cohort are presented in table 1. Majority of the patients with IEM have a congenital defect of phagocyte function. Two patients with glycogen storage disease Ib died due to the complication of neutropenia dysfunction.
In addition, currently three patients with organic aciduria and immune dysfunction are followed at our hospital.

Conclusion: We present Slovenian data on patients with inborn errors of metabolism causing inborn errors of immunity. Presence of recurrent infections or autoimmune findings in a patient with a suspected metabolic disease should suggest that immune deficiency may also accompany the picture, and diagnostic examinations in this regard should be deepened.

Good cooperation and communication between metabolic medicine specialist and immunologist is essential for optimal treatment and prophylaxis where it is possible. In patients with undefined immunodeficiency, comprehensive assessment for evaluating possible IEM should be performed.

Metabolic diseases leading to immunological disorders are probably underdiagnosed. Some patients with IEI can be detected with newborn screening tests for metabolic disease.

POSTER 173 - HUMAN INBORN ERROR OF IMMUNITY IN DEVELOPING COUNTRIES: STIL CHALLENGING

AUTHORS

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AFFILIATIONS

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Biography:
MANSOURI Mariam, I am 28 years old, currently I am a PhD student, I am working on an immune deficiency called hyperimmunoglobulin E syndrome, through my thesis I am trying to make a phenotype-genotype correlation to explain the diversity of clinical pictures of each patient suffering from the same syndrome.

The aim of this study is to provide a comprehensive overview of children patients with inborn errors of immunity, which encompass a diverse range of over 406 diseases and 430 genetic disorders. This research will focus on examining the epidemiological, clinical, immunological, genetic, etiological, and therapeutic characteristics associated with these conditions. This retrospective monocentric descriptive study aims to analyze and characterize all pediatric patients who diagnosed with an inborn error of immunity at the university hospital Ibn Sina of Rabat. The study will encompass a period spanning from January 2010 to January 2022, providing valuable insights into the prevalence, clinical features, and therapeutic approaches for these conditions within the specified timeframe. Our series comprises 204 patients, with a notable male predominance indicated by a sex ratio of 1.31. Parental consanguinity was observed in 40.8% of cases, and 14.7% of patients had a family history of primary immune deficiencies. The median age at diagnosis for our patients was 50 months, ranging from 23 days to 15 years. Significantly varying age ranges were observed across different categories. Initial symptoms appeared within the first year of life for 58% of cases, ranging from the first day to 14 years. The median delay in diagnosis was 8 months, ranging from 7 days to 10 years. Based on the classification by the International Union of Immunological Societies, the distribution of our patients is as follows: 19.1% with combined immunodeficiencies, 25.5% with well-defined syndromes, 16% with predominantly antibody deficiencies, 16% with phagocytic defects, 2.5% with defects of innate immunity, 19.6% presenting auto inflammatory disorders, and 1% with complement deficiencies. The most frequent presentations included respiratory infections in 51% of cases, skin infections in 30%, infectious adenopathy in 19%, and failure to thrive in 18% of patients. The rate of genetic diagnosis was 12.4%. Antibiotic prophylaxis was prescribed for 60.3% of patients, intravenous immunoglobulins for 25.4%, and hematopoietic stem cell transplantation for 2.36%. The overall mortality rate was estimated at 15.8%, with deaths occurring between the first month and 14 years of age. Inborn errors of immunity encompass a diverse group of diseases, characterized by genetic variations and affecting the immune system. While these conditions are presumed to be rare, they exhibit a considerable frequency and diversity within our specific context. Ensuring healthcare professionals possess appropriate and comprehensive training is crucial, as it enables early detection and management of these patients, ultimately leading to improved prognosis and outcomes.

POSTER 179 - DISTINCTION BETWEEN SECONDARY AND PRIMARY HYPOGAMMAGLOBULINEMIA: CHALLENGES IN REAL-LIFE PRACTICE

AUTHORS

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Biography:
Dr Irani obtained her Medicine Doctor Diploma from St Joseph University in Beyrouth. She did Internal Medicine residency Cooper Hospital, USA and the Allergy and Clinical Immunology fellowship a the Hospital University of Pennsylvania, USA . She is an American Board diplomate of Internal Medicine and Allergy/Immunology.

Master of Clinical Epidemiology: AUB, 2017

Associate Professor of Medicine St Joseph University, Beirut since December 2018 and teaches Allergy/Immunology and Autoimmunity at St Joseph University

She is the Head of Department of Internal Medicine & Clincial Immunology at Hotel Dieu De France Beyrouth, Lebanon. She was interested in many researches and had a lot of publications in the Journal of Allergy and Clinical Immunology and other journals.

Fellow of The American Academy of Allergy, Asthma and Immunology and President of the Lebanese Society of Allergy and Immunology, she gained several local and American Awards.

She participated in many clinical trials in Allergy & Immunology. She treats all Allergic diseases such as Urticaria, Allergic Rhinitis, Asthma, Atopic Dermatitis, Food Allergies as well as Primary immunodeficiencies among others.

Rationale: New therapeutic modalities in auto-immune and hematologic lymphoproliferative pathologies are of great importance for a better disease outcome. These advances come with the risk of immunosuppression. Indeed, the distinction between secondary hypogammaglobulinemia (SHG) or unmasking an undiagnosed primary hypogammaglobulinemia (PHG) is challenging. Methods: We report 2 cases of hypogammaglobulinemia consulting after recurrent respiratory and or urinary tract infections requiring frequent hospitalisations for intravenous antibiotics. A 38 y old female with a history of ongoing systemic lupus erythematous (SLE) and a 54 y old male with a history of B-cell lymphoma in remission. Both received Rituximab 5 years prior to consultation. They recalled, after a thorough examination of the medical history, recurrent upper and lower respiratory infections attributed in the past to pollution or allergies. An evaluation showing low Immunolglobulin G level,(<300mg/dl), a poor response after Streptococcus Pneumoniae vaccination and a low CD19 count with an inverted CD4/D8 ratio on flow cytometry confirmed the diagnosis of SHG, or rather an unmasked PHG. Results: The SLE patient received intravenous immunoglobulin (IVIG) at a dose of 600mg/dl/month, a clinical improvement was seen as far as recurrent infections as well as arthralgias after the second course of IVIG. The second patient was switched to subcutaneous immunoglobulins, because of severe side effects during the first course of IVIG, the latter was interrupted because of acute fever, headaches and severe back pain during the infusion. He improved clinically and felt a major improvement of his quality of life and energy level.Conclusion: In conclusion, SHG is usually considered as normal after immunosupressive drugs and is often left untreated. A high index of suspicion should help unmasking PHG or diagnosing SHG in order to start immunologlobulin replacement therapy, and reduce complications in the group of patients presenting with typical clinical features of both conditions. International guidelines are necessary for early diagnosis, screening and better management in such cases.

POSTER 183 - AGAMMAGLOBULINEMIA IN AICARDI-GOUTIÈRES SYNDROME

AUTHORS

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Biography:
Pongsawat Rodsaward is an adult allergist/immunologist from Thailand. Right now, he is studying PhD program at Chulalongkorn University.

Objective: Here we report the case of agammaglobulinemia in the patient with Aicardi-Goutières Syndrome (AGS).

Patient and Methods: The patient was suspected of having autoinflammatory disease since 2 months of age presented with recurrent neutrophilic lobular panniculitis and persistent fever. The complete blood count showed normochromic normocytic anemia and neutrophil predominant leukocytosis. The number of lymphocyte subpopulation and immunoglobulin level were within the normal limit. She got prednisolone 1 mg/kg/day from then on. Later she developed epilepsy with bilateral basal ganglion calcification, organomegaly and lipodystrophy. CANDLE syndrome was a differential diagnosis but the Autoinflammatory/Primary Immune Deficiency Genes Panel shown no likely pathogenic variants. Tocilizumab and colchicine did not improve her symptoms. She was losing follow-up since she was 10 years old. At the age of seventeen, she returned with Nocardia paucivorans preauricular abscess and osteomyelitis. Additionally, she had 2 episodes of acute encephalopathy in two months. Whole genome sequencing was done at this time.

