



IPIC 5TH EDITION

INTERNATIONAL PRIMARY
IMMUNODEFICIENCIES
CONGRESS

DIAGNOSIS
AND CLINICAL CARE

APRIL 27-29, 2022
VILAMOURA - PORTUGAL

an IPOPI event



CONGRESS REPORT





IPIC2023

INTERNATIONAL
PRIMARY
IMMUNODEFICIENCIES
CONGRESS

DIAGNOSIS
AND CLINICAL CARE

NOVEMBER 8-10, 2023

ROTTERDAM
THE NETHERLANDS

an IPOPI event



ABOUT IPOPI

IPOPI is a non-profit international organisation and the leading advocate for primary immunodeficiency (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 primary immunodeficiency patients worldwide through global collaboration.

IPOPI has an increasing membership and currently represents 69 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** organisations to improve living conditions for people living with PID
- 3 - **Educate, promote knowledge and data sharing** to increase understanding of PID, improve clinical care and advance research
- 4 - **Strengthen 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!

 [linkedin.com/company/international-patient-organisation-for-primary-immunodeficiency](https://www.linkedin.com/company/international-patient-organisation-for-primary-immunodeficiency)

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VILAMOURA - PORTUGAL,
27-29 APRIL 2022

IPIC5TH EDITION CONGRESS REPORT SUPPORTING ORGANISATIONS



IPIC5 2022 CONGRESS REPORT (by Dr Helena M Cornelissen*)

IPIC 2022, the 5th International Patient Organisation for Primary Immunodeficiency (IPOI) International Primary Immunodeficiencies Congress (IPIC) was held in beautiful Vilamoura, Portugal in April 2022. Despite facing the many challenges of the COVID-19 pandemic as well as recent unrest in Ukraine a face-to-face congress was made possible. A truly welcome and amazing feat by the organising committee.

IPIC5th saw the joining together of 600 delegates interested in learning more about diagnosis and clinical care of primary immunodeficiencies (PIDs). Over 130 posters for presentation were approved, most presented by young scientists and physicians with an interest in PID.

The program celebrated the inspiring work that has been carried out by the global PID network however also highlighted the many challenges still in? need to be addressed. The strength and success of IPIC lies in its well-balanced scientific program that is clinically orientated with input from key PID stakeholders namely doctors, scientists, patients and nurses, designed to complement other existing international congresses and scientific meetings.

This report presents a summary of the conferences main sessions providing relevant update and highlighting the recent advances in PID.

Key topics that were addressed were:

- PIDs and allergy
- Management of gastrointestinal and hepatic manifestations
- Genetic diagnosis in PID
- The malignancy spectrum of PIDs
- Autoimmunity and autoinflammation manifestations
- Ethical considerations
- Viral infections (including COVID-19 in PID)

Words from an esteemed congress attendee highlight the success of the congress and serve as an excellent introduction to the report; "Many congratulations to you all for a truly amazing congress, which I think has been a tremendous success. Fantastic venue, great program, great company, great food... all credit to the whole team for the herculean efforts behind the scenes and pulling it off in the face of many unprecedented challenges!"

** Dr Helena M Cornelissen is currently a registrar in hematopathology at the National Health Laboratory Service (NHLS), Tygerberg Hospital and Faculty of Health Sciences at the University of Stellenbosch, Cape Town, South Africa. IPOPI wishes to sincerely thank her for the preparation of this congress report*

KEY MESSAGES:

- The non-infectious manifestations of primary immunodeficiencies (PIDs) or inborn errors of immunity (IEI) are increasingly more apparent.
- There are many challenges faced in PIDs, these need to be realized and innovative answers developed
- Early identification and management of PIDs is reaching new strengths, newborn screening is key however also brings to light new questions.
- The soon to be published International Union of Immunological Societies (IUIS) 2022 classification provides a working framework, with phenocopies of PIDs being a growing field.
- Personalised medicine is already applied and growing, highlighting the every-increasing need for equality in access to care.
- The need for collaboration has never been greater.

WEDNESDAY 27 APRIL 2022

OPENING SESSION INCLUDING KEYNOTE ADDRESS 9

Chairs: Dr Nizar Mahlaoui (IPOPI Medical Advisory Panel Chairman) and Ms. Martine Pergent (IPOPI President)

- Opening remarks: Ms Martine Pergent (IPOPI President) and Mr Johan Prévot (IPOPI Executive Director)
- Keynote speech "PIDs across the age spectrum" – Prof Klaus Warnatz

SESSION 1: PIDS AND ALLERGIES – EXPLORING THE CROSS OVER! 11

Chairs: Dr Nizar Mahlaoui and Dr Nicholas Brodzski

- Brief epidemiological overview of PIDs and Allergies – Dr Nizar Mahlaoui
- When is allergy a PID and when is it just allergy? – Prof Anna Sediva
- Asthma, chronic obstructive lung issues and PIDs – Dr Leif Hanitsch
- Dermatological allergic manifestations in PIDs – Prof Raffaele Badolato

THURSDAY 28 APRIL 2022

SESSION 2: MANAGEMENT OF GASTROINTESTINAL AND HEPATIC MANIFESTATIONS IN PIDS ... 16

Chairs: Prof Sergio Rosenzweig and Ms Jose Drabwell

- The interplay between the gastrointestinal tract and the immune system – Dr Fabienne Charbit-Henrion
- How to manage? – Dr Cinzia Milioto
- Explorations and treatment pathways including transplantation and conditioning – Dr Lizzy Rivers
- A Patient Experience – Ms Sian Van den Bogaerd-Rance

SESSION 3: THE USUAL SUSPECTS (WHEN NOTHING IS WHAT IT SEEMS YOU HAVE TO LOOK BEYOND...) 21

Chairs: Prof Stephen Jolles, Ms Roberta Anido de Pena and Prof Stuart Tangye

- Genetic diagnosis – Dr Sophie Hambleton
- Malignancy spectrum of PIDs – Dr Ton Langerak
- Autoimmunity and autoinflammation manifestations – Prof Tadej Avcin

SESSION 4: REGIONAL DIAGNOSIS AND CLINICAL CHALLENGES SESSION 24

Chairs: Prof Martin van Hagen and Ms. Cynthia Olotch

- APSID Lecture Dr Ankur Jindal
- ASID Lecture Dr Helen M Cornelissen
- CIS Lecture Prof Sergio Rosenzweig
- ESID Dr Nizar Mahlaoui
- LASID Prof Gesmar Segundo
- SEAPID Dr Narissara Suratannon

SESSION 5: TREATMENT ADVANCES IN SPECIFIC PID MANAGEMENT 27

Chairs: Dr Virgil Dalm and Ms Martine Pergent

- T-cell lymphopenia: How TRECs modify the management of these patients – Prof Stephan Ehl
- CGD latest management advances – Prof Steven Holland
- ALPS: reaching new heights! – Dr Olaf Neth
- Update on IUIS classification: will it open new PID management pathways? – Prof Steven Holland

FRIDAY 29 APRIL 2022

SESSION 6: PID ECONOMICS, DIAGNOSIS, ACCESS TO CARE: ETHICS BETWEEN THE LINES 32

Chairs: Prof Charlotte Cunningham-Rundles and Dr John Seymour

Invited panel: Prof Alessandro Aiuti, Ethicist Prof James Taylor, Prof Frank Staal, Prof Cornelis Boersma, Dr Adli Ali, Nurse Mary Louise Daly and Ms Otilia Stanga

- Access to new therapies and health economics
- Future of NBS towards genomics
- Expanding Hematopoietic Stem Cell Transplantation to more adult patients with PID: new frontier?

SESSION 7: THE QUEST FOR A CURE TO PRIMARY IMMUNODEFICIENCIES 34

Chairs: Prof Tadej Avcin and Mr Andrea Gressani

- Cell therapy and PIDs – Prof Luigi Notarangelo
- Bone Marrow Transplantation in adults – Prof Felipe Suarez
- Thymic Transplantation – Prof Graham Davies
- Gene Therapy and Gene Editing – Prof Frank Staal

SESSION 8: MANAGEMENT OF VIRAL INFECTIONS IN PIDS 38

Chairs: Prof Steven Holland and Prof Stuart Tangye

- COVID-19 and PIDs! – Dr Virgil Dalm
- CMV and EBV management in PIDs – Prof Jeroen van Kampen
- Management of respiratory and entero-viruses in PIDs – Prof Stephen Jolles

CLOSURE TALK 42

Chair: Dr Nizar Mahlaoui

- “Horizon 2040: what can PID genetics studies tell us about the future?” – Prof Luigi Notarangelo
- Closing remarks – Ms. Martine Pergent

ABBREVIATIONS 44

ABSTRACTS APPROVED FOR POSTER PRESENTATION 48

YOUNG PID INVESTIGATORS: POSTER WINNERS’ SESSION 54

Chairs: Prof Gesmar Segundo and Ms Jose Drabwell

- Poster 1 – “Antibody and T-Cell responses following -COV-2 vaccination in patients with Inborn Errors of Immunity” – Dr T. ALBA CANO
- Poster 2 – “Clinical profile of a multicentre cohort of patients with Common Variable Immunodeficiency (CVID) from India” – Dr Ankur KUMAR
- Poster 3 – “The Haematological features of Primary Immunodeficiency: A retrospective review of the routine laboratory investigations of the South African Primary Immunodeficiency Registry” – Dr H. M. CORNELISSEN

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WELCOMING SESSION

OPENING WELCOME: MR JOHAN PREVOT AND MS MARTINE PERGENT

- We are here! In person! Despite much adversity
- **Let us learn, share, discuss and have FUN!**

In the beautiful setting of the Algarve, Portugal the congress was opened by Mr Johan Prévot (IPOPI executive director) and Ms Martine Pergent (IPOPI president). 2022 celebrates the 30th anniversary of IPOPI and it was very relevant to hold the 5th congress in Portugal as it is the birthplace of IPIC. Face-to-face contact was welcomed after having to postpone the 2021 congress due to the COVID-19 pandemic. Another hurdle faced in organizing the congress was the recent War in Ukraine although 8 representatives from the Ukraine were able to join. The adversity faced has given new strength to assist patients and clinicians, “as the good of humanity depends on peace, hope and action”. With concluding remarks from Ms Martine Pergent of “let us learn, share, discuss and have fun” IPIC5th 2022 was opened.



KEYNOTE SPEECH

PIDS ACROSS THE AGE SPECTRUM – PROF KLAUS WARNATZ

- The timeline is different for each PID
- A different perspective: Hidden, raging, smoldering and accumulative disease
- Realise the challenges and develop different answers

After an introduction from Dr Nizar Mahlaoui, Prof Klaus Warnatz gave the keynote address.

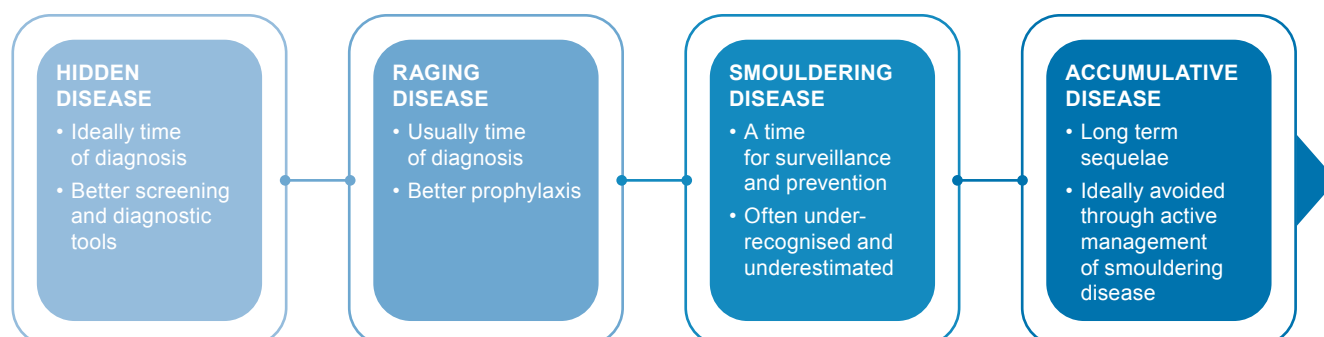
From deep understanding of IEI, a different outlook on the PID timeline was discussed, a timeline that follows core pillars but is different for each disease entity. Four stages across the spectrum of PID were proposed, namely a time of hidden disease, of raging disease, of smoldering disease and finally the effects of accumulative disease. These 4 pillars should be applied in the approach to diagnosis, management and importantly prevention of the sequelae of disease.

The time of hidden disease varies across PIDs where Severe Combined Immunodeficiency (SCID) for example may have a very short period of hidden disease whilst Common Variable Immunodeficiency (CVID) a longer period of hidden disease. It is this time of hidden disease that should ideally be the period when patients are diagnosed. The spectrum then progresses to a stage of raging disease, this is the time when patients usually require hospitalisation and are diagnosed. The disease then goes on to follow a more smoldering course which requires active monitoring and preventative intervention to avoid or dampen the last stage; accumulative disease where there is organ damage.

The disease can also follow a dynamic course where it waxes and wanes between the different stages and so different approaches and answers are needed. Hidden disease requires better awareness and access to diagnostics such as newborn screening, raging disease aggressive intervention such as Hematopoietic Stem Cell Transplant (HSCT), whilst smoldering disease becomes more challenging requiring active prevention so as to avoid the consequences of accumulative disease.



Importantly, CVID should not be applied as an umbrella term. Those with a more combined immunodeficiency or genetic diagnosis need to be teased out as their raging and smoldering disease course may be more aggressive with more dire accumulative consequences. In CVID important sequelae of accumulative disease are Granulomatous-Lymphocytic Interstitial Lung Disease (GLILD) and hepatopathy which ideally should be addressed in the smoldering period, needing close monitoring and active intervention. The talk concluded that “we owe it to our patients to learn from both the living and the dead and we need to try and understand what brought patients to their untimely demise and hopefully apply this to the living to look to the future and improve their outcome”.



SESSION 1: PIDS AND ALLERGIES – EXPLORING THE CROSS OVER

Chaired by Dr Nizar Mahlaoui and Dr Nicholas Brodzski

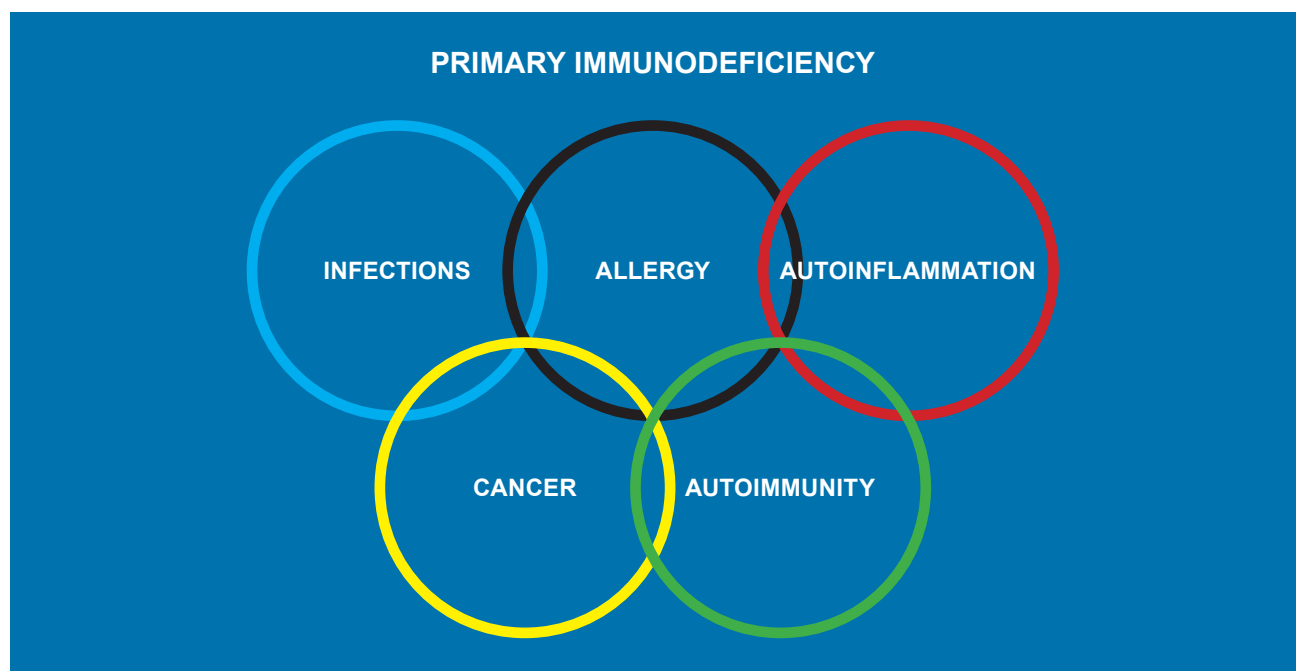
Epidemiological overview of PIDs and Allergies: **Dr Nizar Mahlaoui**, when is allergy a PID and when is it just an allergy: **Prof Anna Sediva**, Asthma, chronic obstructive lung issues and PIDs: **Prof Leif Hanitsch**, Dermatological allergic manifestations in PIDs: **Prof Raffaele Badolato**

- Consider non-infectious manifestations of PID: Overlap between allergy and immunodeficiency
- In allergy, syndromic features are more suggestive of a PID
- Differentiate asthma from COPD (may be an overlap), increased asthma prevalence in PID. Minimize steroid use
- Severe dermatological manifestations unresponsive to treatment should prompt investigation for PID

EPIDEMIOLOGICAL OVERVIEW OF PIDS AND ALLERGIES

DR NIZAR MAHLAOU, PARIS, FRANCE

The first talk of session 1 was opened by **Dr Nizar Mahlaoui** discussing a brief epidemiological overview of PIDs and allergy. He highlighted that non-infectious manifestations of PID are increasingly more apparent. In reference to a recent ESID registry review by Thalhammer et al (DOI 10.1016/j.jaci.2021.04.015) it was proposed that up to 25% of PIDs will be missed if the focus is on infections alone. Although the frequency of clinical manifestations varies per IUIS classification both infections and immune dysregulation predominate. The true prevalence of atopic disorders is difficult to pinpoint however estimated around 24%. B and T cell deficiencies namely CVID and hyper- Immunoglobulin E (IgE) HIGE syndromes most commonly present with atopy. Warning signs for PID are increased IgE, autoimmunity, infections, connective tissue disease and family history. Those presenting with atopy tend to have an older median age at presentation with at least 25% having at least 1 episode of severe allergy. There is no difference in gender and consanguinity tends to have less allergy with no difference in survival compared to those without allergy, however one needs to look at the accumulative incidence over time. PIDs are rare but multiple and complex, prognosis often severe when misdiagnosed and inadequately treated.



WHEN IS ALLERGY A PID AND WHEN IS IT JUST AN ALLERGY?

PROF ANNA SEDIVA, PRAGUE

Prof Anna Sediva provided an approach to a question that often arises – when is allergy a PID and when is it just an allergy? IgE is the best marker for allergy however it is a measure at the end of the immune response. Although IgE is often elevated in PID and allergy, it may be normal even though the patient has an atopic phenotype. Unlike in allergy, where the allergen is the trigger for IgE, in PID it is rather a consequence of immune dysregulation that drives increased IgE levels. Important to consider is the clinical phenotype of the patient, patients with syndromic features are more likely to have an associated PID than those without.

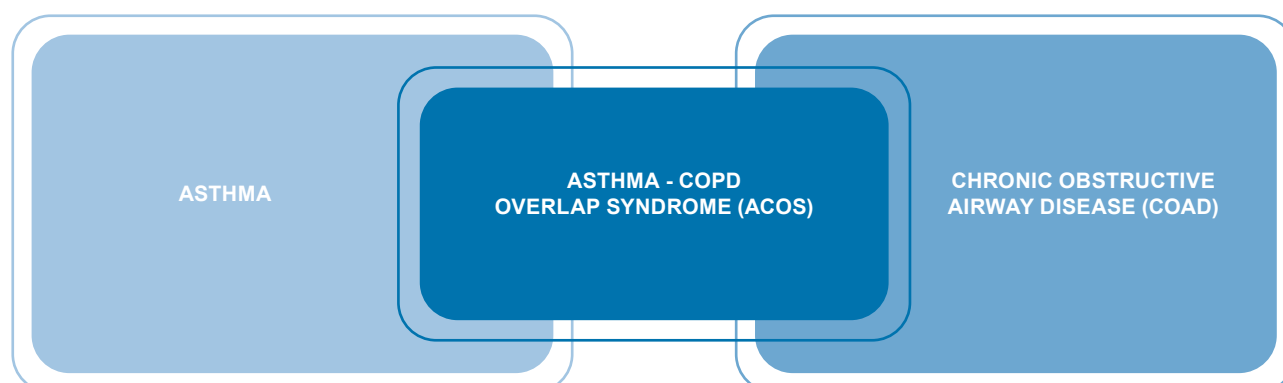
RAISED IGE PLASMA LEVELS	ATOPIC FEATURES (IGE PLASMA LEVELS MAY BE RAISED OR NORMAL)
? Allergy	? Allergy
Hyper IgE syndromes	SCID
Omenn syndrome	Hyper IgE syndromes
WAS	Omenn syndrome
IPEX syndrome	WAS
CGD	Netherton Syndrome

* CGD: Chronic Granulomatous Disease, IPEX: Immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome, SCID: Severe Combined Immunodeficiency, WAS: Wiskott Aldrich Syndrome

ASTHMA, CHRONIC OBSTRUCTIVE LUNG ISSUES AND PIDS

PROF LEIF HANITSCH, BERLIN, GERMANY

Following discussion of allergy in PID **Prof Leif Hanitsch** discussed asthma and Chronic Obstructive Pulmonary Disease (COPD) in PIDs providing a framework for management. The prevalence of asthma is higher than the general population and often occurs independently of IgE levels however is associated with low IgA and IgM. The true prevalence of COPD in PID remains uncertain. Although the clinical presentation is similar, it is important to differentiate between asthma and COPD as the management differs however there may be an overlap namely asthma-COPD overlap syndrome (ACOS). Both XLA and CVID suffer from increased rates of asthma however CVID carries an increased risk for COPD and may have an ACOS profile. Inhalative therapy is the cornerstone of management. In Asthma inhaled corticosteroids are the first line of treatment whilst in COPD long-acting beta agonists (LABA) and long acting muscarinic antagonists (LAMA) are first line. In bronchiectasis there is difficulty in the drug getting into the small airways due to the mucus plug and so it is advised to start with a short acting beta-2 agonist (SABA) followed by saline solution for improved muco-ciliary clearance and then LAMA/LABA/ICS. Macrolides are useful in preventing exacerbations and are important in PIDs acting as both an antimicrobial as well as an anti-inflammatory component.





DERMATOLOGICAL ALLERGIC MANIFESTATIONS IN PIDS

PROF RAFFAELE BADOLATO, BRESCIA, ITALY

Dermatological allergic manifestations are common in allergy however also to PIDs. **Prof Raffaele Badolato** carried along the theme of atopy and discussed the haematological allergic features in PID. A spectrum of dermatologic manifestations was discussed divided into those with predominantly allergy and those with predominately infection. Dermatologic monogenic disorders such as Netherton syndrome and severe skin dermatitis, multiple allergies and metabolic wasting.

SAM syndrome present with predominant atopic dermatitis whilst monogenic IEI with skin infections such as Epidermodysplasia Verruciformis (EV)1 and EV2 have more predominant infection. Mixed and allergic/infections are seen in Hyper IgE syndromes (Loss of function [LoF] STAT3 mutations, ZNF341, IL6R, IL6ST and CARD 11 deficiency) whilst skin infections with cytopenia namely lymphopenia and neutropenia are typically warts, hypogammaglobulinemia, infections and myelokathexis (WHIM) syndrome, EV4 or EV5. The dermatological features often present later in DOCK8 deficiency whilst Omenn syndrome and Wiskott Aldrich syndrome (WAS) have earlier onset dermatological features, all falling in to the category of combined immunodeficiency with hyper IgE. Fungal skin infections are of particular concern and may be associated with syndromic features such as STAT3-LoF. In conclusion severe dermatological manifestations that are not responsive to treatment and associated with infection should prompt further investigation for possible PID.

ALLERGY			INFECTION	
Dermatologic monogenic disorders	Mixed type allergic/ infectious disorders	Combined immunodeficiencies with hyper IgE	Skin infection and lymphopenia/ neutropenia	Monogenic IEI Diseases with skin infections
Netherton syndrome, SAM syndrome	Hyper IgE syndromes STAT3 LoF ZNF341 IL6R, IL6ST, CARD11	Omenn Syndrome, IPEX, Wiskott Aldrich Syndrome, DOCK8 deficiency, MALT1 deficiency	WHIM (CXCR4), EV4 (RHOH), EV5 (IL7)	EV1, EV2





SESSION 2: MANAGEMENT OF GASTROINTESTINAL AND HEPATIC MANIFESTATIONS IN PIDS

Chaired by: Prof Sergio Rosenzweig, and Ms Jose Drabwell.

The interplay between the gastrointestinal tract and immune system: **Dr Fabienne Charbit-Henrion**, How to manage gastrointestinal and hepatic manifestations of PID: **Dr Cinzia Milito**, Explorations and treatment pathways including transplantation and conditioning: **Dr Lizzy Rivers**, A patient experience **Ms Sian Van den Bogaerd-Rance**



- The immune system is not the same in all areas of the gastrointestinal tract
- Gastrointestinal disease affects around half of PID patients
- Inflammasome and autophagy dysfunction are likely important in gastrointestinal pathology and may be potential treatment targets
- There is increased risk for gastric malignancy and liver involvement, particularly CVID
Abdominal ultrasound and upper endoscopy should be performed annually with regular liver function monitoring

THE INTERPLAY BETWEEN THE GASTROINTESTINAL TRACT AND IMMUNE SYSTEM

DR FABIENNE CHARBIT-HENRION, PARIS, FRANCE

Dr Fabienne Charbit-Henrion started session 2 discussing the interplay between the gastrointestinal tract and the immune system. She described 3 main phenotypes; those presenting with epithelial defects who occur early with congenital diarrhea, autoimmune enteropathies that resemble an IPEX like syndrome and colitis that presents with a Chron's like disease. Epithelial defects have a defect in the epithelial lining resulting in intestinal insufficiency, some developing inflammation. In autoimmune enteropathies the proximal gastrointestinal tract is affected. The defect is mainly in the adaptive immune system presenting with chronic diarrhea and villous atrophy however may have an allergy phenotype with hyper IgE. Children typically have an IPEX like phenotype with non-coeliac enteropathy whilst adults are more lymphopenic, with increased risk for malignancy, up to 40% had a molecular diagnosis. The early inflammatory bowel type phenotype affects the more distal bowel, carrying defects in the innate immune system. Defects are usually loss of regulation, inflammasome dysfunction and defects in innate epithelial defense. There are some overlapping syndromes. In conclusion the gastrointestinal tract is a regionalised organ, and the immune system is not the same in all areas.

	AREA OF GASTROINTESTINAL TRACT	IMMUNE SYSTEM AFFECTED	MECHANISMS	MUTATION
Epithelial defects	Epithelial lining	Adaptive immunity	Alteration of apical differentiation	PEX1, PRECC1, EPCAM, MYO5, UNC45A, FARSA, NEUROG3
			Alteration in adhesion	
Auto-immune enteropathy	Proximal and small bowel	Adaptive immunity	Decreased T-regulatory cells	FOXP3 IL2RA MALT1 DOCK8
			Increased T-effector cells	STAT1 GOF STAT3 GOF JAK1 GOF PTPN2 LOF
Colitis and perineal lesions	Distal bowel	Innate immunity	Decreased regulation of macrophages	IL-10 receptor pathway
			Decreased innate effector cells	Chronic granulomatosis disease: NCF1, CYBB, CYBA, NCF4, NCF2 NOD2-XIAP pathway: XIAP, TRIM22, NPC1
Colitis only	Distal bowel	Innate immunity	Decreased regulation of innate pathway	Loss of regulation: TNFAIP3, IL37, ELF4, IPO8 Inflammasome: NLRC4 GOF, MVK LOF, CASPASE 8 LOF
			Decreased innate effector cells	Innate epithelial defense: DUOX2, ALP1

HOW TO MANAGE GASTROINTESTINAL AND HEPATIC MANIFESTATIONS OF PID

DR CINZIA MILITO, ROME, ITALY

Dr Cinzia Milito built on the previous talk and discussed the management of gastrointestinal and hepatic manifestations. About 10% of patients with CVID present with liver involvement, separated into 2 general complications namely liver disease concomitant to CVID and liver disease specific to CVID which includes nodular regenerative hyperplasia (NRH). It is often difficult to diagnose liver involvement as it may be silent. As highlighted by Prof Warnatz in the keynote address, it is often a sequela of accumulative disease after a period of smoldering disease. Liver function tests should be performed 3-4 times per year and trends monitored closely, ultrasound or CT scan are also advised. It should be managed with corticosteroids alone or with immunomodulators. CVID patients develop enteropathy and have increased risk for gastric cancer, the leading malignant cause of death and therefore annual gastric endoscopy was advised.

LIVER DISEASE IN CVID

Liver Disease concomitant to CVID	Liver Disease specific of CVID
HBV, HCV infection	Nodular regenerative hyperplasia (NRH)
Alcohol related liver disease	Liver granulomatosis
NAFLD/NASH	Idiopathic liver disease

** CVID: Common Variable Immunodeficiency, HBV: Hepatitis B Virus, HCV: Hepatitis C Virus, NAFLD/NASH: Non-alcoholic fatty liver disease/ Non-alcoholic steatohepatitis, NRH: Nodular Regenerative Hyperplasia

EXPLORATIONS AND TREATMENT PATHWAYS INCLUDING TRANSPLANTATION AND CONDITIONING

DR LIZZY RIVERS

Continuing the gastrointestinal disease theme **Dr Lizzy Rivers** discussed explorations and treatment pathways in the gastrointestinal manifestations of PIDs. She highlighted that gastrointestinal disease affects up to half of PID patients. The inflammasome is gathering increased interest: as its pathophysiological role is better understood it may serve as a possible therapeutic target. PIDs that develop gastrointestinal complications are WAS where raised IL-18 suggests inflammasome dysregulation. Anti-IL-1 has proven a useful drug to treat gastrointestinal manifestations in WAS. A large proportion of CGD suffers with inflammatory bowel disease (IBD). Unlike WAS, Anti-IL-1 has shown conflicting responses whilst rapamycin/sirolimus seems promising in targeting autophagy stimulation. X-linked inhibitor of apoptosis (XIAP) mutation often has refractory IBD, aside from curative transplant other targeted therapies include anti-γ-IFN and IL-18p. Similarly, in IPEX syndrome HSCT is curative however, rapamycin/sirolimus have shown good results in halting disease progression. There is a rapidly expanding field of targeted medicine and biological therapies. As multiple pathways are often involved combined and multifactorial approaches are needed, the inflammasome and autophagy are likely important treatment targets.

STIMULATORY CYTOKINES	CYTOKINE BLOCKERS	LYTIC ANTIBODIES	SPECIFIC PATHWAY INHIBITORS	OTHER NOVEL AGENTS
Interferon gamma (IFNγ)	Anti-IL-1 (Anakinra, Canakinumab)	Anti-CD20 (rituximab)	mTOR (rapamycin/sirolimus)	CTLA4 fusion protein (Abatacept)
Interferon alpha (IFNα)	Anti-IL-6 (Tocilizumab)	Anti-CD52 (Alemtuzumab)	PI3K δ (Leniolisib, Nemiralisib)	Anti- $\alpha_4\beta_7$ integrin (Vedolizumab)
Interleukin 2 (IL-2)	IL-18 binding protein (IL-18BP) (Tadekinig alfa)	Anti-thymocyte globulin (ATG)	JAK (Ruxolitinib, Baracitinib)	Anti- α_4 integrin (Natalizumab)
	Anti-TNF α (Infliximab, Etanercept)			
	Anti- γ -IFN (Emapalumab)			
	Anti-IL-12/IL-23 (Ustekinumab)			

A PATIENT EXPERIENCE

MS SIAN VAN DEN BOGAERDT-RANCE, NETHERLANDS

Providing an important patient perspective, **Ms Sian Van den Bogaerdt-Rance** discussed her experience in being diagnosed with CVID later in life. She highlighted the fears faced with uncertainty around diagnosis but also the relief both mentally and physically in obtaining a diagnosis and getting the correct treatment. Her positivity and drive for patient advocacy is inspiring and reminds the PID community of the reason for their work.



SESSION 3: THE USUAL SUSPECTS (WHEN NOTHING IS WHAT IT SEEMS YOU HAVE TO LOOK BEYOND...)

Chaired by: Prof Stephen Jolles, Ms Roberta Anido de Pena and Prof Stuart Tangye

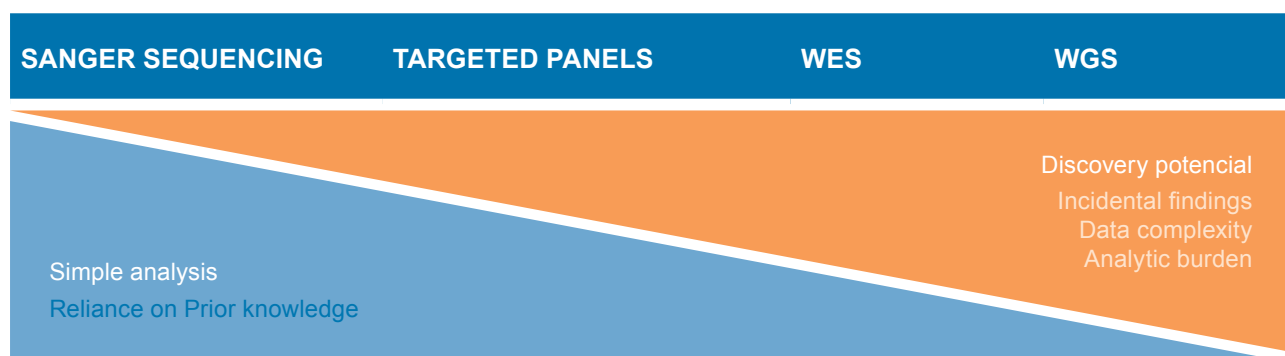
Genetic diagnosis: Prof Sophie Hambleton, Malignancy spectrum of PIDs: Dr Ton Langerak, Autoimmunity and autoinflammation manifestations: Prof Tadel Avcin

- Next generation sequencing (NGS) is a useful diagnostic tool however needs to be placed in the clinical context and may require deeper focused investigation.
- PIDs carry a higher risk for malignancy in particular non-Hodgkin lymphoma. There is a spectrum ranging from benign to malignant.
- Autoimmune manifestations are frequent and often multiple in PID with emerging patient tailored therapies developed based on pathogenic mechanisms

GENETIC DIAGNOSIS

PROF SOPHIE HAMBLETON, NEWCASTLE, UNITED KINGDOM

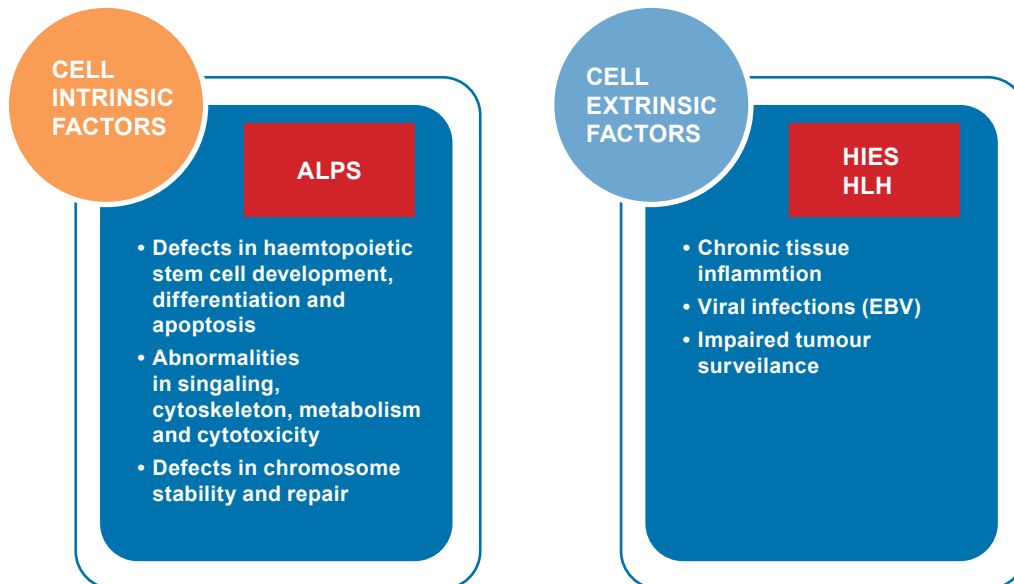
Prof Sophie Hambleton started the third session tackling genetic diagnosis in PID. There are an increasing number of alternative strategies in the contemporary genetic diagnosis of PID. Molecular strategies range from Sanger sequencing, offering simplicity of analysis to targeted PID panels, whole exome sequencing (WES) and now whole genome sequencing (WGS). WGS has expanded the discovery potential in PID facilitating the discovery of an increasing array of genetically distinct IEI. However, it is not perfect with incidental findings raising questions of what to do with the information, the complexity of data interpretation and the analytic burden. Applying such molecular techniques raises the question “how effective are these very expensive methods in providing a molecular diagnosis?” The diagnostic yield ranges from 30-40%, with recent study by Platt et al. (doi:10.1016/j.jaci.2020.08.022) showing an overall diagnostic yield of 56% when WES/NGS PID panel is applied. When applying NGS to PID, although very helpful one needs to put it into context, be aware of its shortfalls and remember the importance of applying the clinical context. A case report was highlighted where the patient had a clinical phenotype of DOCK2 however the PID panel and DOCK2 was negative. Without a high index of suspicion, the patient may have been misdiagnosed as the as the mutation lay outside the filtering process. One may therefore need to look further at cryptic splice sites. Although molecular diagnosis has come a long way the clinical picture should guide variant selection and interpretation, “when the clinical phenotype fits but there is no diagnosis – look deeper look closer”.



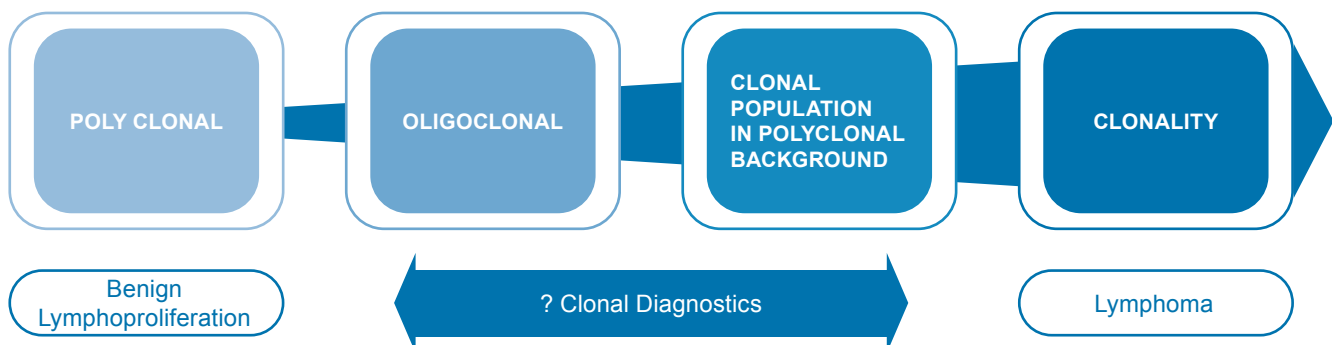
MALIGNANCY SPECTRUM OF PIDS

DR TON LANGERAK, ROTTERDAM, NETHERLANDS

Carrying the theme of “unusual suspects”, **Dr Ton Langerak** followed on from Prof Hambleton, addressing the increasing awareness of non-infectious manifestations in IEI namely, malignancy. There is an 1.4-2.3 fold increased risk for malignancy in those with IEI which varies across the different PID classes. Haematological malignancies, most commonly non-Hodgkin lymphoma or leukaemias are the most prevalent malignancies in PIDs. The mechanisms for PIDs and malignancies could be cellular intrinsic defects or extrinsic defects as seen in Autoimmune lymphoproliferative syndrome (ALPS) and HIES/haemophagocytic lymphohistiocytosis (HLH) respectively.



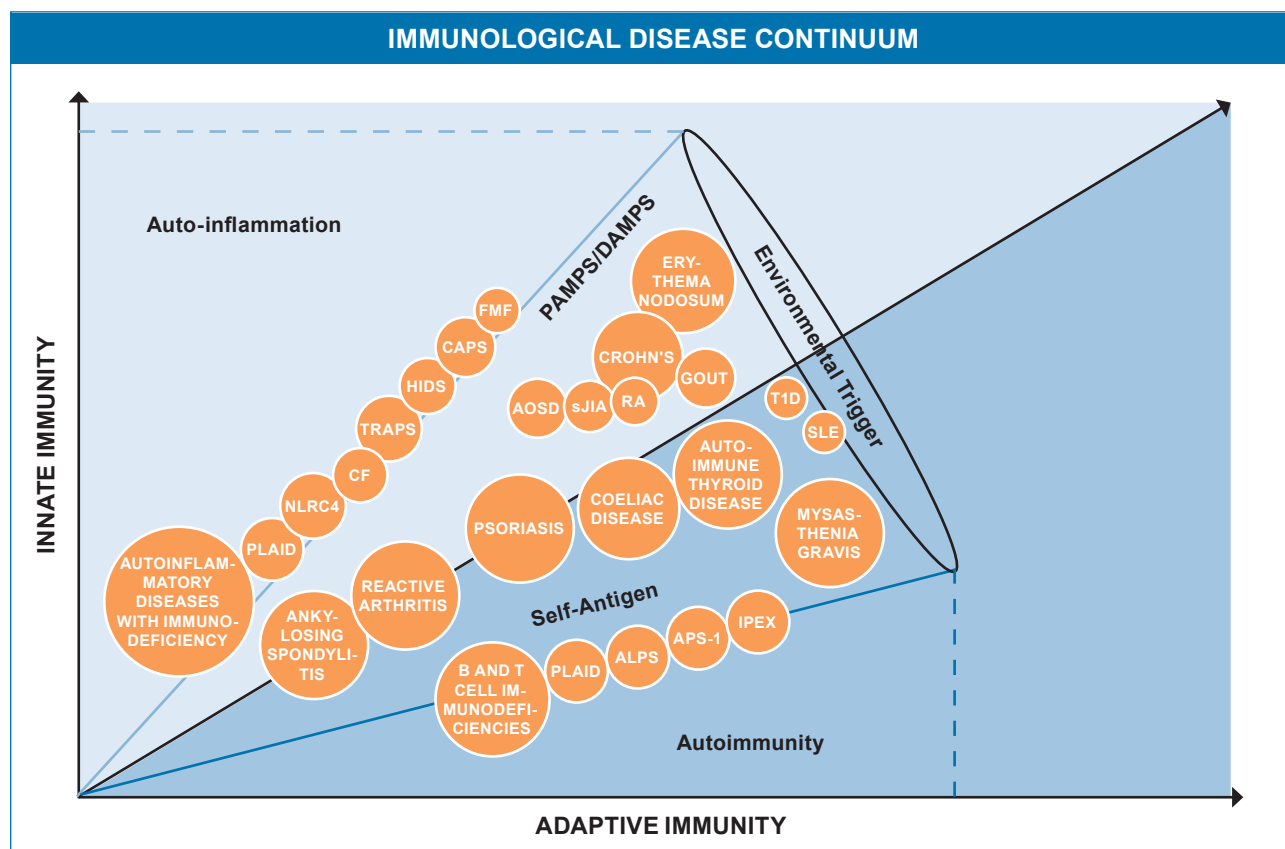
PIDs show a lymphoproliferative spectrum that ranges from benign lymphoproliferation (polyclonal) to lymphoma with expressed clonality. Newborn screening facilitates early diagnosis and timely intervention, ideally before disease onset and consequence thereof. As highlighted in the keynote address there is a need to identify “hidden disease” early. Similarly, there is a need to identify malignancy early before onset, facilitating early interventions. It is proposed that by using standardized techniques, such as EuroClonality (<https://euroclonality.org>), to identify premalignant clones before clinical disease onset comorbidity may be minimised and therefore outcomes improved. The predisposition / high risk of lymphoma in PIDs justifies early identification approaches and immunogenetics have the potential to fulfil that need.