Results: Immunologic work up showed agammaglobulinemia and absence of B lymphocyte. Whole genome sequencing showed new mutation in the intron of IFIH1 gene (c453+625C>T) supporting the diagnosis of AGS. Regular IVIG and Baricitnib were administered. Up to now, 7 months past, she has no episode of acute encephalopathy, panniculitis or any bacterial infection. But the fever still needs to be controlled by NSAIDs.

Conclusions: To our knowledge, this is the first case report of agammaglobulinemia in AGS. The immunologic mechanism of agammaglobulinemia in AGS remains unknown and waiting for more investigations.

POSTER 198 - RADIOLABELED SOMATOSTATIN ANALOG THERAPY IN ERDHEIM- CHESTER DISEASE

AUTHORS

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Biography:
Timo Zondag was born on the 23rd of June in 1993 in Amstelveen in the Netherlands. In 2011 he got selected to attended medical school at the Erasmus University in Rotterdam, where he obtained his medical degree in 2018. During the second year of his medical study, Timo developed an interest in immunology and started a research project at the department of internal medicine, section of Allergy & Clinical Immunology. This would later develop into a PhD- program on histiocytic diseases. He started his clinical career as resident at the Internal Medicine in the Franciscus Gasthuis & Vlietland hospital where he worked for over two years. In 2022 he was allowed to start his specialty training in Internal Medicine at the Erasmus Medical Center in Rotterdam.

Objective: Erdheim-Chester disease (ECD) is a disorder characterized by the accumulation of xanthomatous macrophage-like histiocytes. While targeted therapy seems effective, RAF or MEK blockade does not completely eradicate the disease. Instead, it suppresses the production of somatic mutation-expressing hematopoieitic cells which induce the formation of ECD lesions. Moreover, severe side effects hamper prolonged use of this type of medication.

Method: We explored a novel and potential curative therapy with limited side effects. We here present an ECD patient with a positive somatostatin receptor (SSTR) scintigraphy, who was subsequently and successfully treated with radiolabeled SSTR analog therapy.

Results: A 44-year old male presented with fluctuating vision and progressive diabetes insipidus. The patient developed exophthalmos due to a bilateral intra-conal tumor. A biopsy of the ophthalmic lesion showed a BRAFV600E positive ECD lesion and radiologic evaluation revealed pathologic lesions in the lung, perirenal and periaortic region. Immunosuppressive drugs including corticosteroids, intravenous immunoglobulins, methotrexate, cyclosporine and etanercept could only attain temporary improvement. Targeted therapy (i.e. BRAF/MEK inhibitors) was not available at the time this patient was referred to our hospital and the patient refused chemotherapy. Since the lesions demonstrated somatostatin uptake on indium-111- pentetreotide ([111In-DTPA]-octreotide) scintigraphy, a cycle of 3 administrations of radionuclide therapy with a cumulative dose of 16.5GBq was given. Combined with 7.5mg of prednisone and 100mg azathioprine as maintenance therapy, the ECD lesions stabilized without deterioration for the rest of his life. Moreover, the vision markedly improved and also stabilized throughout his life.

Conclusion: We provide data that support a rationale for somatostatin radionuclide therapy for ECD patients with positive lesions on SSTR scintigraphy. We stress that more research is needed to substantiate the efficacy of this unconventional treatment modality.

POSTER 208 - CD4 LYMPHOPENIA AND SEVERE CHRONIC MUCOCUTANEOUS HUMAN PAPILLOMA VIRUS INFECTION (HPV) IN AN ADULT SUBJECT WITH IL2RG DEFECT

AUTHORS

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Biography:
Pongsawat Rodsaward is an adult allergist/immunologist from Thailand. Right now, he is studying PhD program at Chulalongkorn University.

IL2RG mutations constitute the main cause of X-SCID: a primary immunodeficiency which is usually fatal in the first year of life unless treated by HSCT. We report the case of a man carrying a hypomorphic mutation of IL2RG gene who presented the first signs of the disease in early adulthood.

Clinical data were collected from medical records. Genetic analysis was performed throughout NGS and functional tests were performed by flow cytometry.

A 26-year-old man presented pigmented verrucous papules of the penis since the age of 19 years: the histological analysis confirmed the bowenoid papulosis due to HPV. The types 18, 31, 42, and 53 HPV were detected from genital warts, types 5 and 8 from the arms skin. The lesions were refractory to keratolytic treatment but responded to imiquimod. The patient suffered from pneumonia in his childhood, had varicella in infancy without complications, and presented recurrent mucocutaneous candidiasis. Laboratory tests revealed CD4 lymphopenia (449 cells/mmc), normal CD3, CD8, CD19 and NK cell counts (3150, 2344, 172, and 75 cells/mmc, respectively); extended immunophenotyping showed prevalence of CD8 T cells (CD4+ 19,8%, CD8+ 65%), with a reduction of recent emigrants (CD4+CD45RA+ 13,7%, CD8+CD45RA+ 2,8%, CD19+ RBE 1,7%), and increase of effector cells; he had an expansion of the CD19hiCD21lo subset (20,8%). The molecular analysis of a panel of genes associated to lymphopenia identified a missense mutation in the IL2RG gene (c.C467T:p.A156V), previously reported in an infant with X-SCID. The functional tests showed that proliferation to mitogens was impaired but normalized after adding IL-2. Flow cytometry analysis of IL-2 receptor showed that IL-2R expression and activity (STAT5 phosphorylation) were impaired in EBV immortalized B cell lines, but normal in PHA-T cell lines. Additional analysis identified a second mutation in a PHA-T lymphocytes, which we interpreted as potentially restoring immune function. The patient exhibited mixed chimerism with 11% of PBMCs and 29% of PHA-T cells carrying the original mutation, while the second mutation had 26% of PHA-T cells with the wild type allele.
The patient received the HPV vaccine (Gardasil9®) and was commenced on itraconazole prophylaxis.

We report the case of a combined immunodeficiency due to IL2RG defect that onset in adulthood with HPV infection, harboring a second somatic mutation in the T-cell compartment. Because of the severe epidermodysplasia verruciformis and the T lymphopenia the patient is at high risk of malignancy. Risks and benefits should be evaluated for considering the possibility of HSCT.

POSTER 222 - DISSEMINATED CRYPTOCOCCAL LYMPHADENITIS REVEALS STAT1 GAIN-OF-FUNCION SYNDROME

AUTHORS

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Biography:
Raffaele Badolato works as Professor of Pediatrics at the University of Brescia (Italy), Chief of the Department of Pediatrics of ASST Spedali Civili of Brescia. He is a Pediatric immunologist with a special expertise in the field of Inborn Errors of Immunity.

Background and objective: Patients carrying STAT1-GOF mutations display a wide range of immune dysregulatory features. Chronic mucocutaneous candidiasis is the most common infectious manifestation, however patients may suffer from viral, bacterial and other fungal invasive infections, and present autoimmunity, aneurisms and malignancy. We reviewed two cases of disseminated colliquative lymphadenopathy that revealed the STAT1-GOF syndrome.

Method: Genetic diagnosis was performed throughout mendeliome in P1 (STAT1: c.863C>T; p.Thr288Ile) and Sanger-Sequencing in P2 (STAT1: c.1441 G > T;p.L351F).

Results: P1 was investigated at the age of 16 years for a persistent bilateral cervical lymphadenopathy associated with fever, night sweat and weight loss. In the past medical history she had autoimmune thyroiditis and type 1 diabetes. Imaging showed multiple lymphadenopathies in the mediastinal, supra and sub clavicular districts (Figure 1), with PET CT also showing radiopharmaceutical accumulation. Lymph node excisional biopsy revealed granulomatous lymphadenitis, with colliquative necrosis and positive PCR for Mycobacterium tuberculosis. First line quadruple antitubercular therapy was started, but after 12 months, despite the negative PCR, imaging showed a progression with abdominal lymph nodes involvement. Further microbiological analysis of the lymph node biopsy identified Cryptococcus neoformans; antigenemia resulted positive (1:2048) whereas MRI and lumbar puncture ruled out pulmonary and neurological involvement, respectively. The patient was treated with an induction therapy with fluconazole 15 mg/kg/die and amphotericin B 4 mg/kg/die for 4 weeks, followed by a consolidation phase of fluconazole 12 mg/kg/die for 8 weeks. The infection resolved, and antigenemia halved (1:1024). P2 suffered from chronic mucocutaneous candidiasis, recurrent pulmonary and skin infections since infancy. At the age of 15 years he was admitted to hospital because of fever and multiple lymphadenopathy (neck, axillary and groin) and increased inflammatory markers. Inguinal lymph node biopsy was performed similarly revealing granulomatous necrotizing lymphadenitis due by Cryptococcus neoformans infection, with an antigenemia of 1:10240. The patient responded to intravenous fluconazole and amphotericin B but developed amphotericin-B related renal toxicity (tubular necrosis). P2 also presented autoimmunity with hypothiroidism and Systemic Erythematous Lupus skin lesions.