AUTOIMMUNITY AND AUTOINFLAMMATION MANIFESTATIONS

PROF TADEJ AVCIN, LJUNLJANA, SLOVENIA

Prof Tadej Avcin discussed autoimmune and autoinflammatory manifestations of PID. There is an immunological disease continuum, autoinflammation typically driven by the myeloid lineage and autoimmunity by the lymphoid lineage. Up to 45% of PIDs cause autoimmunity/autoinflammation, these monogenic defects provide a unique insight into the pathogenesis of autoimmunity. There are varying reports of immune dysregulation on registries. In the Slovenian registry 22% had autoimmune manifestations whilst the recent registry review by Thalhammer et al. reported up to 80% presenting with immune deregulatory manifestations.



Peckham et al. J Pathol 2017;241:123–139, DOI:10.1002/path.4812

AOSD, adult-onset Still's disease; ALPS, autoimmune lymphoproliferative syndrome; APS-1, autoimmune polyglandular syndrome type 1; IPEX, immune dysregulation polyendocrinopathy enteropathy X-linked syndrome

Autoimmune manifestations are frequent and often multiple in PID. The autoimmune and inflammatory manifestations include autoimmune phenomena, granulomatosis, HLH syndrome, lymphoproliferation and autoinflammation. Autoimmune disease that is familial, early onset or atypical is highly suggestive of an underlying monogenic PID and should flag further investigation. Monogenic IPI provide unique models to study molecular pathways regulating inflammation and study highlights diseases with combined features of immunodeficiency, autoimmunity, autoinflammation and/or allergy. The field is becoming more complex. JAK inhibitors and type 1 interferons are emerging patient tailored therapies that are based on pathogenic mechanisms.

MECHANISMS OF AUTOIMMUNITY IN PID

Mechanism	PID disease/Gene defect
Exacerbation of type 1 IFN production	Aicardi-Goutières syndrome
Exacerbation of IL-1 production	Autoinflammatory syndromes
Defective negative selection of T/B cells	AIRE, RAG
Defective editing of the B cell receptor	RAG, AID
Defective peripheral antigen-induced death	ALPS (FAS deficiency)
Gain of function of T/B activation/effector molecules	STAT1, STAT3, PI3K

SESSION 4: REGIONAL DIAGNOSIS AND CLINICAL CHALLENGES SESSION

Chaired by: Prof Martin van Hagen and Ms Cynthia Olotch

APSID: Dr Ankur Jindal, ASID: Dr Helena Cornelissen, CIS: Prof Sergio Rosenzweig, ESID: Dr Nizar Mahlaoui, LASID: Prof Gesmar Segundo, SEAPID: Dr Narissara Suratannon

- Call for improved collaboration
- Need to implement regional registries
- Concerns regarding discrepancy of care



Although each region faces different challenges, there are common themes across societies. All regions highlighted the success of summer schools and training programs. Importantly most reported the success of on-going care and training throughout the COVID pandemic, with vaccination triumph. Discrepancy in care amongst different regions was a common thread and concern for many. New-born screening is very much in its infancy in most countries whilst North America, some countries in Europe and Asia have a well-established screening programme. The success of registries was realized; however, most regions reported the need to implement and establish collaborative registries. Overall, there was a call for collaboration with a common goal of promoting research, exchanging ideas, sharing knowledge, and facilitating education. A question was raised regarding adult care of PID patients: Prof Sergio Rosenzweig reminded the audience that the need is a story of our success, patients are surviving into adulthood now. Adults in Asia stay under pediatric care, in Africa it varies according to regional availability of adult immunologists, in Brazil most immunologists are pediatricians and patients remain under pediatric care. In most of Europe, North America and in Thailand there are adult immunology services and patients are transitioned across.



REGIONAL SOCIETY	CHALLENGES	SUCSESSES	NEWBORN SCREENING	IMPACT OF COVID
APSID	<ul style="list-style-type: none"> Regional differences Hong Kong has immunology services now on par with the west Malaysia is split between East and West, often suffering from underdiagnosis and treatment There are 2 centers in India for PID diagnostics many PIDs are still missed, HSCT remains a challenge 	<ul style="list-style-type: none"> Annual APSID schools since 2015. A large number of abstracts have been submitted in regions where there has been an APSID school Plan for a PID registry Post graduate training has been initiated 8 Major PID centers established 	<ul style="list-style-type: none"> Taiwan is the only country doing NBS 	<ul style="list-style-type: none"> Continued virtual meetings through COVID
ASID	<ul style="list-style-type: none"> Should be contributing more PID cases to the global PID population, cases are being missed. Lack of awareness and funding Paucity of diagnostic services and skilled interpretation Overburdened healthcare system distracted by endemic infections 	<ul style="list-style-type: none"> 7 biennial conferences since its inception 15 ASID schools that have been tailored to nurses as well as clinicians in separate sessions A-projects have shown much success with increased PID diagnosis after sessions African specific guidelines are in development ASID registry on its way Sudanese government funded IGRT 	<ul style="list-style-type: none"> No Africa countries with established newborn screening Implementation, follow-up care and immunology services remain concerns 	<ul style="list-style-type: none"> Under vaccinated (less than 1/3rd South Africans vaccinated) Ongoing data collection regarding PID cases with COVID-19 infection
CIS	<ul style="list-style-type: none"> Inequalities between different areas coastal areas benefiting from better specialist access compared to inland Work is still needed to establish a registry 	<ul style="list-style-type: none"> Continued commitment to PID research/care Continued summer and diagnostic schools The Journal of Clinical Immunology 	<ul style="list-style-type: none"> Newborn Screening now well established in the States 	<ul style="list-style-type: none"> Uptake of COVID vaccines has been good with up to 70% vaccinated and only 20% have seen breakthrough infections Sadly 4 COVID related deaths all of whom were vaccinated

REGIONAL SOCIETY	CHALLENGES	SUCCESSES	NEWBORN SCREENING	IMPACT OF COVID
ESID	<ul style="list-style-type: none"> Discrepancies between countries 	<ul style="list-style-type: none"> Strong registry with almost 30 000 patients 21 collaborative publications over the last 5 years 	<ul style="list-style-type: none"> Continues to be piloted and implemented in many European countries however there is still a long way to go 	<ul style="list-style-type: none"> COVID review was published on PID patients in Europe
LASID	<ul style="list-style-type: none"> Regional discrepancies Challenges with diagnostic services with big discrepancy between private and public sectors Access to treatment differs per region Biologics are difficult to obtain 	<ul style="list-style-type: none"> Recent success in plans for new facilities for immunoglobulin production 	<ul style="list-style-type: none"> NBS has been signed by Brazilian government however has not yet been implemented Sao Paulo will start NBS in the near future 	
SEAPID	<ul style="list-style-type: none"> BCGosis remains a challenge as BCG is given at birth as is polio virus Access to diagnostics and even simple measurement of Ig requires referral to specialist center 	<ul style="list-style-type: none"> Efforts to start a patient registry with focus on early diagnosis have begun 	<ul style="list-style-type: none"> No NBS – rely in family history Timing of vaccination and screening is a problem. Careful family history on Early Infant Death should be performed prior to neonatal BCG vaccination 	



SESSION 5: TREATMENT ADVANCES IN SPECIFIC PID MANAGEMENT

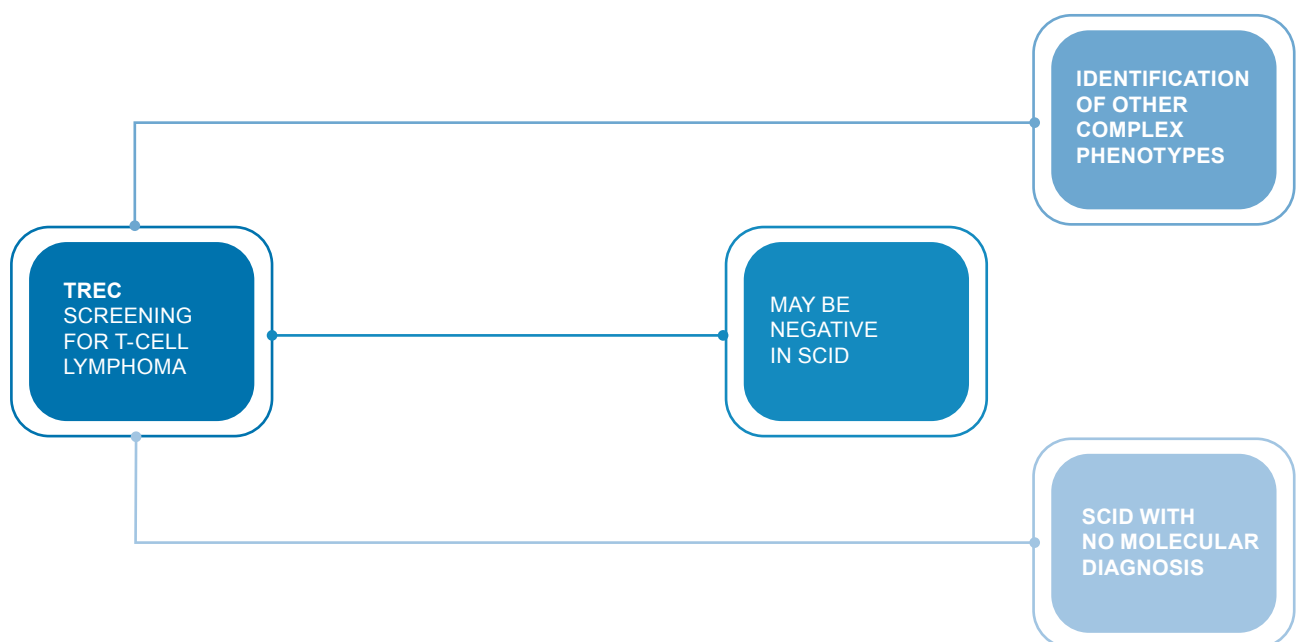
Chaired by: Dr Virgil Dalm and Ms Martine Pergent.

T-cell lymphopenia - How TRECs modify the management of these patients: **Prof Stephen Ehl**, CGD latest management advances: **Prof Steven Holland**, ALPS reaching new heights: **Dr Olaf Neth**, Update on IUIS classification – will it open new PID management pathways: **Prof Steven Holland**

- Improved outcomes when SCID is transplanted <3.5 months
- TRECs screen for T-cell lymphopenia and do not only identify SCID, but other complex phenotypes as well. TRECs may be negative in SCIDs.
- Advances in CGD: transplant, gene therapy and monoclonal antibodies improving outcomes, conventional prophylaxis should not be forgotten.
- Immunotherapy may be a bridge to HSCT in ALPS
- The IUIS classification should be used as a tool to guide diagnosis and research with phenocopies of PID being an expanding new category on the horizon

T-CELL LYMPHOPENIA - HOW TRECS MODIFY THE MANAGEMENT OF THESE PATIENTS PROF STEPHEN EHL, FREIBURG, GERMANY

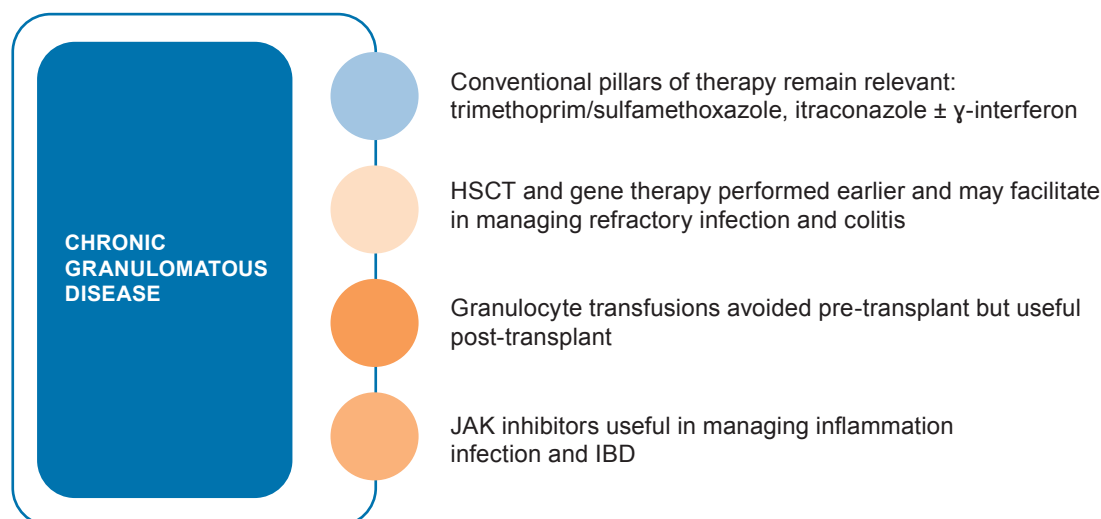
Prof Stephen Ehl started session 5 by discussing TRECs in the identification of T-cell lymphopenia and the German experience with newborn screening (NBS). NBS has been implemented in Germany since 2019. A SCID hotline was established with 42 dedicated immunology clinics, a NBS registry and 12 centers that can validate and treat results. NBS is important as there is clear improved survival when HSCT is performed before 3.5 months of age. However, in performing TREC screening not only SCIDs are identified but also other more complex phenotypes and so should be considered rather a tool for screening for T-Cell lymphopenia. Thymic transplants remain a challenge there is limited availability, the UK providing the only service in Europe but also when to perform the transplant remains a question. Although a useful tool, TRECs may be negative in some SCIDs and so the clinical phenotype should be carefully considered. Another difficulty arises in around 10% of patients who have a clinical and immunological SCID phenotype but have no molecular diagnosis, a watch and wait policy is adopted in Germany and many recover their T-cell function. NBS is a success story but requires careful clinical interpretation. Whether there are other PIDs that could be identified at birth, what methods should be used and how extensive should the panel be are some of the questions to be answered as we look to the future.



CGD LATEST MANAGEMENT ADVANCES

PROF STEVEN HOLLAND, BETHSEDA, UNITED STATES OF AMERICA

Prof Steven Holland followed with an update on the latest advances in chronic granulomatous disease (CGD) management. CGD is almost celebrating its 68th birthday. Infections remain a problem and well-established prophylactic strategies such as trimethoprim/sulfamethoxazole, itraconazole and γ -interferon (although there has been some controversy regarding this in Europe) are still very much still applicable and should not be forgotten however there have been new advances in cure. HSCT with conventional treatment has a better overall survival if transplanted under 8 years. The earlier the transplant the better. Transplant may be done during periods of active infection, including fungal infections and may actually facilitate management of refractory infection. Inflammatory Bowel Disease (IBD) is a common complication and should not be a barrier to transplant. JAK inhibitors show promise in managing inflammation whilst experience with TNF inhibitors has been poor and is not recommended. Granulocyte transfusions are useful in treating infections when used after transplant with improved survival however are not advised pre-transplant. Gene therapy has been successful even in the context of active infection and may help to resolve refractory infection as well as IBD and may be more applicable in those with refractory fungal infection without a good donor match. More than 80% of HSCTs are successful and about 66% of those treated with gene therapy have had successful outcomes, the pillars of prophylaxis remain namely trimethoprim/sulfamethoxazole, itraconazole with/without γ -interferon. CGD is not yet ready for retirement, there's still much to do!



ALPS REACHING NEW HEIGHTS

DR OLAF NETH, SEVILLE, SPAIN

Dr Olaf Neth followed the trend of treatment advances discussing Autoimmune lymphoproliferative syndrome (ALPS) and reaching new heights. ALPS is a complex disease that is difficult to understand, we are likely only at the tip of the iceberg. It is a disease with overlap between immune deficiency, autoimmunity/allergy however not necessarily all or one. It manifests in childhood and is characterised by chronic lymphadenopathy, splenomegaly, multilineage cytopenias and increased risk of B-cell lymphoma due to defective lymphocyte apoptosis, unique expansion of double negative T-cells as a result of mutations in FAS gene. Treatment should be individualized, and disease manifestations managed noting the 10% risk for lymphoma. Sirolimus can be used to manage lymphoproliferation (uncontrolled T-cell proliferation) and mycophenolate for pancytopenias. If intolerant and refractory 3rd line therapies such as vincristine and methotrexate can be applied or 4th line therapy such as rituximab. Although often needed in the acute setting, long term steroids and splenectomy should be avoided, prophylaxis is important namely pneumococcal vaccine and penicillin prophylaxis. Novel therapies are coming into play and immunomodulatory therapy may provide a bridge between HSCT in ALPS and ALPS like syndromes.

DISEASE	DRUG
ALPS	mTOR inhibitors
CTLA4/LRBA deficiency	Abatacept
APDS1/2	Idelalisib and mTor inhibitors
STAT1 GOF	JAK inhibitors
STAT3 GOF	JAK inhibitors

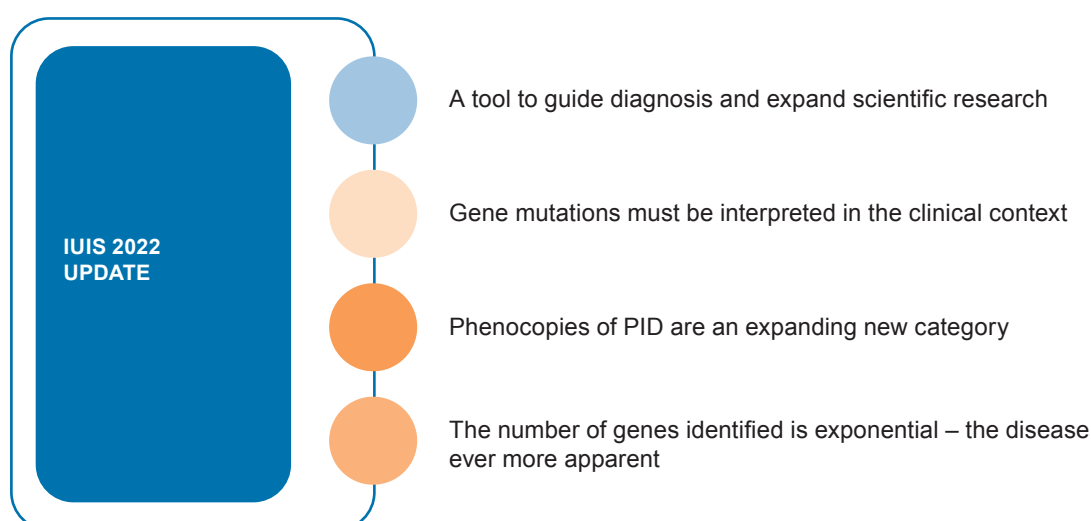
In conclusion there is a big overlap between immune deficiency, autoimmunity/allergy and auto inflammation and we are likely only discovering the tip of the iceberg. Small molecules are likely to be at the forefront of therapy and serve as a bridge to HSCT and possibly gene editing.

UPDATE ON IUIS CLASSIFICATION – WILL IT OPEN NEW PID MANAGEMENT PATHWAYS? PROF STEVEN HOLLAND, BETHESDA, UNITED STATES OF AMERICA

Concluding the session **Prof Steven Holland** provided insight and update into the IUIS 2022 classification. The 2022 update is under review and is soon to be published, an exciting new addition to the scientific community! The number of genes identified is expanding exponentially and it is difficult to keep up. The IUIS classification should be used as a tool to categorize and design diagnosis, it is not aimed to guide treatment. New on the horizon and an expanding category are phenocopies of PID which interestingly tend to present later in life and be more common in males. The mutations are somatic, and a minority of cells carry the mutation, either gained during early embryogenesis or after birth. Somatic TLR8, UBA1 VEXAS (Vacuoles, E1-ligase, X-linked, Auto-inflammatory, Somatic) and autoantibodies to type 1 interferon were discussed.

TLR8 has an early onset that is consistent with an inborn error, it presents with lymphoid proliferation and associated neutropenia. Somatic changes may only be present in a small fraction of the DNA and therefore deep reads are needed to identify the mutation; cases can easily be missed. Contrastingly UBA1 VEXAS presents later in life in adult males and is clearly not inborn. It is a result of a stem cell mutation that results in myeloid expansion and inflammation. All cases are somatic these somatic changes are often present in a large fraction of the DNA and so there does not need to be as much concern around read depth. Autoantibodies to type 1 interferons (IFN) have a later onset and may be relatively common. Infections are likely to be cytokine specific, such as mycobacteria and severe acute respiratory syndrome coronavirus 2 (-CoV-2) infection. Interestingly these patients are at risk of developing more severe COVID, their disease phenotype only manifesting now when the specific dysfunction has been exposed to “the right setting”.

Importantly PIDs are on the rise whilst endemic infections are decreasing due to improved management and prevention strategies. New tools to understand PIDs, that are less rare than previously thought. Genes do not provide all the answers and the IUIS classification should be used to guide the diagnosis and a means to expand scientific research and better understanding, “it is what you put in those genes that gives you what you need to move forward”.







SESSION 6: PID ECONOMICS, DIAGNOSIS, ACCESS TO CARE – ETHICS BETWEEN THE LINES

Chaired by: Prof Charlotte Cunningham-Rundles and Dr John Seymour.

Panel: Prof Alessandro Aiuti a clinician, Prof James Taylor a philosopher and ethicist, Prof Frank Staal a clinician, Prof Cornelis Boersma a health economist, Dr Adli Ali a clinician, Nurse Mary Louise Daly and Ms Otilia Stanga a parent and patient advocate.

- A key problem is equality of access to care. Best care of the patient should be prioritized above budget and policy, unfortunately this is not always the case.
- Patient organisations are paramount in advocating for increased transparency, discussion with stakeholders and improving access to care.
- Informed consent should be at a level understood by the patient even though primary consent may be provided by the primary care givers.
- The overall prognosis of the patient should be taken into consideration when doing organ transplant for chronic sequelae of the underlying immune deficiency.

The last day was started with an interactive and thought-provoking ethical discussion. The first case was presented by **Dr John Seymour**. A case of a neonate identified with ADA-SCID within 48 hours of life as part of newborn screening. The patient was offered enzyme replacement and further investigation done to determine the best option for treatment. It was decided that gene therapy was the best option. However due to uncertainty around residency qualifications and the expense of treatment gene therapy was denied.

Prof James Taylor opened the discussion by identifying 2 key issues. The first around access to healthcare when there is uncertainty around immigration status and residency qualification. There was consensus agreement that this should not be a consideration. Nationality and citizenship should not bear weight in healthcare decisions. The second issue is cost of therapy. **Prof Alessandro Aiuti** reminded us why such therapy is so expensive, and that the follow-up care also needs to be taken into account. As this is a rare disease the cost unfortunately cannot be diluted across many patients. **Ms Otilia Stanga** responded mentioning that she was once such a mother and that patient advocates need to do everything in their power to ensure access to needed interventional care as well as follow-up. **Nurse Mary Louise Daly** echoed this sentiment however highlighted that in reality this is often not the case. Government hands are tied due to budget limitations however there should be increased transparency amongst all stakeholders to understand the true cost of the drug. **Prof Cornelis Boersma** posed the question as to how can treatment be made accessible and affordable for all, future possibilities need to be looked at to make treatment more affordable and accessible. **Prof Frank Staal** advocated that in this case there is a lucky solution as although still expensive HSCT can be offered which is cheaper but still with good outcome. However, he stressed that patient organisations need to put pressure on government to change policy and make treatment more accessible. **Dr Adli Ali** provided perspective from a developing country where the constraints of availability to care are faced daily and one needs to ensure that patients who have the best expected outcome are provided treatment. Therefore, how should patients be prioritised when there is limited availability and access. There was vibrant participation from the floor. The concept of a Casio era was discussed where the majority of patients are lucky and receive treatment whilst the unlucky few with a rare disease do not, their needs swamped by the needs of the many. It was concluded that cost of therapy and its coverage is a problem and we need to provide equitable healthcare for all. There is increased need for close collaboration and increased transparency between the pharmaceutical companies government policy, scientists, researchers, patient advocates and clinicians developing the needed treatment. In the cost benefit analysis society needs to decide what type of society is the goal and this, sometimes trumps the cost. The key problem in this case was access to care and policy affecting care.



Prof Charlotte Cunningham-Rundles introduced the second case; a 22-year-old girl with DiGeorge who is mentally challenged with thrombocytopenia and hepatobiliary syndrome requiring oxygen and a liver transplant. The transplant team and parents are in agreement that the patient should receive a liver transplant however there is concern around the clinical status of the patient namely the existing immune suppression and thrombocytopenia.

Prof James Taylor opened this case discussion highlighting 2 key issues namely informed consent as well as the clinical status of the patient and whether transplant is relevant. **Prof Frank Staal** echoed this sentiment noting that it is important to not only consider the consent but also the fact that the underlying immunological problem cannot be solved and that even if going ahead with the liver transplant the long-term underlying problem will not be resolved. **Prof Alessandro Aiuti** reminded the audience that the family should be given more autonomy in the decision however must be informed that there may not be real long-term benefit. **Dr John Seymour** highlighted that patients need to be given informed consent, even if not providing the primary consent, on a level that is applicable to them and in a way they can understand. **Dr Adli Ali** provided a developing world perspective where often the decision lies with the managing clinician alone, the prognosis of the patient heavily weighting the decision-making process. Whether this is correct is unclear however difficult decisions need to be made to provide care to the most people with the best outcome in a limited budget. From the audience **Prof Luigi Notarangelo** reminded the audience to consider the informed consent of the donor, the donor should be informed that they are providing an organ at a risk to their health to a patient that will very likely have a poor long-term outcome. It was concluded that the family needs to play an important role in the decision-making process and should be given the information and tools to make the most informed decision however responsibility lies with the managing team to consider the clinical status of the patient and whether organ transplant will be of true benefit.

SESSION 7: THE QUEST FOR A CURE TO PID

Chaired by: Prof Tadej Avcin and Mr Andrea Gressani

Cell therapy and PIDs: **Prof Luigi Notarangelo**, Bone Marrow Transplantation in adults with IEI: **Prof Felipe Suarez**, Thymic transplantation: **Prof Graham Davies** and Gene therapy and Gene Editing: **Prof Frank Staal**.

- Monoclonal antibodies as new conditioning regimen in HSCT and virus specific T-cells for treating infection.
- Age is less of a significant barrier to transplant, transplanted patients develop less complications over time when compared to untransplanted.
- Thymic transplants are curative with good outcomes and increasingly applied to non-DiGeorge athymia. Major Histocompatibility Complex (MHC)-matching may influence outcome.
- Gene therapy requires lengthy research and development increasing the cost of treatment, cost cannot be distributed across many. Gene editing new on the horizon.

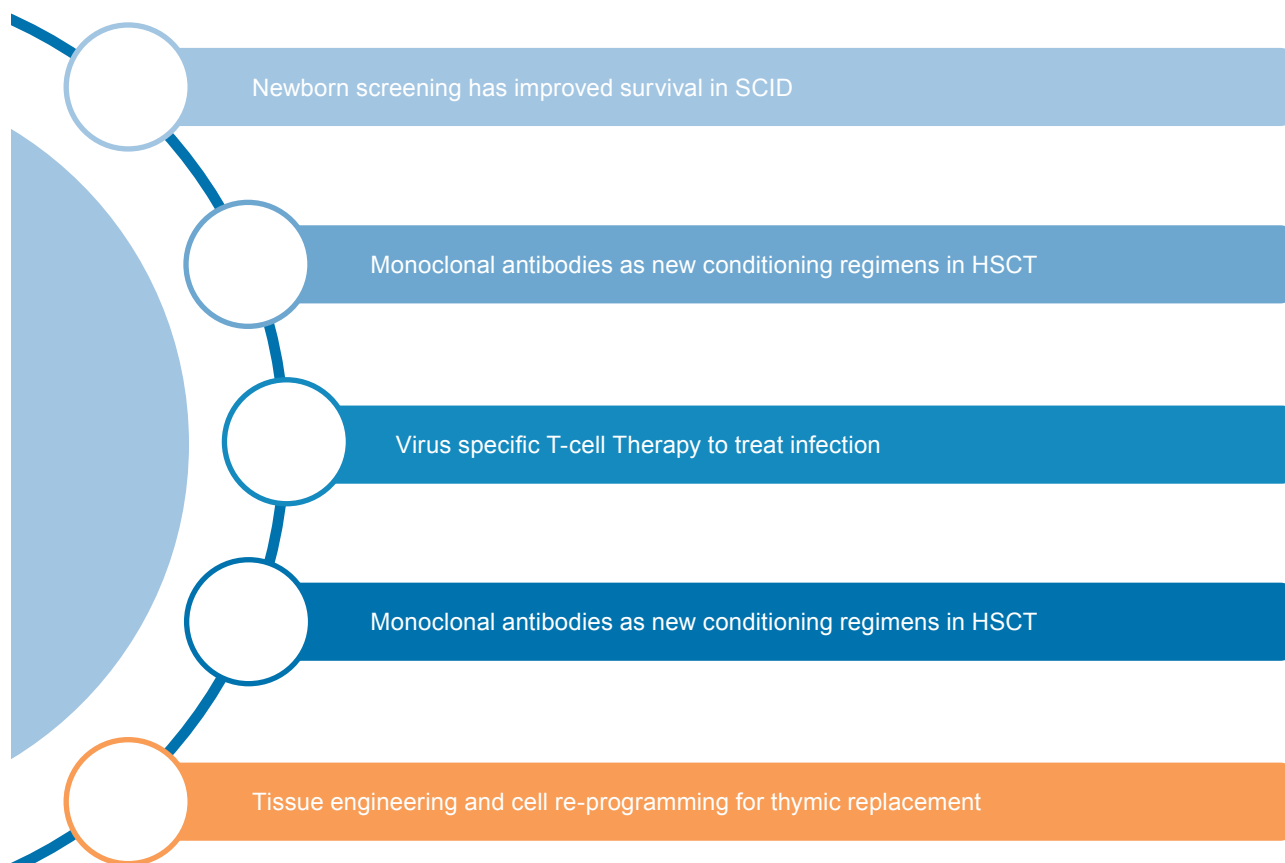


CELL THERAPY AND PIDS

PROF LUIGI NOTARANGELO, BETHESDA, UNITED STATES OF AMERICA

Opening the session on a quest for cure in PID, **Prof Luigi Notarangelo** opened by discussing cell therapy and PIDs. HSCT is an important curative therapy in PID. Improved survival in SCID has only really been seen over the past 10 years with the advent of newborn screening with earlier identification and therefore earlier intervention. The toxicity of conditioning therapy poses a problem in HSCT. Depleting haematopoietic and progenitor cells with monoclonal antibodies may be a new approach to conditioning regimens. C-Kit or CD117 is expressed by HSC, anti-C-Kit given alone as conditioning therapy depletes HSC then followed by donor stem cells is in clinical trial. Another interesting approach is an anti-CD45-drug conjugate targeting myeloid and lymphoid progenitors and can be used if a very profound depleting effect is needed. The safety and efficacy of Anti-CD45 saporin has been demonstrated in RAG1 SCID mice. Another problem faced in HSCT is the prolonged time to immune reconstitution. Culturing HSC in Delta-like-4 (Notch ligand) coated plates with specific cytokines for 7 days has been shown to accelerate immune reconstitution and thus decrease the risk for infection. The need to manage infection pre and post-transplant is often a challenge and virus-specific T cell (VST) therapies may

provide an answer, particularly in the setting of Epstein-Barr Virus (EBV) infection. VST have been shown to have complete or partial response in clearing infection. There is however concern around adding an additional donor therefore increased risk for Graft Versus Host Disease (GvHD) and cytokine release syndrome however this seems to be decreased with if VST are derived from the same donor as the transplant. Cytokine release syndrome can be managed with tocilizumab and anti Tumour Necrosis Factor (TNF)- α . Ideally practicality of VST will improve, with the development of regional banks minimizing the need for patient travel. Tissue engineering and cell reprogramming, particularly in the context of thymic replacement was discussed as a future perspective in cellular therapy in PIDs. With increased NBS the need for thymic transplant is increasing however accessibility is low, thus studies are now looking at the generation of functional thymic cells from induced pluripotent stem cells. The problem however is that the thymus is a complex organ and we are a far way from recapitulating the complexity of the thymus. Novel approaches to managing PIDs are increasingly available and applicable. With new technological advances what is not available now may become available tomorrow.



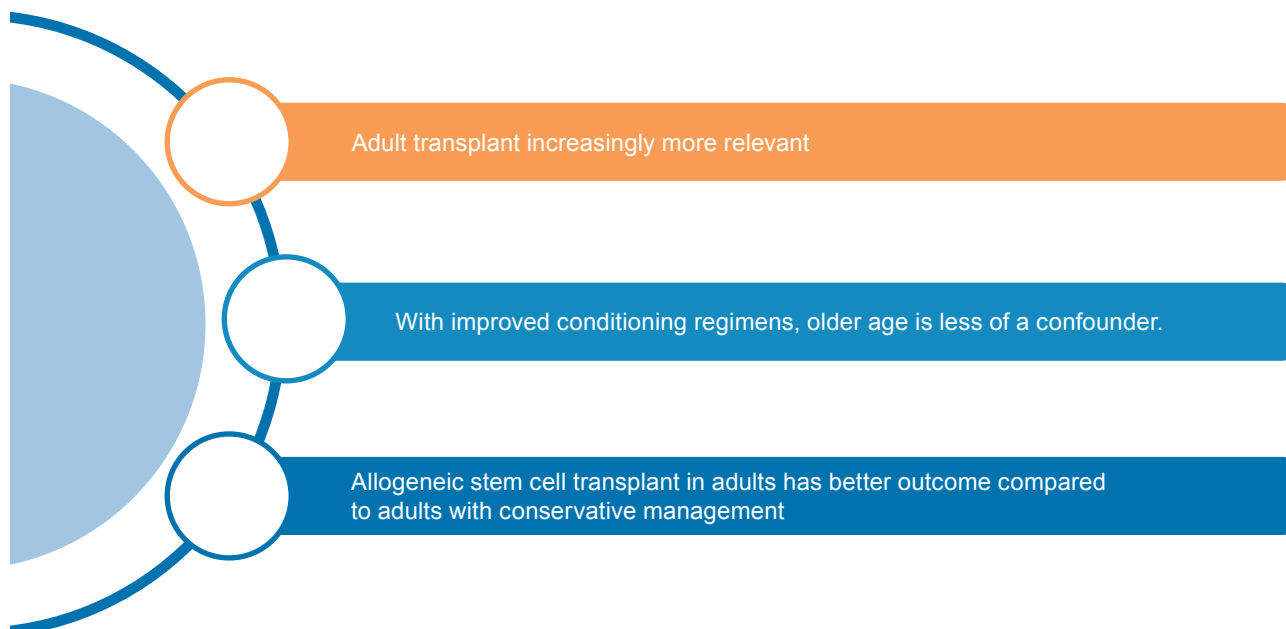
** HSCT: Haematopoietic stem cell transplant, HSC: Haematopoietic stem cell

BONE MARROW TRANSPLANTATION IN ADULTS WITH PIDS

PROF FELIPE SUAREZ, PARIS, FRANCE

Prof Felipe Suarez continued the theme of curative therapy in PIDs by discussing bone marrow transplant (BMT) and its application in adults with PID. Although BMT is mostly used in the paediatric setting there is increased need for adult transplant. As patients are increasingly diagnosed later in life, 25% with first manifestation after 15 years or have worsening severity in the clinical course transplant during adulthood is relevant. There are many other factors influencing age at transplantation. Transplant may be deferred in childhood due to mild initial clinical course, delayed onset of disease, lack of genetic diagnosis with 37% diagnosed after 15 years, or lack of suitable donor. Concerns around transplantation in adulthood are the toxicity, risk of poor immune reconstitution resulting in an even worse prognosis. Reasons for transplantation at an older age may be delayed severe complication, delay in diagnosis, progressive organ damage or late genetic diagnosis. Although older age at transplantation carries increased risks it is still important in preventing progressive organ damage and managing infection and/or inflammatory sequelae. This carries on from the keynote speech, highlighting the need for aggressive intervention in the period of smoldering disease to avoid or minimize the effects of accumulative disease, often seen later in life. Age should be less of a barrier to transplant and even those in their late 60s and 70s could still be offered transplant. The CEREDIH at Paris-Necker experience showed overall good survival of 80%, lower intensity conditioning enabling good response and complete engraftment. Earlier transplant is more ideal,

CGD has the best outcomes whilst CID/severe CVID are more challenging. There is increased risk for mortality within the first 12 months as well as in those with a high morbidity index. When compared to conservative management, adults who underwent allogeneic stem cell transplant fared better than those who did not. Transplant is applicable in adulthood as there is a need to prevent organ damage long term and increased risk for infection.



THYMIC TRANSPLANTATION

PROF GRAHAM DAVIES, LONDON, UNITED KINGDOM

Following discussion around BMT **Prof Graham Davies** discussed thymic transplantation, his hospital being the only facility offering thymic transplant in Europe. The thymus is important in T-cell development. Typical athymia with low T-cells is seen in complete DiGeorge syndrome, other congenital athymias such as CHARGE syndrome are also seen. Atypical athymia seen in Omenn syndrome develop some T-cells with a restricted repertoire. Those can successfully be treated by thymus transplantation using cultured postnatal thymic tissue with the generation of naïve T-cells showing a diverse repertoire. With the dawn of newborn screening there has been a significant difference in age at transplant, median age pre-2019 was 10 months and has decreased to 5 months in 2019-2022 following the implementation of NBS in Germany in 2019.

THYMIC TRANSPLANT

Typical Athymia	Atypical Athymia
<ul style="list-style-type: none"> • Complete DiGeorge syndrome • TBX1 and 2 deficiencies • CHD7 mutations (CHARGE) syndrome • Maternal Diabetes 	<ul style="list-style-type: none"> • FOXP1 deficiency • PAX1 deficiency • Undefined
<ul style="list-style-type: none"> • Improved outcomes with earlier diagnosis • Newborn screening has seen earlier transplant and improved outcome • Prolonged period to immune reconstitution • Complications: Infection, Immune reconstitution syndrome and autoimmunity 	

Patients are now transplanted earlier with less time to develop infections as well as inflammation or autoimmunity. There is typically a long period of reconstitution, with slower immune reconstitution if there has been immunosuppression. Immune reconstitution syndrome post-transplant is a concern, it is often immune driven and associated with delayed reconstitution especially if immunosuppressives are used. Autoimmunity is relatively common after thymus transplant, often easily treated with immune suppression. There does however seem to be an association between MHC matching and autoimmunity, those who did not develop autoimmunity had more than 2 MHC matches and thus having an MHC match maybe helpful. Access to transplant remains a stumbling block and the use of cryopreserved thymic tissue may make it possible for patients to be treated at institutions within their own country and could facilitate the use of at least partially HLA-matched tissue. Other strategies such as engineered thymic stroma may be future directions for thymus replacement therapy.

GENE THERAPY AND GENE EDITING

PROF FRANK STAAL, ROTTERDAM, THE NETHERLANDS

After discussing thymic transplant **Prof Frank Staal** provided insight into the process of gene therapy development and application, why this treatment is so expensive, Gene therapy is suitable for PID as it is a monogenic disease. Patient HSC are mobilized from the bone marrow or peripheral blood enriched for CD34+ cells, genetically modified and then re-infused allowing reconstitution with the gene modified HSCs. Retroviral vectors have now become obsolete and lentiviral vectors are now used. There are now numerous applications for gene therapy largely in SCID and CID but also in sickle cell disease and thalassemia.

THYMIC TRANSPLANT	GENE-MODIFIED BLOOD CELLS	DISEASES
1. HSC collection	Neutrophils	CGD, LAD-1
2. HSC enrichment	Monocytes	(X-ALD, MLD, MPS)
3. Ex-vivo gene modification	Red blood cells	Sickle cell disease and thalassemia
4. IV reinfusion		
5. Expansion of gene modified HSC	Platelets	WAS
	T-cells	SCID, WAS, HLH, IPEX, X-HlgM, XLP
	B-cells	SCID, WAS, XLA
	NK cells	SCID

However, to get to this point is a long pre-clinical development process to ensure safety and efficacy. Gene therapy does not fare worse than patients who have undergone HSCT with a tendency to do better. There is an added advantage of using patient cells with the potential to alleviate the need for patient travel. Gene editing is new on the horizon and is likely to become applicable in PID however cost remains a big hurdle.. Regulation issues are still barriers however with increased conversation, new legislation and better harmonization it is becoming less complex.

GENE ADDITION VS GENE REPAIR (EDITING) IN HSC

Gene Addition	Gene Editing
<ul style="list-style-type: none"> • Efficient • Accepted by regulators • No endogenous regulation • Insertional mutagenesis 	<ul style="list-style-type: none"> • Inefficient • Issues around off target and on target effects • Not yet established by regulators • Regulated expression • Potentially easy vectors

SESSION 8: MANAGEMENT OF VIRAL INFECTIONS IN PID

Chaired by: Prof Steven Holland and Prof Stuart Tangye

COVID-19 and PIDs: Dr Virgil Dalm, CMV and EBV management in PIDs: Prof Jeroen van Kampen, Management of respiratory and entero-viruses in PIDs: Prof Stephen Jolles

- Lymphopenia, comorbidities and absent vaccination associated with severe COVID-19 infection and death. Repeat COVID-19 vaccination is needed.
- EBV is difficult to treat. New oral drugs against CMV (maribavir and lentermovir) are promising.
- Risk/exposure reduction is needed in respiratory infections. There may be a role for nebulized immunoglobulin and HSCT may be needed in some situations.

COVID-19 AND PIDS

DR VIRGIL DALM, ROTTERDAM, THE NETHERLANDS

Starting with the virus that has caused this global pandemic and instigated much fear and concern for PID patients **Dr Virgil Dalm** kicked off the session on managing viral infections in PID by discussing COVID-19. There has been much fear and anxiety from patients around COVID-19 negatively impacting their mental health. However, if the severity of COVID-19 in PID patients is reviewed most who contracted the infection appeared to have mild disease. However, comorbidities, lymphopenia and lower IgG trough levels appear to be markers of disease severity in PID. And so what are the treatment options. Currently recommendations follow non-PID recommendations namely oxygen supplementation, dexamethasone, anti IL-6 and potentially monoclonal antibodies such as Regen-COV®. Regen-COV® is mostly applicable to secondary antibody deficiency and in 37 primary antibody deficiency patients with disease duration >21 days showed response in 97%. Convalescent plasma did show reduction in viral load and improvement in clinical symptoms but data has not been convincing. Vaccination has been addressed by many papers and response varies according to PID class. XLA show almost no response whilst CVID shows a mixed response some mirroring healthy controls and others with non-infectious complications responding more like XLA. Type of vaccine also seems important, Pfizer BioNTech 162b vaccine showed higher chance of seropositivity and neutralising antibodies than AstraZeneca ChAdOx1 nCoV-10 in primary antibody deficiency patients in a UK cohort (Shields et al DOI: <https://doi.org/10.21203/rs.3.rs-1180392/v1>). T-cell responses were comparable to healthy controls, significantly greater T-cell response was seen in those who had had previous PCR positive SARS-CoV-2 infection compared to those who were infection naive. A booster vaccine is recommended and may improve the antibody response.



CMV AND EBV MANAGEMENT IN PIDS**PROF JEROEN VAN KAMPEN, ROTTERDAM, THE NETHERLANDS**

After interesting discussion regarding COVID-19 in PID **Prof Jeroen Van Kampen** discussed the management of Cytomegalovirus (CMV) and EBV in PIDs. Common viruses in a unique host have unique viral syndromes with diagnostic and treatment challenges. Often serological testing is sub-optimal and PCR testing is preferred. Treatment challenges arise in those with infections where there is none or limited treatment options, such as EBV. A case with COVID and chronic norovirus was described after numerous modalities were tried namely Nitazoxanide, Ribavirin and Interferon-alpha with no response gastro-duodenal administration of immunoglobulin significantly reduced the viral load and symptomatic burden. Unique viral syndromes are seen in immunocompromised individuals. CMV in the context of immunodeficiency is typically disseminated namely CMV colitis, CMV retinitis and end organ disease. The drugs available are not without their own side effects as well as problems with administration. Ganciclovir side effects include neutropenia, leukopenia and thrombocytopenia in about 30%, >30% on Foscarnet have nephrotoxicity and electrolyte imbalances and >50% on Cidofovir have nephrotoxicity. Therefore, anticipated treatment side effects further complicate options in patients who often already have organ dysfunction as a result of their underlying disease or concurrent infection. Newer oral drugs such as maribavir and letermovir in CMV have lower toxicity profiles and lower genetic barriers to resistance as well as the added advantage of oral administration. Management pillars in CMV include prophylaxis, pre-emptive therapy when there is CMV replication but not yet disease and treatment when there is active disease.

DRUG	HSV	VZV	CMV	OTHER DNA VIRUSES
Valaciclovir	+	+	-(+/-)	-
Valganciclovir	+	+	+	-
Foscarnet	+	+	+	-
Cidofovir	+	+	+	+
Letermovir	-	-	+	-
Maribavir	-	-	+	-

** CMV: Cytomegalovirus, EBV: Epstein-Barr Virus, HSV: Herpes Zoster Virus

MANAGEMENT OF RESPIRATORY AND ENTERO-VIRUSES IN PIDS**PROF STEPHEN JOLLES, CARDIFF, WALES**

After discussion around CMV and EBV infection **Prof Stephen Jolles** lead the discussion towards the management of respiratory and entero-viruses in PIDs. In respiratory infection, pneumonias are counted but what about viral infections that are actually more common and associated with more significant disease burden? The problem being that viral infections are more difficult to treat than bacterial infections. Study has shown that in comparison to their immunologically competent partners PID patients have similar viruses but more significant symptoms and less symptom free days. Interestingly during periods of lockdown and non-pharmaceutical intervention many PID patients saw improved symptoms and less infections highlighting the need for decreased risk or exposure to infection in these at-risk populations. Regarding COVID-19, as was previously known with rhinoviruses, there seems to be prolonged duration of infection and shedding of virus in XLA patients. A patient was described with 218 days of COVID infection, vaccination was trialed, and the patient improved. Could there be a role for therapeutic vaccination? A collaborative approach is needed in addressing risk and exposure reduction. Combination antivirals may be needed and for longer duration. Monoclonal antibodies may confer more precise management and immunoglobulin therapy is evolving too with nebulized immunoglobulins (IgA and IgM) showing benefit. Vaccinations in PID may harness remaining function and act therapeutically. There is still continued work needed to meet the unmet needs of PID patients in managing their often-debilitating infections.





CLOSING TALK

Closing talk chaired by Dr Nizar Mahlaoui

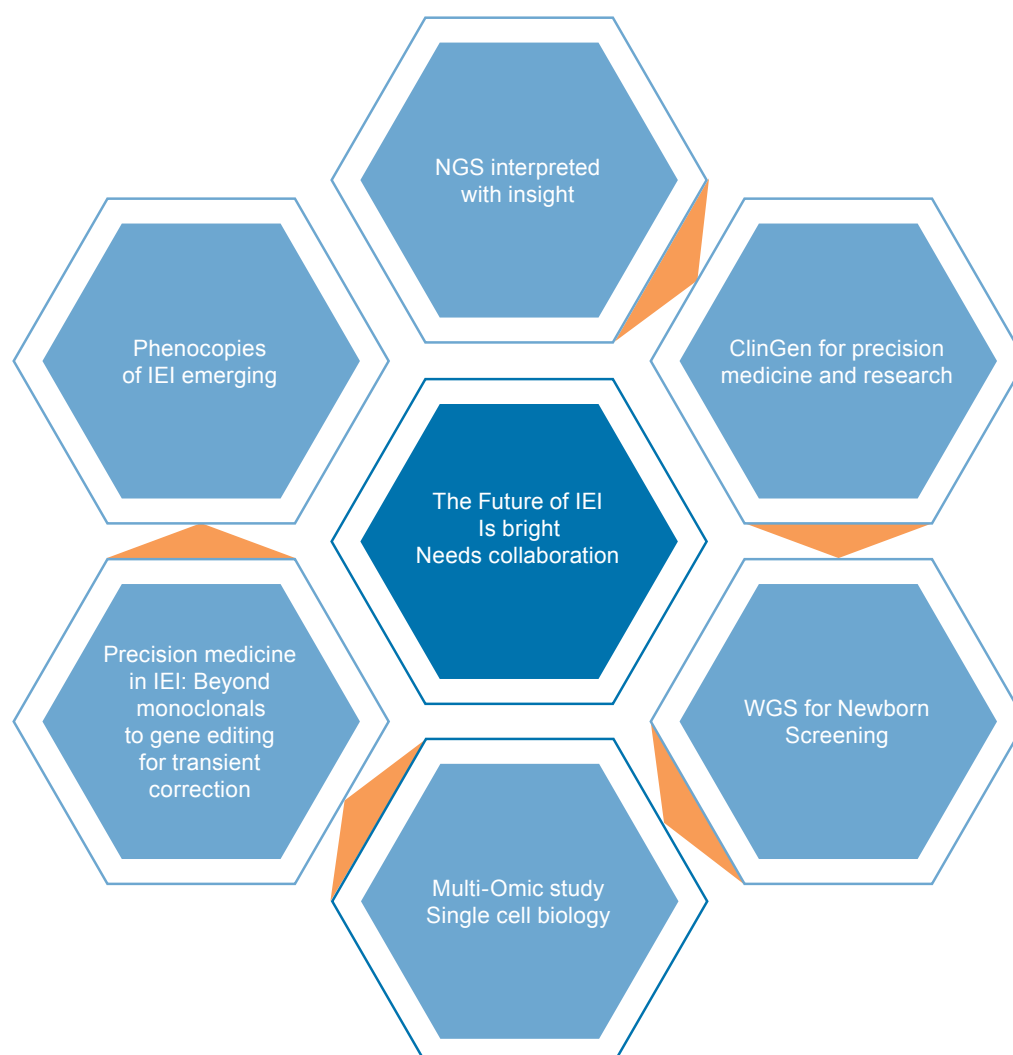
Horizon 2040: What can PID genetic studies tell us about the future? **Prof Luigi Notarangelo**

Closing remarks **Ms Martine Pergent**

HORIZON 2040: WHAT CAN PID GENETIC STUDIES TELL US ABOUT THE FUTURE?

PROF LUIGI NOTARANGELO, BETHESDA, UNITED STATES OF AMERICA

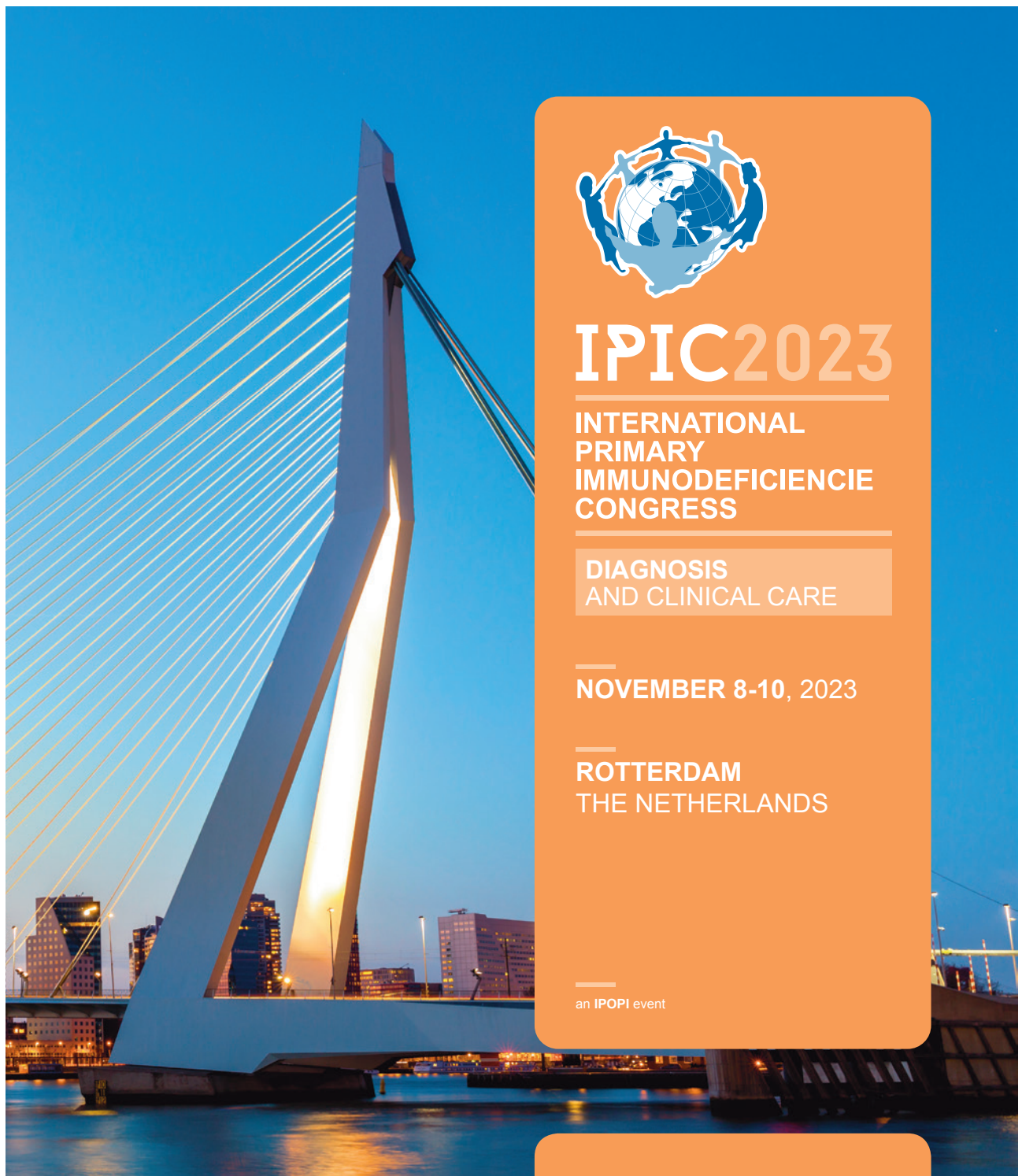
Prof Luigi Notarangelo closed the congress with discussion on PID genetic studies and what they can tell us about the future. PIDs are a continuously evolving story. New genes are being discovered at an exponential rate and now somatic mutations and phenocopies are an emerging field. The approach to diagnosis has now evolved from focused gene sequencing to an unbiased application of whole genome sequencing where sometimes one is surprised by the diagnosis. As was alluded to by Prof Sophie Hambleton earlier in the congress, NGS is not without fault and needs to be interpreted with insight. As results are often ambiguous and the variant identified is the first of its kind there are challenges in defining pathogenicity. There is therefore the need for a resource that will provide comprehensive assessment of the individual variant pathogenicity. ClinGen (<https://clinicalgenome.org/>) and NIH funded resource that defines the clinical relevance of genes for use in precision medicine and research. Newborn screening has been a significant achievement but where do the changes lie? More PIDs should be identified at NBS, WGS is improving, and it is likely that by 2040 NBS with WGS may be routine. But, there is a desire to go beyond genes and integrate multi-omic approaches with epigenome, transcriptome, proteasome and metabiome studies and look at disease on a single cell level with new efforts to integrate multi-omics and clinical data to build deeper understanding.




Such studies however need to be reproduced in multiple settings to achieve meaningful results, requiring collaboration, dedication, and funding. Precision medicine in PIDs is growing from enzyme replacement therapy in ADA-SCID in the late 1980's to application of monoclonal antibodies in current treatment strategies such as JAK-inhibitors and complement inhibitors now to gene therapy and gene editing. The application of gene editing may not only be for cure but also for transient correction of disease phenotype. For example, introduction of normal mRNA copies in CGD to enable cells to produce superoxide and overcome life threatening infection.

We should look with hope at the future management of rare diseases. There is a need for collaboration at all stages from gene discovery and validation to clinical development and launch of new drugs. Patients should be empowered to inform better and facilitate effective trial design. New technologies shortening the diagnostic journey are needed and will stimulate new therapies.

Ms Martine Pergent closed the congress with many thanks and echoed the need for global co-operation between all stakeholders. **See you in Rotterdam on 8-10 November 2023...!**



The poster features a background image of a cable-stayed bridge at night, with its illuminated pylon and cables reflecting on the water. Overlaid on the right side is a large orange rounded rectangle containing the event information. At the top of this rectangle is the IPIC logo, which depicts a globe with silhouettes of people holding hands. Below the logo, the text 'IPIC2023' is written in a large, bold, white sans-serif font. Underneath this, the words 'INTERNATIONAL PRIMARY IMMUNODEFICIENCY CONGRESS' are stacked in a smaller, bold, white sans-serif font. A horizontal line separates this from a white box containing the text 'DIAGNOSIS AND CLINICAL CARE' in orange. Another horizontal line follows, leading to the dates 'NOVEMBER 8-10, 2023' in white. A final horizontal line leads to the location 'ROTTERDAM THE NETHERLANDS' in white. At the bottom of the orange box, the text 'an IPOPI event' is written in a small white font.



IPIC2023

INTERNATIONAL
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DIAGNOSIS
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NOVEMBER 8-10, 2023

ROTTERDAM
THE NETHERLANDS

an IPOPI event

ABBREVIATIONS

ADA2	Adenosine deaminase 2
ADA-SCID	Adenosine deaminase deficient severe combined immunodeficiency
AGS	Aicardi-Goutières syndrome
APDS	Activated phosphoinositide 3 kinase delta syndrome
APLAID	Autoinflammation and phospholipase C γ 2 (PLC γ 2)-associated antibody deficiency
APSID	Asia Pacific Society of Immunodeficiencies
ASID	African Society of Immunodeficiencies
AT	Ataxia Telangiectasia
BAL	Bronchoalveolar lavage
BCG	Bacillus Calmette-Guerin vaccine
BGPI	Brazilian Group of Primary Immunodeficiencies
BKV	BK virus
BMA	Bone marrow aspirate
BMT	Bone marrow transplant
BTk	Bruton's tyrosine kinase
CANDLE	Chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature
CEREDIH	French reference centre for primary immunodeficiencies
CF	Cystic fibrosis
CFTR	Cystic fibrosis transmembrane conductance regulator
CGD	Chronic granulomatous disease
CGH	Comparative genomic hybridization
CID	Combined immune deficiency
CIS	Clinical Immunology Society for North America
CMV	Cytomegalovirus
CNS	Central nervous disease
CNV	Copy number variation
CO	Carbon monoxide
COPD	Chronic obstructive pulmonary disease
CT	Computed tomography
CTLA-4	Cytotoxic T-lymphocyte-associated protein 4
CVID	Common variable immune deficiency
CXCR2	C-X-C motif chemokine receptor 2 (also known as IL-8 receptor beta)
CYBB	Cytochrome B245 beta chain

DHR	Dihydrorhodamine test
EBV	Ebstein Barr virus
ERN	European Reference Network
ERT	Enzyme replacement therapy
ESID	European Society for Immunodeficiencies
EU	European Union
FBC	Full blood count
FcRN	Neonatal Fc receptor for IgG
IgGAM	Immoglobulins G, A and M
GATA2	GATA binding protein 2
GI	Gastrointestinal
GLILD	Granulomatous lymphocytic interstitial lung disease
GM-CSF	Granulocyte-macrophage colony-stimulating factor
GOF	Gain of function
GT	Gene therapy
GVHD	Graft versus host disease
HIES	Hyper-IgE syndrome
HLH	Haemophagocytic lymphohistiocytosis
HOIL-1	Heme-oxidized IRP2 ubiquitin ligase-1
HOIP	HOIL-1 interacting protein
HSCT	Haematopoietic stem cell transplantation
IBD	Inflammatory bowel disease
IFNγ	Interferon gamma
Ig	Immunoglobulin
IgGSD	IgG subclass deficiency
IL-1	Interleukin 1
IL-12	Interleukin 12
IL-18	Interleukin 18
IL-5	Interleukin 5
ILD	Interstitial lung disease
IPEX	Immune dysregulation, polyendocrinopathy, enteropathy, X-linked
IPIC	International Primary Immunodeficiencies Congress
IPOPI	International Patient Organisation for Primary Immunodeficiencies

IRF8	Interferon regulatory factor 8
IRIS	Inflammatory immune reconstitution syndrome
ISG15	Interferon stimulatory gene 15
ITP	Immune-mediated thrombocytopaenia
IUIS	International Union of Immunological Societies
IVIg	Intravenous immunoglobulin
JAK	Janus kinase
JAKINIBS	Janus kinase inhibitors
JCV	JC virus
KRECS	Kappa deleting recombination excision circles
LOCID	Late onset combined immunodeficiency
LOF	Loss of function
LRTI	Lower respiratory tract infection
LSS	Lymphocyte subset
MAS	Macrophage activation syndrome
MD	Myotonic dystrophy
MRI	Magnetic resonance imaging
MSMD	Mendelian susceptibility to mycobacterial disease
NBT	Nitro blue tetrazolium test
NEMO	Nuclear factor-kappa B essential modulator
NET	Neutrophil extracellular traps
NFkB	Nuclear factor-kappa B
NGS	Next generation sequencing
NIH	National Institutes of Health
NLR	Nod-like receptor
NLRC4	NLR family CARD domain containing protein 4
NLRP3	NOD, LRR and pyrin-domain containing protein 3
OS	Overall survival
PID	Primary immunodeficiency
PLAID	PLCG2 associated antibody deficiency and immune dysregulation
PRR	Pattern recognition receptor
RAG1/2	Recombinase activating gene 1/2
RIPK1	Receptor-interacting serine threonine protein kinase 1

ROS	Reactive oxygen species
SAVI	STING-associated vasculopathy with inset in infancy
SCID	Severe combined immunodeficiency
SCIg	Subcutaneous immunoglobulin
SEA	South East Asia
SEAPID	South East Asia Primary Immunodeficiency Network
sIL2R	Soluble IL-2 receptor
sJIA	Systemic onset juvenile idiopathic arthritis
SLE	Systemic lupus erythematosus
smB	Switched memory B cells
SNP	Single nucleotide polymorphisms
SPAD	Specific antibody deficiency
STAT1	Signal transducer and activator of transcription 1
STING	Stimulator of interferon genes
TB	Tuberculosis
TLR	Toll-like receptor
TNF	Tumour necrosis factor
TRECS	T-cell receptor excision circles
TRNT1	CCA-adding transfer RNA nucleotidyl transferase
UK	United Kingdom
USA	United States of America
VEO-IBD	Very early onset inflammatory bowel disease
VZV	Varicella zoster virus
WAS	Wiskott Aldrich syndrome
WCC	White cell count
WDR1	WD repeat domain 1
WES	Whole exome sequencing
WGS	Whole genome sequencing
XIAP	X-linked inhibitor of apoptosis
XLA	X-linked agammaglobulinaemia
X-SCID	X-linked severe combined immunodeficiency

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3 rd PLACE WINNER	HM CORNELISSEN	THE HAEMATOLOGICAL FEATURES OF PRIMARY IMMUNODEFICIENCY: A RETROSPECTIVE REVIEW OF THE ROUTINE LABORATORY INVESTIGATIONS OF THE SOUTH AFRICAN PRIMARY IMMUNODEFICIENCY REGISTRY
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3	R. RIKHI	GENETIC PROFILE OF CHILDREN WITH AUTOIMMUNE MANIFESTATIONS IN WISKOTT-ALDRICH SYNDROME
4	N. KASAP	A CASE OF STAT5B GOF WITH A NEW STAT5B MUTATION PRESENTING WITH TREATMENT-RESISTANT SEVERE ATOPIC DERMATITIS
5	A TAHIAI	THE OCCURRENCE OF AUTOIMMUNE DISEASES IN ALGERIAN PATIENTS WITH HOMOZYGOUS MUTATIONS IN RAG1 AND RAG2
6	F.S. VARGAS CELY	SEVERE AUTOIMMUNITY TRAITS IN A COLOMBIAN BOY: A NOVEL NRAS MUTATION C.182A>G (P.Q61R) CAUSING RAS-ASSOCIATED AUTOIMMUNE LEUKOPROLIFERATIVE DISEASE
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9	T ALEMAYEHU	CHALLENGES IN DIAGNOSING AUTO-INFLAMMATORY DISORDERS IN LOW RESOURCE SETTING
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FRIDAY, APRIL 29, 2022

YOUNG PID INVESTIGATORS: POSTER WINNERS' SESSION

MODERATORS: Prof Gesmar Segundo and Mr Bruce Lim Held in the Plenary Room

ANTIBODY AND T-CELL RESPONSES FOLLOWING SARS-COV-2 VACCINATION IN PATIENTS WITH INBORN ERRORS OF IMMUNITY

AUTHORS

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Objective: To study the immune response after two doses of RNA-based COVID-19 vaccines in patients with inborn errors of immunity (IEI).

Design and method: 90 IEI patients and 33 healthy controls (HC) were studied at least 4 weeks after the second dose of mRNA1273 or BNT162b2 vaccines. 83 patients were categorized as predominantly antibody deficiencies (PAD) (44 common variable immunodeficiency (CVID), 34 isotype or functional deficiencies, 3 agammaglobulinemia and 2 hyper IgM syndromes); 2 patients as diseases of immune dysregulation; 4 were combined immunodeficiencies (2 DiGeorge and 2 Nijmegen syndromes); and 1 had a phagocytic disorder.

Detection of IgG antibodies against SARS-CoV-2 spike protein (S) was performed by using the Abbott's commercial CLIA platform; results are expressed as arbitrary Units (AU)/mL. The coexpression of activation induced cell markers (AIM) CD25 and CD134 (Cytognos) was analysed on gated memory CD4⁺ T-cells by multicolour flow cytometry (BD Bioscience). Results are expressed as the stimulation index (SI) calculated by dividing the percentage of AIM⁺ cells after SARS-CoV-2 pooled peptides (Miltényi Biotec) stimulation with the percentage of AIM⁺ cells from non-stimulated lymphocytes; SI >2 considered positive.

Results: Overall, post-vaccination serum anti-S protein IgG levels were lower in the group of IEI patients than in HC (5039 AU/mL [2930-6473] vs 8154 AU/mL [4452-12135], p=0.03). Within the PAD patients, the subgroup of CVID showed a significant decrease in specific anti-S IgG as compared with HC (4802 AU/mL [2319-6854] vs 8154 AU/mL [4452-12135], p=0.03) while the median concentration in the isotype and functional antibody deficiencies subgroup was similar to HC (6123 AU/mL [2661-10215] vs 8154 AU/mL [4452-12135], p=0.19). Patients with PAD who were previously infected with SARS-CoV-2 (n=8) raised higher anti-S IgG levels than those PAD vaccinated patients naïve to the infection (13581 AU/mL [363-40000] vs 4082 AU/mL [2637-6123], p=0.01).

S-peptides specific CD4⁺ T-cell responses were detected in 68 out of 90 (75.5%) IEI patients tested, showing no differences in SI as compared to HC (3.05 [2.7-3.8] vs 3.2 [1.7-4.1], p=0.79). No statistically significant differences were found in anti-S SARS-CoV-2 cellular responses of IEI patients further stratified by any category and HC.

Conclusions: Vaccine responses to SARS-CoV-2 are not uniformly impaired in IEI. The need of subsequent boosts of COVID-19 vaccination requires an individualized approach in IEI patients, which should include the evaluation of memory specific T-cell induced immunity.

CLINICAL PROFILE OF A MULTICENTRE COHORT OF PATIENTS WITH COMMON VARIABLE IMMUNODEFICIENCY (CVID) FROM INDIA

AUTHORS

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Introduction: There is no exact data on the prevalence of primary immunodeficiency disease (PID) in Germany. The prevalence is indicated as 1: 20.000, excluding IgA deficiencies. Most immunodeficiency syndromes are genetically determined, but the age when PID becomes clinically apparent can be very variable. A few patients show symptoms, like severe infections or failure to thrive, in the postnatal period. Contrary, in more than 30% of the patients the most common antibody deficiencies like B cell deficiencies are diagnosed after the age of 15 years. But also other immunodeficiency syndromes like combined T and B cell deficiencies or phagocyte deficiencies can become clinically apparent in adolescents or adults. In earlier days, only pediatricians were familiar with most of the PID, but today many severely affected children reach adult age and need lifelong treatment. Only a few are cured by bone marrow transplantation (BMT) or gene therapy. But also these patients can be severely affected by graft-versus-host reaction or recurrent infections. Some patients received myeloablative conditioning before BMT or have a PID with a risk of malignancy, and thus needs long term monitoring. Hence, the need of a specialized treatment and support for adolescent and adult patients is high. Colleagues with other medical specializations have access to established special units for adults, but suitable facilities for adult patients with PID are rarely found in Germany.

Methods: A questionnaire about adolescent and adult care was sent to PID pediatric units in Germany. So far about 10 of 13 centers returned their answers; all over they care for 1683 patients with PID. Analyzed were the numbers of patients, their diagnoses, the possible age limit for ambulatory and inpatient treatment as well as existing or potential transition consultation hours.

Conclusion: About one third of all PID patients already has reached adult age and should be transferred to a transition clinic on their way to adult care. In Germany there are only few adult PID units. Most pediatricians continue to take care of their grown-up patients, but inpatient treatment of adults in children's hospitals is rarely possible. Older patients need specialized care in internal medicine.

THE HAEMATOLOGICAL FEATURES OF PRIMARY IMMUNODEFICIENCY: A RETROSPECTIVE REVIEW OF THE ROUTINE LABORATORY INVESTIGATIONS OF THE SOUTH AFRICAN PRIMARY IMMUNODEFICIENCY REGISTRY

AUTHORS

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Background: Primary immunodeficiency diseases (PIDD) or Inborn Errors of Immunity (IEI) are inherited monogenic defects of the immune system resulting in dysfunction of the innate or adaptive immune response. The clinical phenotype ranges from increased susceptibility to infection, to significant immune dysregulation and autoimmunity. Severe, persistent, unusual and/or recurrent peripheral blood cytopenia/s could encompass the spectrum of autoimmunity and malignancy that may constitute the initial presentation. Many cases of IEI remain undiagnosed. Therefore, cost-effective and widely available tools are needed, particularly in resource-constrained settings. These tools could aid early identification of cases for further focused testing. This study aimed to determine the value of routine haematological investigations in the early identification of potential PIDD patients in the South African setting.

Methods: A retrospective descriptive review of routine laboratory parameters of patients on the South African PID registry was conducted. Available patient files, the Tygerberg hospital electronic database and the National Health Laboratory Services (NHLS) laboratory information system were used to supplement patient data. Laboratory parameters closest to date of presentation were recorded. Patients who did not have any full blood count (FBC) parameters available were excluded.

Results: A total of 396 cases were registered, of which 250 (63%) had available FBC parameters. Median age at presentation was 51 months [interquartile range (IQR)(14.5-98 months)]. More than half (59%) presented with a peripheral blood cytopenia. Those with predominantly antibody deficiency constituted 50%, defects in the intrinsic and innate immunity 11%, combined immunodeficiency 13% and immunodeficiencies affecting cellular and humoral immunity 8%. Over one third (37%) presented with lymphopenia [median $2 \times 10^9/L$ IQR(1-3)] and 11% with a neutropenia [median $1 \times 10^9/L$ (0-2)]. Anaemia [median $9g/dl$ (8-10)] was seen in 24% and thrombocytopenia in 5% [median $91 \times 10^9/L$ (44-113)]. Those with a humoral and/or cellular immunodeficiency presented with lymphopenia (84%) or anaemia (62%). In addition, one case with a combined immunodeficiency had a history of a venous thromboembolism and 3 cases a history of lymphoma.

Conclusion: Although infection is one of the more appreciated presentations in IEI, severe, persistent, unusual and/or recurrent cytopenia/s in the absence of other explainable cause may broaden early identifiers of potential IEI in the South African setting and should initiate further investigation.



THURSDAY, APRIL 28, 2022

GUIDED POSTER WALK 1 - AUTOIMMUNITY AND AUTOINFLAMMATION

MODERATOR: Prof Tadej Avčin

POSTER 1 - OVERACTIVE STAT3 DRIVES ABERRANT ACCUMULATION OF AUTOIMMUNE-ASSOCIATED CD21LOW CD23LOW B CELLS

AUTHORS

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Signal transducer and activator of transcription 3 (STAT3) is a latent transcription factor with pleiotropic roles in hematopoietic and non-hematopoietic cells, that regulates gene expression downstream of surface cytokine and hormone receptors. STAT3 constitutive activation and somatic gain-of-function (GOF) SH2 domain mutations recur in B cell malignancies. In addition, germline heterozygous STAT3 GOF mutations were recently shown to cause early-onset multi-organ autoimmune disease. Affected individuals variably present with type-1 diabetes, autoimmune thyroid disease (AITD), rheumatoid arthritis, gut enteropathies and autoimmune cytopenias. The AITD and autoimmune cytopenias, and hypogammaglobulinemia and B cell memory lymphopenia also observed in patients with STAT3 GOF syndrome, point to defects in B cell tolerance checkpoints.

However, little is known of the B cell-intrinsic effects of overactive STAT3. Here, we address this question using mice engineered to carry the most common mutation causing STAT3 GOF syndrome, STAT3T716M, or a mutation at the SH2 domain dimerization interface, STAT3K658N, found in both malignancy and STAT3 GOF syndrome.

We demonstrate that GOF STAT3 causes aberrant accumulation of polyclonal CD21low B cells similar to those previously shown to accumulate in mice and humans with age, chronic infections, immunodeficiency and autoimmune disease. We show that STAT3 GOF allows aberrant accumulation of self-reactive SWHEL B cells recognising a blood cell-surface autoantigen. We use ex vivo cultures, along with B cell receptor deep-sequencing, flow cytometric analyses and high-throughput single-cell RNA sequencing paired with chromatin immunoprecipitation sequencing (ChIP-Seq), to reveal the cell-intrinsic effects of overactive STAT3 in CD21low B cells. Finally, we propose a novel mechanism by which STAT3 may drive aberrant differentiation and accumulation of CD21low B cells. Our findings help explain the over-accumulation of autoantibody-enriched CD21low B cells in autoimmune diseases associated with IL-6 and IL-21 over-abundance. They reveal the landscape of genes and proteins dysregulated by overactive STAT3 in B cells.

POSTER 2 - TREATMENT OF AN IMMUNOLOGIC DOUBLE TROUBLE. JAK1/2INHIBITION IN CHILD WITH STAT1 GOF AND TRISOMY 21

AUTHORS

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Objective: The presence of an additional copy of chromosome 21 (trisomy 21, T21) results in Down Syndrome (DS) a genetic disorder characterized by anatomical abnormalities and a high risk to develop autoimmune and autoinflammatory diseases. Importantly, four of the six receptors recognizing cytokines like interferons (IFN) are encoded on chromosome 21. Previous studies revealed increased IFN induced JAK-STAT1 pathway activation with STAT1 (hyper-) phosphorylation (pSTAT1) and subsequent upregulation of STAT1-dependent genes similar to those characteristically observed in patients with STAT1 gain of function (GOF) mutations. STAT1 GOF patients show a broad clinical phenotype including infection susceptibility and immune dysregulation.

Here we present the case of a child with DS who also carries a STAT1 GOF mutation (c.976C>T) and is under Ruxolitinib treatment (0.5mg/kg/day). Our aim is to evaluate the overlap existing between these syndromes and its likely synergistic effect in terms of IFN responsiveness and the Ruxolitinib treatment effect.

Design and method: Heparinized blood samples were collected from patient 1 (P1, STAT1 GOF/T21), her T21 negative mother with same STAT1 GOF mutation without treatment (P2), person with T21 (P3) and a healthy control (HC). We measured intracellular total STAT1 (n-terminus) in monocytes, CD4+ and CD8+ T cells and pSTAT1 (Tyr701) in monocytes by flow cytometry. To evaluate the functional impact of the directed treatment targeting the JAK-STAT pathway, increasing doses of Ruxolitinib (0.1, 0.5 and 1 µM) were added during IFNγ stimulation.

Results: Total STAT1 protein levels measured in monocytes, CD4+ and CD8+ T cells from P1 were higher than those found for P2 and P3, being all of them than higher those observed in the HC (Figure 1, A). Again after IFNγ stimulation cells obtained from P1, P2 and P3 showed higher pSTAT1 levels when compared to the HC. In vitro treatment with Ruxolitinib effectively normalized the IFNγ induced pSTAT1 levels of P1, P2 and P3 (Figure 1, B).

Conclusions: Increased total STAT1 protein levels found in P1 indicates a potential synergistic effect of the two pathologies whereas pSTAT1 levels were raised in all three probands when compared to the HC. Importantly pSTAT1 levels could be modulated in with in vitro Ruxolitinib treatment suggesting JAK/1 inhibitor therapy to be a viable option for immune dysregulation symptoms often related to these conditions.

POSTER 3 - GENETIC PROFILE OF CHILDREN WITH AUTOIMMUNE MANIFESTATIONS IN WISKOTT-ALDRICH SYNDROME

AUTHORS

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Objective: Wiskott-Aldrich syndrome (WAS) is an X-linked combined immunodeficiency characterized by a triad of thrombocytopenia, eczema, and immunodeficiency. Patients with WAS are not only prone to recurrent infections but are at risk of developing autoimmunity and malignancy. In this study, we report genetic profiles of patients with WAS who developed autoimmune manifestations.

Design & Method: Case records of children with WAS, who were been followed up in Pediatric Immunodeficiency Clinic of Advanced Pediatrics Centre, Post Graduate Institute of Medical Education and Research, Chandigarh, India a tertiary care institute of Northern India were reviewed. Genetic confirmation was done in our in-house setup in most of them. However, in few cases were sent to commercially available NGS panel screening and were further confirmed with Sanger sequencing.

Results: Out of 50 patients diagnosed with WAS and followed up over a period of 12 years, 15 (30%) developed autoimmune manifestations (Table 1). The mean age of the children with autoimmune features was 9 (3-120; IQR: 4.25-57) months. Variants in WAS gene were found in all 15 patients, and 4 (26.6%) of these were novel. Among these 15 patients, 12 (75%), patients had exonic whereas 4 had intronic variants while 1 patient had a reversion mutation. Seven (50%) had variants leading to premature termination [nonsense (n=6/15, 40%); frameshift (n=1)]. Four patients had splice-site variants and 4 had missense variants. Notably, one child presented with infections, bleeding and autoimmune lymphoproliferative syndrome-like disease and was found to have dual pathogenic variants in X-linked inhibitor of apoptosis (XIAP) and WAS gene. WASp protein expression was analyzed in 10 out of 15 patients, 9 patients showed reduced expression. Leukocytoclastic vasculitis was the most common autoimmune manifestation in 9 (60%) patients. Five (33.3%) patients had autoimmune hemolytic anemia (AIHA) with a positive direct Coombs test. Two (13.3%) patients developed Non-Hodgkin lymphoma on follow-up. Stem cell transplantation was carried in 2 children but both died during the post-transplant period. Glucocorticoids were used in 11 (73.3%) patients, while 14 (87.5%) patients were on Intravenous Immunoglobulin therapy.

Conclusion: Most patients with autoimmunity in WAS had premature termination variants in initial exons. Leukocytoclastic vasculitis was the commonest autoimmune manifestation in our cohort.

POSTER 4 - A CASE OF STAT5B GOF WITH A NEW STAT5B MUTATION PRESENTING WITH TREATMENT-RESISTANT SEVERE ATOPIC DERMATITIS

AUTHORS

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Introduction: Signal transducer and activator of transcription 5B (STAT5B) is involved in signaling many families of cytokines. Neonatal onset urticaria, dermatitis, granulomatous skin infections, diarrhea, autoimmunity, and recurrent infections have been reported in the literature with genetic mutations causing increased STAT5B activation (gain-of-function (GOF)), and the number of reported cases is only two. Here, we present a patient with severe atopic dermatitis diagnosed with a novel STAT5B mutation.

Case: A 6-year-old female patient; had atopic dermatitis onset at 40 days of age and allergic asthma symptoms beginning at age three years. The patient had treatment-resistant severe atopic dermatitis, hair loss, and angioedema attacks. She had a history of topical corticosteroids, calcineurin inhibitors, and intermittent systemic corticosteroid use for more than two years. The SCORAD index was 86 (Figure 1). Laboratory findings revealed eosinophilia (5200/mm³) and IgE elevation (17818IU/kL). Other immunoglobulins and lymphocyte subgroup analyses were normal. Regulatory T (Treg) cell levels were higher than the healthy control, and CD4+ and IL4+CD4+ cells were lower than the healthy control (Figure 2). Basal and after stimulation with IL-2 and IL-7 cytokines, the patient's and father's samples showed significantly increased STAT5B phosphorylation than healthy controls (Figure 3). With CD3, CD28, PHA, PMA-Ionomycin, and IL-2 stimulation, the healthy control's cells proliferated at a high level, while the patients were moderate (Figure 4A). RORC, FOXP3, IL-22, Amphiregulin, IL4, IL5, IL13, GM-CSF, IL5, IL13, and IL4 genes were studied by real-time qPCR in skin biopsies taken from the patient, the patient's father, and healthy controls and an increase in IL22 and Amphiregulin genes was detected (Figure 4B). In the genetic analysis of the patient, STAT5B c.650 G>A p.Arg217His mutation was detected. According to functional studies, it is verified that the patient has the STAT5B GOF mutation.

Conclusion: STAT5B GOF is a newly defined primary immunodeficiency with an unknown clinical spectrum. Our case provides new information about STAT5B GOF disease.

POSTER 5 - THE OCCURRENCE OF AUTOIMMUNE DISEASES IN ALGERIAN PATIENTS WITH HOMOZYGOUS MUTATIONS IN RAG1 AND RAG2

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Introduction: Biallelic RAG1 and RAG2 mutations have been associated with a wide range of clinical and immunological phenotypes. While null mutations result in severe combined immunodeficiency (SCID), with the absence of T and B cells (T- B- NK+ SCID), hypomorphic mutations allowing for residual protein function are associated with atypical forms, including OS and leaky SCID.

Objective: We aimed to study the occurrence of autoimmune diseases (AIDs) in Algerian patients with RAG deficiency.

Methods: We have retrospectively screened 10 patients with homozygous RAG1/2 mutations, presenting with SCID, OS or leaky SCID, for the occurrence of AIDs.

Results: Among the ten patients with RAG deficiency (6 males, 4 females, mean age: 12 months, interval: 1 - 72), seven had homozygous mutations in RAG1, while three had biallelic variants in RAG2. RAG deficiency resulted in T-B- NK+ SCID in three patients, OS in five patients and leaky SCID in two others. None of the three patients with SCID had AID, while six out of the seven patients (85.7%) with hypomorphic mutations presented with AIDs, including dermatitis in 5 patients (71.4%), autoimmune hemolytic anemia in two patients (28.6%), idiopathic thrombocytopenic purpura in one patient (14.3%), and juvenile arthritis in one patient (14.3%).

Conclusion: AIDs were absent in RAG-deficient patients presenting with typical SCID but very frequent in patients with hypomorphic RAG1/2 mutations. Given the high frequency of autoimmune cytopenia in OS and leaky SCID, autoimmune origin should be viewed as the main etiology of anemia and thrombocytopenia in patients with such diseases.