Conclusion: Patients with STAT1-GOF syndrome exhibit increased susceptibility to intracellular pathogens, and we suggest that this rare inborn error of immunity should be investigated in cases of Cryptococcus neoformans infections, particularly in patients with concomitant manifestations of autoimmunity.

POSTER 227 - BREAKING PARADIGMS. ECZEMA IS MORE THAN JUST ATOPY

AUTHORS

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Biography:
He is a surgeon from the Autonomous University of Guerrero. Paediatrician graduated from the National Institute of Pediatrics, endorsed by the National Autonomous University of Mexico.
Certified by the Mexican Board of Paediatrics. Allergy specialist and Pediatric Clinical Immunology by the National Institute of Pediatrics. Certified by the National Board of Clinical Immunology. High Specialty in Immunodeficiencies primaries by the National Institute of Pediatrics. Diploma in Medical Education

Background: Skin affection has been described in different inborn errors of immunity (IEI). Traditionally it has been described as hardto-control atopic dermatitis (AD); however, this definition is only sometimes met. The idea of eczema associated with IEI (EA-IEI), defined as erythematous skin with a moist appearance that does not respond to adequate treatment and, despite it, progresses to chronicity with lichenification and desquamation, suits better the skin affection.We present 7 patients with severe eczema as the initial manifestation of IEI.

Method: Retrospective review of the records of patients diagnosed with severe atopic dermatitis referred to the immunodeficiency research unit of a tertiary care center in 2022.

Results: We identified the causative gene variant in all cases through IEI directed panel evaluating 574 genes (Table 1). The mean age of onset and at diagnosis were 6.6 years and 47.5 months, respectively. The median SCORAD was 82.3, and all patients had eosinophilia. The other features are described in Table 1.

Discussion: Severe eczema is usually the initial manifestation in multiple IEIs; when classified as severe AD, it can delay the diagnosis; keep in mind that only 5% of all AD are severe.It is necessary to understand severe AD as a systemic inflammatory state triggered by immune dysregulation; This dysregulation can be triggered either by a skin barrier disorder that has not improved and produces severe symptoms or by a defect in the immune system itself. Whenever treatment to mend the skin barrier has been established without improvement, the intentional search for underlying causes should be the norm. Another factor to consider is the unusual topography that EA-IEI presents; the topography in AD is well-established. However, our series shows that the topography differs from AD in most cases of EA-IEI. Finally, when AD is associated with systemic manifestations (recurrent diarrhea, endocrinopathy, autoimmunity, recurrent viral infections, delayed neurodevelopment, and food allergies, among others), the differential diagnosis of IEI should be included.IEI timely diagnosis is especially relevant currently since we have curative therapies, such as transplantation and gene therapy, whose success is closely related to timely diagnosis, the presence/absence of complications, and the optimal beginning of treatment with immunosuppression/immunomodulation.

POSTER 232 - A GERMLINE STAT6 GAIN-OF-FUNCTION VARIANT IS ASSOCIATED WITH EARLY-ONSET ALLERGIES

AUTHORS

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Biography:

- *Assistant Professor, Division of Allergy, Immunology and Rheumatology, Department of Pediatrics, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand*
- *Head, Center of Excellence for Allergy & Clinical Immunology, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand*
- *Group Leader, Clinical Immunology Interest Group, Allergy, Asthma and Immunology Society of Thailand*
- *Member, Southeast Asia Primary Immunodeficiency (SEAPID) network*
- *Chair, Education and Training Working Party, Asia Pacific Society for Immunodeficiencies*

Background: The signal transducer and activator of transcription 6 (STAT6) signaling pathway plays a central role in allergic inflammation. To date, however, there have been no descriptions of STAT6 gain-of-function (GOF) variants leading to allergies in humans.

Objective: In this study, we report a STAT6 GOF variant associated with early-onset multi-organ allergies in a family with three affected members.

Method: Exome sequencing and immuno-phenotyping of T-helper (Th) cell subsets were conducted. The function of the STAT6 protein was analyzed by western blotting, immunofluorescence, electrophoretic mobility shift assays, and luciferase assays. Gastric organoids obtained from the index patient were used to study downstream effector cytokines.

Results: We identified a heterozygous missense variant (c.1129G>A;p.Glu377Lys) in the DNA binding domain of STAT6 which was de novo in the index patient's father and was inherited by two of his three children. Severe atopic dermatitis and food allergy were key presentations.
Clinical heterogeneity was observed among the affected individuals. Higher levels of peripheral blood Th2 lymphocytes were detected. The mutant STAT6 displayed a strong preference for nuclear localization, increased DNA binding affinity and spontaneous transcriptional activity.
Moreover, gastric organoids showed constitutive activation of STAT6 downstream signaling molecules.

Conclusion: We demonstrate for the first time that a germline STAT6 GOF variant results in spontaneous activation of the STAT6 signaling pathway and is associated with an early-onset and severe allergic phenotype in humans. These observations enhance our knowledge of the molecular mechanisms underlying allergic diseases and will potentially contribute to novel therapeutic interventions.

POSTER 236 - CASE REPORT: INBORN ERRORS OF IMMUNITY CAUSE OF CHRONIC MUCOCUTANEOUS CANDIDIASIS IN A 6TH YEAR OLD BOY

AUTHORS

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AFFILIATIONS

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Biography:
From 2014 University Assistant in Pediatrics

From 12/2014 PhD title University of Medicine and Pharmacy "V. Babes" Timişoara

From 2010 MD Specialist in pediatrics

IIIrd Pediatric Clinic, Children's Emergency Clinical Hospital Timişoara

Introduction: The most common IEI with chronic mucocutaneous candidiasis (CMC) are signal transducer and activator of transcription 1 (STAT1) gain of function (GOF) mutations, with an important role of IL-17 mediated immunity in protection against fungal infections. The patients with an autosomal dominant (AD) STAT1 GOF mutation present most commonly with early onset, especially in the first 2 years of life.

Case presentation: A 6-year-old boy from a non- consanguineous family, presented in our pediatric emergency room with respiratory failure, chronic cough and failure to thrive. He had recurrent, pruriginous and extensive facial eczema, florid dental caries. Moreover he had clinical and radiological features of chronic respiratory disease, with hippocratic fingers. From his medical history we noticed recurrent otitis, pneumonia, oral and pharyngeal candidiasis, onychomycosis with Candida Albicans and recurrent oral thrush.
Laboratory findings where suggestive for combined primary immunodeficiency (PID), chest X- ray demonstrated bronchopneumonia with left massive pleural effusion. We performed genetic tests and the result was positive for STAT1 GOF. This variant is not present in population databases, but missense change is observed in individuals with autosomal dominant chronic mucocutaneous candidiasis.
We started immunoglobulin substitution in order to prevent severe infections, knowing that the management of these patients is challenging. Hematopoietic stem cell transplantation (HSCT) is the only curative treatment option, but just on selected cases. JAK-1inhibitors is a good treatment choice for some patients.

Conclusions: The medical team must make the necessary efforts to diagnose immunological diseases as early as possible. Although CMC is a rare disease, it should be suspected in patients who associate the symptoms mentioned above, necessitating clinical, immunological and genetic investigations in order to reach the diagnostic. In will be possible to prevent severe complications and to initiate certain life-saving therapeutic strategies knowing that antifungal drugs are important to reduce morbidity and prevent mucosal inflammation which can increase the risk for squamous cell carcinoma in those patients which is not curative.