POSTER 6 - SEVERE AUTOIMMUNITY TRAITS IN A COLOMBIAN BOY: A NOVEL NRAS MUTATION C.182A>G (P.Q61R) CAUSING RAS-ASSOCIATED AUTOIMMUNE LEUKOPROLIFERATIVE DISEASE

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Objective: Describe an unusual case of a male patient affected by an early onset of severe autoimmunity that was ultimately diagnosed with a new genetic variant of a primary immunodeficiency disorder-associated gene

Design: Case report

Methods: Retrospective description of clinical records

A 1-year-old male patient displayed 10 days of fever, vomiting, diarrhea, and poor feeding. Previous complete blood count (CBC) evidenced leukocytosis 44,200/mm³, lymphocytosis 19,500/mm³ and monocytosis 4,300/mm³

He was the only child of non-consanguineous parents with unremarkable medical records. Vaccination schedule was updated. Physically the child had multiple non-tender neck, supraclavicular and groin lymphadenopathies and hepato-splenomegaly

CBC displayed similar findings as the previous CBC. Blood cultures and tumoral lysis profiles were negative. Serological studies for chronic infections were negative. Molecular studies in stool sample identified *Campylobacter* and *Giardia lamblia* which were treated properly

Anemia evaluation fulfilled the criteria for autoimmune hemolytic anemia. Serum immunoglobulin levels displayed hypergammaglobulinemia with IgG 1,805 mg/dl, IgM 381 mg/dl, IgA 101 mg/dL and IgE 344 UI/ml along with high antinuclear antibodies in a titer of 1:2,560, low complement C3: 69 mg/dl and C4: 8 mg/dl, CH50 (<10 U/ml) and negative profile for autoimmune hepatitis.

Peripheral blood immunophenotype surprisingly revealed an increased TCRab+CD3+ cells 9,200/mm³ with a remarkably high proportion of double negative TCRab cells 1.8% of total lymphocytes and 3.5% of total CD3+ lymphocytes (normal < 1.5% of total lymphocytes and <2.5% of total CD3+ lymphocytes) with moderate B-cell expansion and normal kappa/lambda distribution. Bone marrow aspiration and biopsy were done discarding malignant transformation

The findings of early autoimmunity and chronic leukoproliferation with high double negative TCRab cells increased the suspicion for a primary immunodeficiency disorder (PID) related to NRAS, KRAS genes. Thus a whole exome sequencing was done finding a new pathogenic NRAS heterozygous mutation c.182A>G (p.Q61R) in peripheral blood. Somatic mutation diagnosis was done due to presence of this mutation in hematologic cells but not in mouth swab sample. With that molecular confirmation a diagnosis of RAS-associated autoimmune leukoproliferative disease (RALD) was done for the very first time related with a somatic mutation in codon 61.

Unfortunately, the patient passed away due to a *Candida parapsilosis* fungemia despite adequate immune modulatory and fungicidal treatment.

Conclusion: PID's and particularly RALD must be considered in patients displaying early autoimmunity features alongside leukocyte proliferation of unknown etiology.

POSTER 7 - AIHA IN WISKOTT-ALDRICH SYNDROME

AUTHORS

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Objective: Wiskott-Aldrich syndrome (WAS) is an X-linked combined immunodeficiency disorder with an incidence of 1-10 per 100,000 live births. Patients with WAS are not only predisposed to recurrent infections but are also at an increased risk of developing autoimmunity and malignancy. The immune-pathogenetic mechanism of autoimmunity in WAS remains unclear. We report clinical and genetic profile of 5 patients with WAS who developed autoimmune hemolytic anemia (AIHA).

Design and Method: Case records of children with WAS, being followed up in Pediatric Immunodeficiency Clinic of Advanced Pediatrics Centre, Post Graduate Institute of Medical Education and Research, Chandigarh, India who had developed AIHA were reviewed. Clinical manifestations, investigations, treatment, and outcomes were analyzed.

Results: Out of 50 patients with X-linked thrombocytopenia (XLT)/WAS followed-up for 14 years, 15 patients (30%) developed one or more autoimmune manifestation. Among these, 5 children (33.33%) had AIHA. Mean age of these children was found to be 37.12 ± 30.21 months (range: 4.5 to 84 months). All children presented with rapidly evolving pallor with (n=5) or without bleeding (n=4) manifestations. Time from diagnosis of XLT/WAS to the development of AIHA varied from 3 to 11 years in 3 patients. Other patients presented with AIHA and diagnosis of WAS was established during this illness. Direct Coombs test was positive in all 5 patients. Additionally, skin vasculitis was observed in 3/5 patients. Genetic evaluation revealed nonsense mutation in 2 patients and missense mutation in 3 patients each in exon 1 and 2 respectively. Combination of glucocorticoids and intravenous immunoglobulin (IVIG) were used for initial treatment in 3 patients while other two children were treated with IVIG alone. All patients responded to treatment. However, 4 patients died with subsequent illness while waiting for hematopoietic stem-cell transplantation (HSCT).

Conclusion: Autoimmune manifestations can occur in 30% patients with XLT/WAS spectrum and AIHA accounts for 33.33% of these. Development of AIHA may be associated with poor outcomes.

POSTER 8 - POTENTIAL ROLE OF ORAL, LUNG AND GASTROINTESTINAL MICROBIOTA IN THE PATHOPHYSIOLOGY OF COMMON VARIABLE IMMUNODEFICIENCY

AUTHORS

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Objective: To compare the bacterial composition of lung, gastrointestinal, and oral microbiome of patients with Common Variable Immunodeficiency (CVID) with dysimmune disorders vs CVID patients who only suffered infections.

Design: Fecal, saliva, and sputum samples were collected from 19 patients diagnosed of CVID followed in a PID unit. A retrospective cross-sectional study was conducted. Cases (12) were defined as CVID with polyclonal lymphocytic infiltration, autoimmune or autoinflammatory diseases, non-infectious enteropathy and/or tumors. Controls (7) only presented infectious comorbidity.

After DNA extraction, V3-V4 hypervariable regions were amplified with 16S rRNA gene universal primers. Illumina Miseq was used for high-throughput sequencing. Reads were quality-filtered and end-trimming, and PCR quimeras were eliminated. High-quality sequences were transferred to Dada2 pipeline analysis obtaining genus- and species taxonomy (Amplicon Sequence Variants or ASVs) (Fig. 1).

Results: Chao1 biodiversity index, providing an estimation of the number of species from each sample, statistically differed in oral ($p=0.027$) and lung microbiome composition ($p=0.05$) between cases and controls. No statistically significant differences were found in the gastrointestinal microbiome ($p=0.81$), in contrast with previously published studies (Fig. 2). Regarding the lung microbiota, *Streptococcus* spp. was the most frequent genus found both in cases and controls. Interestingly, *S. pneumoniae*, the main causing etiological agent of community-acquired pneumoniae (CAP), was the second most frequent microorganism in the lung microbiota of cases (7% vs 0.06% respectively, $p=0.05$). In addition, *Mycoplasma* spp., also related with atypical CAP, was more frequently found in CVID cases showing a statistical trend (0.03% vs 0.001% respectively, $p=0.057$) (Fig. 3).

Streptococcus spp. was also the most frequent genus isolated in the oral microbiome of cases and controls. Alkalophilic species seemed to be more present in CVID controls than CVID cases (0.61% vs 0.086% respectively, $p=0.006$ for *Prevotella salivae*). In contrast, acidogenic species were more frequently associated with CVID cases (0.204% vs 0.04% respectively, $p=0.05$) (Fig. 4). Strikingly, *Campylobacter* spp., a well-known genus related to CVID gastrointestinal infections, accounted for 0.19% of the oral microbiome of CVID cases vs 0.06% of controls ($p=0.029$).

In conclusion, our findings suggest a potential role of members of the oral and lung CVID microbiome, never analysed until date, in the pathophysiology of the dysimmune disorders associated to CVID, and expands the scarce evidence regarding gastrointestinal microbiome in CVID patients (Fig. 5). Future clinical and experimental work should test this hypothesis.

POSTER 9 - CHALLENGES IN DIAGNOSING AUTO-INFLAMMATORY DISORDERS IN LOW RESOURCE SETTING

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Objective: With increasing awareness of the syndromes and their presentation, more children with primary immunodeficiencies are being diagnosed in Ethiopia with each passing year. The aim in discussing this clinical presentation of a young Ethiopian boy suspected of having an autoinflammatory disorder is to outline the diagnostic and therapeutic challenges for such disorders in a low income country.

Design and method: The presentation of a three year old Ethiopian boy with recurrent respiratory and intestinal infections starting from two years of age is summarized. Episodes were notable for subcutaneous nodules shifting positions with each febrile episode, arthralgia, marked leukocytosis and neutrophilia, normal serum immunoglobulin levels and remaining hematologic parameters, normal chest x-ray but mesenteric adenitis, varying levels but persistently elevated CRP even during periods between febrile episodes, negative autoimmune and oncologic markers and negative markers for HIV, TB and other infectious illnesses. He had no atypical post vaccine reactions and his maternal uncle has a high predisposition for illnesses. He was circumcised at ten days of age (uneventful) and shed his umbilicus at one week of age. Febrile episodes are being managed with short term oral steroids while exploring ways to do genetic testing for auto-inflammatory disorders.

Results: There are numerous autoinflammatory disorders and are increasing in number by the year. Though some members of this group are associated with specific communities – familial Mediterranean fever among Mediterranean populations, hyperimmunoglobulin D syndrome among north Europeans etc - some others like Tumor necrosis factor receptor associated periodic syndrome can be diagnosed globally. Clinical features of autoinflammatory disorders overlap and genetic analysis for known mutations is vital for diagnosis.

Conclusion: A paucity of genetic labs makes confirmation of auto-inflammatory disorders difficult in Africa. But continuing education will help identify common clinical features and avoid unnecessary work-up and antimicrobial treatment for similar patients.

POSTER 10 - CASE REPORT OF AUTOIMMUNE THROMBOPENIA AND NEUTROPENIA IN ASSOCIATION TO AUTOINFLAMMATORY CLINICAL MANIFESTATIONS

AUTHORS

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Objective: Describe a case report of a patient with early debut of autoimmune thrombopenia and neutropenia, in association to autoinflammatory clinical manifestations.

Method: Collection of data from the electronic personal health record.

Results: We present a 19-year-old male who debuted in 2014 with severe thrombopenia and neutropenia (6000platelets/mm³ and 100Neu/mm³), implying a hospital admission. As significant clinical manifestations we can outline the appearance of spontaneous bruises, epistaxis, recurrent fever episodes and aphthae.

In the initial study, we objectified a normal count of immunoglobulins, with normal C3 and a mild decrease of C4; decreased CD4/CD8 quotient; absence of B lymphocytes and CD4 cells; and lymphocyte policlonality. Additionally, NK lymphocytes are barely represented although they preserve perforine and granzyme B expression.

We could also objectify a positive direct Coombs, negative C3 and negative indirect Coombs. In the bone marrow (BM) study, we found a normocellular BM with erythroid hyperplasia and megakaryocytic thrombopenia. IgM serologies for EBV, CMV, HAV, HBV, HCV, HIV, B19 Parvovirus, HHV8 and HHV6 were negative. Additionally, we started an early diagnosis study to determine the presence of a possible Autoimmune Lymphoproliferative Syndrome (ALPS), concluding that the patient did not fulfil the diagnostic criteria for this syndrome, as he presented a T alpha/beta CD4-/CD8- normal count; normal sFASL levels; normal B12 vitamin levels; normal IL-10 levels; absence of visceromegaly or lymphadenopathies; or any previous lymphoma history.

Furthermore, we obtained a positive determination of antineutrophil antibodies (anti-HNA) and a negative determination of antiplatelet antibodies.

Finally, several genetic studies were done:

- Study of genes codifying for FAS, CTLA-4, NRAS and KRAS; without any mutations.
- Gene panel testing (NGS), where we could not find any pathogenic or potentially pathogenic allelic variation.

We started treating this patient with IVIG without obtaining any clinical response, so we modified it to Sirolimus and Prednisone, achieving a regular disease control with at least 2 annual bicytopenia flare-ups, with the need to use high doses of Prednisone.

Conclusions: We consider the presentation of this case report to be relevant because it implies a possible ALPS diagnose in a patient that, at present, does not fulfil the necessary criteria, with a difficult control of his basal bicytopenia and an excessive use of corticoids. Therefore, it is required to consider an alternative biological therapy and a close follow-up of this patient, due to the probable association of his clinical presentation with an underlying immunodeficiency, yet to be characterized.

POSTER 11 - PRIMARY IMMUNODEFICIENCY DISORDERS PRESENTING WITH AUTOIMMUNE MANIFESTATIONS IN THE ADULT INTERNAL MEDICINE WARD OF A TERTIARY CARE CENTRE IN SOUTH INDIA- A CASE SERIES.

AUTHORS

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Objective: The presentation of primary immunodeficiency disorders in the adult internal medicine ward may be different, as autoimmunity may be the sole manifestation. We describe a series of 3 patients who were evaluated for various autoimmune features in adult internal medicine ward and were subsequently diagnosed as primary immunodeficiency disorders.

Design and method: This is a case series of 3 patients admitted in adult internal medicine ward of a tertiary care hospital in South India between October 2020 and October 2021.

Results:

Case 1: 35-year- old male was admitted with chronic fatigue, small bowel diarrhea and bilateral genu valgum deformity from 12 years of age. Upon examination, evidence of vitamin B12 deficiency and bilateral genu valgum deformity were noted. Investigations revealed megaloblastic anemia, low serum calcium, vitamin D and globulin levels. Immunodeficiency workup revealed pan hypogammaglobulinemia with low class switched memory B cells and poor vaccine response confirming a diagnosis of common variable immunodeficiency. Upper GI endoscopy showed autoimmune enteropathy of CVID with gastric dysplasia (Fig 1a-d). He was treated with monthly IVIG and prednisolone with improvement in bowel symptoms and anemia.

Case 2: 18-year- old female was admitted with severe fatigue for 1 year and was found to have direct Coombs test positive autoimmune hemolytic anemia and leukopenia. She had low complement levels with negative anti- nuclear antibody (ANA). She had history of multiple hospital admissions with lower respiratory infections since the age of 5 years. Primary immunodeficiency was suspected and on testing she had pan hypogammaglobulinemia with poor vaccine response to pneumococcal vaccine confirming a diagnosis of CVID with autoimmune cytopenias. She improved with oral prednisolone and monthly IVIG.

Case 3: 18-year- old female known case of ataxia telangiectasia from 8 years of age, was admitted with high blood sugars and chronic cough. She had chronic generalized eczematous rash from the age of 5 years. On evaluation she had low serum IgA with normal IgG, IgM and IgE. CT chest did not show bronchiectasis. Evaluation for type 1 diabetes showed anti IA-2 antibody positivity leading to a diagnosis of Ataxia telangiectasia with selective IgA deficiency and autoimmune type 1 diabetes. She was initiated on co trimoxazole prophylaxis and insulin.

Conclusion: Autoimmune features may constitute the predominant manifestation of PID patients attending the adult internal medicine ward and a high index of suspicion is needed to make a timely diagnosis.

POSTER 12 - ASYMPTOMATIC SARS COV-2 INFECTION IN A 59 YEAR OLD WOMAN WITH AN AUTOINFLAMMATORY DISEASE DUE TO SOMATIC NLRC4 MOSAICISM.

AUTHORS

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Objective: The Centers for Disease Control and Prevention has acknowledged an increasing incidence of multisystem inflammatory syndrome in adults (MIS-A) in patients with Sars Cov 2. This severely progressive disease requiring hospitalization in intensive care seems related to a deregulation of cytokines with very high levels of IL-6, IL-2, IL-7, IL-10 and TNF-alpha. This study was developed to characterize an asymptomatic Sars Cov 2 infection in a woman with an autoinflammatory disease and the inflammatory response produced in the context of her pathology.

Design and method: We collected clinical data and performed immunological tests to see the response to the virus.

Results: A 59 year old woman who had reported recurrent episodes of fever, thrills, myalgias, arthralgias and systemic inflammation since the age of 47 was studied in the Department of Immunology. Genetic studies identified the p.Ser-171Phe NLRC4 variant compatible with gene mosaicism, which causes an activation of the NLRC4 inflammasome with a subsequent IL-18 overproduction. She was being treated with Canakinumab once a month and appeared to be relatively well controlled. Although she had a positive PCR against SARS-Cov2 in January 2021, the clinical picture remained very mild and she only produced low quantities of IgM against the virus. IgG was initially negative. However, after vaccination, she developed a considerable IgG response. The other biochemical and immunological parameters such as lymphocyte subpopulations obtained by flow cytometry and humoral immunity, remained similar to her previous results.

Conclusions: Despite the patient's pro-inflammatory status added to the virus' pathophysiology, the patient did not produce a pathologic immune response. This situation could be influenced by her Canakinumab treatment. However, the absolute absence of immunological response remains surprising. It would be of interest to know more about the relationship between Sars Cov-2 and other autoinflammatory diseases, and therefore have a clearer vision of how the virus behaves in these enigmatic syndromes.

POSTER 13 - NEONATAL ONSET MULTISYSTEM INFLAMMATORY DISEASE (NOMID)- A SERIES OF TWO PATIENTS FROM A TERTIARY CARE CENTER IN NORTH INDIA.

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Objective: Neonatal onset multisystem inflammatory disease (NOMID) is the most severe form of NLRP3 associated autoinflammatory disease characterized by recurrent fever, chronic urticarial rash, arthropathy and neurological symptoms. We report 2 cases of NOMID which were diagnosed elsewhere as juvenile idiopathic arthritis and referred to our centre.

Design and method: This is a case series study of two patients with NOMID who were admitted in the department of Clinical Immunology and Rheumatology at a tertiary care centre in North India during the one- year period from April 2018 to April 2019.

Results:

Case 1: 5- year-old male child born of a non- consanguineous marriage, presented with urticarial lesions since birth, episodic fever with each episode lasting for 2-3 days and bilateral knee joint pain with swelling for last 18 months. Family history was unremarkable. He was treated elsewhere as oligoarticular juvenile idiopathic arthritis (oligo JIA) without any clinical improvement. Upon examination, there was stunting, frontal bossing, generalized urticarial lesions, lymphadenopathy and hepatosplenomegaly. Bilateral knee joints were swollen and tender (figure 1a,1b). Investigations revealed neutrophilic leukocytosis, raised erythrocyte sedimentation rate (ESR) and C- reactive protein (CRP). Bilateral knee joint X-ray showed grossly enlarged epiphysis and patella (figure 1 c), confirming a clinical diagnosis of NOMID. MRI Brain, vision and hearing assessment were normal. Due to non- availability of IL1 blockers, he was started on oral colchicine.

Case 2: 4-year-old male child born of non- consanguineous marriage, with history of gross developmental delay was brought with generalized urticarial lesions, progressive deforming arthritis of bilateral knee, elbow and ankle joints and recurrent fever from 1 month of age. He was treated elsewhere as a case of systemic onset juvenile idiopathic arthritis (SOJIA). Upon examination, there was stunting, generalized urticarial lesions, frontal bossing, depressed nasal bridge, hepatosplenomegaly and fixed flexion deformities of bilateral elbow and knee (figure 2d,2e). Investigations revealed anemia, leukocytosis and elevated ESR. X ray of bilateral knee joints showed grossly enlarged patella (figure 2f) consistent with the diagnosis of NOMID. He was started on oral colchicine, as IL1 blockers were not available. As both the patients were lost to follow up, genetic testing could not be done.

Conclusion: Though rare, NOMID should be thought of in any child with neonatal onset urticaria, deforming arthropathy and typical radiological changes. NLRP3 gene sequencing is not mandatory to make a diagnosis and 40-50% of cases may lack an identifiable NLRP3 mutation.

POSTER 14 - PRIMARY IMMUNE REGULATORY DISORDERS WITH AN AUTOIMMUNE LYMPHOPROLIFERATIVE SYNDROME-LIKE PHENOTYPE: IMMUNOLOGIC EVALUATION, EARLY DIAGNOSIS, AND MANAGEMENT

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Objective: Primary immune regulatory disorders (PIRD) are associated with autoimmunity, autoinflammation and/or dysregulation of lymphocyte homeostasis. Autoimmune lymphoproliferative syndrome (ALPS) is a PIRD due to an apoptotic defect in Fas-FasL pathway and characterized by benign and chronic lymphoproliferation, autoimmunity and increased risk of lymphoma. However, clinical manifestations and typical laboratory biomarkers of ALPS have also been found in patients with a gene defect out of the Fas-FasL pathway (ALPS-like disorders). The objective of this work is to identify the genetic defects that could be presented with an ALPS-like phenotype.

Design and method: The literature search was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta analyses (PRISMA) guidelines. Clinical ALPS-like criteria were immune dysregulation defined as autoimmunity and lymphoproliferation. The genes in which genetic defects gave rise to an ALPS-like phenotype were selected based on the IUIS classification and a literature search.

Results: We identified more than 600 patients suffering from 24 distinct genetic defects described in the literature with an ALPS-like clinical phenotype, corresponding to phenocopies of primary immunodeficiency (NRAS, KRAS), susceptibility to Epstein Barr virus (MAGT1, PRKCD, XIAP, SH2D1A, RASGRP1, TNFRSF9), antibody deficiency (PIK3CD and CARD11 gain of function (GOF), PIK3R1 loss of function), regulatory T-cells defects (CTLA4, LRBA, STAT3 GOF, IL2RA, IL2RB, DEF6), combined immunodeficiencies (ITK, STK4), defects in intrinsic and innate immunity and predisposition to infection (STAT1 GOF, IL12RB1) and autoimmunity/autoinflammation (ADA2, TNFAIP3, TPP2, TET2). CTLA4 and LRBA patients correspond around to 50% of total ALPS-like cases. However, only 100% of CTLA4, PRKCD, TET2 and NRAS/KRAS reported patients had an ALPS-like presentation, while the autoimmunity and lymphoproliferation combination resulted rare in other genetic defects. Recurrent infections, skin lesions, enteropathy and malignancy were the most common clinical manifestations. Flow cytometry assays could be useful for the immunological study and identification of ALPS-like patients, such as protein expression assays for NKG2D, XIAP, SAP, CTLA4 and LRBA deficiencies or studies of AKT, STAT1 and STAT3 phosphorylation, between others.

Conclusions: Patients suspected to suffer from one of these disorders require rapid and correct diagnosis allowing initiation of tailored specific therapeutic strategies and monitoring thereby improving the prognosis and their quality of life.

POSTER 15 - AUTOIMMUNITY AND AUTOINFLAMMATION IN ROMANIAN PRIMARY IMMUNODEFICIENCY PEDIATRIC PATIENTS: RETROSPECTIVE ANALYSIS

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Objective: Immunodeficiency and immune dysregulation overlap and the rate of their coexistence is higher than expected. We aimed to determine the incidence of autoimmunity and autoinflammation along with treatment regimens in a cohort of pediatric patients with primary immunodeficiency (PID) from a tertiary center in Romania.

Design and methods: We reviewed retrospectively medical records of PID patients diagnosed since 2015 in the Pediatric Immunology Department of INSMC Alessandrescu Rusescu, Bucharest. We collected and analysed data on PID diagnosis, underlying genetic defects, type of autoimmune and autoinflammatory manifestations. We compared the time onset of each manifestation to the time of PID diagnosis. We also discussed treatment strategies in the study group patients.

Results: 33 pediatric patients were diagnosed with PID over 5 years (26 males, 7 females), median age 13 years (range 0.5, 22 years). The most frequent PID was X-linked agammaglobulinemia (8 patients). Autoimmune manifestations included celiac disease, cytopenias, alopecia, endocrinopathies and were present in 4 (12%) patients. Autoinflammatory manifestations included systemic hyperinflammation, skin and central nervous system vasculitis, generalised exfoliative erythroderma, arthritis, inflammatory bowel disease and were present in 10 (30%) patients. Immune dysregulation response preceded PID diagnosis in 7 patients, with up to 144 months. Diagnosis of PID in association with autoimmunity and/or autoinflammation was genetically confirmed in 91% of patients (11 out of 12). Treatment regimens varied from corticosteroids to TNF alpha inhibitors in the study group patients.

Conclusions: In our cohort, 36% of PID patients associated autoimmunity or autoinflammation stating these patients' high risk of developing such complications. Maintaining the balance between effective immunosuppressive treatment and serious infections avoidance is a continuous challenge in these patients.

POSTER 16 - AUTOIMMUNE MANIFESTATIONS IN A LARGE MULTI-CENTRE COHORT OF PATIENTS WITH COMMON VARIABLE IMMUNODEFICIENCY IN INDIA.

AUTHORS

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Objective: To report the autoimmune manifestations in a multi-centre cohort of patients with CVID from India.

Design and Methods: A predesigned Microsoft Excel sheet was circulated via email to all centres across the country who are involved in the care of patients with PIDs. Data were collected from centres who agreed to take part in this multicentre study. Diagnosis of CVID was based on the European Society for Immunodeficiency (ESID) 2014 classification criteria.

Results: In this multi-centre cohort, we included clinical details of 126 patients diagnosed to have CVID based on (ESID) 2014 criteria. Median age at onset of symptoms and diagnosis was 7 years and 15 years respectively. Autoimmune manifestations were seen in 43 patients (34.12%) [19 females and 24 males]. 16.27% patients had only autoimmune manifestation but no infections. Autoimmune hemolytic anemia and autoimmune hepatitis were the most common autoimmune manifestation (5.55% each) followed by autoimmune thrombocytopenia, inflammatory arthritis and systemic lupus erythematosus (3.96% each), autoimmune thyroiditis (3.17%), celiac disease and alopecia areata (2.6% each) and autoimmune neutropenia, pure red cell aplasia, chronic inflammatory demyelinating polyneuropathy (1.58% each). Vasculitis, psoriasis, antiphospholipid antibody positivity, inflammatory Bowel Disease (IBD) were seen in one patient each

We compared the clinical and immunological profile of patients with CVID with and without autoimmunity. We found that patients with CVID who had autoimmune manifestations had significantly higher recurrent infections (76.74% vs 72.15%, p value 0.02) and fungal infections (9.30% vs 7.59%, p value 0.02) when compared to patients with CVID who had no autoimmune manifestations. Patients with CVID who had autoimmune manifestations had significantly higher mean IgG (338.29±367.54 vs 300.29±248.52, p value 0.021) and low mean IgM levels (52.25±78.14 vs 76.25±119.98, p value 0.010) when compared to patients with CVID who had no autoimmune manifestations. 50% of patients with CVID with autoimmune manifestations were detected to have a monogenic defect as compared to 66% of patients with CVID who had no autoimmune manifestations. Patients with CVID who had autoimmune manifestations were managed using intravenous immunoglobulin therapy 400 mg/kg every 3-4 weeks, corticosteroids, mycophenolate mofetil, azathioprine and sirolimus.

Conclusion: This is the first large multicentre cohort of patients with CVID from India. Autoimmune manifestations are common and are seen in 1/3rd of all patients with CVID. Patients with CVID with autoimmune manifestations have significantly higher recurrent infections and fungal infections, have higher serum IgG levels and reduced IgM levels.

POSTER 17 - AN UNUSUAL CASE OF HEPATOMEGALY, PANCYTOPENIA AND AUTOINFLAMMATORY SYNDROME IN A COLOMBIAN GIRL: ABOUT A CASE OF PSTPIP1-ASSOCIATED MYELOID-RELATED PROTEINEMIA INFLAMMATORY SYNDROME.

AUTHORS

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Objective: Describe an unusual case of a patient affected by hallmark chronic systemic inflammation that ultimately was diagnosed with a genetic confirmed primary immunodeficiency disorder (PID)

Design: Case report.

Methods: Retrospective description of clinical records.

Results: A 17-year-old female had a 2-month history of periodic fevers, malaise, fatigue, odynophagia and lymphadenopathy. She had been diagnosed with myelodysplastic syndrome since 10-year-old due to chronic pancytopenia, aseptic pyogenic arthritis of the knee 5 years before, periodontal disease, recurrent chalazion and aseptic rectal fistula. She had a sister who apparently died at adolescent age due to systemic lupus erythematosus complications. At physical evaluation the patient had normal vital signs but was pale, had a cervical lymphadenopathy measuring 4cm2, active periodontal disease, pharyngeal erythema without exudate and marked hepatosplenomegaly (Figure 1). Infectious and hematologic etiologies were considered. Laboratories displayed leukopenia with severe neutropenia, chronic infections were ruled out, C-reactive protein was mildly elevated but procalcitonin and cultures were negative. Node biopsy exhibited reactive hyperplasia with parafollicular expansion and bone marrow evaluation didn't exhibit any abnormality suggestive of malignancy.

It was concluded that she had features of systemic chronic inflammation without clear microbiologic triggering, as well as features of immune dysregulation that pointed towards an autoimmune process or a PID. Immunologic profile was evaluated. Immunoglobulins showed IgG and IgA hypergammaglobulinemia supporting chronic inflammation, auto-antibodies were negative, erythrocyte sedimentation rate was high, and complement fraction C4 was slightly low, with T-cell and NK cell lymphopenia. (Table 1).

With this information rising alarms about a PID a whole exome sequencing (WES) was done. WES showed a pathogenic heterozygous germline mutation c.748G>A (p.E250K) in PSTPIP1 gene confirmed by Sanger, identified as causative of PSTPIP1-associated myeloid-related proteinemia inflammatory (PAMI) syndrome. Given those results, zinc and calprotectin serum levels were performed, displaying five-fold the upper normal limit of zinc with borderline calprotectin levels, eliciting a PAMI metabolic confirmatory diagnosis. Nowadays the patient is under clinical remission of its systemic inflammatory features just with short courses of non-steroidal inflammatory drugs and being considered for bone marrow transplantation.

Conclusions: PAMI syndrome must be considered in patients displaying features of periodic inflammation of uncertain etiology and hematologic abnormalities as chronic neutropenia once other more frequent etiologies had been ruled out.

POSTER 18 - IDENTIFICATION OF HETEROZYGOUS PSTPIP1 AND WAS VARIANTS IN A PATIENT WITH RECURRENT INFECTIONS AND INFLAMMATORY-ASSOCIATED SYMPTOMS.

AUTHORS

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Objective: To report the analysis of the genetic screening for immunodeficiencies of a patient with complex inflammatory disorder in association with recurrent infections.

Case report: 40-years-old woman was referred to the Immunology department due to clinical history of psoriatic arthropathy, recurrent respiratory infections and recurrent herpes simplex in association with secondary optic neuritis. She also complained of chronic fatigue and intermittent low fever. Different biological treatments were attempted without success. Laboratory screening during follow-up did not provide evidence of immunodeficiency, and a genetic study was requested in order to exclude any underlying immunological disorder.

Design and Methods: Genomic DNA from peripheral blood of the patient was isolated and Next Generation Sequencing (Gene Systems) was performed using a screening panel of 200 genes associated with immune deregulation.

Results: Genetic analysis revealed two heterozygous variants in PSTPIP1 gene (p.Arg405Cys) and WAS gene (p.His-180Asn). Both of them are described as mutations with conflicting pathogenicity interpretations according to genomic databases.

Published functional studies with PSTPIP1 variant suggest altered interaction of the protein with the cytoskeleton and other molecules of its pathway. It was also found evidence of reduced expression of WASP protein in association with p.H180N WAS variant in the literature.

Conclusion: Monoallelic mutations in PSTPIP1 gene are implicated in a spectrum of clinical disorders termed PST-PIP1-associated inflammatory diseases. Among other functions, PSTPIP1 is an adaptor protein which is able to interact with WASP molecule allowing successful activation and migration of lymphocytes.

In this case we present two heterozygous mutations in PSTPIP1 and WAS genes in a patient with recurrent infections and inflammatory-related symptoms.

POSTER 19 - EARLY ONSET AMYLOIDOSIS IN COPA SYNDROME: FIRST CASE REPORT

AUTHORS

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Copa syndrome is inherited in an autosomal dominant pattern with variable penetrance. Patients with Copa syndrome develop pulmonary symptoms, arthritis, and renal disease. Most present early in life with 76% exhibiting signs and symptoms of disease under age of 5 years of age. Amyloidosis in Copa syndrome is not reported. We report the first case report of amyloidosis in Copa syndrome.

Case Report: Child was symptomatic since 3 years during which he presented with high grade fever, evanescent rash and poly-arthritis with a waxing and waning course and diagnosed as systemic onset juvenile idiopathic arthritis. Bone marrow examination was normal, FNAC from cervical lymph node was suggestive of reactive lymphadenopathy. Child was initiated on naproxen on which fever spikes came down and activity improved significantly. Later on child was started on methotrexate, thalidomide, and oral steroids.

Child was again admitted at 5 years with the complaints of pain and swelling of joints for 2 months, at that time child was febrile and he had severe pallor, hepatosplenomegaly and polyarthritis. The possibility of SJIA with active flare up was considered. There were no features suggestive of macrophage activation syndrome (MAS). During the course of hospital stay swelling of joints resolved and child became afebrile and spleen size regressed. Child was discharged on oral Prednisolone at 2mg/kg/day for one month followed by tapering of the dose. Now the patient had nephrotic range proteinuria so an initial possibility of nephrotic syndrome was considered and the workup was done. Biopsy done from the duodenum and rectum was suggestive of amyloidosis. Colchicine was added in view of amyloidosis. Genetic analysis done suggested COPA gene mutation at c.3100C>A(p.Leu1034Ile), heterozygous mutation.

Discussion: Copa syndrome is a primary immunodeficiency characterized by immune dysregulation with autoinflammation and autoimmunity. Persistent inflammation can lead to amyloidosis in these cases, much earlier than other autoimmune-inflammatory diseases. Steroids are useful in other autoimmune components such as arthritis, which has been additionally approached with arthritis-specific disease modifying agents. Remissions in both arthritis and pulmonary disease can often be achieved using these medications. However, due to the progressive nature of Copa syndrome several patients have died during acute exacerbations. Maintenance therapies have usually consisted of either methotrexate or azathioprine with intermittent pulses and gradual tapering oral steroids. Other maintenance therapies may include hydroxychloroquine, etanercept, and IVIG at immuno-modulatory dosages. So prompt management may reduce the rapid progression of the disease.

POSTER 20 - MONOGENIC AUTOIMMUNE HEMOLYTIC ANEMIA: EXPERIENCE FROM A TERTIARY CARE CENTER FROM NORTH INDIA.**AUTHORS**

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Objective: Autoimmune hemolytic anaemia (AIHA) is classified as either isolated primary or secondary AIHA. Corticosteroids remain the cornerstone in managing children with AIHA; however, it is a nonspecific immune-suppressive strategy. Secondary AIHA due to underlying autoimmune illness or immunodeficiency is usually less responsive to corticosteroids than primary AIHA. Recently, with more understanding of molecular and genetic etiologies of AIHA, a more specific, and targeted immunomodulatory therapy is considered for secondary AIHA. Herein, we report our experience with 16 patients with monogenic AIHA.

Design and methodology: Retrospective review of case records of all children diagnosed with AIHA with proven monogenic PID in the Allergy-Immunology Unit, Department of Pediatrics, Postgraduate Institute of Medical Education and Research, Chandigarh, India.

Results: We enrolled 16 patients of AIHA with underlying PID. The diagnosed PID include Wiskott-Aldrich syndrome (WAS) (n=4, 23.5%); Autoimmune lymphoproliferative syndrome (ALPS) (n=4, 23.5%); Lipopolysaccharide-responsive and beige-like anchor protein (LRBA) deficiency (n=3, 17.6%); Severe combined immunodeficiency [SCID, n=2 (12%); STK defect (1), and NHEJ1 defect (1)]; STIM1 defect (n=1, 5.8%); CD40L defect (n=1, 5.8%); and ACP5 defect (n=1, 5.8%). AIHA was seen in the initial presentation of the disease in patients with CD40L defect, LRBA defect (n=3), ALPS (n=4), ACP5 defect, STIM1 defect, and in 1 patient with WAS. Corticosteroid was the first-line agent used (n=11/ 16, 68.7%), whereas 3 patients were managed without corticosteroid [18.7%, SCID (2), and CD40L defect (1)]. Other agents utilised include Mycophenolate mofetil (MMF) (n=7, 41.1%); Azathioprine (n=2, 12.5%); Sirolimus [n=6, 37.5%; ALPS (3); LRBA (2); STIM1 defect (1)]; and Rituximab [n=2, 12.5%; ALPS (1); STIM1 defect (1)]. Complete remission of AIHA was achieved with Corticosteroid alone (n=1, 6.2%); IVIg with corticosteroids (n=3, 18.7%); and MMF (n=2, 12.5%). All patients administered with Sirolimus had achieved either partial or complete remission without further blood product transfusions or additional immunosuppressants. Of the 4 patients with ALPS, the newly diagnosed patient was considered for Sirolimus with corticosteroids upfront as a first-line agent due to the published evidence for Sirolimus. AIHA in patients with WAS and SCID were corticosteroid responsive and did not require further immunosuppressive therapy for AIHA.

Conclusion: Experience gained from our cohort revealed variable severity of AIHA in various PIDs with variable treatment responsiveness. This study also shows clinical improvement with targeted therapy which implies the need to elucidate the underlying genetic cause in patients with secondary AIHA.

THURSDAY, APRIL 28, 2022

GUIDED POSTER WALK 1B - GENETIC DIAGNOSIS A

MODERATOR: Prof Stuart Tangye

POSTER 21 - MONOGENIC SUSCEPTIBILITY TO MYCOBACTERIAL DISEASES IN MOROCCAN PEDIATRIC PATIENTS

AUTHORS

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Objective: The most pathogenic of *Mycobacterium* species are *M. tuberculosis*, *M. leprae* and *M. ulcers*. However, environmental and individual factors, including the host genetic, play a crucial role in the outcome of exposure to mycobacteria. The first molecular evidence of a monogenic predisposition to mycobacteria came from the study of mendelian susceptibility to mycobacterial disease (MSMD), a rare group of inborn errors of interferon gamma (IFN γ) immunity, with 33 different genetic disorders of 18 genes, predisposing to weakly virulent mycobacteria and recurrent salmonellosis. We studied the immunological and genetic features of clinically diagnosed MSMD patients.

Design and method: Patients presented with clinical features of MSMD, including complicated local or systemic reactions to BCG vaccination, unusual severe, persistent and/or recurrent infections with mycobacteria and/or salmonella, were recruited into this study. Immunological examinations, functional exploration of the IL-12/IFN- γ axis and genetic analyses were performed for all patients and their family members where available. HIV-positive patients were excluded from the study.

Results: Our study involved 14 children from 12 unrelated families. Their mean age at diagnosis was 4 years (1-17 years) and the median age at onset is 6 months. Nine patients (64%) were born to consanguineous parents. Ten patients had BCG infections, three had severe fatal tuberculosis and one patient had recurrent salmonellosis. Immunological results were within the reference ranges, but all patients had impaired or abolished IFN- γ production in response to IL-12, except one patient who had increased IFN- γ level. Nine different mutations were found in 5 genes, including IL12RB1 in 7 patients, STAT1 in 3 patients, SPPL2A in two patients, IFNGR1 and TYK2 in one patient each. The identified variants abolish or impair the production of IFN- γ or the cellular response to this cytokine, resulting in a monogenic predisposition mainly to mycobacteria and to other pathogen in particular genetic etiologies.

Conclusion: Our study confirm that the integrity of IFN γ -mediated immunity is required for host defense against mycobacterial infection. In response to activation signals induced by mycobacterial antigens, IL-12, IL-23 and ISG15 are secreted by dendritic cells, macrophages and neutrophils. These cytokines bind to their receptors on T-helper and NK cells, inducing the production of IFN- γ , IL-17, and TNF α . As well, secreted IFN- γ binds to its receptor (IFN γ R) on the surface of macrophages and dendritic cells enhancing the production of IL-12 and their ability to eliminate intracellular microorganisms, such as *Mycobacteria* and *Salmonella* sp.

POSTER 22 - 10 YEARS OF MOROCCAN EXPERIENCE IN THE GENETIC DIAGNOSIS OF PRIMARY IMMUNODEFICIENCIES

AUTHORS

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Objective: to assess the Moroccan experience in molecular diagnosis in patients with primary immunodeficiencies (PIDs).

Design and method: In this retrospective study, we present the Moroccan experience in molecular diagnosis of PIDs patients over the last decade. 630 cases of PIDs from the 5 university hospitals of Morocco were included in the study. Their molecular test results were classified according to the 2019 classification presented by the International Union of Immunological Societies (IUIS).

Results and conclusions: 119 (19%) patients had a molecular diagnosis. 70 pathogenic mutations were identified, including 38 new ones. The most used detection technique is Sanger sequencing followed by whole-exome sequencing (WES). The most molecularly detected categories of PIDs are combined immune deficiencies with syndromic features (30%) and combined immune deficiencies (21%), followed by congenital phagocyte defects (19%) and antibody predominant deficiencies (16%). Defects in intrinsic and innate immunity (9%) and immune dysregulation diseases (4%) are less common in our department. Promoting the use of WES may facilitate molecular detection of PIDs and increase the number of newly identified genes and mutations. WES has the potential to provide rapid and accurate molecular diagnosis, which would reduce diagnostic delays and improve therapeutic intervention.

Keywords: Genetic diagnosis - primary immunodeficiencies - whole-exome sequencing - Sanger sequencing

POSTER 23 - UTILITY OF MULTIPLEX LIGATION DEPENDENT PROBE AMPLIFICATION FOR DETECTING COPY NUMBER VARIATIONS IN PRIMARY IMMUNODEFICIENCY DISEASE

AUTHORS

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Background: Primary immunodeficiencies also referred as inborn errors of immunity manifest as an increased susceptibility to infectious diseases, autoimmunity, auto inflammatory diseases, allergy, and/or malignancy. These conditions are caused by monogenic, germline gene variants that result in loss of expression, loss-of-function or gain-of-function of the encoded protein. Multiplex Ligation Dependent Probe Amplification (MLPA) is a molecular technique based on semi-quantitative PCR for detection of copy number variants like duplications and deletions in the genome.

Methods: MLPA probe sets for determining the copy number variations in different Primary immunodeficiency's diseases were used in study. This Included SALSA MLPA Probemix P250 for DiGeorge syndrome (DGS); SALSA MLPA Probemix P368 for DCLRE1C for Severe combined immunodeficiency disease (SCID); SALSA MLPA Probemix P243-B1 SERPING1-F12 for Hereditary Angioedema, SALSA MLPA Probemix P454 for Chronic Granulomatous Disease (CGD); SALSA MLPA Probemixes P385 DOCK8 and P386 DOCK8-STAT3 Autosomal Recessive hyper IgE syndrome (AR-HIES). MLPA was performed according to the manufacturer's instruction and ABI 3100 Genetic Analyzer was used for fragment separation. Coffalyser software (MRC Holland) was used for data analysis.

Results: We report our 3-year experience in setting up facilities for MLPA for diagnosis of PIDs in Chandigarh, North India. Out of 53 patients who were suspected to affect with Primary Immunodeficiency diseases were checked with MLPA, we observed a copy number variations in 24 of these 53 patients. 11 patients affected with T-B-NK+ SCID had a homozygous deletion in 1-4 of DCLRE1C gene and parents were heterozygous carriers for this deletion. 2 patients with Hereditary Angioedema have a heterozygous deletion in Exon 8 of SERPING1 gene and 1 with a heterozygous deletion in Exon 6 of F12 gene. 5 patients were observed affected with DiGeorge syndrome sharing a common hotspot heterozygous deletion in TBX gene (Exon 2, 7). One female patient with CGD was found to be a carrier for CYBB gene (Exon 7-8 deletion). Her mother and sister were also found to have a similar heterozygous deletion in the CYBB gene; one patient was affected with Autosomal Recessive hyper IgE syndrome found to have homozygous deletion in DOCK8 gene (Exon 12-48).

Conclusion: MLPA is a rapid, economical, and reliable method to detect deletions, carrier screening and prenatal diagnosis in the patients affected with Primary immunodeficiency diseases.

POSTER 24 - PITFALLS OF TARGETED NEXT GENERATION SEQUENCING FOR DIAGNOSIS OF INBORN ERRORS OF IMMUNITY: PRELIMINARY EXPERIENCE FROM A TERTIARY CARE CENTRE AT CHANDIGARH, NORTH INDIA

AUTHORS

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Purpose: Inborn errors of immunity (IEI) are a heterogeneous group of genetic diseases that include primary immunodeficiencies (PID) and other disorders affecting different aspects of the immune system. Next-Generation Sequencing (NGS) is an essential tool to diagnose IEI.

Methods: We report our 3 year experience with NGS for diagnosis of IEI in Chandigarh, North India. We used a targeted, customized gene panel of 44 genes known to result in IEI on Ion S5 NGS system from Thermo Fisher Scientific, USA. Variant analysis was done using Ion Reporter software. The in-house NGS has enabled us to offer genetic diagnoses to patients with IEI at affordable costs.

Results: Of 122 patients who were included, pathogenic variants were identified in 77 patients. These included patients with Chronic Granulomatous Disease (CGD), Severe Combined Immune Deficiency, leukocyte adhesion defect, X-linked agammaglobulinemia, Ataxia Telangiectasia (AT), Hyper-IgE syndrome, Wiskott Aldrich syndrome, Mendelian susceptibility to mycobacterial diseases, Hyper-IgM syndrome, autoimmune lymphoproliferative syndrome, and GATA-2 deficiency. Major pitfalls in the diagnosis were failure of detection of copy number variations such as large deletions which were later found on visualisation of the BAM files on Integrated Genomics Viewer. Genes with pseudogenes such as the NCF1 gene also posed a significant challenge. There were no reads from Exon 2 of the NCF1 gene in all patients with common NCF1 Exon 2 GT deletion, later confirmed by Gene Scan. In one instance an insertion deletion of IL2RG gene was misinterpreted as two variants in close proximity. In a young girl with CGD a heterozygous deletion in CYBB gene was suspected based on reduced number of reads from Exon 7 and 8 of the gene when compared to other samples from the same run. This was later confirmed by Multiplex Ligase Dependent Probe Amplification (MLPA). Variants of undetermined significance were also found in some of the undiagnosed cases. In one patient with suspected autosomal dominant Hyper IgE syndrome a variant of undetermined significance was detected in the CYBB gene. However, upon functional validation with dihydrorhodamine (DHR) assay it was inferred as benign since the DHR was normal. Unexpected results were also found, a ATM gene variant was detected in a case of autosomal recessive Hyper IgM syndrome.

Conclusion: NGS is a powerful and useful tool for genetic diagnosis of inborn error of immunity. However, it is also important to appreciate its limitations for its optimal and effective use for diagnosis of IEI.

POSTER 25 - NOVEL IRF7 MUTATION IN A CHILD WITH RECURRENT PNEUMONIA

AUTHORS

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Objective: Defects in the type I interferon (IFN) response cause selective susceptibility to severe viral infections, including influenza, herpesviruses, SARS-CoV-2 and live attenuated vaccines. We investigate a 5-year-old child with recurrent severe viral infections for underlying inborn errors of immunity.

Design and method: We performed a trio exome sequencing-based primary immunodeficiency panel.

Results: The patient is a girl of Belgian descent, without relevant family history. She received her routine vaccinations without adverse reactions. Since the age of 6 months, she suffered recurrent episodes of radiologically confirmed pneumonia with elevated serum inflammatory markers, requiring admission to hospital for intravenous therapy. In 4 of the 6 episodes, a viral cause was identified (respiratory syncytial virus n=1, influenza A n=2, adenovirus n=1). Additionally, she was admitted once for bacterial parotitis, otitis media and periorbital cellulitis, and once for fever without focus and high serum inflammation parameters. On this occasion, her serology showed a recent seroconversion for Epstein-Barr virus. Genetic analysis revealed a novel mutation in IRF7 (c.312G>A, p.Trp104*) in the child. Family segregation is ongoing. This is a stopgain mutation, probably pathogenic, with an allele frequency of 10⁻⁵ and a CADD score of 37 (MSC 3.313). Further functional validation of the mutation is ongoing.

The child is now doing well and has not suffered from additional severe infections during the pandemic. She receives yearly the influenza vaccination, and she has been recently vaccinated against SARS-CoV-2.

Conclusions: We here present a novel pathogenic mutation in IRF7, underlying severe recurrent viral pneumonia, including with influenza A, in a young child.

POSTER 26 - IL12RB1 MUTATION PRESENTING WITH THE HYPER Ig E SYNDROME PHENOTYPE

AUTHORS

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Introduction: Primary immunodeficiencies such as DOCK8 deficiency, STAT3 deficiency, IPEX syndrome usually present or complicate with atopic dermatitis-like eczematous lesions.

Case Report: Three-year-old boy was admitted to our hospital with complaints of disseminated eczematous lesions since newborn period and recurrent bronchiolitis. Developmental milestones were normal for age. The parents were from the same village. Two siblings (1 boy, 1 girl) were healthy.

Physical examination findings were as follows; weight 14.5 kg (50%), height 36,3 cm (25%), vital signs were normal. There were eczematous lesions all over the body including the scalp and papillary lesions resembling warts on the neck. Laboratory examinations showed eosinophilia with elevated IgE levels (WBC 14200/mm³ (PNL 52%, lymphocyte 24%, eosinophils 24%), Hb 12.5 g/dl, PLT 437 000/mm³, IgG 1190 mg/dl, IgM 46 mg/dl, IgA 93 mg/dl, IgE 7598 ku/l, fx5 (-), dermatophagoides (+++)). Lymphocyte subsets were normal except inverted CD4/CD8 ratio (CD3 T lymphocyte 69%, C19 B lymphocyte 22%, CD3+CD4+ T Helper 34%, CD3+CD8+ T Cytotoxic 30%, NK 5%).

Regular IVIG and prophylaxis with trimethoprim-sulfamethoxazole and fluconazole therapy were started with the preliminary diagnosis of DOCK8 deficiency. Eczematous lesions regressed and IgE level showed a slight decrease under regular therapy. During the 6-year follow-up period, the patient had rare upper respiratory tract infections. The last laboratory analysis showed high IgE and low IgM levels for age (IgG: 1380 mg/dl, IgM: 27 mg/dl, IgA: 264 mg/dl, IgE: 4470 mg/dl). Next-generation sequencing revealed a homozygous mutation in the IL12RB1 gene (c.684_685insT amino acid change: p.Val229fs (Frameshift Insertion) of 662 a.a).

Conclusion: Interleukin-12 receptor b1 (IL12RB1) deficiency, is the most common genetic etiology of mendelian susceptibility to mycobacterial disease, which is characterized by the selective predisposition to clinical disease caused by weakly-virulent mycobacteria, such as Bacillus Calmette-Guérin (BCG) vaccines, and environmental non-tuberculous mycobacteria (NTM). The patient did not have any mycobacterial disease up to now. Regular screening tests for mycobacteria such as ppd and Quantiferon TB tests were all negative. The case is presented to emphasize the importance of genetic tests in the exact diagnosis of patients with inborn errors of immunity.

POSTER 27 - A 14-YEAR-OLD BOY WITH SEVERE COMBINED IMMUNODEFICIENCY

AUTHORS

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Objective: Atypical presentations should not be overlooked.

Design & methods: A 14 year old boy from a consanguineous family, presented with a history of recurrent draining ears since the age of 3 years. Repeated hospital admissions at the age of 6 years with pneumonia complicated with lung abscess, and at the age of 8 years, bilateral pneumonia with pleural effusion. The patient suffered from occasional anemia and thrombocytopenia which was diagnosed at that time as immune thrombocytopenic purpura. At the age of 12, the patient started to suffer from persistent cytopenias; BMA and BMB revealed markedly hypocellular bone marrow, chromosomal breakage studies was normal. By examination the boy was microcephalic and was below percentiles for age for weight and height. Immunological work up done revealed low IgG and IgA levels, markedly low CD19 0.2%, CD3 76%, CD4 45%, CD8 28.5% CD56 5.4%. Hematopoietic stem cell transplant was considered in this patient from a related donor, the only fully matched sibling was a 4 year old girl whom by chance was discovered to be suffering from repeated chest infections and draining ears, by examination she had similar phenotypic appearance, microcephaly and stunted growth.

Results & conclusion: NGS panel sequencing revealed homozygous pathogenic variant identified in NHEJ1 gene, diagnosing an autosomal recessive form of SCID; Cernunnos/XLF deficiency.

POSTER 28 - THREE PATIENTS WITH SEVERE DEFECTS IN INTERFERON GAMMA RECEPTOR SIGNALING: A CHALLENGING DIAGNOSIS

AUTHORS

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Objective: Defects in IFN- γ receptor (IFN- γ R) signaling via STAT1 leads to susceptibility to infection by otherwise weak pathogenic mycobacteria, resulting in mendelian susceptibility to mycobacterial disease. We identified three patients presented with disseminated mycobacterial infections caused by *M. avium*, *M. persicum* or *M. bovis* BCG respectively. Whole-exome sequencing (WES) was used as the first line diagnostic approach, however in all patients additional analysis was crucial to make the definite diagnosis.

Design and Method: WES, SNP array and long range PCR were performed to identify the genetic defects. Expression of IFNGR1, STAT1, CD64, SOCS1 and phosphorylation of STAT1 were determined after stimulation with IFN- α or IFN- γ .

Results: In Patient 1, only one heterozygous variant p.(Val63Gly) in the IFNGR1 gene was identified by WES. Additional genetic analysis identified a second complex Alu-insertion in IFNGR1. Patient 2 was compound heterozygous for the null p.(Val68Lysfs*6) variant and the hypomorphic p.(Ile37Thr) variant in IFNGR1. In Patient 3 a novel variant in the STAT1 gene p.(Asn460Ile) was identified. Patients 1 and 2 had reduced expression of IFN- γ R1. All patients had reduced phosphorylation of STAT1 and absent induction of SOCS1 after IFN- γ stimulation. While STAT1 phosphorylation was normal after IFN- α stimulation in Patient 1 and 2, and mildly reduced in Patient 3.

Conclusion: We conclude that functional assays are crucial to assess the extent of IFN- γ R signaling defects when new combinations of bi-allelic or non-conclusive genetic variants are found, which is important in the determination of clinical treatment.

POSTER 29 - CASE REPORT OF A POLYMORPHISM IN HOMOCYGOSIS IN THE MEFV GENE IN THE CONTEXT OF AN AUTOINFLAMMATORY SYNDROME.

AUTHORS

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Objective: Describe a case report of a patient with a suspected autoinflammatory disease in association to recurrent outbreaks of fever, generalized erythroderma, and myalgia.

Method: Data collection of the electronic medical record.

Results: We present a 49-year-old man who presented 4 episodes per year of generalized erythroderma and skin peeling, associated with fever spikes and generalized myalgia of 5 days of duration, starting at the age of 34. As initial treatment, antihistamines were used, with a partial clinical response.

During the outbreaks, there was evidence of increased acute phase reactants with leukocytosis with neutrophilia and increased C-reactive protein, absence of concomitant infectious symptoms (multiple serologies negative), negative results for autoimmunity tests and mild C3 hypocomplementemia.

As relevant studies, a skin biopsy was performed where both acute and chronic superficial perivascular dermatitis were observed, which was compatible with the clinical diagnosis of an autoinflammatory disease. Moreover, we carried out a mutational test by Sanger of the coding sequences of exons 3-10 of the MEFV gene, as well as the coding sequences of exons 1-7 of the TNFRS1A gene, exons 2-9 of the CIAS1 gene and the complete coding sequence of MVK gene without detecting any pathogenic mutation.

Due to the continuity of the outbreaks, treatment with corticosteroids was indicated in case of an outbreak (at a dose of 1mg/Kg/day) for 2 days, as well as daily colchicine with good clinical response, reducing the number and severity of annual outbreaks.

Given that the mentioned clinical features and the good response to the indicated treatment seemed compatible with an autoinflammatory disease, we decided to characterize it by performing massive sequencing, where we detected a missense polymorphism in the homozygous MEFV gene that replaces the arginine located at position 202 of the pyrin protein with a glutamine (p.Arg202Gln). This change is associated with the Familial Mediterranean Fever syndrome characterized by recurrent fevers, abdominal pain, arthritis / arthralgia, erythema and, less frequently, severe myalgias.

Conclusions: We consider the presentation of this case report relevant because it shows the importance of the use of massive sequencing techniques in the molecular diagnosis of autoinflammatory syndromes, among others, as they allow us to make a complete reading of the genes associated with these kinds of syndromes. Otherwise, with the use of the Sanger technique, many of these genetic variations would remain undiagnosed because they are infrequently associated with pathogenic mutations. Family segregation of the patient is pending.

POSTER 30 - IDENTIFICATION OF A NOVEL NLRP12 VARIANT IN ASSOCIATION WITH A CASE OF SEVERE SARS-COV2 INFECTION

AUTHORS

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Background: NLRP12 is a protein that plays an essential role as a potent mitigator and also inductor of inflammation. Mutations in NLRP12 have been previously described in patients with familial cold autoinflammatory syndrome 2. Here we report a case of a paediatric patient who debuted with a severe case of SARS-COV2 infection.

Case Presentation: An 11 years old girl, without family history, was admitted to the Intensive Care Unit after a Multi-system inflammatory syndrome associated with COVID-19 infection. The patient had a clinical history of urticarial flares in relation with cold exposure; however, after the acute episode, the patient also developed generalized arthromyalgias.

Methods: Genomic DNA from peripheral blood of the patient was isolated and Next Generation Sequencing (Gene System) was performed using a screening panel of 200 genes associated with immune dysregulation.

Results: There were not any abnormal immunological results except an increase of proinflammatory cytokines (IL1B, TNF, IL8) and acute phase reactants.

After the genetic analysis, it was identified a heterozygous mutation in NLRP12, p. Ser659Arg. This variant has not enough evidence to establish a definitively molecular diagnosed, but the patient's symptoms are suggestive of a cryopyrinopathy: early debut of her clinical manifestations, arthromyalgias and abnormal skin reaction to cold.

Conclusion: Although no direct association has been described between SARS-COV2 infection and the allelic variant detected in our patient, recent studies show that the SARS-CoV2 protease NSP5 cleaves NLRP12, a critical modulator of the inflammatory pathway.

POSTER 31 - NOVEL STIM1 MUTATION

AUTHORS

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Primary immunodeficiencies associated with genetic channelopathies are uncommon, however, several types have been described, such as mutations associated with calcium channels STIM1 and ORAI1.

We present the case of a 55-year-old male patient recently diagnosed with a previously undescribed mutation in STIM1. The patient began in adulthood with a myopathy characterized by an increase in creatine kinase (around 700), pseudomyotonia in the electromyography and abnormalities in the muscle biopsy. The genetic test showed a missense heterozygous mutation at position L303 of the STIM1 gene. The mutations described in this protein can be due to gain or loss of function. While both present platelet and muscle malfunction, only the latter have been associated with immunodeficiency to date.

Previously, the patient had 3 episodes of lower respiratory infections per year, and is referred to us due to suspicion of primary immunodeficiency. The basic study including immunoglobulins, complement, lymphocyte subpopulations, antibody production test, NK cell activity and mitogen lymphoproliferation test did not show alterations, however, a maintenance deficit of polysaccharide antibodies was detected.

In turn, a functional study of the STIM1 protein was carried out. The levels of this protein in PMBCs were within normal limits compared to healthy patients, however, an alteration in calcium homeostasis was found, with the channel presenting a gain of function.

This case-report on a previously undescribed mutation contributes to a better understanding of STIM1 mutations, their pathophysiology and possible therapeutic implications.

POSTER 32 - GENETIC PROFILE OF HEREDITARY ANGIOEDEMA IN A SINGLE CENTRE COHORT FROM NORTH INDIA

AUTHORS

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Objective: To report the genetic profile of patients with hereditary angioedema from a single centre cohort from North India.

Patients and Methods: Diagnosis of HAE was based on presence of suggestive clinical manifestations, low C1-inhibitor and/or low C4. Sanger sequencing for all 8 exons of SERPING1 gene was carried out in the Allergy Immunology Laboratory, Department of Pediatrics, Postgraduate Institute of Medical Education and Research, Chandigarh, India. Multiplex Ligation Dependent Probe Amplification (MLPA) and whole exome sequencing (WES) was carried out in patients in whom no pathogenic variants were detected on Sanger sequencing.

Results: A cohort of 91 individuals with symptoms of recurrent familial angioedema from 35 non-related families was studied. The study identified 28 different mutations (15 missense, 3 frameshift deletion, 7 splicing defects and 2 large indels) responsible for the disease in 28 HAE families. 6 of the mutations in this cohort are novel and 3 are confirmed de novo cases. In the remaining 9 families no molecular alteration could be detected and subjected for whole exome sequencing and MLPA, SALSA MLPA Probemix P243-B1 SERPING1-F12 were used for MLPA. 2 patients with Hereditary Angioedema have a heterozygous deletion in Exon 8 of SERPING1 gene and 1 with a heterozygous deletion in Exon 6 of F12 gene.

Conclusion: Recurrent episodes of acute non-itchy soft tissue swellings, a positive family history and low serum C4 levels are important clues for the diagnosis. In a suggestive clinical setting, a low C1-INH level confirms the diagnosis of hereditary angioedema (HAE). These results highlight the heterogeneity of mutations in the C1NH gene causing C1INH deficiency and HAE. With the advent of available genetics method it is possible to provide a genetic diagnosis to the patient with HAE and helps to provide a carrier screening and prenatal diagnosis.

POSTER 33 - NOVEL FERMT-3 GENE VARIANT IN A CHILD WITH LEUCOCYTE ADHESION DEFICIENCY TYPE-III.

AUTHORS

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Objective: Leukocyte adhesion deficiency (LAD) syndrome is a rare inborn error of immunity characterized by dysfunction in activation and adhesion of leucocytes affecting their subsequent migration to the site of injury. Till date, four classes of LAD have been discovered with LAD type-III being caused by variants in FERMT-3 gene resulting in platelet dysfunction along with immunodeficiency. We report clinical and genetic profile of a child with LAD Type-III.

Design and Method: Index case was being followed up at the Pediatrics Immunodeficiency Clinic, Advanced Pediatrics Centre, Post Graduate Institute of Medical Education and Research, Chandigarh, India. Clinical manifestations, investigations, treatment, and outcomes were analyzed.

Case summary and results: A 3 and half year-old girl presented with history of skin bleeds since early infancy and recurrent epistaxis from 18 months of age. She had history of one episode of ear infection with discharge at 2 years of age. There was no history suggestive of umbilical sepsis or delayed cord fall. Laboratory investigations showed neutrophilia (TLC count: 29×10^9 /L), normal platelet count (249×10^9 /L) and increased prothrombin time (12.3s). Activated Partial Thromboplastin Time (28.9s), Fibrinogen assay (438 mg/dl), FXIIIa antigen assay (68.1%), VWF antigen assay (127%) and VWF Ristocetin cofactor assay (102.5%) were within normal range. Platelet aggregation studies performed twice were consistent with Glanzmann's thrombasthenia with low levels of aggregation with Arachidonic acid (5%), ADP (0%), Collagen (1 %), and Epinephrine (1%). Aggregation with Ristocetin (1.25mg/ml) - 85% was normal. (Normal >60%). Flow cytometric analysis of platelets showed increased CD42b positive expression (98.8% platelets), CD41a positive (99.9% platelets) and CD61 positive (99.8% platelets) as compared to Control > 90%. Molecular analysis by next-generation sequencing revealed the novel homozygous splice variant in FERMT3 (c.895-3T>G) which was confirmed by Automated Sanger sequencing.

Conclusion: Leukocyte adhesion deficiency type-III should be suspected in children who present with bleeding diathesis and recurrent infections. Platelet aggregation studies can confirm the platelet dysfunction. However, molecular analysis by NGS or Sanger sequencing is required for genetic confirmation.

POSTER 34 - BILATERAL CORNEAL ULCER IN PROLIDASE DEFICIENCY – A NOVEL ASSOCIATION

AUTHORS

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Introduction: Prolidase deficiency (PD) is a rare autosomal recessive disorder that has symptoms such as chronic skin ulcers, dysmorphic facies, cognitive retardation, hematological anomalies, splenomegaly, and chronic infection. Bilateral corneal opacity in prolidase deficiency is not reported in literature.

Case summary: Our patient is the third born child of a third degree consanguineous marriage with one male sibling death in infancy. This boy is symptomatic since infancy when he developed generalized severe eczema and pustular lesions over the face trunk and extremities along with bilateral ear discharge. The skin lesions will improve with topical steroids and again reappear with increased intensity. Since 5 years of age, the child developed recalcitrant ulcers over both foot which was gradually progressive and non-healing with pus discharge. He also has delay in cognitive milestones. On examination he has abnormal facies with deformed pinna. In the eye he has developed bilateral corneal opacity with muddy sclera and loss of eye lashes. There is moderate pallor with hepato-splenomegaly in the child. Immunological investigations revealed a very high IgE level in serum with hyper-gammaglobulinemia and normal lymphocyte subsets. Phosphatase 3 was normal but Th17 cells were reduced. Genetic analysis showed homozygous mutation in PEPD c825del(p.Phe275Leufs*46), which is reported to be pathogenic.

Discussion: The incidence of PD is of 1–2 per 1 million births, but is more frequent in some populations, as the Druze and Arab Muslim minority in Israel. Prolidase plays a pivotal role in collagen metabolism, mainly in recycling collagen via its degradation and resynthesis. Corneal opacity may be due to defect in collagen metabolism in prolidase deficiency. There is neither definitive cure for PD nor consensus for treatment. As described below, different approaches were thought to slightly improve the dermatological symptoms in PD: enhancing collagen metabolism with oral supplementation of ascorbic acid or glycine/proline, improving prolidase activity and stability with manganese chlorite and diminishing the immunological reaction by antihistaminic and corticosteroids

POSTER 35 - GENETIC BASIS OF COMMON VARIABLE IMMUNODEFICIENCY (CVID): A MULTICENTRE EXPERIENCE FROM INDIA

AUTHORS

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Objective: To elucidate the genetic basis of CVID in the multicentre cohort from India.

Design and methods: A predesigned Microsoft Excel sheet was circulated via email to all centres across the countries who are involved in the care of patients with PIDs. Data were collected from centres who agreed to take part in this multicentre study. Diagnosis of CVID was based on the European Society for Immunodeficiency (ESID) 2014 classification criteria.

Results: In this multicentre study, we included 126 patients diagnosed to have CVID. Genetic testing (whole-exome sequencing or targeted next-generation sequencing) could be performed in 34 patients. In 20/34 patients, no pathogenic variant was observed. Of these 20 patients, 6 (30%) had autoimmune manifestations and 3 (15%) had bronchiectasis while IgG, IgM, and IgA levels were found to be reduced in 100%, 85%, and 100 % respectively. A pathogenic variant was observed in 14/34 patients (41%). These included pathogenic variants in following genes: LRBA (n=3), IRF2BP2 (n=2), XIAP (n=2), DCLRE1C (n=1), WAS (n=1), SH2D1A (n=1), STXBP2 (n=1), DOCK2 (n=1), AICDA (n=1) and PI3KCD (n=1). In the monogenic cohort 6/14 cases (42.85%) had autoimmune manifestations and 5/14 (36%) had bronchiectasis. IgG, IgM, and IgA levels were reduced in 100%, 86%, and 86%, respectively in the monogenic cohort. Infections were observed in all cases. In the monogenic group, B-cells were reduced in 6/14 (43%), and switched memory B cells were reduced in 7/8 (87.5%) cases. T cells were normal in all; however, reduced levels of natural killer cells were observed in 6/14 (42.85%). Intravenous immunoglobulin (IVIg) was given to all patients with CVID who had monogenic causes.

Conclusions: This is the first study to evaluate the genetic basis of CVID in India and first attempt to collect nationwide data on CVID. Pathogenic variants were reported in 41% of patients with CVID. LRBA gene variants were the most common pathogenic variant followed by XIAP gene defects. Epigenetic alterations may contribute to the disease pathogenesis in 60% of patients in whom no pathogenic variants were identified. However, this aspect needs to be explored in our cohort.



THURSDAY, APRIL 28, 2022

**GUIDED POSTER WALK 2 - MANAGEMENT OF INFECTIOUS
AND NON-INFECTIOUS COMPLICATIONS**

MODERATOR: Prof Steven Holland

**POSTER 36 - CLINICAL PROFILE OF A LARGE SINGLE CENTER COHORT OF HEREDITARY ANGIOEDEMA
FROM NORTH INDIA**

AUTHORS

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Objective: To report the clinical and laboratory data on a single center cohort of patients with HAE.

Design and methods: Medical records of patients diagnosed to have HAE and being followed up in the Pediatric Immunodeficiency Clinic, Department of Pediatrics, Postgraduate Institute of Medical Education and Research, Chandigarh, India were analyzed in detail. Diagnosis of low C1-inhibitor (C1-INH) HAE was established based on clinical symptoms +/- a positive family history with low C1-inhibitor antigen levels +/- low C4 levels while patients with symptoms consistent with HAE but with normal C1-INH and normal C4 were classified as normal C1-INH HAE. SERPING1 gene sequencing was carried out in all patients with suspected HAE.

Results: We enrolled 110 patients from 39 families (37 females and 73 males) diagnosed to have HAE. The median age at onset of symptoms was 12 years and median age at diagnosis was 24.5 years. Of the 39 families, 35 had low C1-INH HAE while 4 had normal C1-INH HAE. Most common presenting manifestation (108 out of 110 patients, 98.1%) was found to be recurrent swelling of face and limbs. Only 2 (1.8%) patients were asymptomatic and were diagnosed by the laboratory parameters because of a positive family history. Laryngeal edema was seen in 30 patients (27.3%) and abdominal pain was observed in 33 (30%). Prodromal symptoms were seen only in 7 patients (6.3%) with heaviness of the extremity being the most common prodromal symptom. Erythema marginatum was seen 3 (2.7 %) patients only. Because of lack of first line treatment for HAE, all patients were managed using attenuated androgens, tranexamic acid (long-term prophylaxis) while fresh frozen plasma was used for acute management of laryngeal edema. One patient in our cohort died while 11 families reported death of at least one family member in the past because of laryngeal edema.

Conclusion: There is paucity of data on HAE from India. We previously reported our clinical experience on 32 patients with HAE. With increase in awareness and support from national and international societies, increasing number of patients with HAE are now being identified. There is an urgent need to provide first line treatment options for patients with HAE in India.

POSTER 37 - NOVEL MUTATIONS IN THE TET2 GENE IN TWO UNRELATED PATIENTS WITH AUTOIMMUNE LYMPHOPROLIFERATIVE SYNDROME-LIKE (ALPS-LIKE) PHENOTYPE AND SUSCEPTIBILITY TO HEMATOLOGIC MALIGNANCY

AUTHORS

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Objective: Somatic mutations in TET2, a regulator for DNA demethylation, have been associated with hematologic malignancies. Recently, biallelic germinal mutations have been described in 3 children with an ALPS-like phenotype (immune dysregulation, lymphoproliferation and autoimmunity) and lymphoma. We report two unrelated ALPS-like patients who presented with T-cell lymphoma associated to biallelic or monoallelic mutations in TET2.

Design and method: Molecular studies were performed through Next Generation Sequencing and comparative genomic hybridization array. Immunophenotype, western blot, gene expression and DNA methylation assays were also performed.

Results: P1, a 27 years-old woman, with history of B-cell lymphoma in remission for 10 years was diagnosed in October 2020 of anaplastic large-cell lymphoma, in addition of inflammatory analytical findings, hypergammaglobulinemia, lymphadenopathies and hepatosplenomegaly. Molecular studies revealed two heterozygous mutations in TET2 that led to a complete TET2 deficiency. Although maybe conditioned by the treatment received, the immunophenotype showed decreased dendritic and naïve T-cells, while TEMRA CD8+ and regulatory T-cells were elevated. Some ALPS-biomarkers (vitamin B12, double negative T-cells and IL-10) were elevated. Interestingly, the healthy carrier P1's brother also presented with an expansion of TEMRA CD8+ T-cells and elevated IL-10 in serum. P1 died in the context of highly aggressive refractory T-cell malignancy. P2, a 56 years-old woman, with chronic tonsillitis and adenoiditis progressively, developed cytopenia, lymphadenopathy, splenomegaly and T-cell lymphoma. She underwent a stem cell transplantation. Molecular studies revealed a large heterozygous germinal deletion affecting the TET2 gene. The immunophenotype study was performed in bone marrow at diagnosis showing a decreased naïve CD8+ T-cell compartment. Both P1 and P2 had somatic mutation restricted to the T-cell lymphoma in other genes previously associated with malignancies (STAT3 and KMT2D, TET2 and DNMT3A, respectively). Hypermethylation of DNA was observed in P1 but no alterations in P2.

Conclusions: mutations in TET2 have been associated with myeloid and lymphoid malignancies. We described two patients with biallelic or monoallelic mutations in TET2 that presented with ALPS-like phenotype and T-cell lymphoma. These findings highlight the role of TET2 in the homeostasis and function of the immune system and may imply dysregulation of cytotoxic lymphocyte maturation and function, according to the increase of the exhausted CD8+ T-cells phenotype observed in P1 and her healthy carrier brother. However, the study of a larger number of patients is necessary to elucidate the role of TET2 in the innate and adaptive immunity.

POSTER 38 - SERUM IMMUNOGLOBULINS AND PNEUMONIA RISK AND LUNG FUNCTION IN MIDDLE-AGED AND ELDERLY INDIVIDUALS: A POPULATION-BASED STUDY

AUTHORS

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Objective: Immunoglobulins (Igs) play an important role in host defense and prevention of infections, including respiratory tract infections. Higher age influences serum Ig levels, but the association between Igs and pulmonary outcomes in older individuals from the general population is unknown.

Design and Method: We aimed to evaluate the association of serum IgA, IgG, and IgM with pneumonia and lung function in community-dwelling middle-aged and elderly individuals from the Rotterdam Study. We performed Cox proportional hazards regression analyses for the association of Igs with risk of pneumonia and related mortality. We performed linear or binomial logistic regression analyses for the association between Igs and spirometry measurements. Associations were adjusted for multiple covariates including age, sex, smoking, comorbidities, and C-reactive protein.

Results: We included 8,766 participants (median age 62 years, 57% women) with baseline IgA, IgG, or IgM measurements. After six years of follow-up, an increased pneumonia risk was reported with higher IgA (hazard ratio [HR]: 1.15; 95% confidence interval [95% CI]: 1.00-1.32) and IgG (HR: 1.13; 95% CI: 1.06-1.19). Higher IgG was furthermore associated with an increased risk of pneumonia related mortality (HR: 1.08; 95% CI: 1.01-1.16) and recurrent pneumonia (incidence rate ratio [IRR]: 1.04; 95% CI: 1.00-1.09). Higher IgA and IgG were also associated with a lower forced expiratory volume in one second (FEV1), a lower forced vital capacity (FVC), and an increased odds of preserved ratio impaired spirometry (i.e. FEV1 <80% and FEV1/FVC ratio \geq 70%) (odds ratio [OR] for IgA: 1.14; 95% CI: 1.00-1.31 and OR for IgG: 1.11; 95% CI: 1.05-1.17).

Conclusions: Higher serum IgA or IgG levels were associated with an increased risk of pneumonia, recurrent pneumonia, pneumonia related mortality, and a restrictive spirometry pattern in our general population cohort of middle-aged and elderly individuals. We hypothesize that underlying chronic inflammation could play a role, although our findings need to be replicated and pathophysiological mechanisms need to be elucidated.

POSTER 39 - HUMORAL IMMUNE RESPONSE AFTER ONE AND TWO DOSES OF ADJUVANTED INFLUENZA VACCINE IN PATIENTS WITH COMMON VARIABLE IMMUNE DEFICIENCY

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Objective: The problem of vaccination of patients with primary immunodeficiency, and especially patients with humoral defects of immunity, who respond with a low level of specific antibodies or even a complete absence of antibody synthesis after vaccination, is especially urgent now, when vaccination is assigned the main role in preventing the spread of infectious diseases.

Design and methods: In the prospective, single-center study, formation of humoral response in patients with common variable immune deficiency (CVID) after adjuvant influenza vaccines administration in hemagglutinin inhibition test was studied. In 2018-2019 influenza season 6 patients with CVID received 1 dose of the adjuvant subunit quadrivalent influenza vaccine, and in 2019-2020, 9 patients with CVID received 2 doses of the adjuvant subunit trivalent influenza vaccine. Blood samples were taken before and 3 weeks after vaccination. Intravenous immunoglobulin therapy (IVIG) was suspended for 7 weeks - 4 weeks before and 3 weeks after vaccination. Geometric mean titer (GMT) and geometric mean ratio (GMR) were estimated.

Results: Statistically significant increase in GMT relative to baseline to A/H1N1 and A/H3N2 (25 [12; 54] to 34 [16; 75] ($p = 0.02$) and 11 [6; 19] to 17 [10; 29] ($p = 0.05$), respectively) and in GMR - 1.36 [1.03; 1.80] versus 0.79 [0.55; 1.16] ($p = 0.03$) and 1.59 [1.00; 2.52] versus 1.00 [0.63; 1.58] ($p = 0.07$), respectively was observed in the group of patients vaccinated with 2 doses. An increase in GMT to strain B/Colorado in the group of vaccinated with 2 doses was also statistically significant: from 7 [5; 10] to 11 [7; 18] ($p = 0.02$). Cochran-Mantel-Hensel criterion showed that the chance of an increase in antibodies as a result of vaccination with two doses is in 9.3 [1.6; 51.4] times higher (the Mantel-Hensel odds ratio) than after single dose vaccination ($p = 0.02$), regardless of the strain.

Conclusions: Immunogenicity of simultaneous administration of two doses of influenza vaccines is higher in patients with CVID than after single dose. But the search for new vaccination schemes is the subject of further investigations, as well as the effectiveness of boosterization with immunoadjuvant vaccines in patients with CVID.

POSTER 40 - COMMON VARIABLE IMMUNODEFICIENCY IN ADULTS PATIENTS AND LIVER DISORDERS

AUTHORS

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Introduction: Common variable immunodeficiency (CVID) encompasses a heterogeneous group of disorders with humoral defect, characterized by hypogammaglobulinemia.

As part of the complications in CVID, liver alterations have been reported, with presentation ranges between 10-33.8% of patients. Liver damage has been attributed to immune dysregulation.

Objective: To determine the frequency and type of liver abnormalities in adult patients with CVID.

Material and methods: a cross-sectional, descriptive study was carried out, including patients from the Primary Immunodeficiency Clinic, Hospital de Especialidades, with a definitive diagnosis of CVID, according to the ESID criteria. Liver function tests were performed: total proteins, albumin, globulins, AST, ALT, FA, GGT, DHL, uric acid. In addition to a liver ultrasound, performed and interpreted by an expert radiologist.

Results: 36 patients with a diagnosis of CVID were included, 27 women and 9 men. Median age of 30 years, range 20 to 79 years.

Of the 36 patients, 27.7% of the patients, with liver abnormalities, elevated liver enzymes one standard deviation above the normal value for age: AST, ALT and GGT; by ultrasound 3 with hepatic steatosis and 7 with hepatomegaly, and data in relation to nodular regenerative hyperplasia. 5 also with portal hypertension, the presence of collateral venous network and esophageal varices were documented.

100% with splenomegaly, immune thrombocytopenia, and 2 with a history of splenectomy.

80% corresponded to the Freiburg IA phenotype.

Conclusions: the presentation of liver damage in CVID does not have an established prevalence, it ranges from elevated alkaline phosphatase to nodular regenerative hyperplasia, liver cirrhosis and portal hypertension.

The most common form of presentation of liver damage in patients with CVID is nodular regenerative hyperplasia (NRH). It has been established that it is produced by immune dysregulation in these patients. Its detection is important due to the morbidity and mortality implications of these patients.

POSTER 41 - INTEGRATING CLINICS, LABORATORY, AND IMAGING FOR THE DIAGNOSIS OF COMMON VARIABLE IMMUNODEFICIENCY-RELATED GRANULOMATOUS-LYMPHOCYTIC INTERSTITIAL LUNG DISEASE

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Objective: Granulomatous lung interstitial disease (GLILD) is a non-infectious complication that develops in 9 to 30% of patients with common variable immunodeficiency (CVID). Often related to extrapulmonary dysimmune disorders, it is associated to long-term lung damage and poorer clinical outcomes. The aim of this study was to explore the potential use of the integration between clinical, laboratory, and developed CT scan scoring systems to improve the diagnostic accuracy of non-invasive tools.

Design and methods: A retrospective cross-sectional study of 50 CVID patients was conducted in a referral unit of primary immune deficiencies. Clinical, analytical, and functional parameters were collected. The Baumann's GLILD score system was externally validated by two observers in high-resolution CT (HRCT) scans. We developed an exploratory predictive model by elastic net and Bayesian regression, assessed its discriminative capacity, and internally validated it using bootstrap resampling.

Results and Conclusions: Lymphadenopathies (adjusted OR 9.42), splenomegaly (adjusted OR 6.25), Baumann's GLILD score (adjusted OR 1.56) and CD8+ cell count (adjusted OR 0.9) were included in the model. The larger range of values of the validated Baumann's GLILD HRCT scoring system gives it greater predictability. The Cohen's k statistic was 0.832 (95% CI 0.70-0.90), showing high concordance between both observers. The combined model showed a very good discrimination capacity with an internally validated AUC of 0.969.

Models integrating clinical, laboratory, and CT-scan scoring methods may improve the accuracy of non-invasive diagnosis of GLILD and might even preclude aggressive diagnostic tools such as lung biopsy in selected patients.

POSTER 42 - SKIN DISORDERS AND IMMUNOLOGICAL FEATURES IN AZERBAIJANI PATIENTS WITH HYPER IGE SYNDROME.

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Objective: HIES (Hyper-IgE Syndrome) is one of the rare primary immunodeficiency, characterized by recurrent eczema, pruritus and/or abscesses, respiratory infections, stable eosinophilia, and high serum IgE levels. The clinical course, depending on the variant different types of inheritance - autosomal dominant and autosomal recessive of the alleged disease, creates a serious problem for clinicians and delays the time of establishing the correct diagnosis.

Design and method: In 2010-2021 years 7 patients with HIES were examined at the Azerbaijan Medical University, of which there were 6 boys and one girl. 4 patients were born from a close relative marriage. No family history of PID was found in any of the patients. Clinical and instrumental examination, CBC, blood biochemistry, serological and immunological tests were performed. X-ray of the lungs and ultrasound examination of the lymph nodes and abdominal organs were used. Genetic analysis using Sanger sequencing was done.

Results: From the first years of life, patients complained of dry and itchy skin, multiple rashes. They had a peculiar facial structure (flat nose, wide forehead, wide-set eyes). Two patients were not vaccinated due to the signs of eczema observed from the first day of life. All patients had lymphadenopathy, 2 patients -hepatomegaly, 1 patient -splenomegaly. 2 patients had episodes of conjunctivitis, 1-'cold' skin abscess. Serologic tests were positive for CMV in 3 patients, for EBV in 2, for Herpes simplex in 2 patients. Streptococcus aureus was found in 2 patients and Streptococcus hominis in one patient. Immunological analysis: in two patients, there was a decrease in T-lymphocytes and their subpopulations (CD3+ and CD4+), also a number of B-lymphocytes (7-14%). In 5 patients the phagocytic activity of neutrophils was significantly reduced (40-49%). Although serum levels of IgA, IgM and IgG were within the normal range, IgE significantly exceeded the normal range (1101-8243 U/ml, while the norm was 20-60 U/ml). Severe eosinophilia (16-35%) was registered in 6 patients. Genetic analysis was performed in 1 patient and revealed a heterozygous mutation in the ADAR, BLOC1S6, IL7R, ITK, MAP3K14, ORAI1, PARN genes and a homozygous mutation in the DOCK8 gene. One of the patients died.

Conclusion: Most clinicians diagnose hyper-IgE syndrome based on key clinical signs, high IgE levels, eosinophilia and family history. In doubtful cases, it is necessary to look for the STAT3 and/or DOCK8 mutation. Patients with HIES require management with the different specialists to organize timely and success treatment and prevent life-threatening complications.

POSTER 43 - MENDELIAN SUSCEPTIBILITY TO MYCOBACTERIAL DISEASES IN A THIRTEEN YEAR OLD ETHIOPIAN GIRL WITH AUTOSOMAL DOMINANT INTERFERON GAMA RECEPTOR ONE DEFECT

AUTHORS

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Objective: The diagnosis of primary immune deficiency in resource limited setting

Design And Method: This is a case report on primary immune deficiency,autosomal dominant mendelian susceptibility to mycobacterial disease in a 12 year old female patient from Adama,Ethiopia.