POSTER 243 - CHRONIC OBSTRUCTIVE PULMONARY DISEASE IS PRIMARY- SECONDARY IMMUNODEFICIENCY

AUTHORS

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AFFILIATIONS

[1]Vitebsk State Medical University

Biography:
Prof. Aksana ishchanka MD, candidate of sciences (Ph.D.), doctor of sciences (D.Sc.)

CURRENT POSITION
Head of Department of Clinical Immunology and Allergology Vitebsk State Medical University, Belarus
Exclusive director WAO Excellent Center of the Vitebsk State Medical University

TRAINING
Graduated with honors from the Vitebsk State Medical Institute, Belarus, in 1995. After graduating from the institute, she completed an internship in the specialty "therapy". She began her career with the general hospital staff of the Vitebsk Regional Clinical Hospital, then worked as a doctor allergist-immunologist in the allergology department Vitebsk Regional Clinical Hospital, Belarus.

Since 2002 she has been working at Vitebsk State Medical University, first as an Assistant at the Department of Clinical Immunology and Allergology, since 2004 as a Senior Lecturer, since 2009 as an Associate professor, since 2020 as a Professor, 2021 as a Head of Department.

In 2005 she completed her PhD, in 2020 - her doctoral dissertation, specializing in Clinical Immunology and Allergology.

She is specialist in the development of programs and the implementation of clinical trials GCP.

Member of the House of Delegates of the World Allergy Organization (WAO) in 2018-2019, 2019-2020, 2020-2021, 2021-2022 Member of the Russian Society of Allergology and Clinical Immunology (RAACI), European Academy of Allergology and Clinical immunology (EAACI) and the American College of Allergy, Asthma and Immunology (ACAAI).

SCIENTIFIC INTERESTS AND PUBLICATIONS
Scientific and clinical interests of Prof. Ishchanka are immunodeficiency and autoimmune diseases, COPD, immunotherapy. More than 70 publications have been published on the topics of scientific research, 6 patents.

EDITORIAL ACTIVITY
Dr. Ishchanka is Deputy Chief Editor of "Immunopathology, Allergology, Infectology" and a member of the editorial board of "Russian Journal of Allergy", "Bulletin Vitebsk State Medical University"

Background: COPD is one of the symptoms of Common Variable Immunodeficiency associated with NFKB1 mutation. On the other hand, COPD is a manifestation of HIV infection, with up to 25% of HIV-infected patients suffering from COPD. At the same time, COPD is a pollutant- induced disease, exacerbations of which are often associated with recurrent respiratory infections, and the development of emphysema is associated with autoimmune mechanisms.

Objective: This study assesses the immune status of COPD patients during an exacerbation

Method: We performed open cohort prospective study in the pulmonology and allergy departments of the Vitebsk Regional Hospital. We examined 100 patients: 53 COPD patients, 47 patients with COPD and asthma (ACOS). The study examined the immune status of patients: phenotype blood leukocyte and lymphocyte cells (CD3, CD4, CD8, CD13, CD14, CD20, CD25, HLA-DR, CD34, CD38, CD69, CD71), the serum levels of IgG, IgM, IgA, IgE,
interferon-α and interferon-γ, cytokines (IL-1β, IL-2, IL-4, IL-6, IL-12, TNF-α, TGF-β1).

Results: W Upon admission in the hospital, all patients had type I inflammation and needed antibiotic therapy. Pathogenic microflora in the amount of 106 CFU/ml or more was found in sputum of patients The COPD patients, including ACOS

during exacerbation had signs of immunodeficiency: the reduction of natural killer cells; decrease of expression CD71+ lymphocytes, with a strong depression in the COPD group ($p = 0.045$); decreased expression of CD95 + relative to the reference values; reducing the number of CD8 + cells in the ACOS ($p = 0.001$). The T lymphocytes in COPD patients were increased, whereas B lymphocytes were increased in the ACOS patients. In the group of patients with significant depression CD16+ lymphocytes (<70%) we observed reduction of the CD25+, CD69+ (COPD), CD71+, CD95+ (in both groups), increased expression of HLA-DR+ (ACOS), increasing CD4+ cells (Fig.1). The serum levels of IL-1β and TGF-β1 were significant increase. The IgG1 serum level was decreased and IgA level was increased in COPD patients compared with a ACOS. Total IgE in the ACOS group exceed the reference values more than doubled.

Conclusion: These data indicate the presence of immunodeficiency in COPD patients with frequent exacerbations. Patients with COPD have recurrent infections caused by opportunistic microflora, persistent immunological disorders, systemic inflammation, and autoimmune inflammation. Therefore, we designate immunodeficiency in COPD as “primary-secondary”, having a primary genetic predisposition, but realized under the influence of pathogenic factors, which, as a rule, do not induce the disease without this predisposition.

POSTER 244 - CARMIL2 deficicency: a variable phenotype of the same disease.

AUTHORS

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Biography:
Professor of pediatrics, infectious disease departmen and clinical imunology unit.
PhD in immunology and genetics in 2022 hematopoeitic stem cell transplant diploma
Moroccan society for pimary immunodeficiency treasurer
African sociey for primary immunodeficiency, training responsable

Introduction: CARMIL2 is a primary immunodeficiency related RLTPR gene. Carmil 2 is a protein implicated in the cytoskelet organisation and cellular migration which plays a role of CD28 lymphocytes T cosignalisation. Recently, carmil2 protein mutations have been repoted as responsible of a variable phenotype.
We report here seven cases of CARMIL2 deficiency.
Famille2: Fille de 2 ans, mariage consanguin de 2ème degré.Pneumonies à répétition, recto- colite ulcérocongestive, atteinte cutanée compatible avec psoriasis, taux bas d'IgG. Suspecter une immunodéficience primaire, nécessitant un traitement approprié. Famille3: Trois sœurs issus d'un mariage consanguin de 2ème degré présentent des symptômes variés incluant des éruptions cutanées pustuleuses, des abcès cutanés, des infections respiratoires et ORL à répétition, des onycomycoses,une gingivostomatite herpétique sévère et un AVC ischémique avec sténoses multiples des artères cérébrales. Une immunodéficience primaire est suspectée.

First family: 1st degree consanguineous family with a sibling of three. The eldest brother who died at the age of 16 and a half presented with an esophageal stenosis treated by dilatations and had a dilated cardiomyopathy. The two twin sisters have been followed since the age of 2 for repeated oral candidiasis, onychomycosis, an episode of CMV pneumonia treated in addition to psoriasis. One of the twins was complicated by candida esophagitis associated with duodenal stenosis which was activated with good evolution.

Second family: E 2-year-old daughter, 2nd degree consanguineous marriage. She presented recurrent pneumonia, rectocolitis ulcerocongestive with psoriasis, low IgG levels. She was treated by infleximab, antibioprophylaxis, intravenous immunoglobulin.

Third family: Three sisters from a 2nd degree consanguineous marriage present with various symptoms including pustular rashes, cutaneous abscesses, recurrent respiratory and ENT infections, onychomycosis, severe herpeticgingivostomatitis and ischemic stroke with multiple stenoses of the cerebral arteries.

Conclusion: Cutaneous, vascular and digestive disorders are reported in carmil2 deficiency.Colitis especially was common then esophageal stenosis, often complicating candida infections.

POSTER 245 - INFANTILE NEPHROTIC SYNDROME AS A PRESENTING MANIFESTATION OF WISKOTT-ALDRICH SYNDROME

AUTHORS

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AFFILIATIONS

[1]PGIMER

Biography:
MD PEDIATRICS from the Madras Medical College, Chennai, India

Currently DM: Senior resident Fellow
Pediatric Clinical Immunology and Rheumatology
Allergy Immunology Unit
Postgraduate Institute of Medical Education and
Research Chandigarh, India

Objective: To report an unusual presenting manifestation of Wiskott-Aldrich syndrome.