Result And Conclusion: A 12 year old female patient has multiple hospital visits since the age of 6months. The most striking diagnosis was repeated mycobacterial infections: at 1year and 2months of age and at the age of 3years and 1 month she was treated for Tb lymphadenitis and pulmonary and lymph node tuberculosis respectively. At 4years and 9m she again was diagnosed to have a probable diagnosis of multidrug resistant tuberculosis, (MDR-TB) after she presented with lymph node, chest wall abscess and was treated with second line anti-TB drugs. Again at the age of 8years, she was treated for scalp and skin TB after biopsy confirmation with first line anti-TB drugs; despite the treatment, the scalp and skin lesion persisted heal. At 11year of age she was again diagnosed with sacro-iliac arthritis with adjacent epidural abscess and multiple deeply ulcerated deep scalp lesions with pus formation secondary to tuberculosis and now she still taking anti Tb for the fifth time. She has taken all childhood vaccines, including BCG.

Genetic sequencing: showed autosomal dominant (MedGen UID: 863300) Mendelian susceptibility to mycobacterial disease due to c.819_822del (p.Asn274Hisfs*2) IFNG-R1 defect. to the authors knowledge this is the first case report of Mendelian Susceptibility to Mycobacterial Diseases secondary to Interferon Gama receptor 1(IFNG-R1) defect from Ethiopia.

Key words: Primary Immune Deficiency, Mendelian Susceptibility to Mycobacterial Diseases, Interferon Gamma –receptor -1 defect, Bacillus Calmette-Guérin (BCG) vaccines

POSTER 44 - LATE DIAGNOSIS OF COMMON VARIABLE IMMUNODEFICIENCY (CVID): A PENDING PROBLEM.

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Objective: Describe the clinical and analytical alterations in a CVID patient diagnosed at the age of 43 years.

Method: Collection of data from the electronic personal health record including clinical data, blood analysis and imaging tests.

Results: 43-year-old female who was admitted in October 2021 to our hospital due to a parapneumonic pleural effusion. She presented a previous history of recurrent pneumonia (1 episode every 3-4 years since she was 20 years old), occasional episodes of otitis and conjunctivitis and continuous productive cough since she was 14 years old.

Upon the patient's arrival to the emergency department, she referred moderate exertion dyspnoea and severe chest pain. The physical examination was completely normal. We initially requested blood tests, a chest x-ray test and an electrocardiogram. In the x-ray we objectified a bilateral pleural effusion, in association to paratracheal adenopathies and a pulmonary nodule of uncertain aetiology.

In the initial blood tests, the patient presented leucocytosis with polymorphonuclear predominance and increased acute phase reactants.

Additional tests were done: an antigen test for SARS-CoV2, which was negative; the pleural fluid was cultivated, being positive for *S. pneumoniae*; and the blood culture was also positive for *S. pneumoniae*.

In addition to these tests, a chest computed tomography (CT) was done, showing a left hydropneumothorax chamber, with thickening and parietal enhancement of organized appearance, which presented a greater loculated fluid component in the most posterior region, in relation to evolving empyema. It also showed passive atelectasis of the LII and hypodense consolidated in lingula, in relation to probably necrotizing pneumonia.

In relation to her immunocompetence status, she presented an undetectable count of immunoglobulins (IgG: <33.3 mg/dL; IgM: <6.7 mg/dL; IgA: 6.8 mg/dL) and an altered immunological memory profile (B Naive cells: 96.1 %; B IgM memory cells: 3.0 %; B Switched memory cells: 0.7%), so we have also requested a gene panel testing.

Therefore, we decided to start replacement therapy with 20g of intravenous immunoglobulin during the admission, achieving post-infusion IgG levels of 491 mg/dL. She will receive this dose every 21 days.

Conclusions: We consider the presentation of this case report to be relevant because, unfortunately, late diagnosis of CVID still occur nowadays, implying the appearance of severe infections which can endanger the patients' health condition. Therefore, we should emphasize in the need of an early testing of immunoglobulin levels in patients with recurrent infectious processes.

POSTER 45 - DERMATOLOGICAL MANIFESTATIONS DURING PRIMARY IMMUNE DEFICIENCY IN DARK SKIN

AUTHORS

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Objective: to describe the dermatological manifestations during primary immune deficiency in dark skin.

Design and method: This is an open cohort study started in 2018 on children aged 0 to 18 years with dermatological manifestations suspected of primary immune deficiency at the Albert Royer Children's Hospital in Dakar. The diagnosis of primary immune deficiency was made according to the criteria of the phenotypic classification of the International Union of Immunological Societies (IUIS).

Results: 64 patients were followed up, including 35 girls. The average age was 6 years. The age of onset of symptoms was: in the neonatal period in 4.69%; less than 3 years in 67.19%; between 3 and 10 years and greater than 10 years in 14.06%. Dermatologic manifestations were: viruses (condyloma in 21.87%, kaposi's disease and disseminated warts in 3.12% ; malignant varicella and disseminated molluscum contagiosum in 1.56%); bacteria (pyodermitis in 21.87%, bacterial dermohypodermatitis in 3.12%; disseminated BCGitis and scrofuloderma tuberculosis in 1.56%); mycosis (Oral-esophageal candidiasis in 1.56%); inflammatory (atopic eczema in 21.87%, acute lupus in 12.5%, erythroderma in 9.37%, severe psoriasis in 4.69%, PAA or Pyoderma-Acne-Arthritis syndrome, diffuse lichen planus and diffuse fixed urticaria in 1.56%); acrodermatitis enteropathica in 4.69%. Extradematological manifestations were among others: Altered general condition in 40, 63%; pneumonia in 15,63% including 1 with covid 19; sepsis, arthritis and diarrhea in 14,06%; otitis in 6,25%; purulent conjunctivitis in 4,69%. 31 cases benefited from basic exploration for the immunological typing of the deficiency. This exploration revealed in 30 of them: hyperIgE syndrome in 46.67%; auto-inflammatory disease in 23.33%; congenital zinc deficiency in 10%; predisposition to mycobacterial infections and epidermodysplasia verruciformis in 6.67%; deficiency expression to CMHII class and primary deficiency of C2 complement. For some of this patients, a genetic investigation is in progress. After 3 years of regular follow-up of the cohort, we had 8 lost to follow-up, 4 deaths including 2 by sepsis, 1 by metastasis of neoplasia and 1 at home of unknown cause. 1 case of worsening of molluscum contagiosum tumor and 7 cases of recurrence and worsening of condyloma.

Conclusion: we noted the diversity of skin manifestation. All the cases except 1, having do a basic immunological assessment, could be classified according to the 10 tables of the IUIS phenotypic classification 2019. This result suggests a high sensitivity of dermatological manifestations for the diagnosis of primary immune deficiencies. This finding should be confirmed by further studies.

POSTER 46 - LONG-TERM SURVIVAL IN A PATIENT WITH COMMON VARIABLE IMMUNODEFICIENCY AFTER LUNG TRANSPLANTATION: POSSIBLE ROLE OF A HIGH-DOSE INTRAVENOUS IMMUNOGLOBULIN PROTOCOL

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Objective: Describe the case of a CVID patient who had a lung transplantation (LT) in 2004, since when he has been treated with a high-dose IVIG protocol, maintaining a good life style basis in the present day.

Method: Collection of clinical data from the electronic personal health record.

Results: We present a 56-year-old male who was diagnosed in 1988 with CVID. Our patient presented a history of recurrent upper and lower respiratory tract infections, toxoplasmosis and possible tuberculosis. He also presented bilateral basal bronchiectasis with destruction of the lung parenchyma and severe respiratory failure. In addition, he had chronic leukopenia and thrombopenia, chronic liver CVID-associated disease, portal hypertension, immunoglobulin hypercatabolism, psoriasis, CVID-associated lymphoid hyperplasia (with splenomegaly > 20 cm), retractile capsulitis of the shoulder. No systemic autoimmune processes.

Despite replacement therapy with IVIG and a constant protocol of rotating treatment with antibiotics, he evolved into terminal pulmonary disease with 24-hour oxygen requirement and prognosis of 6 months of life. He was rejected for LT in several occasions. Finally, he had a double lung transplant on December 18, 2004 in the Puerta de Hierro University Hospital in Madrid.

He received the following high-dose IVIG protocol:

- Reconditioning phase before the LT: 1.2g/kg/month.
- Immediate post-LT phase (first month): 2.3g/kg/month.
- Maintenance period after LT (from the first month after LT until December 2009): 1.1g / kg / month.
- Long-term maintenance period after 5 years of LT until now: 650mg - 1g / kg / month.

The doses were calculated assuming the patient's high IgG catabolism, expecting to have IgG levels over 1000mg/dl all the time.

17 years after LT, he receives 30g of IVIG every 21 days and he has not presented any health issues lately.

Conclusions: We consider the presentation of this case report to be relevant because the intensification of IVIG therapy could be one of the keys for the successful and prolonged survival and acceptable quality of life in a CVID patient after LT.

POSTER 47 - EXTENDED LYMPHOCYTE IMMUNOPHENOTYPING FOR IMMUNODIAGNOSIS OF RECURRENT RESPIRATORY INFECTIONS IN THE ABSENCE OF PRIMARY IMMUNODEFICIENCY

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Objective: Standard lymphocyte immunophenotyping (SLI) (T-CD3+, T-CD4+, T-CD8+, B, NK cells) contributes to the diagnosis or exclusion of primary immunodeficiencies (PID). In PID-unrelated recurrent infections (RI), SLI may be inconclusive, therefore we investigated some supplementary lymphocyte subgroups with impact in RI pathogenesis: immature B cells (CD19+CD10+), naive B cells (CD19+sIg+), memory B cells (CD19+CD27+), plasma cells (CD19+CD38+), T-double negative (T-DN) cells (CD3+CD4-CD8-), NKT cells (CD3+CD16/56+CD4±CD8±CD1d+). The objective was to guide diagnosis by extended lymphocyte immunophenotyping (ELI), revealing usually untested subgroups that showed significant changes.

Design and method: SLI and ELI was applied in 25 children aged 1-9 years, presenting PID-unrelated RI; control group consisted of 18 healthy subjects. The determinations were made from EDTA-collected fresh whole blood, using 8-color methodology. Data acquisition and analysis of results was performed with Becton-Dickinson equipment: FACSCanto II flow cytometer, compensation microspheres (Anti-Mouse Ig/Negative Control Particles Compensation Set), FACSDiva 6.1 software.

Results: CD19+ lymphocytes (B cell population) were low in 67% of cases, especially by lowering naive B cells (50% cases). Immature B cells and memory B cells decreased in either 11% cases. CD3+ lymphocytes (T cell population) were low in 11% cases, mainly by decreasing T-CD4+ cells (helper T cells) in 28% of cases. T-DN lymphocytes were high in 22% of cases, 75% of these being associated with T-CD4+ cell decreases. NK cells were high in 39% cases; NKT cells showed no modification. The overall improvement of ELI was obtained in 22% cases with T-cell modifications and 72% cases with B-cell deficiencies. ELI alone was useful only in 28% patients with B-cell modifications.

Conclusions: ELI determines more accurately the origin of the lowering of different types of lymphocytes in RI, proving usefulness in lowering B and T-CD4+ cells. Diagnosis features can consequently be varied and adapted to each case.

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POSTER 48 - THE CHALLENGES OF DIAGNOSING PRIMARY IMMUNODEFICIENCY SPOTTED AFTER B-CELL LYMPHOPROLIFERATIVE MALIGNANCY

AUTHORS

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Objective: To raise awareness of the potential clues for diagnosis of a common variable immunodeficiency (CVID) debuting as a lymphoma in a lady, with a medical history of recurrent respiratory infections from childhood and the relevance of immunological studies at lymphoma diagnosis and before chemotherapy.

Design and methods: Complete clinical and immunological work-up and follow-up by haematologists and immunologists care team was conducted at malignancy diagnosis. Genetic studies were performed.

Results: A 65-years-old female patient diagnosed with a follicular lymphoma IV stage in 2003 treated with 5 cycles of fludarabine and rituximab, with complete remission in 2004. She suffered a recurrence 2 years later and was treated with rituximab. Clinical history was relevant for recurrent upper and lower infections since childhood and malabsorption syndrome with growth retardation. Severe panhypogammaglobulinemia was spotted, T-cell and neutrophils count was normal, and increasing NK cell numbers since diagnosis (726 cell/uL). She showed partial specific antibody responses after remission, with very low B cell counts, IgG, IgA and IgM levels and undetectable free serum light chains to date. She has experienced recurrent pneumonias, herpes zoster, three episodes of bacteraemia and two additional primary neoplasia, despite immunoglobulin replacement therapy after lymphoma diagnosis and treatment.

Subtotal mucosal villous atrophy (Marsh B3) and non-celiac lymphocytic infiltration (without plasma cells) was detected in a duodenal endoscopy. Genetic study revealed the presence of mutations in two genes: a heterozygous missense mutation of LRBA, usually associated with CVID, and a heterozygous missense mutation of IFIH1 associated in some cases with immunodeficiency and a higher risk of suffering respiratory infections. Ongoing functional and protein expression LRBA analysis.

Conclusions: This is an eloquent case of the relevance of immunological work-up at lymphoma diagnosis before initiating therapy. Patient's clinical features and mutations reveal a possible underlying CVID. The hematological malignancy could be the trigger for an in-depth study of the patient in which the CVID suspicion may modify the diagnostic and therapeutic decisions and more close follow-up. The crossovers between immunodeficiency and hematological malignancy will enlighten the complex genetic and immunological pathways background.

POSTER 49 - SELECTIVE IMMUNOGLOBULIN A DEFICIENCY IN ASSOCIATION WITH BURKITT'S LYMPHOMA

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Objective: We present the case of a 10-year-old girl with selective IgA deficiency (SIgAD) who suffered from Burkitt's lymphoma while having positive Epstein-Barr virus (EBV) antibodies (IgM and IgG). Also a familial history of a mother diagnosed with hypogammaglobulinemia.

Design And Method: Clinical case presentation. We present a follow-up case of a 10 years old girl with SIgAD and diabetes mellitus type 1 who was diagnosed with Burkitt's lymphoma and positive IgM and IgG EBV antibodies. Laboratory test results, imaging studies and treatment were followed-up until resolution.

Result: The patient was brought to the ER due to dizziness, abdominal pain, vomiting, and dysphagia. No fever, weight loss, diaphoresis or pruritus. Physical examination reported a palpable mass in the hypogastrium, no signs of internal organs involvement. Bilateral inguinal lymphadenopathies were also found. Rest of physical exam within normal. Abnormal laboratory findings: Hemoglobin 10.9 gr/dL, VCM 75 fl, Platelets 614000/mm³, VSG 51 mm, LDH 410 UI/L, PCR 46.9 mg/dl, IgG 1561 mg/dl, IgM 80.9 mg/dl, IgA < 5mg/dl, Fe: 19 ng/ml Transferrin 216 mg / dl, Ferritin: 30 ng / ml. Lymphocyte subpopulations: normal. Neuronal specific enolase 19.7 ng / ml, Infectious serology 31/10/2019: AC AntiHBs <2 mUI / ml, Hepatitis A, B and C virus serologies negative. Cytomegalovirus IgG Positive 70.6 U / ml and IgM negative, Epstein Barr Virus IgG Positive (231U / ml) and IgM Positive (24.5 IU / ml) Imaging studies: A hypermetabolic mass of 8.7x6.7 cms in adjacent hypogastrium / dependent on intestinal loops was detected, accompanied by hypermetabolic areas in the left cardiophrenic recess and both parietocolic gutters, all of this suggestive as first choice of malignant nature but without apparent infiltration. Pelvic mass biopsy: High-grade non-Hodgkin B lymphoma with medium-large cell morphology germinal center immunophenotype and Burkitt lymphoma immunohistochemistry (positive for CD20, PAX5, CD10, Bcl 6, cMyc (80%) and P53 (80%). Ki-67 proliferative index: 100%. After the diagnosis was confirmed, started on November 6 2019 treatment with the R-COPAD-M2 (Rituximab, Cyclophosphamide, Doxorubicin, Vincristine, Prednisone and Methotrexate) protocol. Currently in maintenance with rituximab and complete remission by PET-CT

Conclusions: We consider that the association between LB and SIgAD is a rare condition with few cases described. The mother's hypogammaglobulinemia made us contemplate the existence of a common genetic defect, over 200 genes were studied by NGS and no pathogenic mutation was found

POSTER 50 - IMMUNOLOGICAL ABNORMALITIES IN CHILDREN PRESENTING WITH DISSEMINATED STAPHYLOCOCCUS INFECTION. A SINGLE UNIT EXPERIENCE FROM NORTH INDIA.

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Objective: To screen children presenting with disseminated staphylococcus infection for presence of immunological abnormalities

Design and method: This was a prospective observational study carried out in the Pediatric Allergy Immunology Unit, Advanced Pediatric Centre, Postgraduate Institute of Medical Education and Research, Chandigarh, India. We included 30 children with disseminated staphylococcus infection. Disseminated staphylococcal infection was defined as the involvement of at least two distant sites with presence of gram-positive cocci in cluster and/or growth of *Staphylococcus aureus* from at least one normally sterile body fluid. Following laboratory investigations were carried out:

1. Complete blood count, absolute lymphocyte count, absolute neutrophil count
2. Lymphocyte subset (CD3+ T cell, CD19+ B cell, CD56+ NK cell)
3. Immunoglobulin profile (IgG, IgA, IgM)
4. Nitroblue tetrazolium dye (NBT) test
5. CD62 ligand shedding assay (for screening of Toll-like receptor pathway defect)

CD62 ligand shedding was assessed using standard protocol. Phorbol Myristate Acetate (PMA), TLR 2/6 agonist and TLR 4 agonist were used to stimulate neutrophils. Abnormal CD62 ligand shedding was defined based on the difference in percentage shedding between cases and control >20% and based on the shift seen in the flow plot.

Results: Most common site of infection in our cohort was soft tissue infection (43.33%), pulmonary involvement (33.33%) followed by musculoskeletal system involvement (30%). Blood culture grew *Staphylococcus aureus* in 53.33%. Eight out of thirty children had abnormal lymphocyte subset (5 had low B cells, 2 had low NK cells and 1 had low T cells) during active infection. Of these, lymphocyte subset abnormalities normalised in 4 patients while repeat testing could not be performed in remaining 4 patients. Immunoglobulin profile and NBT was normal in all patients. Six out of 30 children had abnormal CD62 ligand shedding assay. There was statistically significant difference in median age between patient with normal and abnormal CD62 ligand shedding (1 vs 3 years, p value 0.045). Other clinical and laboratory parameters were comparable between the 2 groups. Two children died in the entire cohort (both had abnormal CD62 ligand shedding). We were able to perform genetic testing in 2/6 patients with abnormal CD62 ligand shedding (MYD88 gene Sanger sequencing in 1 and whole exome sequencing in 1). Both showed no pathogenic variants.

Conclusion: Children with disseminated staphylococcal infection may have underlying immunological abnormalities. TLR pathway defect may be the commonest immunological abnormality.

POSTER 51 - MID-REGIONAL PROADRENOMEDULLIN (MR-PROADM) LEVELS IN PRIMARY IMMUNODEFICIENCIES COMPLICATED WITH PULMONARY MANIFESTATIONS

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Background: The development of lower respiratory complications in primary immunodeficiencies (PID) significantly contributes to morbidity and mortality. The inflammatory response that develops throughout the clinical process can cause the release of several biomarkers. The aim of this study was to evaluate the inflammatory biomarker mid-regional proadrenomedullin (MR-proADM) levels in parallel of the distribution of lower respiratory tract complications in children with PID disorders.

Material-Methods: A total of 155 PID patients who were diagnosed according to IUIS (International Union of Immunological Societies)/ESID (European Society of Immunological Diseases) criteria were included in the study. Demographic and clinical data were recorded from the patient files. All initial admission (complete blood count, immunoglobulin levels, lymphocyte subsets) and follow-up laboratory and radiological imaging data (chest X-ray, high-resolution computed tomography imaging), clinical findings, complications during follow-up (organomegaly, musculoskeletal/cardiovascular, respiratory system complications, autoimmune disease, malignancy) were recorded. Plasma MR-proADM levels of each case were measured with a commercial microELISA kit.

Results: Plasma MR-proADM levels were measured in two groups with (n:52) and without (n:103) lower respiratory tract complications. The complicated group was also categorized into infectious (11 bronchitis-bronchiolitis, 9 pneumonia) and non-infectious (19 atelectasis, 5 bronchiectases, 1 interstitial lung disease, 3 parenchymal nodule, 4 chronic changes) groups. The Median MR-proADM level was 143.1 (26.1-562.6) ng/L in respiratory complicated patients and was 104.1 (11.3-477.9) ng/L in non-complicated group. The difference between the two groups was not statistically significant (p:0.175). The median level was 205.5 (73.4-562.6) ng/L in the infectious group while it was 96.1 (26.1-43.3) ng/L in the non-infectious group and the difference between the two groups was statistically significant (p:0.003). When the predictive values of inflammation markers in the infectious group were evaluated, MR-proADM (AUC:0.749,p:0.003) had statistically significance by comparison to CRP (AUC: 0.330, p: 0.040) and SAA (AUC:0.261,p:0.004).

Conclusion: MR-proADM is found to be higher in infectious complicated patients and correlates with other inflammatory markers more often in non-infectious complicated patients. However, it has been thought that more new studies are needed for the use of MR-proADM as a biomarker in chronic lung inflammation.

POSTER 52 - MALIGNANCIES IN CHILDREN WITH INBORN ERRORS OF IMMUNITY - OUR EXPERIENCE AT CHANDIGARH, INDIA.

AUTHORS

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Objective: To study the clinical profile and outcomes of occurrence of malignancy in children with Inborn Errors of Immunity (IEI).

Design: Retrospective review of the case records.

Methodology: Case records of children with IEIs who developed malignancies and where been followed up in Pediatric Immune Deficiency clinic of Post Graduate Institute of Medical Education and Research, Chandigarh, India a tertiary care Institute of Northern India were reviewed and analyzed.

Results: Nine children developed malignancy in our IEI cohort (n=9; Male:7). Consanguinity and family history of IEI was present in 2 patients. Median age at onset for any symptom which led to the diagnosis of IEI was 17 months (range: 2-216 months). Median age at diagnosis of IEI was 54 months (range: 3-240 months). While the median age at diagnosis of malignancy was 96 months (range, 24 -240). Diagnosed IEI with malignancy include: Combined Variable Immunodeficiency(CVID) (n=2), Wiskott-Aldrich syndrome (2), X-linked lymphoproliferative syndrome (1), Ataxia telangiectasia (1), Autoimmune Lymphoproliferative syndrome (1), Combined Immunodeficiency (1), Deficiency of Adenosine Deaminase 2 (1). Lymphoma was the most commonly encountered malignancy (n=7), followed by EBV related leiomyoma of liver (n=2). Among the 7 children who developed lymphoma, mixed cellularity and nodular sclerosis variant of Hodgkin lymphoma was found in 1 patient each while 5 patients had Non-Hodgkin's lymphoma (NHL). Both T and B cell type of NHL were seen in liver (n=2) and CNS (n=2). High grade B cell lymphoma of liver and central nervous system (CNS) was seen in patient with X-linked lymphoproliferative syndrome and Wiskott-Aldrich syndrome. Two patients with CVID developed T cell NHL of Liver and CNS. Epstein Barr virus was positive in 3/7 patients. Six patients were commenced on chemotherapy. At the time of analysis, only 1/9 patient (11.1%) is alive and receiving second course for relapse of HD. Mortality in the cohort 8/9 (88.8%).

Conclusions: Lymphoid malignancies were observed in our cohort of IEI patients. Management of malignancies with underlying IEI remains a challenge and is responsible for high mortality.

POSTER 53 - DEFICIENCY OF ADENOSINE DEAMINASE 2: MYRIAD FACES IN A SINGLE FAMILY

AUTHORS

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Objective: Lymphoreticular neoplasms in association with deficiency of adenosine deaminase 2 (DADA2) are rare and occasional cases have been reported recently. We report a family of 3 children with ADA2 gene mutation with varied haematological manifestations, including fatal Hodgkin lymphoma.

Design and methodology: Retrospective review of case record to describe the clinical course of 3 children in a family with ADA2 gene mutation.

Results: A 10-year-old boy (Index patient [Pt. 1], first in birth order), born to a non-consanguineously married couple, had presented with fever and generalized lymphadenopathy for four months. On examination, he had pallor, generalized lymphadenopathy, and massive hepatosplenomegaly. His younger brother (Pt.2, birth order 2 and aged five years) was having clinically asymptomatic splenomegaly (5 cm below the costal margin). The youngest brother of index child (Pt.3; birth order 3 and aged 18 months) was diagnosed with pure red cell aplasia and was transfusion dependent from 2 months of age.

Laboratory investigations of Pt.1 revealed pancytopenia (Table 1). Cervical lymph node excision biopsy showed Hodgkin lymphoma (Nodular sclerosis) (Figure 1A-D). He had pan-hypogammaglobulinemia and elevated Epstein Barr virus viral load (1.7 million copies/ml). On day 4 of his hospital stay, his fever increased along with clinical and laboratory features of hemophagocytic lymphohistiocytosis (HLH) (Table 1). He was administered 1 g/kg of intravenous immunoglobulin and pulse methylprednisolone (30 mg/kg/dose for 5 days); however, he was nonresponsive and succumbed to HLH. Clinical exome sequencing revealed compound heterozygous mutations in exon 5 of ADA2 gene [nonsense mutation: c.806dup, (p. Tyr269Ter)]; and a frameshift mutation with premature truncation: c.777_780dup, (p. Asp261ProfsTer2)].

The plasma ADA2 level of Pt.2 was markedly low (4.4 mU/g protein, N: 76-183) and both Pt. 2 and Pt. 3 were identified compound heterozygous for the same variant as index child. Father was heterozygous carrier of frameshift mutation in exon 5 of ADA2 gene [c.777_780dup, (p. Asp261ProfsTer2)]. The plasma ADA2 levels of father and mother were comparable with normal range of heterozygous carriers of ADA2 defect (51.5, and 31.9 mU/g protein, respectively; N: 33.3-77.3 mU/g protein).

After establishing the diagnosis of DADA2, patient 3 was initiated on oral prednisolone at 2 mg/kg/day, and he is being evaluated for hematopoietic stem cell transplantation. Patient 2 is being kept on close follow-up.

Conclusion: To conclude, we report novel mutations in ADA2 with an index child manifested with Hodgkin lymphoma and 2 other younger brothers with various haematological manifestations.

POSTER 54 - X- LINKED LYMPHOPROLIFERATIVE SYNDROME -1: ONE CASE IN A MILLION

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Objective: Describe the first case of XLPS1 in El Salvador

Design and method: We looked for information in the clinical file by making a descriptive presentation of the clinical case.

Results (Case Report): A 9- years old boy was referred to immunology team to our hospital because for the previous 4 years he had been treated for suspected infection for EBV due he presented classical symptoms of this infection but was not possible to identified the virus. The first manifestation was a Burkitt lymphoma so that he received antineoplastic drugs (Ifosfamide- carboplatin and etoposide) getting remission. A few months later our patient presented a relapse and infiltration of Burkitt lymphoma in the soft tissues and parotid gland for that reason a new cycle of antineoplastic was performed and he reached again his remission. A year later the patient returned to our hospital presented thrombocytopenia in his blood count, a bone marrow aspiration was made and did not revealed abnormalities; in order to research his atypical evolution, the patient was referred for immunological evaluation and genetic test was performed that reported: A Likely Pathogenic variant, c.201+2T>C (Splice donor), was identified in SH2D1A.

Conclusions: We are presenting the first case of XLPS1 in our country and for us this is great step in the immunological field in El Salvador. The understanding of the molecular and cellular pathology in XLPS1 continues to expand; novel treatments including gene therapy has been developed. The literature report that analyses of mutations are in the spectrum of deletions, splice site, nonsense, and missense changes in SH2D1A, but so far, there has not been a clear correlation between mutations and the severity of phenotypes identified. The patients can progress from one phenotype to another, and different clinical features are seen within members of the same family; the oncology manifestations are one the most frequently and this is how our patient was identified.

POSTER 55 - GATA2 DEFICIENCY AND HIDRADENITIS SUPPURATIVA IN A YOUNG ADULT: A THERAPEUTIC CHALLENGE

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Objective: to describe the clinical spectrum and the immunologic features of a young adult with GATA2 deficiency.

Design and method: case report based on medical record from Immunology Unit in San Martin Hospital of La Plata, Argentina.

Case report: A 24 years old woman from non-consanguineous parents without family history of immunodeficiency. She had history of recurrent cellulitis (4 episodes), mainly in feet associated with lymphangitis in the lower limb. The radio isotopic lymphography showed absence of lumbo-aortic iliac and left inguinal ganglion groups. Primary lymphedema was diagnosed. At 12 years old she had haemorrhagic chickenpox, esophageal and vaginal candidiasis which cured with medical treatment. She has had papilloma plantar wart until today. During her adolescence, developed severe cystic nodular facial acne, sicca syndrome and a severe hidradenitis suppurativa.

At the age of 20, laboratory measurements showed persistent pancytopenia. Bone marrow aspirate reported few hematopoietic precursors, granulocytic dysplasia and signs of bone marrow failure. Biopsy revealed hypocellular bone marrow with dyshemopoietic features and myeloid series with delayed maturation. Immunophenotype: decreased monocytes with mild maturation alterations. Neutrophils with aberrant patterns and decreased CD10+ expression. CD3+ increase gamma/delta (9,6%). Absence of lymphoid precursors B. FISH test without chromosome 7 abnormalities.

Immunological assessment: monocytopenia, global lymphopenia, hypergammaglobulinemia with variable response to protein and polysaccharide antigens. B- and NK-lymphopenia with T cell profile according to her age. NKdim: 100%, NKbright: absent. Dendritic Cells (DC) functional study: DCm: 0.001%, DCp: 0%.

The genetic study by massive sequencing confirmed the diagnosis of GATA2 deficiency: c.1064_1084up (p. Arg361_Arg362 InsProThrThrThrLeuTrpArg).

Azithromycin prophylaxis was indicated. She received HPV vaccine. Hidradenitis suppurativa was treated surgically with poor outcome and we planned to start immunosuppressive therapy. Hematopoietic stem cell transplantation (HSCT) was proposed but the patient refused.

Conclusions: We report a young adult with combined immunodeficiency, myelodysplasia, primary lymphedema and severe hidradenitis suppurativa with confirmed diagnosis of GATA2 deficiency. The challenge nowadays is to find a suitable treatment for hidradenitis with the hope of improving her quality of life and avoiding future complications.

POSTER 56 - A CASE REPORT CHRONIC MUCOCUTENOUS CANDIDIASIS (CMCC) WITH MANIFESTATION OF RECURRENT INVASIVE STAPHYLOCOCCUS AUREUS INFECTION

AUTHORS

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Chronic Mucocutaneous Candidiasis (CMCC) is a rare entity of primary T-cell defect disease resulting in non-invasive *Candida* species infection. It may cause significant morbidity and mortality. Most patients with CMCC have a mutation in the AIRE or STAT1 gene with typically encompassed endocrinopathy, autoimmunity, and chronic infection of the skin, nail, oral or genital mucosa. However, there is some selective immune defect of T-cells such as Interleukin-17 Receptor A (IL17RA) deficiency associated with staphylococcus aureus infection as a manifestation of CMCC

A 9-years-old Chinese girl was presented with recurrent joint and skin infection since the age of 4 years. She has underlying asthma and chronic eczema with no significant family history of autoimmune or immunodeficiency disease. She underwent multiple procedures including incision drainage, joint arthrotomy washout, and was treated with multiple courses of antibiotics before referring to the Immunological team for further investigation of immunodeficiency disease. Several immunodeficiencies work up and genetic analysis was done, revealed of Interleukin 17 receptor deficiency heterozygous pathogenic variant.

This case report provides valuable possible differential diagnosis within line with her atypical presentation, emphasizing diagnostic challenges as she not presented with classical CMCC and the importance of genetic analysis in patients with recurrent infection.

POSTER 57 - DONOR-DERIVED T CELL IMMUNOGLOBULIN AND MUCIN DOMAIN 3 DEFICIENCY UNDERLYING POST-TRANSPLANT INFLAMMATORY BOWEL DISEASE

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T cell immunoglobulin and mucin domain 3 (TIM-3) is expressed by a variety of immune cells. TIM-3 belongs to the family of immune checkpoint proteins executing immune regulatory functions. Treatment with checkpoint inhibitors has been demonstrated to increase T cell-mediated clearance of cancer but was also associated with T cell-mediated inflammation manifesting in the intestine and other organs. Germline loss-of-function mutations in TIM-3 are linked with systemic immune activation and T cell lymphoma. In the present report, we describe a patient with severe inflammatory bowel disease manifesting following hematopoietic stem cell transplantation due to rare T cell lymphoma (Prolymphocytic T cell leukemia). Donor derived hematopoietic cells were identified to carry a rare loss-of-function mutation in HAVCR2 encoding TIM-3. TIM-3 expression following in vitro stimulation of T cells was absent while CD25 up-regulation was intact. Immune-histology revealed that in sharp contrast to healthy controls and patients with inflammatory bowel disease, Tim-3 expression was virtually absent in the inflamed intestinal tract of the patient. This is to our knowledge the first report of hematopoietic cell-restricted TIM-3 mutation/deficiency associated with inflammatory bowel disease.

POSTER 58 - CROSS-TALK BETWEEN NOX AND AUTOPHAGY TO MAINTAIN THE LONG-TERM B CELL MEMORY IN PATIENTS WITH CHRONIC GRANULOMATOUS DISEASE

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Background: Implication of NADPH oxidase (NOX) has not been explored in sustaining memory B-cell generation in CGD.

Objective: To investigate the biological significance of NOX in B-cell, generation of regulatory B-cells, and sustaining long-term memory. Moreover, study has also examined the implication of autophagy in maintaining the overall homeostasis of B-cell functions in a wide spectrum of NOX mutations identified in CGD patients.

Design and Methods: This is a prospective observational study that has been conducted on CGD patients (n=30). The proportion of B-cell subsets were assessed in mutation-proven CGD [X-linked, AR, and carrier CGD] and were compared with age-matched healthy controls. Investigation of B-cell proliferation and generation of regulatory B-cell was also examined in different groups of CGD patients. To examine the cross-talk between proliferation potential of B-cells and autophagy we have assessed the late autophagy markers (e.g. LC3 and Lysotracker Green) in different sub-groups of CGD patients and compared with controls.

Result: A significant reduction in activated memory B cells proportion was observed in the test group compared to controls. While comparing sub-groups with healthy control, there was a significant reduction in both total memory cells and activated memory B cells in patients with X-linked CGD as compared to the control. Similarly, patients with AR-CGD showed significantly low activated memory B cells and resting memory B cells when compared to control. XL-CGD has revealed a significantly reduced proportion of activated memory B cells while comparing to AR and X-linked carrier CGD. B regulatory cells were only significantly reduced in AR CGD group when compared to the control. Expression of Ki67 (proliferation marker) in overall B-cells has also been found to be reduced in CGD patients as compared to healthy controls. While analysing the expression of Ki67 in different subsets of memory B-cell has also demonstrated the lower expression of the same in XL-CGD and AR-CGD as compared to healthy controls which suggests the retarded proliferation ability in a wide spectrum of NOX mutation. Moreover, expression of LC3 and lysosome activation have also shown a drastic shift in patients with XL-CGD and AR-CGD as compared to controls and found to be concordant with proliferation ability in different NOX mutations.

Conclusion: Results indicated the biological significance of NOX in B-cell activation, proliferation, and generation of regulatory B-cells. Altered autophagy are also suggesting the differential cross-communication of NOX-autophagy axis in maintaining the overall homeostasis of memory B-cells and subsequent humoral response.

POSTER 59 - NON-TRAUMATIC FRACTURES AND OSTEOSARCOMA YEARS AFTER HAEMATOPOIETIC STEM CELL TRANSPLANTATION FOR PRIMARY IMMUNODEFICIENCY REVEAL UNEXPECTED DIAGNOSIS OF OSTEOGENESIS IMPERFECTA**AUTHORS**

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A 20-year-old gentleman underwent haematopoietic stem cell transplantation (HSCT) at the age of 15 years for undefined primary immunodeficiency (PID). Post-HSCT, he developed non-traumatic fractures and secondary osteosarcoma. Genetic analysis revealed osteogenesis imperfecta. Initially he presented at the age of 6 years with history of recurrent chest infections and extensive molluscum contagiosum since the age of 5 months. Laboratory evaluation showed normal full blood counts with raised IgG (37 g/dl), IgA (2.76 g/dl) and normal IgM. Lymphocyte subsets showed normal T-cell counts with slightly reduced naïve CD4 (51%) and CD8s (24%), low B cells (0.14 x10⁹/L), normal NK cells (0.09 x10⁹/L), and reduced TREC counts (15000 TRECs/ millions of CD3 cells) for age. T-cells showed dysregulation with increased (30%) gamma-delta expression. Proliferation assays showed suboptimal responses to CD3/CD28 and PHA stimulation. Whole exome sequencing failed to identify a pathogenic variant that explains his underlying immune defect. At the age of 11, he developed abdominal pains with vomiting. Blood PCR showed EBV viraemia, gastrointestinal endoscopy showed gastric and duodenal ulcers with EBV positive cells on gut biopsy. Being diagnosed with EBV lymphoproliferative disease (LPD), he received Rituximab with good response. At the age of 14, he developed diffuse large B cell lymphoma of the left femur treated with chemotherapy and localised radiotherapy. He underwent successful TCR alphabeta/CD19 depleted haploidentical transplant (father) with T-cell add-back at the age of 15.

At the age of 16, he developed non-traumatic fractures of the left femur and humerus. Family history was positive for repeated fractures in both his younger brother. Genetics revealed a homozygous mutation in COL1A1 c.2167 G>A p(Ala-723Thr) in both the patient and younger brother with carrier status in both parents.

At the age of 18, he developed a high-grade osteosarcoma in the distal left femur (same site of previous lymphoma) requiring above knee amputation. 12 months later, CT chest confirmed localised pulmonary metastasis that were surgically resected. Six months later, he developed recurrence in his stump- requiring resection. He is now 20-year-old with no active disease and remains 100% donor engrafted.

Conclusion: The onset of fracture and osteosarcoma of the left femur, both at the same site of previous lymphoma, might have been triggered by localised radiotherapy and surgical intervention (left femur pen insertion) in a background of homozygous mutation in COL1A1. This case highlights the ongoing need for close surveillance to diagnose and manage rare post-HSCT complications.

POSTER 60 - NINE-MONTH TREATMENT FOR A PATIENT WITH X-LINKED AGAMMAGLOBULINEMIA AND SARS-COV-2 INFECTION USING MULTIPLE THERAPEUTIC APPROACHES

AUTHORS

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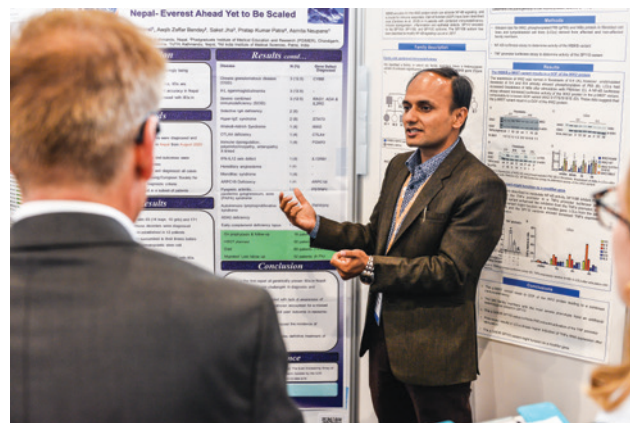
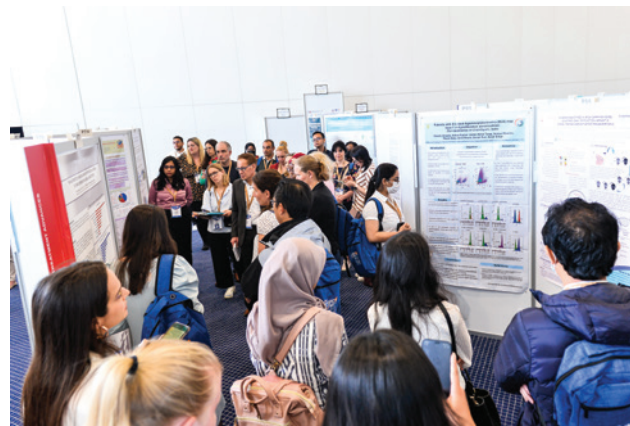
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Outcomes following severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in individuals with primary immunodeficiencies (PID) still remains uncertain. Contrary to expectations, patients with X-linked agammaglobulinemia (XLA) early in the pandemic have been reported to have less severe COVID-19.

We report a case of 35-year old male patient diagnosed with XLA at the age of 13-months. He suffered from chronic sinusitis and bronchiectasis. The patient was on regular subcutaneous immunoglobulin replacement therapy. He presented in early April 2020 with a one-week history of low-grade fever and dry cough. Nasopharyngeal swab tested positive for SARS-CoV-2 RNA. The patient was admitted to the hospital. CT chest scan showed widespread patchy ground-glass opacities in the lower lobes with underlying interstitial pattern. Despite all the treatments fever persisted with rapidly increasing CRP and IL-6 levels and patient required supplemental oxygen. Tocilizumab was administered on the eight day of hospitalization. He was also treated with COVID-19 convalescent donor plasma and methylprednisolone. On day 22 after admission the patient remained asymptomatic and chest CT showed almost complete resolution. However, SARS-CoV-2 RNA was subsequently found on multiple nasopharyngeal swabs for five weeks. After this acute illness, the patient relapsed every month with fever, elevated inflammatory parameters and pneumonitis confirmed by CT scans. He was treated with antimicrobials, COVID-19 convalescent plasma and methylprednisolone. SARS-CoV-2 RNA became undetectable on nasopharyngeal swabs from the early May. Given the unusual course COVID-19 in our patient with three relapses with undetectable viral RNA, the possibility of reactivation of latent SARS-CoV-2 infection or triggering of chronic inflammatory processes by this infection is being considered. With the written consent of the patient and the approval of the Ethics Committee, therapy was started with monthly administration of tocilizumab at a dose of 800 mg. The patient remained asymptomatic for three consecutive months. Three weeks after receiving a reduced dose of 400 mg tocilizumab, the patient experienced a new relapse of the disease. A sputum sample tested positive for SARS-CoV-2 RNA, and the patient commenced a 10 day course of remdesivir with favorable clinical, radiological and laboratory response.