Design and method: A case report of a 6-month-old boy who was admitted in the in-patient unit of the Allergy Immunology Unit, Advanced Paediatrics Centre, Post Graduate Institute of Medical Education and Research, Chandigarh, India

Results: A six-month-old boy first born of a non-consanguineous marriage presented to our institute with an acute febrile illness and generalized body swelling with decreased urine output. A possibility of nephrotic syndrome (NS) was considered, and he was evaluated. Investigations revealed albuminuria (3+) with an increased urine protein-creatinine ratio (19), hypercholesterolemia (2.77 g/L), and hypoalbuminemia (0.9g/dl). However, he also had a history of recurrent episodes of blood-mixed stools since the neonatal period. There was a history of early childhood deaths among three maternal uncles due to thrombocytopenia and infections. Further investigations revealed normocytic normochromic anemia with thrombocytopenia (51 x 109/L) and a mean platelet volume of 8.1 fl. A clinical possibility of Wiskott-Aldrich syndrome (WAS) was also considered. Subsequent immunological investigations revealed reduced WAS protein expression (by flow cytometry) [0.59 (S.I >0.65)]. Whole exome sequencing showed a hemizygous variant in the WAS gene with a pathogenic 5' splice variant (c.777+1G>A) at intron 8, confirming the Wiskott-Aldrich Syndrome diagnosis.
Other causes of NS, such as cytomegalovirus infection, human immunodeficiency virus, hepatitis B, and hepatitis C, were ruled out. We started the child on oral glucocorticoids at 2mg/kg/day, and he achieved remission within a week. Steroids were gradually tapered and stopped after 12 weeks. He is currently well at follow-up and is being planned for a hematopoetic stem cell transplant.

Conclusion: Autoimmune renal manifestations in WAS can occur as early as infancy. Timely diagnosis and appropriate immunosuppression of NS in WAS may result in rapid remission.

POSTER 246 - POIKILODERMA WITH NEUTROPENIA AND HYPOGAMMAGLOBULINEMIA IN A CHILD WITH USB1 MUTATION

AUTHORS

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Biography:
Full Name: Ilknur KULHAS CELİK Date of Birth: 01.11.1983 Nationality: Turkish
Academic Title: Associate Professor
Present Position (including name and address of the institution): Selcuk University, Pediatric Allergy Immunology
Starting Date in this Position: 30.11.2021

Relevant Professional Qualifications (Post Graduate Training):
Qualification
Pediatrics resident, Ondokuz Mayıs University School of Medicine 2009-2013
Pediatric allergy immunology resident, Ankara Children's Hematology Oncology Research and Training Hospital 2016-2019

Relevant Experience / Positions (Responsibility/Years):
Experience
Specialist Of Pediatrics, Osmancık/Corum Public Hospital 2013-2016
Fellowship of Pediatric allergy immunology, Ankara Children's Hematology Oncology Research and Training Hospital 2016-2019
Specialist of Pediatric Allergy Immunology, Ankara City Hospital 2019-2021
Associate Professor, Selcuk University School of Medicine 2022-

Introduction: Poikiloderma with neutropenia (PN) is a rare autosomal recessive hereditary disease caused by biallelic mutations of the USB1 gene. It is characterized by poikiloderma, chronic noncyclic neutropenia and recurrent sinopulmonary infections with bronchiectasis. Here we report a case with homozygous c.531delA mutation in USB1 gene.

Case: An 18-month-old boy was admitted to our clinic with skin hyperpigmentation, growth retardation and recurrent lower respiratory tract infections. The medical history revealed that he was hospitalized six times due to pneumonia since the age of three months. His physical examination showed facial dysmorphism with trainguler face, depressed nasal bridge and frontal bossing. He also had poikiloderma in the whole body. Skin biopsy was performed and showed only hyperkeratosis. His weight and height were below the 3 percentile. He is the first child of his consangenius parents. In the laboratory findings; he has mild neutropenia (1100 / mm3), hypogammaglobulinemia (serum IgG:351 mg/dl, IgA:17 mg/dl, IgM: 20mg/dl) and, peripheral lymphocyte subset analysis was normal. Neutropenia was also observed in previous examinations (neutrophil counts:980-560-840/mm3). Immunoglobulin replacement therapy and antibiotic prophylaxis were started. Exome sequence analysis showed the presence of known homozygous variant (c.531delA) in USB1 gene.

Conclusion: Poikiloderma with neutropenia mainly affects the myeloid lineage. Apart from other patients in literature, we observed hypogamaglobulinemia in addition to neutropenia in our patient. We think that hypogamaglobulinemia may contribute to the infection severity.

POSTER 254 - MACULOPAPULAR PURPURIC RASH (HSP-LIKE) IN IL 12RB1 DEFICIENCY. IS IT A SIGN OF PERSISTENT SMOLDERING INFECTION OR AUTOIMMUNITY?

AUTHORS

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Biography:
Dr Pallavi L Nadig completed her MBBS from Bangalore Medical College and Research Institute, Bangalore, Karnataka, India in 2015 and her MD in Pediatrics from the Post Graduate Institute of Medical Education and Research (PGIMER), Chandigarh, India in the year 2018.
She is currently pursuing her post-doctoral three-year fellowship in Pediatric Clinical Immunology and Rheumatology from PGIMER, Chandigarh, India, under the mentorship of Prof Surjit Singh.

Introduction: Mendelian susceptibility to mycobacterial diseases predisposes the individual to increased susceptibility to environmental mycobacterial infections. Maculopapular rashes have occasionally been seen in patients with IL12RB1 deficiency with evidence of leukocytoclastic vasculitis on histopathology. Here we describe a case of transient maculopapular rash in a patient with IL12RB1 deficiency.

Case details: A 3-year-old girl born to 3rd degree consanguineous marriage, presented with low-grade fever, neck swellings, recurrent episodes of transient pedal oedema and maculopapular non-palpable rash involving bilateral lower limbs up to knee joint for the past 2 months. She was treated with anti-tubercular medications for BCG adenitis at 3 months of age. She had pallor, generalized lymphadenopathy, hepatosplenomegaly, and non-blanchable maculopapular-purpuric lesions over the bilateral lower limb and presacral area with non-pitting oedema. Urinalysis was normal. She was worked up for possible causes of vasculitis; ANA-2+ cytoplasmic, positive DCT, normal complements and negative ANCA. Skin biopsy showed mild vascular proliferation in the upper dermis and minimal perivascular infiltrates of lymphocytes and occasional eosinophils. Given BCG-related complications, she was worked up for primary immunodeficiency disease: hypergammaglobulinemia, with normal lymphocyte subset analysis Dihydro-Rhodamine assay. Flowcytometric expression of IL12RB1 and PhosphoSTAT4 were reduced on PBMCs suggesting IL12RB1 deficiency; confirmed by genetic analysis. FNAC lymph node showed reactive lymphoid hyperplasia. She was started on antitubercular therapy with suspicion of disseminated BCGiosis. Lymph nodes regressed in size along with organomegaly with no recurrence of skin lesions at 3 months follow-up.

Conclusion: Cutaneous vasculitis can be seen in MSMD, particularly in patients with IL12RB1 deficiency, caused by a persistent infection, usually salmonella species. A possible mechanism is hypothesized to be secondary to the secretion of IL-12 resulting in INF-Gamma release promoting T cell activity and possible autoimmunity. However, such manifestation can appear even in mycobacterial infections.

POSTER 255 - A CASE OF MASSIVE SPLENOMEGALY AND SMOULDERING HEMOPHAGOCYTOSIS - A DIAGNOSTIC CHALLENGE.

AUTHORS

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She is currently pursuing her post-doctoral three-year fellowship in Pediatric Clinical Immunology and Rheumatology from PGIMER, Chandigarh, India, under the mentorship of Prof Surjit Singh.

Introduction: Hemophagocytic lymphohistiocytosis in X-linked inhibitor of apoptosis deficiency is generally a milder disease which is more frequent and recurrent. Occasionally it can present with HLH-like illness characterized by fever, cytopenias and splenomegaly and may not always fulfil the HLH 2004 diagnostic criteria. Here, we describe one such case who presented since infancy with recurrent episodes of cytopenias and was later diagnosed to be a case of XIAP deficiency.

Case details: A A 5-year-old boy, presented with progressive abdominal distension, splenohepatomegaly, and progressive pallor since early infancy. He had mild anaemia, leukopenia and thrombocytopenia and elevated transaminases. Bone marrow examination was normal. Liver biopsy showed evidence of extramedullary hematopoiesis and a focus of hemophagocytosis. However, serum ferritin, triglyceride, and fibrinogen were normal.
Laboratory workup for infections, thalassemia, autoimmune hepatitis and targeted genetic sequencing for hemolytic anaemia and storage disorders yielded negative. He continued to have progressive abdominal distension secondary to massive splenic enlargement.
Immunological work-up showed hypergammaglobulinemia, normal lymphocyte subsets and double-negative T-cells. Whole exome sequencing was initially negative. At the age of 4 years, considering hypersplenism he underwent splenectomy; transfusion requirements were reduced. Histopathology of the spleen and liver showed fibro-congestive changes and hemosiderosis.
During follow-up, he was noted to have lymphomatous enlargement of retroperitoneal lymph node; biopsy showed reactive lymphoid hyperplasia. Given developing HLH, steroids, and cyclosporine. A repeat targeted exome sequencing for IEI identified a pathogenic hemizygous variant in XIAP [c.990_991del (p.Leu331Argfs*18)]. The mother was also confirmed to be the carrier for the same variant. The patient is being prepared for transplantation.

Conclusion: XIAP deficiency is a rare inborn error of immunity characterised by HLH, inflammatory bowel disease, hypogammaglobulinemia, cytopenias and susceptibility to infections, especially Epstein-Barr virus and has not been known to develop lymphomas. Unlike other causes of primary HLH, these patients may not fulfil the criteria for HLH and thus may be overlooked causing delays in diagnosis.

POSTER 256 - RITUXIMAB TO TREAT VASCULITIS AND CUTANEOUS ULCERATIONS IN PROLIDASE DEFICIENCY: A CASE STUDY

AUTHORS

Sogkas G[1,2], Fedchenko M[3], Atschekzei F[1,2]

AFFILIATIONS

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Biography:
Georgios Sogkas completed his medical degree at the University of Thessaly (Larissa, Greece) and after that moved for postgraduate studies to Oxford (University of Oxford, UK; MSc in Integrated Immunology) and then to Hannover (Hannover Biomedical Research School, Germany; PhD in Immunology). He specialized in Internal Medicine and Rheumatology as well as in Clinical Immunology at the Hannover University Hospital. Since 2021 he works as a consultant Rheumatologist and Immunologist at the outpatient clinic of the Department of Rheumatology and Immunology at the Hannover University Hospital. His main research focus is the investigation of the relevance of the mechanisms of immune dysregulation in inborn errors of immunity (IEIs) in systemic rheumatic disorders

Objective: Prolidase deficiency (PD) is a rare autosomal recessive inborn error of immunity (IEI) caused by biallelic homozygous or compound heterozygous loss-of-function mutations in PEPD, the gene that encoded prolidase. PD typically manifests with variable dysmorphic features, chronic cutaneous ulcers, recurrent infections and features of autoimmune connective tissue diseases. Proposed targeted treatment approaches, such as gene and enzyme replacement limited efficacy or accessibility and so far, there is no consensus regarding treatment of PD and its autoimmune manifestations.

Case description: Here, we present a currently 28-year old female patient with PD due to a novel copy number variation in PEPD gene (NC_000019.10 :g.[33989982_33992982del]; [33989982_33992982del]). The patient displayed treatment refractory chronic mucocutaneous ulcerssince the age of 3.6 years. At the age of approximately 7 years, she was diagnosed with an undifferentiated connective tissue disease, that apart from its early onset would be consistent with the diagnosis of Sjögren's syndrome. Clinical findings leading to the diagnosis of undifferentiated connective tissue disease included keratoconjunctivitis sicca, Raynaud's phenomenon and cutaneous vasculitis. Biopsy of septal nasal mucosa confirmed vasculitic etiology of mucosal ulcerations revealing immunoglobulin and complement deposition.
Immunological laboratory investigations revealed a polyclonal hypergammaglobulinemia, hypocomplementemia, antinuclear antibodies with positive SS-A and SS-B antibodies.
Treatment with diverse csDMARDs (methotrexate, azathioprine, ciclosporin, cyclophosphamide), steroids and high-dose intravenous immunoglobulin failed to control vasculitis, which led to repetitive lower extremity amputations and wound debridements. Besides the patient displayed infectious complications during treatment with steroids and csDMARDs, including a CMV colitis. At the age of 25 years, a rituximab (RTX) treatment was introduced, leading to recession of cutaneous ulceration, preventing the appearance of new ones and enabling tapering of steroids.

Conclusion: The present case expands the genetic spectrum of PD by the indentification of novel large-scale mutation, abrogating prolidase expression. Further, it suggests the therapeutic efficacy of RTX in treating autoimmune manifestations of PD and consequently the immunopathogenic role of CD20 positive B cells in PD, through their representing intermediary cells for plasma cells or through their alternative functions, such as their antigen-presenting role.

POSTER 259 - HAEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS IN CHILDREN: AN ADDITIONAL WARNING SIGN FOR INBORN ERRORS OF IMMUNITY

AUTHORS

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AFFILIATIONS

[1]Immunology Unit - Meyer Children's Hospital, IRCCS - University Of Florence, [2]Hematology Unit - Meyer Children's Hospital, Irccs

Biography:
Expert in:

molecular diagnosis of invasive bacterial disease
IEIs: newborn screening, diagnostic and specific treatment
vaccines in pediatric population at risk

Author of 94 english publication in peer-reviewed journals, h-index 16 (Scopus, 05 July 2023).

Speaker at national and international conferences on paediatric infectious diseases, vaccines and primary immunodeficiencies (more than 40).

Participation as principal investigator, Co-Pi and sub investigator in national and international clinical studies in pediatric field (IEIs, vaccination, epidemiology).

Objective: Haemophagocytic Lymphohistiocytosis (HLH) is a potentially fatal condition characterised by severe impairment of immune homeostasis. The objective of this study is to evaluate and characterize in clinical practice the possible association between HLH and IEIs, beyond the known forms of FHLH.

Design and methods: A This is a single-centre retrospective study that included patients from March 2013 to March 2023. Demographic, clinical and laboratory data were obtained by medical record review and stored after anonymization. Inclusion criteria were paediatric cases (0-16), with a genetic diagnosis of IEIs and HLH (at least 5 criteria), exclusion criteria the diagnosis of an IEIs belonging, according to the 2022 classification of the International Union of Immunological Societies, to the class of FHLH.

Results: Eight patients with a non-FHLH IEIs who presented with a complete HLH episode during their clinical history or at onset were identified. Specifically, the subjects identified were affected by primary immunodeficiencies belonging to 5 different groups of IEIs:2 cases affected by severe combined immunodeficiency (SCID), 3 cases affected by X-linked immunodysregulation forms (XLP1/XLP2), 1 case affected by interferon gamma receptor defect (INFGR), 1 case affected by combined immunodeficiency forms with syndromic traits, 1 case affected by autoinflammatory disorder. The median age of onset was 6 months (IQR 4.5-37.5), in 75% of the included subjects HLH was the sign of disease onset and in all cases the genetic diagnosis of IEIs was obtained after the episode of HLH. In 5/8 subjects an often-multiple infectious trigger was identified. All patients required intensive care while the HLH94/04 protocol was applied in two patients (XLP1/IFNGR1) both of whom died.3/8 underwent haematopoietic stem cell transplantation (HSCT), one subject with XLP2 and history of recurrent HLH is currently silent with target therapy (ruxolitinib). 4/8 subjects presented fatal outcome.

Conclusion: The results of our study, although limited in number confirm that HLH is a highly complex clinical manifestation and can often be associated with IEIs, beyond FHLH. In addition to the 10 warning signs of Jeffrey Modell Foundation manifestations of immune dysregulation such as HLH could effectively be included as an 'eleventh sign', often representing its clinical onset (figure 1). Relying solely on genetic testing for FHLH or the search for EBV alone appears limited, as different IEIs and different infectious triggers can trigger HLH. Early recognition of IEIs can guide towards correct family genetic counselling and a more 'tailor-made' therapeutic approach by improving safety and efficacy.

POSTER 270 - DEMOGRAPHIC, CLINICAL, IMMUNOLOGICAL, AND MOLECULAR FEATURES OF IRANIAN NATIONAL COHORT OF PATIENTS WITH DEFECT IN DCLRE1C GENE

AUTHORS

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Background: A mutation in the DCLRE1C gene causes Artemis deficiency, a severe form of combined immunodeficiency (SCID). An inadequate DNA repair process and an immature adaptive immunity contribute to T-B-NK+ immunodeficiency and radiosensitivity. Patients with Artemis are prone to recurring infections early in life.