To our knowledge this is the first case to show that inflammation in COVID-19 infection can be kept under control with tocilizumab. However, the patient's failure to clear RNA viral infection appears to be caused by a lack of antibodies to SARS-CoV-2. Our case further confirms previous findings on the beneficial effect of remdesivir in patients with PID.



THURSDAY, APRIL 28, 2022

GUIDED POSTER WALK 3 - DISEASE SPECIFIC

MODERATOR: Dr Adli Ali

POSTER 61 - A NOVEL PATIENT WITH COMPLETE STAT2 DEFICIENCY PRESENTED WITH HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS AND IMPAIRED IFN- α SIGNALING

AUTHORS

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Objective: Human inborn errors of innate immunity affecting the type I interferon (IFN-I) pathway have been associated with severe susceptibility to viral illness. Hemophagocytic lymphohistiocytosis (HLH) is a life-threatening systemic hyperinflammatory syndrome that has been increasingly associated with inborn errors of IFN-I-mediated innate immunity. The objective of this work is to characterize, at functional and molecular level, a 2-years old girl suffering HLH after mumps-measles-rubella (MMR) vaccination at 12 months of life.

Design and method: Immunophenotype of peripheral blood lymphocytes, functional and molecular studies such as Targeted Next Generation Sequencing (NGS) gene panel, gene and protein expression, protein phosphorylation and NK-cell degranulation assays were carried out.

Results: NGS revealed a novel homozygous loss of function variant (c.633+2T>C) in the STAT2 gene. This variant caused the complete deficiency of the STAT2 protein due to abnormal splicing and the deletion of exon 7 at RNA level, which results in a premature stop codon. In this case, the STAT2 deficiency abolished the immune response induced by IFN-I. Expression of interferon-stimulated genes such as IRF7, ISG15 and IFIT1 were severely decreased in the patient compared to healthy donor. Additionally, STAT2 deficiency prevented a correct production of IFN- α , since the IFN- α 2 gene expression after stimulation with soluble IFN- α 2 and with poly I:C was dramatically decreased in the patient compared to healthy donor. In addition, a mild impairment of NK-cell degranulation was observed during HLH presentation, with full recovery afterwards. The patient required immunosuppression including steroids, IL-1 blockade and IVIG. However, she is no longer requiring neither immunosuppression nor immunoglobulin replacement therapy.

Conclusions: we report a novel case of STAT2 deficiency in a patient who presented with HLH after routinely MMR vaccination. The loss of function mutation impaired the correct IFN-I-induced immune response, as well as the production of IFN- α after stimulation of the anti-viral pathway. These results led us to speculate that a deficient production and response to IFN- α together with a transient defect in the NK-cell activity could be the hallmark of HLH triggering. Defining the molecular consequences of variants in STAT2 and other IFN pathway-related genes provides insight into the involvement of interferons in human innate immunity.

POSTER 62 - SOLUBLE SURFACE MOLECULES IN SERUM SUGGEST INVOLVEMENT OF ACTIVATED T-CELLS AND MACROPHAGES IN NON-INFECTIOUS COMPLICATIONS IN CVID

AUTHORS

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Objective: Common Variable Immune Deficiency (CVID) is characterized by antibody deficiency and susceptibility to infections. However, during the disease course more than 60% of CVID patients experience non-infectious complications (NIC). These include autoimmune disease, granulomatous complications, and malignancy. NIC are associated with high morbidity and mortality. Currently, it is unknown which patients are at risk for developing NIC, and what type of NIC they might develop. The aim of this study was to determine whether serum levels of soluble surface molecules, representing T-cell and macrophage activation, differ between CVID patients with infections only (IO) and CVID patients with NIC.

Design and method: Soluble (s) surface molecules were determined in serum of 56 CVID patients and 12 healthy controls (HCs) using ELISA. The CVID patients were grouped in CVID+IO (N = 37), and CVID+NIC (N = 21). The CVID+NIC contained CVID patients with granulomatous disease (CVID+gran, N = 8), CVID patients with autoimmune disease (CVID+AI, N = 10) and CVID patients with malignancy (CVID+mal, N = 3). sCD4, sCD8 and sIL-2R were used as markers for T cell activation, sCD14, sCD163 and sCD206 were used as markers for macrophage activation.

Results: Principal component analysis (PCA) involving sIL-2R, sCD163, sCD206, sCD14, sCD4 and sCD8, showed CVID patients to cluster away from the HC. Focusing on the CVID patients, a heterogeneous group was observed with partial overlap between CVID+NIC and CVID+IO. Unsupervised hierarchical clustering showed that sIL-2R, sCD163 and sCD206 were important for clustering of the CVID patients with NIC, more so than sCD14, sCD4 and sCD8. sIL-2R appeared significantly elevated in all CVID patients versus HCs. Significant elevation of sIL-2R and sCD163 was observed only in CVID+gran, compared to CVID+AI, CVID+mal and CVID+IO. sIL-2R correlated positively with sCD163 in all CVID subcategories (CVID+IO: 0.63; CVID+AI: 0.59; CVID+gran: 0.73), while moderate negative correlation was observed in HCs (0.35). sCD206 showed an overall positive correlation with sIL-2R in all CVID subcategories (CVID+IO:0.45; CVID+AI: 0.58; CVID+gran:0.60), although expression levels did not differ significantly per subcategories. A less strong correlation was observed between sIL-2R and T-cell associated markers sCD4 and sCD8.

Conclusions: sIL-2R seems the most discriminating soluble surface molecule in serum of CVID patients concerning NIC, especially regarding granulomatous disease. The macrophage biomarkers sCD163 and sCD206 seemed more informative and also to correlate more strongly with sIL-2R as did sCD4 and sCD8. This could suggest that tissue macrophage activation is of importance in CVID+NIC.

POSTER 63 - ACTIVATED PI3K-DELTA SYNDROME, AN IMMUNODEFICIENCY DISORDER, LEADS TO SENSORIMOTOR DEFICITS RECAPITULATED IN A MURINE MODEL

AUTHORS

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The phosphoinositide-3-kinase (PI3K) family plays a major role in cell signalling and is predominant in leukocytes. Gain-of-function (GOF) mutations in the PIK3CD gene lead to the development of activated PI3K-delta syndrome (APDS), a rare primary immunodeficiency disorder. A subset of APDS patients also displays neurodevelopmental delay symptoms, suggesting a potential role of PIK3CD in cognitive and behavioural function. However, the extent and nature of the neurodevelopmental deficits has not been previously quantified. Here, we assessed the cognitive functions of two APDS patients, and investigated the causal role of the PIK3CD GOF mutation in neurological deficits using a murine model of this disease. We used p110-delta E1020K knock-in mice, harbouring the most common APDS mutation in patients. We found that APDS patients present with visuomotor deficits, exacerbated by autism spectrum disorder comorbidity, whereas p110-delta E1020K mice exhibited impairments in motor behaviour, learning and repetitive behaviour patterning. Our data indicate that PIK3CD GOF mutations increase the risk for neurodevelopmental deficits, supporting previous findings on the interplay between the nervous and the immune system. Further, our results validate the knock-in mouse model, and offer an objective assessment tool for patients that could be incorporated in diagnosis and in the evaluation of treatments.

POSTER 64 - DIVERSE PHENOTYPES IN MICE CARRYING NOVEL LEU387ARG GAIN-OF-FUNCTION VARIANT IN SIGNAL TRANSDUCER ACTIVATOR TRANSCRIPTION 3

AUTHORS

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Objective: Signal transducer activator transcription 3 (STAT3) is a transcription factor that regulates various genes associated with cell growth, cell survival, and immune regulation. Patients with gain-of-function (GOF) mutations in STAT3 exhibit different clinical phenotypes, including immunodeficiency, malignancy, autoimmunity, and short stature. A novel heterozygous STAT3 L387R variant was discovered in a Dutch family with six affected individuals. The clinical symptoms of these patients include recurrent infections with hypogammaglobulinemia, immune thrombocytopenia, dermatitis, interstitial lung disease, and retinal vasculitis. HEK293 cells expressing STAT3 L387R displayed enhanced STAT3 activity upon IFN-alpha or IL-6 activation in the cellular study. However, cellular manner can not fully describe all spectrums of this disease. To better understand the effect of this mutation on the diversity of clinical manifestations and pathological aberrations, we generated a knock-in mouse model with the L387R mutation corresponding to the patients.

Design and method: L387R mutation of STAT3 was introduced in the exon 13 using a standard CRISPR-mediated genome editing technique (Cyagen Biosciences Inc.). Mice were bred and backcrossed under the pathogen-free condition at the animal facility, Faculty of Veterinary, Chulalongkorn University, Thailand. Sanger sequencing was performed to determine genotypes of L387R STAT3 and WT STAT3 mice. Clinical phenotypes including growth and survival of all mice were observed. Organs of the mice will be examined for pathological changes. Primary bone marrow-derived macrophage and fibroblast from mice will be collected to investigate STAT3 phosphorylation, dimerization, nuclear migration, and target gene activation.

Results: Two homozygous L387R STAT3 mice died right after birth. Heterozygous L387R STAT3 mice developed diverse phenotypes, including congenital blindness and dermatitis lesion on the flank and neck.

Conclusions: This study could extend the insight of the pathophysiologic mechanisms underlying the L387R STAT3 GOF variant. Understanding the biological functions of STAT3 could provide future therapeutic options for these patients.

POSTER 65 - PATIENTS WITH X-LINKED AGAMMAGLOBULINEMIA (XLA) MAY HAVE T CELL PROLIFERATION ABNORMALITIES: OUR EXPERIENCE AT CHANDIGARH, INDIA

AUTHORS

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Objective: To assess T cell proliferation responses through a carboxyfluorescein succinimidyl ester (CFSE) based flow assay in patients with XLA.

Methodology: All patients with XLA were diagnosed based on clinical features with low immunoglobulins, low B cells and a pathogenic variant in BTK gene. We performed in vitro T cell proliferation using peripheral blood mononuclear cells that were isolated using Ficoll-Paque gradient centrifugation. Flow cytometry was used for the assessment of T cell proliferation in response to antigens or mitogens using CFSE that integrates with intracellular proteins of the cell. When T lymphocytes are stimulated with mitogens e.g phytohemagglutinin (PHA) or anti CD3CD28 beads, cells divide and the dye gets apportioned equally between two daughter cells.

Results: In this study, we included 5 patients diagnosed to have XLA. Molecular confirmation showed exonic variants in 4 and 1 had an intronic mutation in BTK gene. Age of onset varied between 2-36 months. In vitro T cell proliferation response to phytohemagglutinin (PHA) were normal in all 5. Percentage proliferation of T cells using PHA varied from 94.72% to 66.05%. However, defective T cell proliferation was observed in 1/5 patients when stimulated with CD3/CD28 beads. In this case, 66.44% of cells proliferated when stimulated with PHA while only 10.27% of T cells proliferated from anti CD3CD28 beads indicating defective T cell proliferation response.

Conclusion: This is the first study to demonstrate in vitro T cell proliferation abnormalities in patients with XLA. Our preliminary work suggests reduced T cell proliferation to CD3CD28 beads while normal proliferation following PHA indicating a milder form of T cell proliferation abnormality in patients with XLA. Abnormal T cell proliferation response in XLA patients suggest that function of T cell compartment is influenced by B cells.

POSTER 66 - X-LINKED LYMPHOPROLIFERATIVE SYNDROME: EXPERIENCE FROM A TERTIARY CARE CENTER FROM NORTH INDIA.

AUTHORS

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Objective: X-linked lymphoproliferative syndrome (XLP) is a rare primary immune deficiency (PID) disorder characterized by fatal infectious mononucleosis, hypogammaglobulinemia, lymphoproliferation, and hemophagocytic Lymphohistiocytosis (HLH). There are 2 genetically distinct types of XLP (XLP1 and XLP2) with considerable clinical and immunological overlap.

There is a paucity of literature on XLP from developing countries, including India. Herein, we report the clinical, immunological, genetic details, and outcomes of patients with XLP from a single centre in North-West India.

Design and methodology: Retrospective review of case records of all children diagnosed with XLP in the Department of Pediatrics, Advanced Pediatrics Centre, Postgraduate Institute of Medical Education and Research, Chandigarh, India.

Results: Six children were diagnosed to have XLP [XLP1 (n=3); and XLP2 (n=3)]. The median age of onset of symptoms was 4.5 months (range: 1 month- 4 years), and 4 (66.6%) were symptomatic from infancy. The median age at diagnosis was 3.5 years (4 months- 7 years) with a median delay in diagnosis of 2.4 years. Five patients (83%) had recurrent episodes of infections (Table 1), and 4 patients (75%) had HLH, wherein 2 of them had recurrent HLH. Epstein Barr virus (EBV) was isolated in 2 patients who had HLH (Table 1). Other associated manifestations include celiac disease and hypothyroidism (Pt.1); EBV related lymphocytic cholangitis (Pt.4); and Wiskott-Aldrich Syndrome (Pt.3). Hypogammaglobulinemia was seen in 3 patients [50%, XLP-1 (n=2), and XLP-2 (n=1)]. Genetic analysis showed previously reported variants in 5 children, while one had a novel variant in exon 7 of XIAP gene [c.1370dup p. Asn457Lysfs Ter16] (Table 1).

Episodes of HLH were managed with intravenous immunoglobulin (IVIg, 1g/kg; n=4); Pulse methylprednisolone/ Dexamethasone (n=3); Oral prednisolone (2 mg/kg/d, n=1). Two patients (33%) required additional immunosuppressants for control of HLH [Cyclosporine, n=2; Rituximab, n=1]. Patient 2 had a relapsing course of inflammatory bowel disease managed with oral prednisolone and azathioprine (2.5 mg/kg/d) without any future relapses. One patient with XLP-2 and COVID-19 triggered MIS-C was treated with IVIg alone. None of these patients underwent hematopoietic stem cell transplantation (HSCT) either due to financial constraints or due to the unavailability of a matched donor. Patient 3 had succumbed to the HLH illness, and the rest 5 patients (83%) were asymptomatic at 10.2 patient-years of follow-up (median follow-up: 18 months).

Conclusion: We report the largest single-centre cohort of patients with XLP from India.

POSTER 67 - THE FIRST PATIENT FROM THE NATIONAL IRANIAN REGISTRY WITH PROTEIN KINASE C-DELTA DEFECT, AND REVIEW OF THE LITERATURE

AUTHORS

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Objective: Protein kinase C is a family of serine/threonine kinases that regulates the adaptive immune responses, as well as growth, differentiation, and apoptosis of a variety of cell types. Homozygous mutations of the Protein Kinase C Delta (PRKCD) gene result in clinical features of immune dysregulation and increased susceptibility to Epstein-Barr virus infection. Nevertheless, a few patients represent autoimmune lymphoproliferative syndrome (ALPS).

Design and Method: The data were collected by direct interview and reviewing the patient's clinical records. To identify the patient's underlying genetic mutation, whole-exome sequencing was performed. Additionally, we searched in PubMed, Web of Science, and Scopus databases for previously reported ALPS-like patients.

Results: In the current study, we reported a 13-year-old boy who presented with lymphoproliferation, autoimmunity, cardio-myopathy, recurrent pneumonia, and dermatological manifestations. He had elevated numbers of double-negative T cells, CD8+ T cells, and serum IgG level along with a decreased NK cell count. The genetic evaluation confirmed a homozygous frameshift mutation (c.1293_1294insA) at exon 13 of the PRKCD gene. The literature search revealed 39 ALPS-like patients with monogenic defects which only six (15.3%) of them were due to PRKCD genes. Organomegaly (89.2%) and autoimmune (88.0%) complications were the most prevalent clinical manifestations. Despite an increased level of double-negative T cells in 24 patients (70.6%), Laboratory indices were mainly normal in ALPS-like patients.

Conclusions: PRKCD should be considered in the setting of ALPS clinical manifestations with prominent dermatological involvements, especially in conjunction with EBV lymphoproliferation and decreased NK cell count or function.

POSTER 68 - IS MORTALITY AVOIDABLE IN PATIENTS WITH HEREDITARY ANGIOEDEMA IN THE 21ST CENTURY?: A DEVELOPING COUNTRY PERSPECTIVE

AUTHORS

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Objective: To report our experience with mortality in patients with hereditary angioedema and to report factors associated with death in these patients.

Methods: We reviewed the medical records of all patients diagnosed to have HAE in the Pediatric Immunodeficiency Clinic, Department of Pediatrics, Postgraduate Institute of Medical Education and Research, Chandigarh, India. Medical records of families who reported atleast 1 death attributable to HAE were analysed in detail.

Results: Of the 39 families (110 patients), 11 families (23 patients) reported death of at least 1 family member because of HAE. All these family members died of laryngeal edema. Age at death was known in 20 patients out of 23 patients with median age at death of 31 years. Except 1 patient who died while she was taking treatment for HAE, the diagnosis was not established prior to death in others. At the time of death of these patients, atleast 1 another family member was symptomatic and even then the diagnosis was not established.

In our cohort, only 1 patient died during follow up. This was 17 year old female who was diagnosed at 10 years of age and was on long term prophylaxis with Stanazolol and Tranexamic acid. However, the drug compliance was not adequate because of the adverse effects in the form of amenorrhea and hirsutism. She developed an episode of laryngeal edema and died on way to the hospital.

In addition, we carried out quality of life assessment in 32 patients in our cohort using angioedema quality of life scale (AE-QoL). We observed that 29 out of 32 had severe impairment in the quality of life while 2 had no impairment.

Conclusion: HAE is a rare genetic disorder with significant mortality especially in developing nations like India. Laryngeal edema is commonest cause. Early diagnosis and treatment may prevent this catastrophic outcome.

POSTER 69 - CASE REPORT. NEW DIAGNOSTIC OF A 65-YEAR-OLD WOMAN WITH PAUCISYMPTOMATIC COMMON VARIABLE IMMUNODEFICIENCY (CVID) WITH VERY LOW LEVELS OF IGG (50 MG/DL), BUT NORMAL LEVELS OF IGA AND IGM

AUTHORS

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Objective: The objective of this case is to describe the case of a 65-year-old woman who shows very low IgG levels with normal IgA and IgM levels in a routine blood test..

Design And Method: We compiled the clinical data from our consultation and conducted the immunodeficiency study protocol, which included humoral immunity (turbidimetry), lymphocyte populations by flow cytometry, and response to polypeptide and polysaccharide vaccines (ELISA). Differential diagnosis with secondary immunodeficiencies was also performed.

Result: A 65-year-old female patient who was admitted to the Emergency Room with a 5-day history of fever. Her laboratory tests showed lymphopenia with very low levels of IgG. She was then referred to our department for further evaluation after being treated in ER.

She has shown moderate symptoms of respiratory infections such as recurrent otitis and tympanic perforation since her early childhood. She underwent surgery at the age of 10 years to treat said perforation and experienced residual deafness. She suffered from recurrent tonsillitis and was surgically treated at the age of 20, as well as recurrent bronchitis which was treated with oral antibiotics 3 to 5 times a year. No hospital admissions for pneumonia or other recurrent or severe infections has been required. No other otorhinolaryngologic infections were reported. Lymphoproliferative syndromes and myeloma, as well as protein-losing enteropathy, such as chronic diarrhea or kidney failure, were ruled out.

Other surgical interventions: Hysterectomy.

Family history: Daughter with idiopathic thrombocytopenia.

Laboratory results:

- Serum proteins: Decreased IgG with normal IgA and IgM (Table 1).
- Lymphocyte populations: Decreased B memory and switched B memory lymphocytes (Table 1).
- Autoimmunity tests: Negative
- Vaccine response (pre and post vaccination): Absence of response to polysaccharide and peptide vaccines (Table 2).
- We were able to recover the result of a 35-year old proteinogram (1986) where a gamma fraction of 5.7%= 350 mg/dL was already appreciated.
- Genetic study NGS panel of 200 genes associated to primary immunodeficiencies was negative

Conclusions: We have presented the case of a patient who may have had an isolated IgG hypogammaglobulinemia since she was at least 30 years of age with decreased memory-B lymphocytes and absence of response to peptide and polysaccharide vaccines. Even when her IgG was so low, we were surprised to see she had normal levels of IgA and IgM and had experienced very mild clinical features over her lifetime.

POSTER 70 - FUNCTIONAL EVALUATION OF NEUTROPHIL USING NITROBLUE TETRAZOLIUM TEST: 12 YEARS REVIEW IN A TERTIARY REFERRAL CENTRE IN MALAYSIA

AUTHORS

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Neutrophil dysfunction is one of the disorders of innate immunity which may present with defective microbicidal oxidative burst activity. Hence, measuring the ability of neutrophils to kill microbes provides a valuable index of its functional capacity in the immune system. The Nitroblue Tetrazolium (NBT) test is one of the tests available for evaluating phagocytic oxidase function of cells, making it an invaluable tool in assessing neutrophil function, specifically in the diagnosis of chronic granulomatous disease.

Objective: This study aims to review the demographic profile, indications, and clinical profile of patients investigated with NBT in our centre.

Design and Method: Profile of pediatric patients (below 12 years) who had performed NBT in Hospital Canselor Tuanku Muhriz UKM (HCTM), Malaysia from January 2010 to October 2021 were reviewed retrospectively.

Results: The data revealed a cohort of 44 patients with an average age of 24.6 months (2.05 years) and 63.64% were male. More than half of the patients (53.13%) had recurrent infections including multiple recurrent abscesses (37.50%), skin and gastrointestinal infections (28.13%), and upper respiratory tract infections (21.88%). The mean absolute neutrophil counts of this cohort of patients was $3.9 \times 10^9/L$ (range $1.5 - 8.5 \times 10^9/L$), with most having relatively higher absolute lymphocyte count than the expected value for their age. NBT tests performed revealed most of the results were within the normal range with an average of 89.55% of PMA stimulated neutrophils. Only 2 patients had lower than normal NBT results (15-30% of PMA stimulated neutrophil), with one of them being diagnosed to have a novel neutrophil dysfunction. With an exception of one syndromic patient who had a low B cell count, all the other patients had normal serum immunoglobulin levels (IgG, IgA, and IgM) and lymphocyte subsets counts (T-cell (including CD4 and CD8), B-cell, and NK cell).

Conclusion: Upon review, all the 44 patients had strong clinical indications for the request of NBT tests, having fulfilled the 10 warning signs criteria for PID, with most presenting with recurrent abscesses. It is important to note that HCTM is a tertiary referral centre for PID, in which referred cases were mostly complex with diagnostic dilemmas. Classical cases of PID including CGD were mostly diagnosed before being referred to the centre, thus explaining the lower positive rate of the test despite the strong clinical indications of a possible defect in the neutrophil cases.

POSTER 71 - CASE REPORT: COMMON VARIABLE IMMUNE DEFICIENCY WITH THE SAME GENOTYPE AND TWO DIFFERENT CLINICS SEEN IN TWO SIBLINGS

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CVID, is a heterogeneous group of immunodeficiency disorders, characterized by decreased serum immunoglobulin levels, abnormal antibody responses, and increased susceptibility to recurrent bacterial infections. In this case report, two siblings with CVID which have the same genotype and two different clinics are presented.

Case 1: 29 years old male patient, who had repetitive upper respiratory tract infections (10 times per year in approximately 10 times a year) and the person has a history of admission to the hospital of pneumonia were only low Ig A in laboratory values. At that time, this situation is evaluated as a selective IgA deficiency. With the past 20 years after the patient, a certain story of one time pneumonia and tonsillitis per year. The last patient who started working as a doctor about 5 years ago had a persistent cough with sputum complaint, and after that, a chest X-ray taken in a patient who applied to various clinics revealed infiltrations consistent with pneumonia and then, for this reason, he received antibiotic treatment. He hasn't received benefits from this treatments. After that, the patient was applied pulmonology clinic to request sputum culture and ARB evaluation; the result was detected ARB(+). After that, anti-tuberculosis treatment was started. In routine follow-up, which were examined three weeks after the start of treatment were elevated liver enzymes detected, the treatment was interrupted for a while. Serological examination of hepatitis etiology has revealed Anti-CMV-IgM(+) and abdominal ultrasound examination revealed splenomegaly, hepatomegaly and hepatosteatosis. In addition, the immunoglobulin levels were found low. It was decided to start immunoglobulin therapy. At the first stage, 60 g intravenous immunoglobulin therapy was given, and the IgG value after treatment was reached normal range. In addition, flow cytometry and Immunoglobulin values at the time of diagnosis and after the immunoglobulin treatment are shown in table 1. Subsequently, the patient's immunoglobulin therapy was arranged as subcutaneous administration. The genetic examination of both cases have shown table 1.

Case 2: 44 Year old female individual; the sister of case 1. Case 2 was screened for immunodeficiency after Case 1 is receiving diagnosis and she has a history of recurrent urinary tract infection, vaginitis and repeated antibiotic use for them since six years. Other than that, she doesn't have any other history of infection in her story. In the genetic examination as the same as the case. Since the patient's IgG values (Table 2) are close to the lower limit and she does not have a serious infection; in addition, it was planned to start immunoglobulin administration if any serious infection develops due to a history of cardiovascular disease in the individual.

POSTER 72 - A SLOVENIAN EXPERIENCE OF NETHERTON SYNDROME PATIENTS IN THE LAST 30 YEARS

AUTHORS

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Objective: Netherton syndrome is a rare autosomal recessive genodermatosis characterized by congenital ichthyosiform erythroderma, trichorrhexis invaginata and immune dysregulation caused by SPINK 5 mutation leading to reduction of LEKTI inhibition of proteolytic enzymes in the skin. Most complications of the disease occur in the first months of life with dehydration, failure to thrive and recurrent infections. Homozygous mutation and mutations located upstream in LEKTI seem to correlate with more severe phenotypes. In addition, more severe phenotype is observed in mutations that abolish LEKTI expression. We present clinical and genetic data of Slovenian Netherton patients treated in the University Medical Center Ljubljana, Slovenia in the last 30 years.

Design And Method: We have analyzed clinical documentation of Netherton patients treated in the University Children's Hospital and the Dermatology and Venereology Clinic. We have compared their clinical picture, time to clinical and genetic diagnosis and their mutations. We have classified patients into 5 different groups based on their clinical severity score in the first 5 years and later on.

Results: In this study, we report on 6 unrelated patients with Netherton Syndrome aged 4 months to 30 years, who are all still alive at the time of writing. In the table 1 we present the genetic mutations, clinical picture, clinical severity score and course of disease in the first 5 years and later on. All of our patients had more severe clinical course in the first five years of life. They all had failed to thrive, three of them had a severe bacterial infection in the first months of life. We have three patients with a homozygous mutation in our cohort with different clinical course. The most severe disease course has our youngest patient with c.1431-12G>A – homozygous mutation.

Conclusions: A Slovenian cohort of patients with Netherton syndrome has similar course of disease and its complications can be compared to complications seen in Netherton syndrome patients described in the literature. According to our experience, patients with different SPINK 5 homozygous mutations can have different clinical course. The patient with the most severe course has an intronic homozygous mutation that leads to the absence of the LEKTI expression. Two patients with a homozygous mutation nearer NH2 end of the protein have a milder clinical picture. Some, if not all Netherton patients could probably benefit from active antimicrobial prophylaxis and immunoglobulin prophylactic treatment in the first months of life.

THURSDAY, APRIL 28, 2022

GUIDED POSTER WALK 3B - GENETIC DIAGNOSIS B

MODERATOR: Prof Frank Staal

POSTER 73 - GENETIC LANDSCAPE OF PRIMARY IMMUNODEFICIENCIES IN UKRAINE

AUTHORS

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Background: Ukraine with a population of about 42 million belongs to the countries, information on the incidence of PID, prevalence of certain nosologies and their genetic variants, is poorly represented on the world map.

Purpose: The aim of study was to determine the incidence of PID and genetic landscape in Ukrainian population.

Methods: This study involved 1304 patients from the Ukrainian National Registry of primary immunodeficiencies. The genetic data are available for 305 pts – 23,3% of all patients in the PID Registry and 42% among patients with severe forms of PID.

Results: The overall prevalence of PID in Ukraine is 2 cases per 100000 inhabitants. Among 305 patients with genetically verified diagnosis the mutations were detected in 62 genes, responsible for the development of 75 nosologies. Predominantly antibody deficiencies are the most common subcategory of PID (52,54%), followed by combined immunodeficiencies with associated or syndromic features (21,73%), combined immunodeficiencies (7,3%), congenital defects of phagocyte number and function (7,66%), diseases of immune dysregulation (2,54%), complement deficiencies (1,78%) and autoinflammatory disorders (1,34%). The most common of the genetically verified nosologies are XLA (67; 22%), CGD, Di George (73; 24%), Nijmegen syndrome (55; 18%), Ataxia-teleangiectasia (40; 13,2%), Wiscott- Aldrich syndrome (29; 9,6%). The majority of patients with Nijmegen syndrome and ATA are from the western Ukraine, 75% and 71,9%, respectively. In general, in Western Ukraine there is a predominance (60%) of autosomal recessive forms of primary immunodeficiencies, while in the Central and Eastern parts of the country there is a different distribution with a predominance of up to 70-75% of PID with X-linked and AD type of inheritance. SCID with different genes affected accounts for 68 cases (5,2% from all PID) with most frequent affected IL2RG gene, followed by RAG1 with the majority of mutations presented as c.256_257delAA, which was suggested as Founder Variant in Slavic Countries.

Conclusions: Distribution between the main groups of PID in Ukraine is similar to the structure in the European countries but the incidence of PID remains lower. The peculiarity of the genetic landscape is a significant number of patients with Nijmegen syndrome, which reflects its Slavic origin. The Founder Variant study on individual nosologies is of interest for further research, just like the differences in the distribution of inheritance types across the country.

POSTER 74 - EVALUATION OF INBORN ERRORS OF IMMUNITY IN CHILDREN WITH SUSPECTED MENDELIAN SUSCEPTIBILITY TO MYCOBACTERIAL DISEASE

AUTHORS

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Objective: Identification of genetic variants of the IFN gamma or IL 12 pathway in children with suspected Mendelian susceptibility to mycobacterial disease and their functional characterization

Design: Prospective observational study

Method: 32 patients with disseminated tuberculosis, extra-pulmonary forms of tuberculosis excluding tubercular meningitis and lymph node TB, disseminated BCGosis and non-tubercular mycobacterial infections, non-typhoidal Salmonella and intramacrophagic bacterial and fungal infections were subjected to targeted next generation sequencing (NGS) using the Ion Torrent S5 system for genetic analysis. Flowcytometric evaluation of the IFN gamma or IL 12 axis was done for functional validation of identified variants.

Results: Of the 32 patients who underwent NGS, 15 patients (46.87%) had mutation proven MSMD. The median age at disease onset in mutation proven MSMD was 7 years. The clinical features include: BCG adenitis (6/15; 40%), BCG local site reaction (3/15; 20%), disseminated TB (12/15; 80%), skeletal TB (9/15; 60%). Organisms identified include MTB (5/15; 33.33%), Mycobacterium bovis (3/15; 20%), Mycobacterium avium complex (1/15; 6.66%), Salmonella typhi (1/13; 6.66%) and Salmonella sp.(2/13; 13.33%), Psuedomonas sp. (1/15, 6.66%), Cytomegalovirus (CMV) (1/15, 6.66%). Thirty-three percent of patients in our cohort were infected by more than one organism. Family history of mycobacterial infections was reported in 8 patients. Among the patients IL12RB1 mutations were identified in 6 (40%), IFNGR1 mutations in 5 (33.33%), IFNGR2 mutations in 2 (13.33%), ISG15 mutation in 1 (6.66%) and IL12B mutation in 1 (6.66%). Protein expression of IL12RB1 (CD212) or IFNGR1 (CD119) was decreased in all patients with IL12RB1 or IFNGR1 (except 1) mutation, respectively, as indicated by flow cytometer. CD119 expression was increased in one patient with partial dominant IFNGR1 mutation in the cytoplasmic domain, resulting in cell surface expression of truncated molecules. Flowcytometric assay revealed reduced phosphorylation of STAT4 and STAT1 in all patients with IL12RB1 and IFNGR1 mutation, respectively.

Conclusion: It is important to have a clinical suspicion of MSMD in patients presenting with disseminated forms of mycobacterial infections. Flowcytometric evaluation for IL 12/IL 23/ISG15/IFN gamma circuit should be done in all patients with BCGosis for rapid MSMD diagnosis and provides important clues to the underlying genetic defect.

POSTER 75 - CLINICAL HETEROGENEITY IN A FAMILY WITH A GAIN-OF-FUNCTION VARIANT IN IKBKB: DOES SP110 FUNCTION AS A MODIFIER GENE?

AUTHORS

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Objective: IKBKB encodes for the IKK2 protein which can activate NF- κ B signaling, and is crucial for immune responses. We identified a family in which six family members have a heterozygous variant of unknown significance (VUS) (c.194T>C) in the IKBKB gene. Three family members without the IKBKB variant were clinically and immunologically unaffected. Six family members with the IKBKB variant had reduced absolute T- and B lymphocytes and hypogammaglobulinemia. However, the clinical phenotype was highly variable. The proband developed lethal CMV disease at 48 years of age and her daughter (26y) suffered from colitis and warts. The brother (55y) of the proband and his son (15y) had recurrent upper respiratory tract infections. Two other family members (18y, 21y) with the IKBKB variant displayed an aberrant immunological phenotype but no clinical features. The proband and her daughter, who were clinically most severely affected, harbored an additional heterozygous VUS in the SP110 gene (c.1447G>A). SP110 protein has been described to modulate NF- κ B signaling. Therefore we hypothesized that SP110 may function as a modifier gene of NF- κ B activity.

Design and method: Western blot analysis, phosphoflow, and stimulation assays on fibroblasts and EBV immortalized lymphoblastoid cell lines (LCLs) were conducted to explore NF- κ B activity. Luciferase assays were performed to measure IKBKB and SP110 function.

Results: Expression of IKK2 protein was not altered, but fibroblasts and LCLs from the family members with the IKBKB variant had constitutive phosphorylation of P65, increased degradation of I κ B α , and increased secretion of IL-6 and IL-8 after stimulation. Furthermore, overexpression of the IKBKB variant in an luciferase assay showed increased NF- κ B activity. Interestingly, LCL from the proband (with additional VUS in SP110) displayed higher secretion of IL-6 and IL-8 than LCLs from family members with only the IKBKB variant. This data suggests that the VUS in SP110 further enhances activity of the NF- κ B pathway. Therefore, we are currently investigating if the variant in SP110 indeed has functional consequence on the NF- κ B pathway.

Conclusion: The c.194T>C variant in IKBKB results in increased NF- κ B activity, suggesting a gain-of-function of the IKK2 protein, leading to a combined immunodeficiency with a highly variable clinical presentation. Our observations raise a number of intriguing questions: 1) whether a clinical phenotype will develop in the clinically unaffected family members and/or how this is triggered 2). if the variant in SP110 acts as modifier gene of NF- κ B pathway activity and 3). how these patients should be monitored and treated.

POSTER 76 - PROFILE OF INBORN ERRORS OF IMMUNITY (IEI) IN NEPAL- EVEREST AHEAD YET TO BE SCALED

AUTHORS

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Background: Inborn errors of immunity (IEIs) are increasingly being diagnosed in various regions of the world. With increasing awareness, and diagnostics, IEIs are diagnosed with increasing frequency and accuracy in Nepal. Besides, IEIs are also being evaluated in children presenting with autoimmune manifestations. We describe the profile of patients diagnosed with IEIs in Nepal during 2020-2021.

Methods: Records of all patients with IEIs who were diagnosed and treated at our tertiary care centre in Nepal from August 2020 to October 2021 were analysed. Lead author (DB) has examined and diagnosed all cases. IEIs were diagnosed as per European Society for Immunodeficiencies (ESID) diagnostic criteria based on clinical and laboratory evidence including flow-cytometric and genetic analysis.

Results: Twenty-four patients with IEI (14 boys; 10 girls) and 171 children with autoimmune disorders were diagnosed during the study period. Genetic analysis was done in 10 patients. The profile includes patient with chronic granulomatous disease (12.5%), X-linked agammaglobulinemia (12.5%), severe combined immunodeficiency (RAG and IL2RG gene defects) (8.3%), Common variable immunodeficiency (8.3%), Job syndrome (8.3%), Selective IgA deficiency (8.3%), Wiskott-Aldrich Syndrome (4%), IFN-IL12 pathway defect (4.1%), MonoMac syndrome (4.1%), Leukocyte adhesion defect (4.1%), hereditary angioneurotic edema (4.1%), early-complement deficiency lupus (4.1%), autoimmune lymphoproliferative syndrome (4.1%) and unclassified IEI (12.5%). Both patients of SCID succumbed to their illness before exploring the scope of hematopoietic stem cell transplantation (HSCT). In addition, 171 cases of autoimmune disorders were diagnosed. It included connective tissue disorders (Childhood lupus (n=23), dermatomyositis (n=4), and scleroderma n=2), autoinflammatory disorders (3%), juvenile idiopathic arthritis (53%), interferonopathy (0.58%), multisystemic inflammatory syndrome in children (10%) and autoimmune vasculitis (7%). All patients with IEIs are on antimicrobial prophylaxis. All children with humoral immunodeficiencies are commenced on regular intravenous immunoglobulin replacement. Two patients with IEIs are planned for HSCT.

Conclusion: We present our experience of IEIs in resource-limited settings. Socio-economic status and limited resources coupled with lack of awareness of IEIs among laity and pediatrician accounted for a missed diagnosis, late diagnosis, and poor outcome in Nepal. Antimicrobial prophylaxis reduced the incidence of breakthrough infections.

POSTER 77 - THE MULTIFACETED SYNDROMIC IMMUNODEFICIENCIES: A SINGLE INSTITUTION'S 15-YEAR EXPERIENCE

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Syndromic immunodeficiencies are conditions with immunodeficiencies overlapping with other multisystem clinical manifestations which are not necessarily associated with the immunologic deficit. We performed a retrospective case series of patients with syndromic immunodeficiencies in our institution from 2006 to 2021. 47 patients were identified and included in the study. Mean age was 11.7 +/- 7.4 years. Median ages of primary immunodeficiency (PID) (n=47) and genetic diagnosis (n=44) were 5 years (range 0.1-17 years) and 2 years (0-16 years) respectively. Majority of the patients presented with recurrent/severe infections before 1 year old (27/41; 66%). 8/41 (20%) developed infections between 1 and 5 years old whilst only 6/40 (15%) after 5 years of age. There were 24 different genetic syndromes associated with PIDs. 8/47 (17%) had genetic diagnosis which were not commonly associated with PIDs: 2p16.3 deletion syndrome, supernumerary ring chromosome 20 syndrome, Arboleda-Tham syndrome, microcephalic osteodysplastic primordial dwarfism type 1, Myhre syndrome, Noonan syndrome, trisomy 22 and trichothiodystrophy/Cockayne syndrome complex. Two patients with protein kinase C delta deficiency, two patients with Wiskott-Aldrich syndrome (WAS) and one with sideroblastic anaemia with B cell immunodeficiency, periodic fevers and developmental delay (SIFD) had undergone haematopoietic stem cell transplant. One patient with WAS had lentiviral-mediated gene therapy and one DiGeorge syndrome (DGS) patient received thymic transplant. 7/47 (15%) died: DGS (n=1), SIFD (n=2), supernumerary ring chromosome 20 syndrome (n=1), activated PI3 delta syndrome (APDS) (n=1), deficiency of adenosine deaminase 2 (DADA2) (n=1) and cartilage hair hypoplasia (n=1). Our study demonstrated that syndromic immunodeficiencies have wide spectrum of presentations, affecting multi-organ systems. This raises the need to ensure these children are cared by multidisciplinary teams (including paediatric infectious diseases and immunologists), overseen by general paediatricians in view of their management complexities and varying degree of prognosis. Patients with inborn errors of immunity should be thoroughly assessed for syndromic features besides infections, autoinflammation, autoimmunity, immune dysregulation, lymphoproliferation, malignancy and allergy.

POSTER 78 - IL-6 MEDIATED STAT3:NFKB SIGNALLING CASCADE IN LOSS OF FUNCTION STAT3 HYPER IGE SYNDROME PATIENT: CROSSTALK, DYNAMICS & SIGNAL INTEGEARTION

AUTHORS

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Introduction: Long treatment with IL-6 in LOF-STAT3-HIES patients (n=5) leads to impaired cellular accumulations of unphosphorylated STAT3: unphosphorylated NFkB (U-STAT: U-NFkB) resulting in significant downregulations of genes (RANTES, IL-6, IL-8, STAT3) on mRNA levels & protein levels. Jurkat E6-1 cells were transfected with different STAT3 mutants in CC domain, TA domain and SH2 domain, results showed significant downregulation of RANTES, IL-6, IL-8, STAT3 and other kb dependent genes.

Objective: To assess the mechanism of U-STAT3: U-NFkB complex activation pathway in response to IL-6 in LOF STAT3-HIES patients.

Methodology: Cohort of 40 suspected HIES subjects on basis of clinical & laboratory phenotype (recurrent infections, eczema) NIH score ≥ 20 and Th17 cells $\leq 0.5\%$, 5 genetically confirmed cases were recruited along with 10 controls to analyze U-STAT3: U-NFkB complex activation pathway. mRNA expression of genes (RANTES, IL6, ICAM1, SOCS3, ZFP36L2, CSF1, STAT3, IL8 & IFN-B1) was performed in 05 LOF-STAT3-HIES patients & control, after long treatment of IL-6 (36hrs). 04 different STAT3 mutants in AT (K49R), CC (K140R), TA (K685R) and SH2 (Y705F) domain were transfected in Jurkat cells to examine mRNA expression of genes by qRT-PCR and protein expression were analyzed by western blot with or without IL-6 treatment. ChIP qPCR analysis were performed in 05 patients after treatment with IL-6. Quantification of fold enrichment in patient & control relative to nonspecific IgG as negative control and normalized with input DNA.

Result: mRNA expression of genes (RANTES, IL6, ICAM1, SOCS3, STAT3 & IL8) were analyzed using qRT-PCR showed significant down-regulation of above mentioned genes in 05 patients (P1:R518X, P2:T714I, P3:E466D, P4:R455Q, P5:R382W) compared to controls after treatment with IL-6. Flow-cytometry analysis of STAT3, showed reduced expression pSTAT3 & total STAT as compared to controls. pSTAT3 was found to be reduced in 60% of cohort. ChIP qPCR showed significant down-regulations of RANTES & STAT3 in patient. Jurkat cells were transfected with different STAT3 mutants, there was significant downregulation of all above mentioned genes.