Methods: From 1999-2022, 9 Iranian patients (33.3% female) with confirmed DCLRE1C mutations were identified among 5373 patients registered. A retrospective review of medical records and next-generation sequencing were used to collect demographic, clinical, immunological, and genetic information.

Results: There were seven patients born into a consanguineous family (77.8%). Median onset age was 6.0 months (5.0-17.0). Clinically, severe combined immunodeficiency (SCID) was detected at 7.0 (6.0-20.5) months after a median diagnostic delay of 2.0 (1.0-3.5) months. A pneumonia (44.4%) and an otitis media (3.33%) was the most common first presentation, followed by BCG lymphadenitis (22.2%) and gastroenteritis (11.1%). A respiratory tract infection (including otitis media) and chronic diarrhea were the most prevalent symptoms. 2 patients also had juvenile idiopathic arthritis (P5), celiac disease, and idiopathic thrombocytopenic purpura (P9) as autoimmune disorders. A reduction in the number of B CD19+ and CD4+ cells was observed in all patients. There was an IgA deficiency in 77.8% of the participants.

Conclusions: In the case of patients born to consanguineous parents with recurrent infections, particularly respiratory tract infections and chronic diarrhea, inborn immune errors should be suspected, even if growth and development are normal.

POSTER 271 - GATA 2 DEFICIENCY PRESENTING WITH GENERALIZED VERRUCOSIS: case report

AUTHORS

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Generalized verrucosis is a clinical manifestation of human papillomavirus infection. Patients with generalized verrucosis present with over 20 verrucae distributed over more than one site of the body. This clinical manifestation occurs in association with several genetic syndromes of immunodeficiency, including GATA2 deficiency. We report here a 26-year-old Moroccan women with GATA2 deficiency and generalized verrucosis . The patient was from a consanguineous marriage parents. She presented in dermatology consultation of the university hospital centre ibn rochd for profuse polymorphous verruciform lesions.

These dermatological disorders have been evolving since the age of 15 years old, the patient doesn't had any reccurent infections, secondary immunodeficiencies or similar lesions in her family , the physical examination showed: profuse polymorphous verruciform lesions in the upper and lower limbs and at the face, which probably causes functional and aesthetic damage, laboratory studies showed a monocytopenia; 0.01 10 3 /mm³; (NV: 0.2-1 10 3 /mm³), lymphocytes subpopulations count: NK lymphopenia: CD16+, CD56+ =64/ mm³; (NV:94/ mm³- 348 mm³), B cell lymphopenia : CD19+= 9/mm³; (NV: 47/ mm³-243/ mm³). the skin biopsy confirmed the diagnosis of warts, GATA2 mutation was confirmed by exome sequencing: GATA2 (c.1070C>T, p.3571). GATA2 deficiency is an inborn error of immunity characterized by hematological cytopenias, including those of B lymphocytes, natural killer cells (NK), and dendritic cells. Patients are prone to developing myeloid leukemia and opportunistic infections, including mycobacterial, HPV, and opportunistic fungal infections.

Despite the emergent findings, the exact pathogenetic mechanism underlying these alterations is still not fully understood. Also, there are still many gaps regarding the optimal management of patients with GATA2 deficiency, highlighting the need for dedicated guidelines.

THE NURSES PERSPECTIVES ON PID DIAGNOSIS AND MANAGEMENT

POSTER 164 - MANAGEMENT AND EARLY DETECTION OF SEVERE ADVERSE REACTION TO INTRAVENOUS IMMUNE GLOBULIN: THE ROLE OF THE EXPERT NURSE

AUTHORS

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Transfusion Related Acute Lung Injury (TRALI) is an infrequent complication that may arise from the use of blood products. Here, we discuss a case of TRALI after intravenous immune globulin (IVIG) infusion in a patient diagnosed with Common Variable Immunodeficiency, secondary hypersplenism, and thrombocytopenia. This patient was receiving a 10% IVIG replacement therapy every 4 weeks at the Immunology Day Hospital. During a session, the patient experienced feverish sensation and breathlessness, his vital signs showed low (82%) peripheral oxygen saturation, though heart rate and blood pressure remained normal. The infusion was immediately stopped, and the patient was taken to the Emergency Room for evaluation. He did not suffer from any loss of consciousness or chest pain, nor were there any skin or gastrointestinal symptoms. Anaphylaxis was ruled out. A chest X-ray showed bilateral opacities, leading to the suspicion of COVID-19 infection.
This was later disproved when a SarsCoV-2 PC result negative. The laboratory workup showed an increased white blood cell count with lymphocytopenia, as well as elevated acute phase reactants (CRP, fibrinogen, D-Dimer). These results were compatible with the clinical and laboratory criteria for TRALI. Both patient serum and IVIG batch samples were sent to the Transfusion Center, which tested and confirmed the presence of anti-HNA 1a, 1b, 1c, 3a, and 3b IgG antibodies. After the acute event, replacement therapy was switched to hyaluronidase- facilitated subcutaneous immune globulin (fSCIG). The patient was trained to self-administer fSCIG at home by the specialized nursing staff at the Immunology Day Hospital and, since then, he has self-administered several doses without complications. This case report emphasizes the importance of being aware of this complication of IVIG administration, as well as the need for knowledge concerning infusion reactions and their potential danger signs. Moreover, early recognition and management by experienced nursing staff has a positive effect on patient prognosis. Finally, switching to facilitated subcutaneous immune globulin is a viable strategy in cases of IGIV related TRALI.

POSTER 209 - KNOWLEDGE AND SKILLS OF NURSES REGARDING PRIMARY IMMUNODEFICIENCIES

AUTHORS

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Biography:
Dr Hariyan graduated from I.Horbachevsky Ternopil National Medical University in 2000 and since 2007 she has been working as an assistant, a lecturer, and an associate professor of this higher school. Mrs Hariyan has been keen on children immunology and screening of severe combined immunodeficiency in newborn babies in Ukraine for 6 years. General paediatry is the area of her interest for 23 years.

The aim of research is to determine the knowledge and skills of nurses regarding some primary immunodeficiencies (PID).

Materials and methods: An anonymous and voluntary survey of nurses was conducted at the regional children's clinical hospital from April to May 2023. The survey involved 63 nurses from the hospital. The questionnaire consisted of 27 questions related to the socio-demographic data of the respondents and rare diseases. The most commonly encountered rare diseases in the practice of nurses at the hospital were primary immunodeficiencies.

Research results and their discussion: Among the respondents, the majority were female (96.8%), aged between 31 and 50 years (63.5%), and employed in the hospital setting (90.5%). Most of them were experienced workers with more than 20 years of work experience (52.4%). Overall, the majority of respondents (71.0%) identified correctly which diseases belong to rare diseases. The percentage of correct answers regarding knowledge of rare diseases ranged from 47.9% for PID to 77.5% for SB, while correct answers regarding skills ranged from 41.3% for PID. Overall, nurses demonstrated better knowledge than skills regarding rare diseases (p=0.0003). The most problematic issues were that HIV/AIDS was assigned as PID (31.7%), unfamiliarity with the technique of subcutaneous immunoglobulin administration (87.3%).
Respondents indicated that frequent respiratory viral infections can be a sign of PID (in 90.5%); allergic manifestations and the risk of oncopathology were indicated much less often. Lack of awareness has been demonstrated regarding the diseases that belong to PID, particularly regarding ataxia-telangiectasia. Only 36.5% of respondents indicated this disease, although it is not uncommon in our population. However, the most worrying is the fact that 31.7% of nurses attributed HIV/AIDS to PID, while this disease is acquired and does not belong to PID, which are caused by genetic defects and cannot be transmitted to other people through blood, saliva or other biological liquid A total of 6.4% of respondents believe that PID can be infected.

Conclusion: The study showed insufficient awareness among nurses regarding specific rare diseases. The lowest knowledge was demonstrated regarding primary immunodeficiencies. There is a need to improve the knowledge and skills of nurses regarding rare diseases, which can enhance the quality of nursing care for patients with rare diseases and their families. The development of educational interventions for nurses can help increase their awareness of rare diseases.

POSTER 212 - FROM CASE MANAGER NURSE TO ADVANCED PRACTICE NURSE IN A PAEDIATRIC PRIMARY IMMUNODEFICIENCY REFERRAL UNIT

AUTHORS

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Biography:
Nurse specialist in pediatrics. Professional with more than 16 years of experience in the area of hospitalization and children's outpatients. Currently dedicated to the work of nurse manager in the Functional Unit of Clinical Immunology and Primary Immunodeficiencies. and Primary Immunodeficiencies Unit. I am part of the management committee of the immunology nursing group (GEIE) of theu immunology (GEIE) of the Spanish Society of Immunology (SEI).

Background: Advances in diagnosis, therapeutic improvements and hospital caseloads are leading towards a change in Inborn Errors of Immunity (IEI) patients, where the nursing model develops an expert knowledge role in harmony with the multidisciplinary team.
Nursing care for chronic paediatric patients leads us to prioritise training families and patients in their care. Home treatment training, infection prevention measures, early detection of warning signs, as well as disease monitoring and ensuring the transition to adulthood are essential. In addition, in patients with IEI, who have increasing needs due to their improved survival, quality of life (QoL) is essential.
The nurse figure is described in different accreditations as a professional from the basic and complementary multidisciplinary team who has experience in IEI to guarantee comprehensive, quality and expert care. In April 2018, a paediatric expert nurse became part of the Immunology Unit with a patient manager role, thus obtaining XUEC (2019), CSUR (2021) and ERN-RITA (2022) accreditations.

Objectives: Our goal is to analyse the changes in the advanced practice nurse's role and functions in a paediatric reference Immunology Unit over the last 4 years.

Methods: Descriptive, observational, cross-sectional study with two cut-off points: 2018 and 2022. Anonymised data on the nurse's daily activity was extracted from the electronic medical record with the following variables: face-to-face follow-up visits, telephone visits, telematics consultations and number of subcutaneous immunoglobulin (sc) administrations. Additionally, in 2021 the adult transition programme was implemented as well as health education visits for patient in transition to the haematopoietic stem cell transplant (HSCT) Unit from the Immunology Unit (IMM).
Changes in activity between the two time points was analysed and the new health programmes implemented were described.

Results: (Image1)

Conclusions: The IEI population's, given their chronicity, complexity and low prevalence require personalised and specialised attention, focusing on integrating different care team's attention and the patient's particular needs.
The nurse's role is essential to guarantee the quality of care for these patients. Care activity has increased in recent years, with a clear rise in telematic visits. In addition, there has been a boost in the diversity of functions, with the emergence of the transition to adulthood programme, to guarantee a continuity of care and the internal transition to HSCT, which aims to improve the patient and family's experience in relation to this transcendental process.

POSTER 237 - SUBCUTANEUS IMMUNOGLOBULINS REPLACEMENT THERAPY: RE- TRAINING TO IMPROVE SAFETY AND QUALITY OF LIFE

AUTHORS

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Biography:
I am a nurse who have been working since 2008 at the Primary Immunodeficiencies adult center at Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico of Milan, Italy. In the ten previous years I cared patients with lymphoma/leukaemia and BMT at the haematology department.

In the latest 10 years I developed my skills in the care of patients with Primary Immunodeficiencies, I improve my knowledge of these rare and complex disorders. As our center is part of a Unit where other rare disorders are managed, as thalassemia, I also have experience in these disorders. I'm also involved in my Institution PICC team. I recently renewed my INGID membership.

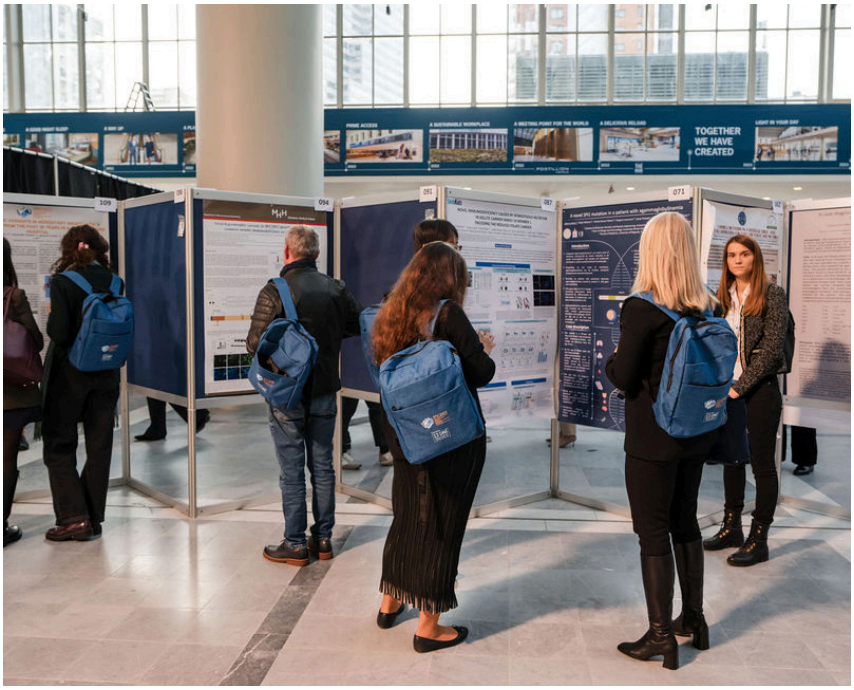
Background: Patients with severe primary antibody immunodeficiency (PAD), as common variable immunodeficiency or X-linked agammaglobulinemia, need life-long immunoglobulins replacement therapy. These patients' quality of life has been improved since the introduction of home therapy with subcutaneous immunoglobulins (SCIG). Hence, it is of pivotal importance to train patients for self-administration at home. Despite adequate training and good performance was achieved initially, some patients reported adverse reactions that were consequence of mistakes in the procedure. In 2018 the team of nurses dedicated to patients with inborn errors of immunity decided to plan a dedicated and periodical refreshment of the SCIG self-administration procedure for every PAD patient in order to reduce the discomfort of home therapy and avoid severe adverse reactions.

Aims: This study aims to describe the mistakes reported by the PAD patients who are under replacement therapy with SCIG/fSCIG and the results of the periodical refreshment after 5 years of its introduction.

Patients and methods: All the PAD patients under replacement therapy with SCIG or facilitate SCIG (fSCIG) and cared at our Center for Inborn Errors of Immunity (ERN-RITA Center Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico of Milan, Italy) have been enrolled. All the patients have been evaluated for every steps of the procedure and their mistakes or accident reported.

Results: We evaluated 50 PAD patients who are under replacement therapy with SCIG or fSCIG. The 72% have been trained to the first administration by our team and the 28% arrived to our center after been trained at other centres. In 2018 we re-trained 20 patients, 8 patients did mistakes, and the most common mistake was "the lesser maneuver" (89%).
In 2023 we started the re-training, so far only 5 patients did the refresh of the procedure and we found that 4 patients did mistakes and the most frequent now is "the site chosen for infusion".
During the COVID-19 pandemia, we had to address PAD patients to home therapy with SCIG/fSCIG in a rush with no time to do the training as in the past. These patients are going to be retrained in the next weeks.

Conclusion: All the patients have been very happy to do the refresh of the SCIG/fSCIG self-administration and they feel more confident to perform the procedure at home. The patients themselves asked to be periodically re-trained in order to avoid passages of the procedure that can lead to infections or dangerous mistakes for their health.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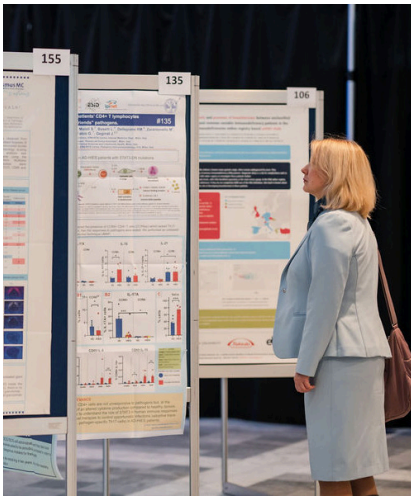
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