Conclusion: This was a first study ever human study conducted showing a novel role of U-STAT3: U-NFkB in LOF STAT3 HIES patient, showing impaired regulation of STAT3: NFkB complex activation pathway that resulted in down-regulations of RANTES, STAT3, IL-6, IL-8, CSF1, ZFP36L2 and other kb dependent genes after IL-6 treatment indicating that U-STAT3: U-NFkB pathway was under-utilized in the LOF STAT3 HIES patients. STAT3 mutant transfection studies further confirmed impaired response of U-STAT3: U-NFkB complex pathway.

POSTER 79 - A NOVEL MUTATION IN A TURKISH CHILD PRESENTED WITH HIGH IGM LEVELS AT ADMISSION AND DIAGNOSED AS XLA FOR A LONG TIME

AUTHORS

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Agammaglobulinemia or hypogammaglobulinemia is a rare inherited immunodeficiency disorder. Mutations in the BLNK gene cause low levels of mature B lymphocytes in the peripheral blood leading to recurrent infections. We present a Turkish boy who had recurrent respiratory tract infections for six months. He had low IgG (81 mg/dl) and IgA levels (<5 mg/dl) with high IgM (258 mg/dl). Flow cytometric analysis of lymphocyte subsets showed low CD19+ B cells (0.05%). Homozygous c.790C>T (p.Gln264Ter) mutation was detected in the BLNK gene with Targeted Next Generation Sequencing (TNGS).

Agammaglobulinemia may be due to different genetic etiologies together with complex genetic events. Although the first diagnosis to be considered in boys is Bruton's agammaglobulinemia, patients with normal BTK sequence and/or expression should be investigated with a large genetic study such as TNGS in the early period to reach a definitive diagnosis. This case of agammaglobulinemia, observed in a 4-year-old male patient, highlights the necessity of considering BLNK mutations in children with B cell deficiency, even though they are known to be rare causes of agammaglobulinemia.

POSTER 80 - CONGENITAL NEUTROPENIA DUE TO HOMOZYGOUS MUTATION IN GLUCOSE-6-PHOSPHATASE CATALYTIC SUBUNIT 3 DIAGNOSED IN AN ADULT.

AUTHORS

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Objective: To report the case of an adult with a late diagnosis of congenital neutropenia.

Clinical Case: A 34-year-old female without consanguinity, mother with a history of an abortion. Personal history of low height and weight. Diagnosed with ventricular septal defect at 8 months, maxillary sinusitis, bronchitis and pharyngitis at 4 years, complicated pneumonia at 9, 26 and 30 years, bronchiectasis over infected at 14. All required hospitalization and intravenous antibiotic. Pulmonary tuberculosis at age 9. Menarche at 12, later with amenorrhea, diagnosed with hypotrophic hypogonadism secondary to infant uterus and ovaries. Sent at 25 years of age to hematology for neutropenia 400 cells/mm³, lymphocytopenia 1300 cells/mm³ and thrombocytopenia 97,200 cells/mm³. Normal bone marrow biopsy. They start filgrastim with a favorable response. Diagnosed with chronic bronchopulmonary aspergillosis, treated with voriconazole at age 30, she is sent to immunology, she is found with CD4 259 cél/mm³, CD8 376 cél/mm³, CD16+ CD56+ 290 cél/mm³, CD19 155 cél/mm³. IgA 79 mg/dl IgG 1818 mg/dl, IgM 214mg/dl.

Due to the presence of repeated sinopulmonary infections, infection by mycobacteria and fungal, low levels of CD4, initially combined immunodeficiency was suspected, however, by the presence of neutropenia below 500 cells / mm³ on 3 continuous occasions, and the exclusion of secondary causes, sequencing is performed, homozygous mutation of glucose-6-phosphatase catalytic subunit 3 (G6PC3) is detected.

Discussion: the mutation in G6PC3: is causing congenital neutropenia, severe recurrent infections, hormonal deficiency, growth retardation, heart and genital condition, as documented in this patient, It is a mutation generally of heterozygous origin, however, in this clinical case, it stands out to be homozygous, hoping to cause congenital neutropenia of greater severity with poor prognosis. However, the patient was diagnosed late in adulthood, resulting in complications.

Conclusion: There are few reported cases, the screening of immunodeficiencies combined with neutropenia just at a high suspicion, and the comprehensive identification of the morphological alterations, will contribute to the underdiagnosis and will have important prognostic implication in the diagnosis of G6PC3 deficiency.

POSTER 81 - PATHOGENIC VARIANT IN TLR3 IN TWIN GIRLS WITH VIRAL ENCEPHALITIS AND OVERWHELMING INFLAMMATION

AUTHORS

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Objective: TLR3 defects underlie severe viral infections, such as herpes virus encephalitis and influenza pneumonia. We investigated MCDA twins with viral encephalitis and multi-organ failure upon overwhelming inflammation to screen for inborn errors of immunity.

Design and method: We performed a trio exome sequencing-based primary immunodeficiency panel.

Results: Both children were admitted to the intensive care at the age of 8 months and 12 months, respectively, with encephalitis. P1 had also hepatitis, pleural effusion, and positive cytomegalovirus (CMV) PCR in blood and cerebrospinal fluid. She recovered within 3 weeks on ganciclovir and Megalotect and was discharged on IV immunoglobulins (IVIG) and valganciclovir. P2 had encephalitis with tonic-clonic seizures, hepatitis, myocarditis, and pericarditis. The respiratory panel was positive for parechovirus, rhino/enterovirus, and coronavirus NL63. CMV PCRs were negative in all tested fluids. She recovered with supportive therapy and was started on IVIG. Three months later, both children developed severe systemic inflammation with acute hepatitis, myocarditis, and cardiogenic shock during a respiratory tract infection with respiratory syncytial virus (RSV) and succumbed despite intensive treatment.

A clinical exome sequencing identified a pathogenic heterozygous variant in TLR3 in both sisters (c.1660C>T, P554S). TLR3 restricts early viral replication by controlling IFN- β production in infected cells and TLR3 deficiency underlies life-threatening infections with several viruses, including SARS-CoV-2, influenza, and herpes.

Conclusions: Despite prophylactic treatment with IVIG, the course of viral infections was extremely severe in these patients, with multi-organ failure due to associated systemic inflammation and myocarditis. The clinical course of these patients demonstrates the crucial importance of an intact TLR3-mediated antiviral response, not only in case of herpes or influenza infection, but also for other double stranded or single stranded RNA viruses (such as CMV and RSV).

POSTER 82 - MONOGENIC DISORDER ASSOCIATED WITH AUROIMMUNE LYMPHPPROLIFERATIVE SYNDROME -LIKE PHENOTYPE

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Objective: Autoimmune lymphoproliferative syndrome (ALPS) is a congenital disorder that results in an apoptosis impairment of lymphocytes, leading to chronic Lymphoproliferation and autoimmunity, mainly autoimmune cytopenia. Some of the autoreactive T cells cannot apoptosis in activation-induced cell death (AICD) pathway; therefore, they have accumulation of autoreactive CD4- and CD8- (double-negative) T cells, leading to cytopenia, splenomegaly, lymphadenopathy, autoimmune disorders, and a greatly increased lifetime risk of lymphoma. FAS, FASL, CASP8, and CASP10 gene defects are often responsible for the disease, the phenotype of which can vary from asymptomatic/mild forms to severe disease. More rarely, defects are associated with other genes involved in the ALPS-like phenotype.

Design and method: A systematic literature search was performed in Web of Science, PubMed, and Scopus from the earliest available date to March 2021 with standard keywords to find patients with ALPS-like phenotypes. Demographic, clinical, immunological, and molecular data were extracted.

Results: In this systematic review we reported 61 patients with genetically determined ALPS-like. Most of the ALPS-like cases carry mutations in the STAT3 (n=15), LRBA (n=11), and CARD11 (n=8) genes. The most common presentation was splenomegaly and lymphadenopathy followed by hepatomegaly. The most common autoimmunity was autoimmune hemolytic anemia and immune thrombocytopenic purpura followed by autoimmune neutropenia. Elevated serum immunoglobulin was reported especially in IgG, IgM, and IgA. An increased proportion of DNT cells was reported in almost half of patients.

Conclusions: Our results showed that all of the ALPS-like cases carry one or more mutations in the STAT3, LRBA, CARD11, KRAS, CTL4, ADA2, RASGRP1, STK4, TNFAIP3, PRKCD, NRAS, PIK3CD and UNC13D, RAGs, RELA, PIK3CD genes.

POSTER 83 - COMBINED IMMUNODEFICIENCY IN A PATIENT WITH KABUKI SYNDROME

AUTHORS

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Background: Kabuki syndrome (KS) is a rare congenital multisystem disorder. KS is caused by germline mutations encoding proteins for histone modification such as KMT2D or KDM6A. Abnormalities in KS include skeletal abnormalities, craniofacial defects and varying mental disability. Immunological abnormalities underlying susceptibility to infections are increasingly described in patients with KS.

Methods: We characterized a patient with KS like craniofacial dysmorphism and skeletal abnormalities. Recurrent infections suggested primary immunodeficiency (PID). Extensive immunologic phenotyping and genetic analysis using whole exome sequencing (WES) and Sanger sequencing were performed. The patient was treated with subcutaneous immunoglobulin replacement therapy which ameliorated the susceptibility to infections.

Results: We report a 51 year old male patient with congenital characteristic KS like skeletal morphology of the upper limbs and craniofacial abnormalities. He had repetitive bacterial airway infections requiring multiple antibiotic treatment. Immunologic phenotyping indicated a common variable immunodeficiency (CVID) defined by hypogammaglobulinemia, severe B cell and T cell lymphopenia and skewed B- and T-cell differentiation. WES demonstrated a heterozygous mutation in KMT2D (OMIM #147920) near the splicing site of exon 34/35 (c.21661C>T; p.Arg2789Trp). Sequencing of cDNA could exclude exon skipping and we did not observe a disadvantage of the mutated allele on cDNA level.

Conclusion: We present a novel rare KMT2D mutation associated with KS in a patient with PID. KS patients are prone to respiratory infections and repeatedly demonstrate immune deficiencies according to CVID equivalent immunophenotypes. Whether epigenetic abnormalities due to abnormal histone modifying function on KMT2D protein level cause dysregulation in B cell and T cell development should be further investigated.

POSTER 84 - GENOMIC RESULTS OF A PAEDIATRIC PATIENT WITH CENTRAL NERVOUS SYSTEM LYMPHOMA

AUTHORS

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Objective: To report the case of a patient with CNS lymphoma and the relation with his genomic analysis results.

Case Report: A 7-year-old boy diagnosed with stage IV primary CNS lymphoma is being followed up by Immunodeficiencies unit due to suspicion of primary immunodeficiency. The patient's parents are blood relatives and two sisters died in early infancy.

IgA and IgG hypogammaglobulinemia and increased IgM levels were detected in the immunological screening. In addition, in vitro lymphoproliferation capacity of CD4+ T cells was reduced and very low thymic production was observed.

Design And Method: Genomic DNA was isolated from peripheral blood and Next Generation Sequencing (GeneSystems) was performed using a library enriched in 200 genes associated with immunodeficiencies.

Results: The sequencing results allowed the detection of a homozygous allelic variant in ATM gene (p.Arg2849Ter) which was previously described as pathogenic for Ataxia-Telangiectasia (AT) Syndrome in databases and was also reported in AT-affected patients in the literature.

In addition, it was identified two heterozygous variants in LIG4 gene, both probably located in the same allele, as suggested by the software analysis. One of them, p.Met127Ile2, was previously reported as a variant of uncertain significance for LIG4 syndrome; and the other, p.Gly103Arg, had no records in genomic databases.

Conclusions: Both ATM and LIG4 genes are related to the DNA double-strand repair pathway. The identification of this ATM variant in homozygosis in our patient is compatible with the diagnosis of ataxia-telangiectasia. In addition, the LIG4 variants could have an additive effect on the dysfunction of the DNA-repair pathway.

POSTER 85 - HYPOGAMMAGLOBULINEMIA AND TRICHTHODISTROPHY: AN UNEXPECTED ASSOCIATION?

AUTHORS

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Objective: Trichothiodystrophy is a rare, autosomal recessive multisystemic disorder in which the main feature is brittle, short and sulfur deficient hair. The spectrum of clinical features varies from mild disease with only hair involvement to severe disease with profound developmental defects, recurrent infections and a high mortality at a young age. According to the literature it is seldom associated with immunodeficiency.

Methods: The authors reviewed clinical and laboratory data from medical records.

Results: We present a 5-year-old girl who had severe atopic dermatitis, photosensitivity, short and brittle hair, peculiar facies, development delay, failure to thrive and short stature. She had a deceased sibling with multiple congenital anomalies of unknown etiology.

At the age of 2 she was diagnosed with multiple severe IgE mediated food allergies with high levels of IgE (4348 kU/L). The child was hospitalized at 22 and 26 months for diarrhea, with identification of *Salmonella typhimurium* and *Aeromonas hydrophila* respectively. On the second admission she presented bacterial enterocolitis with suspicion of severe allergic enteropathy, hypoalbuminemia and hypogammaglobulinemia (IgG 82 mg/dL). She was given antibiotics, a restricted diet, corticoid therapy and high dose IVIG with initial clinical and nutritional recovery. She maintained hypogammaglobulinemia and continued treatment with frequent IVIg and systemic corticotherapy. No further serious infections occurred. Attempts to reduce corticotherapy resulted in worsened hypogammaglobulinemia and eosinophilia.

Whole exome based Mendeliome testing found compound heterozygous variants in the ERCC2 gene and cytogenetics studies found increased cellular sensitivity to UV light, both in favor of the diagnosis of trichothiodystrophy. Hair examination under polarized light microscopy revealed tiger-tail banding pattern, supporting the diagnosis of trichothiodystrophy. Immunophenotyping of B cells showed decreased CD19 levels (6,64% - 272/mm³). Next Generation Sequencing (NGS) panel for SCID, CID and predominantly antibody deficiencies presented some pathogenic variants of uncertain clinical significance.

Conclusions: Immunodeficiency is often associated with multiple genetic syndromes. Immunological studies should always be performed in patients with trichothiodystrophy as the diagnosis and treatment of hypogammaglobulinemia improves the prognosis of these children.

POSTER 86 - GENETIC DEFECTS IN INNATE AND ADAPTIVE IMMUNITY

AUTHORS

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Innate immunity is composed of phagocytic cells e.g., macrophages, dendritic cells, neutrophils, or intermediate cells (bridging innate and adaptive immunity cells) e.g., delta-gamma T cells, natural killer (NK) cells, and NK-T cells accompanied by natural barriers (skin epithelial layers and antimicrobial secretions and gastrointestinal and respiratory mucosa), cytokines and chemokines. Innate immunity receptors that are known pattern recognition receptors (PRRs) are either cell-associated (e.g., Toll-like Receptor) or soluble (e.g., complement proteins) that can recognize numerous pathogen-associated molecular patterns (PAMPs) or damage-associated molecular patterns (DAMPs). Every defect in each one of this integrated defense system may lead to pyogenic infections. Hence, we have provided a thorough or timely diagnosis and management guideline of innate immunodeficiency, which may improve the outcome of the disease treatment as well as we have provided deeper insight into introducing cost-effective and accurate predictive, diagnostic, and prognostic approaches to reduce the burden of the disease for patients, their families, and healthcare systems in the future.

POSTER 87 - UNUSUAL PRESENTATION OF AN UNCOMMON PRIMARY IMMUNODEFICIENCY

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A 2 year 11 month old girl presented with abdominal distension for 1 year, and multiple neck swellings, intermittent fever and progressive pallor for 3 months. She was given anti-tubercular treatment for 3 months prior to coming to us. Her elder brother had died at the age of 3 months due to pneumonia. On examination, she had pallor, generalized lymphadenopathy, eczematous skin rashes, tachypnea and spleno-hepatomegaly. Laboratory investigations showed anemia (57 gm/L) and thrombocytopenia (30×10⁹/L) with elevated inflammatory markers (Erythrocyte sedimentation rate- 28 mm/1st hr and C-reactive protein- 65mg/L). Infective work up including tuberculosis, kala-azar, cytomegalovirus and HIV came negative. Beta-D glucan was within normal limits. Contrast enhanced computed tomography showed patchy consolidation with ground glass opacities in dependent region of both lungs. Fine needle aspiration from lymph node was suggestive of granulomatous inflammation. Immunological work up showed decreased proportion of naïve helper (CD3+CD4+CD45RA+) and cytotoxic T lymphocytes (CD3+CD8+CD45RA+) and increased proportion of memory helper T lymphocytes (CD3+ CD4+CD45RO+). Lymph node biopsy and bone marrow biopsy showed infiltration of mixed histiocytic population without any evidence of malignancy. So, initially possibility of LCH vs non-LCH histiocytosis were kept. But, characteristics (including CD markers) of histiocytic population were not consistent with LCH. So, the child was started on oral prednisolone and whole exome sequencing was sent. Whole exome sequencing revealed a homozygous c.201-2A>G splice variant in intron 2 of IFN- γ R1 gene. This splice variant skips from end of exon 2 to middle of exon 3 and omit bases 201–302. The observed variation has previously been reported in patients with nontuberculous mycobacterial infections with mendelian susceptibility to mycobacterial diseases (MSMD). Therefore, immunological work up for MSMD were sent that showed reduced expression of phospho STAT-1 and phospho STAT-4 on gated monocytes and decreased IFN- γ receptor 1 expression on activated granulocytes and monocytes in the index child compared to control (by Flow-cytometry). So, diagnosis of MSMD was considered. However, no acid fast bacilli could be isolated either from gastric lavage or from lymph node biopsy of the index child.

The child was started on anti-tubercular treatment with isoniazide, rifampicin, levofloxacin and ethambutol. Although the child responded initially, there was recurrence of fever, rashes and organomegaly 4 months after initiation of anti-tubercular treatment. Therefore, the child was started on injection amikacin and oral azithromycin in addition to isoniazide, rifampicin and ethambutol (HRE). The child is doing well at 1 month of follow up.



FRIDAY, APRIL 29, 2022

GUIDED POSTER WALK 4 - TREATMENT ADVANCES

MODERATOR: Prof Klaus Warnatz

POSTER 88 - DEVELOPMENT OF A NOVEL BTK LENTIVIRAL VECTOR FOR GENE THERAPY OF X-LINKED AGAMMAGLOBULINEMIA

AUTHORS

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Background: X-linked agammaglobulinemia (XLA) is a rare X-linked genetic disorder resulting from mutations in the Bruton's tyrosine kinase (BTK) gene. These mutations lead to the failure of afflicted individuals to generate mature B cells as well as other immunological dysfunctions mainly in NK and myeloid cells. Current therapy consists of immunoglobulin replacement and targeted antimicrobial agents. This therapy is insufficient, as treated XLA patients continue to suffer from low quality of life and recurrent complications. To overcome this insufficiency, Lentiviral (LV)-based gene therapy has previously been demonstrated in various XLA mouse models. Interestingly, in terms of expression cassette design, most efforts focused on the inclusion of generic elements to increase BTK expression with less regard to expression specificity.

Objective: We hypothesized that by using the human BTK endogenous promoter, we would be able to maintain the tight physiological regulation of BTK gene expression while producing therapeutic Btk protein levels in the desired target cell populations.

Design and methods: To study the endogenous BTK promoter in depth, we dissected the proximal and distal regions into several fragments based on bioinformatic analysis. The constructs that included the dissected promoters were tested for expression levels and specificity in healthy human CD34+ cells. Next, we designed a BTK lentiviral vector with a codon optimized BTK transgene under the control of the endogenous BTK promoter (NTX109). NTX109 was tested in vitro and in vivo in XLA mouse model (Xid) for expression specificity, integration events and functional restoration.

Results: Transduction of NTX109 at escalating doses into CD34+ cells resulted in Btk expression which was 2-3fold higher compared to endogenous levels at a clinically relevant MOI and average vector copy number (VCN) of <2 (Fig. 1A and B). Transduction of Lin- cells derived from Xid mice with NTX109 resulted in substantial restoration of BTK expression leading to correction of B cell development in-vitro. Transplantation of NTX109 transduced Xid lin- cells to lethally irradiated Xid mice led to specific BTK expression in myeloid and B cells with no expression in T cells (Figure 1C). Furthermore, engrafted mice demonstrated a strong selective advantage of corrected cells. Therefore, treated animals were able to successfully restore B cell differentiation and antibody secretion in response to LPS stimulation (Figure 1D).

Conclusions: Our data demonstrates that NTX109 LV is a good candidate for development of a clinically safe and efficient XLA gene therapy.

POSTER 89 - PEGYLATED RECOMBINANT ADENOSINE DEAMINASE (ELAPEGADEMASE) MAINTAINS DETOXIFICATION AND LYMPHOCYTE COUNTS IN PATIENTS WITH ADENOSINE DEAMINASE-DEFICIENT SEVERE COMBINED IMMUNODEFICIENCY**AUTHORS**M Dorsey ¹, A Rubinstein ², H Lehman ³, T Fausnight ⁴, J Wiley ⁵, E Igboekwe ⁶, E Haddad ⁷**AFFILIATIONS**¹ University of California San Francisco Medical School, San Francisco, UNITED STATES,² Montefiore Medical Center/Albert Einstein College of Medicine, New York, UNITED STATES, ³ University of Buffalo, Jacobs School of Medicine and Biomedical Sciences, Buffalo, UNITED STATES, ⁴ The Penn State Milton S. Hershey Medical Center, Hershey, UNITED STATES, ⁵ Leadiant Biosciences, Inc., Gaithersburg, UNITED STATES, ⁶ Chiesi USA, Inc., Boston, UNITED STATES, ⁷ University of Montreal, Montreal, CANADA

Objective: Enzyme replacement therapy (ERT) is the first-line therapy for metabolic detoxification and immune recovery in patients with adenosine deaminase-deficient severe combined immunodeficiency (ADA-SCID). Previously, the only ERT available was pegademase, which had a short shelf life, unreliable production, and the theoretical risk of bovine spongiform encephalopathy transmission. Elapegademase is a PEGylated recombinant bovine adenosine deaminase (ADA) ERT developed to replace the bovine-derived ADA used in the manufacture of pegademase. This study (NCT01420627) was a multicenter, open-label, crossover from pegademase to elapegademase in patients with ADA-SCID to evaluate the ability of elapegademase therapy to maintain metabolic detoxification (trough erythrocyte total deoxyadenosine nucleotides [dAXP] LE. 0.02 mmol/L). Secondary objectives included assessment of trough plasma ADA activity, CD4+ and CD19+ lymphocyte counts, safety, and development of anti-drug antibodies (ie, anti-elapegademase and anti-pegademase IgG, IgM, and anti-PEG antibodies).

Design and Method: Once pegademase dosage was adjusted to achieve full therapeutic metabolic detoxification (dAXP LE. 0.02 mmol/L and ADA activity GTE. 15 mmol/h/L), patients began elapegademase therapy at an equivalent enzymatic dose to pegademase and discontinued pegademase. The study population consisted of 7 patients (mean age [SD]: 21.3 [9.5] years) with ADA-SCID at 6 different US centers.

Results: Upon switching to elapegademase, 1 patient withdrew after 2 doses due to injection site pain caused by EDTA in the original formulation; EDTA was removed from the formulation for the 6 subsequent patients enrolled. The 6 remaining patients completed 71 to 216 weeks of elapegademase therapy, with 3 patients completing GTE. 212 weeks. All 6 completer patients met the criteria for maintenance of full therapeutic metabolic detoxification during elapegademase therapy, with minor exceptions at 1–3 time points in 4 patients. Elapegademase therapy resulted in an increase in CD4+ and CD19+ lymphocyte counts compared with pegademase therapy, though the degree of the increase varied between patients. Elapegademase had a comparable safety profile to pegademase; no patient developed a severe infectious complication during the study. The most common adverse events during elapegademase therapy were cough and vomiting (3/7 patients for both); they were considered unrelated to therapy. Three of the 7 patients had transient, non-neutralizing anti-drug antibodies without effect on ADA levels or activity.

Conclusion: In this study elapegademase was well tolerated, maintained metabolic detoxification, and was associated with improvements in CD4+ and CD19+ lymphocyte counts compared with pegademase in patients with ADA-SCID.

POSTER 90 - EFFICACY AND SAFETY OF ROMIPILOSTIM IN TREATMENT OF THROMBOCYTOPENIA IN PATIENTS WITH WISKOTT-ALDRICH SYNDROME.

AUTHORS

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Objective: Hematopoietic stem cell transplantation (HSCT) is the treatment of choice for patients with Wiskott-Aldrich syndrome (WAS) and is highly successful. Yet, in patients awaiting HSCT, or in whom it cannot be offered for various reasons reduction of bleeding symptoms caused by thrombocytopenia is of paramount importance. Thrombopoietin receptor agonist (TPO-RA) romiplostim demonstrated its efficacy in small groups of WAS patients. Here, we report treatment efficacy and safety of romiplostim in a large cohort of pediatric WAS patients.

Design and methods: 67 eligible patients ages 16 days to 14.9 years (median, 1.3 years) with genetically confirmed WAS received romiplostim at 9 µg/kg weekly for 1-12 months (median, 8 months) between March 2012 and December 2019. Primary response was assessed at 4 weeks, long-term response – at 2-12 months of treatment. Response was classified as complete (platelets > 100 x 10⁹/L), partial (increment >30 x 10⁹/L but < 100 x 10⁹/L), or no response.

Results: Complete or partial primary platelet responses were observed in 22 (33%) and 18 (27%) subjects, respectively. Importantly, bleeding severity score (World Health Organization grades 1-4) decreased in both responders and non-responders. Platelet response persisted long-term in 38 (95%) responders. The number of patients who had grade 2 bleeding declined from 63% to 21% after 1 month of treatment.

There were no apparent severe adverse effects associated with romiplostim administration. No cytopenia or decrease in bone marrow cellularity were observed in patients' bone marrow aspirates, assessed after the median treatment duration of 12 months (range, 1 month to 2.8 years).

Given that 40% of the patients were non-responders, we also assessed the factors predictive of response. The only statistically significant parameter, affecting the probability of achieving a complete response was the median pretreatment platelet count (OR 1.8 with an increase in the number of platelets by 10 x 10⁹/L, p = 0.005) (Table 1). Also, missense mutations in WAS gene were present more often in patients with complete response, while truncating mutations were frequently found in partial and non-responders, but this trend did not reach statistical significance in multivariate analysis (OR 2.8, p = 0.124).

Conclusions: Romiplostim is safe and effective in managing thrombocytopenia and bleeding in most WAS patients. The responses tend to be durable and stable over time, with no considerable fluctuations. Clinical and laboratory predictors of response to romiplostim require further investigation.

POSTER 91 - MANUAL ADMINISTRATION OF SUBCUTANEOUS IMMUNOGLOBULIN 20% IN CLINICAL PRACTICE IN PATIENTS WITH IMMUNODEFICIENCIES

AUTHORS

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Objective: Although subcutaneous immunoglobulin (SCIG) is typically administered via an infusion pump, manual administration using a syringe and butterfly needle has emerged as an alternative technique that may be preferred by some patients. This analysis of the CUNCUN study (NCT03716700) evaluated manual administration of Immune Globulin Subcutaneous (Human) 20% Solution (Ig20Gly) in clinical practice in Canada.

Design and Methods: CUNCUN was a noninterventional, multicenter (n=6), prospective study that enrolled patients with primary immunodeficiencies (PID) or secondary immunodeficiencies (SID) who had transitioned to Ig20Gly from another SCIG. Data on Ig20Gly infusion parameters, dosing and adverse events (AEs) were collected from patient medical records at Ig20Gly initiation and 3, 6 and 12 months post-initiation; patient satisfaction and quality of life (QoL) were assessed 12 months post-initiation. Data were analyzed according to whether patients infused Ig20Gly manually or using a pump.

Results: Of 125 patients enrolled, 61 had PID (mean age 55 years; includes 1 patient with PID and SID) and 64 had SID (mean age 69 years). Of these, 43% (n=54) infused Ig20Gly manually. Compared with patients using an infusion pump, patients infusing Ig20Gly manually did so at lower median infusion volume per infusion and shorter infusion duration, were more likely to use two or fewer infusion sites, and typically infused more frequently (Table). In both groups, the abdomen was the most common infusion site and the median weekly dose was 8 g. Manual administration tended to be used more frequently by patients with PID than those with SID (43% vs 35%). Most AEs were mild or moderate in severity. Patients in both groups expressed overall satisfaction with Ig20Gly at 12 months post-initiation, with all respondents indicating they would like to continue Ig20Gly. Patient-reported QoL outcomes were comparable between the two groups.

Conclusions: This real-world study confirms the feasibility and tolerability of infusing Ig20Gly manually or via a pump in patients with PID or SID.

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POSTER 92 - SUSTAINED CLINICAL IMPROVEMENT IN THREE PATIENTS AFFECTED BY ACTIVATED PHOSPHOINOSITIDE 3-KINASE DELTA SYNDROME (APDS) TREATED BY THE SELECTIVE PI3KDELTA INHIBITOR LENIOLISIB

AUTHORS

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Introduction: Activated PI3-kinase-delta syndrome (APDS) is a primary combined immunodeficiency disease with variable clinical features mainly represented by sinopulmonary infections and non-neoplastic lymphoproliferation with high incidence of bacterial and viral infections and B cell-lymphomas. Clinical trials using selective p110d inhibitors have been initiated in adult patients. Here we present the follow-up of 3 patients treated by the p110d specific inhibitor Leniolisib (Novartis Pharmaceuticals).

Methods: The agreement for Temporary Use Authorisation of Leniolisib was obtained by French authorities in order to treat 3 patients presenting severe APDS disease despite Ig replacement therapy and the long-term immunosuppressive treatment.

Results: Patients of 4, 7 and 27 years old, started Leniolisib treatment in April 2019 and December 2020. The pediatric patients (P1 and P2, siblings) harbor a heterozygous mutation for p.E1021K in PIK3CD gene while the adult patient (P3) harbors a splice-site mutation in the PI3KR1 gene causing APDS2. P1 presented severe broncho pneumopathy and lymphoproliferation despite sirolimus treatment which had to be stopped because of renal toxicity; P2 presented several episodes of lung and renal bacterial infections with a severe involvement of the ENT sphere; P3 presented a life-threatening condition with severe lung and gastrointestinal infections, colitis, lymphoproliferation and fluctuating pancytopenia. Leniolisib was orally introduced with increasing doses in order to reach the daily dose of 140 mg for P3 and 60 mg and 80 mg for P1 and P2 accordingly to their weight. The treatment was well tolerated; no related toxicity was detected after respectively 30 months of treatment for P1 and P2 and 11 months for P3. To date all 3 patients presented a significant clinical improvement: only 1 severe adverse event unrelated to treatment was noticed (for P2, post-traumatic tibia osteomyelitis successfully treated by antibiotic therapy); the lymphoproliferation and splenomegaly significantly decreased as demonstrated by medical imaging. No other severe bacterial or viral infections were detected. The quality of life globally improved, P3 recovered normal job activity and family life. So far, no movement to normalisation or no negative impact on T and B cell subsets of the leniolisib treatment was observed.

Conclusion: Leniolisib is a well tolerated PI3Kd inhibitor even in pediatric APDS patients with favorable benefit-risk profile and clear improvement of the clinical status. In-depth analysis of the immunological profile is needed in order to better characterize the variable responses. Leniolisib represents a targeted treatment with new robust prospects for APDS treatment.

POSTER 93 - IN VITRO EFFECT OF RUXOLITINIB ON SIGNAL-TRANSDUCER-AND-ACTIVATOR-OF-TRANSCRIPTION 1 HYPERACTIVATION IN PATIENTS WITH DOMINANT NEGATIVE STAT3 MUTATIONS

AUTHORS

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Objective: Diseases caused by STAT1 gain-of-function (GOF) and dominant negative (DN) STAT3 mutations share clinical manifestations including infectious and inflammatory events. Targeted treatment with Janus-kinase (JAK) inhibitors shows promising results in treating STAT1 GOF-associated symptoms. However, management of DN STAT3 patients is mostly supportive. We aimed to determine the response of DN STAT3 patient cells to STAT1-activating cytokines as well as the impact of JAK inhibition in STAT1 activation and regulation of downstream genes.

Design and Method: Heparinized fresh whole blood samples were collected from DN STAT3, STAT1 GOF and healthy donors. Levels of basal STAT1 and phosphorylation (pSTAT1) following type I/II interferons (IFNs) or interleukin (IL)-6 stimulation were analyzed by flow cytometry. To evaluate the impact of ruxolitinib, whole blood or peripheral blood mononuclear cell (PBMC) were stimulated with IFN-I, IFN-II or IL-6 in presence of increasing doses of ruxolitinib. The cytokine-induced pSTAT1 and downstream effector molecules were quantified using flow cytometry, qPCR and ELISA techniques.

Results: DN STAT3 and STAT1 GOF mutations resulted in a common cellular phenotype characterized by increased total STAT1 levels and phosphorylation (pSTAT1) in response to IFN alpha (CD3+ cells) and IFN gamma (CD14+ monocytes). STAT1-downstream gene expression and C-X-C motif chemokine 10 secretion were higher in most DN STAT3 patients upon stimulation compared to healthy controls. In vitro treatment with the JAK1/2-inhibitor ruxolitinib reduced cytokine responsiveness and normalized STAT1 phosphorylation, being similar in DN STAT3 similarly and STAT1 GOF patient' cells. In addition, in vitro treatment was effective in modulating STAT1 downstream signaling in DN STAT3 patients, suggesting ruxolitinib as a potential therapeutic option.

Conclusions: In the absence of effective directed treatment options for AD-HIES at present, modulation of the JAK/STAT1 pathway with ruxolitinib may be further explored particularly in those AD-HIES patients with autoimmune and/or autoinflammatory manifestations.

POSTER 94 - FACILITATED SUBCUTANEOUS IMMUNOGLOBULIN TREATMENT IN PATIENTS WITH PRIMARY AND SECONDARY IMMUNODEFICIENCIES: THE FIGARO STUDY

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Objective: Facilitated subcutaneous (SC) immunoglobulin (fSCIG), a dual-vial unit of immunoglobulin G (IgG) 10% and recombinant human hyaluronidase (rHuPH20) is approved in Europe as replacement therapy for primary immunodeficiency (PID) and secondary immunodeficiency (SID) in adults, children and adolescents. The objective of the FIGARO study was to provide insights on the real-world utilization and tolerability of fSCIG in patients with PID and SID.

Design and method: FIGARO (NCT03054181) was a prospective, multicenter (n=14), observational study conducted across Europe under the auspices of the European Society for Immunodeficiencies (ESID). Study initiation was December 2016. Database closure was May 2021. Patients who received ≥1 fSCIG infusion for PID or SID and provided informed consent were eligible and followed for ≤3 years. Data were analyzed by age (pediatric [≤18 y], adult [18–64 y], and older adult [≥65 y]) and are presented here up to 1 year of follow-up.

Results: 156 patients were enrolled: 15 pediatric, 120 adult, and 21 older-adult patients. 1-year follow-up data were available for 128 patients. fSCIG was mainly prescribed for PID among patients aged <65 years (pediatric: 93.3% PID; adults: 87.5% PID), and for SID among older adults (71.4%). fSCIG administration parameters at inclusion and 1-year follow-up are shown in the table.

At inclusion, 75.6% received their fSCIG infusion at home, and 78.7% self-administered. Adults were more likely to receive their initial infusion at home and self-administer (81.7% and 86.6%, respectively) than pediatric patients (53.3% each) and older adults (57.1% and 52.4%, respectively). At 1 year, the proportion of patients infusing at home and self-administering increased to 85.8% and 88.2%, respectively. At both time points, >80% of patients infused every 3–4 weeks, and the median number of infusion sites was 1.0.

At 1 year, 21 patients (16.5%) reported adverse drug reactions (ADRs) associated with fSCIG. Of these, 15 had local ADRs (pediatric [n=1], adult [n=14], and older adult [n=0]) and 11 had systemic ADRs (0, 10 and 1, respectively).

Conclusions: FIGARO provides insights on the real-life utilization of fSCIG in a broad and unselected sample of patients with PID and SID, and confirms the feasibility and tolerability of fSCIG across the age spectrum. Regardless of age, most patients were able to self-administer the full fSCIG dose at home every 3–4 weeks and required only 1 infusion site. Baxalta Innovations GmbH (a Takeda company) funded this study; Takeda Development Center Americas, Inc. funded medical writing support.

POSTER 95 - USE OF VIRUS SPECIFIC T CELLS FOR EBV+ LYMPHOPROLIFERATION PRETRANSPLANTATION IN AN ARPC1B DEFICIENT PATIENT

AUTHORS

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Background: Homozygous mutations in the ARPC1B cause an autosomal recessive syndrome of combined immune deficiency with impaired T-cell immunity, defective phagocyte function and abnormal thrombocytes. The disease has similar clinical presentation as more known actinopathies (e.g., Wiscott-Aldrich Syndrome) with progression to severe autoimmunity and malignancy. Allogeneic hematopoietic stem cell transplantation can be curative for the disease.

Virus specific T cells (VST) have been used successfully in adults and children to combat resistant virus infections such as CMV, EBV, adenovirus in the context of long-term post transplantation immune deficiency. In only rare cases VST was used before allogeneic stem cell transplantation for primary immunodeficiency to control the viral infection.

Methods: Here we present a case of a patient with ARPC1B deficiency who received several infusions of VST for uncontrolled EBV lymphoma in the pretransplant period.

Family donors were typed for HLA at allelic level and screened for EBV seropositivity (VCA IgG and EBNA1 IgG). HLA typing of the chosen donors showed haplocompatibility. Mononuclear cell collection was performed the day before immunoselection which was done on Clinimacs Prodigy (Miltenyi Biotec). Cytokine Capture System (CCS) with EBV Peptivator Select was used to positively isolate EBV specific lymphocytes with IFN gamma secretion. Positive cell fraction from target cell bag was taken to flow cytometry for lymphocyte subpopulations analysis and was released for clinical use.

Results: 28y old male patient with several complications of ARPC1B deficiency presented with EBV+ lymphoma after 10 years of mild clinical course of his disease. We were able to control his disease with antiviral therapy and anti-CD20 monoclonal antibodies for the first year. After SARS-CoV2 infection his disease relapsed, we combined chemotherapy with VST as method to control the disease while we were preparing him for HSCT.

Treatment course with complications is presented in Picture 1.

Conclusions: There are many examples of patients receiving VST after allogeneic HSC transplantation due to malignant disease as well as primary immunodeficiency. In our case we have had a partial response in controlling EBV+ lymphoproliferation with pretransplant VSL. We have observed neurological and ophthalmological complication after VSL infusions. ARPC1B deficiency exhibits several immune - dysregulation manifestations such as autoinflammation and autoimmunity which could possibly lead to strong alloreactive anti-lymphocyte responses causing rejection of infused VST. In addition, progressive T cell dysfunction and chemotherapy can be an additional trigger for Varicella Zoster virus reactivation.

POSTER 96 - EFFICACY AND SAFETY OF SUBCUTANEOUS HUMAN IMMUNOGLOBULIN (16.5%) IN PEDIATRIC PATIENTS WITH PRIMARY IMMUNODEFICIENCIES: DATA FROM TWO PHASE 3 STUDIES

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Objective: To assess pharmacokinetics (PK), efficacy and safety of Cutaquig® in pediatric patients with primary immunodeficiency (PI).

Design and Method: Two prospective, open-label, multicenter phase 3 trials have been completed. The pivotal study (NCT01888484) assessed the pharmacokinetics (PK), efficacy and safety of Cutaquig® in pediatric and adult PI patients which was extended (NCT03907241) to ascertain medium-to-long-term safety and efficacy.

Results: The pivotal study included 38 pediatric patients (76% male) in 3 subgroups: 12 young children (2 to 5yrs), 14 older children (6 to 11yrs) and 12 adolescents (12 to 16 yrs). Of the 38 children, 10 continued in the extension study. Pediatric patients received a total of 3,283 SCIG infusions. Weekly SCIG administration resulted in flat PK profiles with lower fluctuations at steady state after SCIG administration than after IGIV. No SCIG patient had IgG trough levels below 5 g/L. Clinical efficacy of SCIG was confirmed by zero SBI serious bacterial infection (SBI) in either study. Overall rate of infections was similar across the age groups at between 2 and 4 infections/person-year in the pivotal study with the highest rate in young children (4.2). In the 10 pediatric patients in the extension study the rate of infections/person year was highest in the adolescent group (2.9). Most common infections were respiratory infections. PID children in the study, treated with SCIG, had infection rates no different from normal, non-immunodeficient age comparable children. The number of days absent from school/person-year was 8.5 in the youngest group, 3 in older children and 4 days in adolescents in the pivotal study. Similar findings were observed in the extension study. SCIG administration was well tolerated with no related serious adverse reactions reported in pediatric patients in either study with 5 related adverse reactions in both the primary and extension study (none in the youngest subjects). Infusion site reactions were reported in 25 (66%) pediatric patients during the pivotal study and in 7 (70%) in the extension study (all except one of mild/moderate intensity).

Conclusion: Data from both phase 3 studies demonstrate similar efficacy and safety of SCIG administration in pediatric patients as in adults with PI.

POSTER 97 - USE OF IMMUNOGLOBULIN REPLACEMENT THERAPY: REAL-LIFE EXPERIENCE OF AN IMMUNODEFICIENCY UNIT

AUTHORS

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Objective: The objective of this work is twofold. First, the description of the clinical characteristics and the immunoglobulin (Ig) replacement therapy used by patients treated in the Primary Immunodeficiency Unit. Second, the comparison of their clinical, analytical, and therapeutical characteristics as well as the effects on their quality of life according to the Ig administration route.

Material And Methods: This is a retrospective observational study including 104 patients diagnosed with primary or secondary immunodeficiency during a follow-up period of 14 months. Patients were divided according to their treatment administration route. Data regarding their clinical characteristics (age, sex, diagnosis and comorbidities), treatment posology (previous treatment, tolerance, training visits, number of medical consultations related with their pathology or treatment) and clinical results (blood-through Ig levels and number of working days lost) were collected. The descriptive and inferential statistical analysis was performed with the R statistical software (4.0.0 version).

Results: The most frequent diagnosis was common variable immunodeficiency (44.76%). Sixty-nine percent of all patients used a subcutaneous (SC) administration route. Patients under SC Ig replacement therapy were in average significantly younger than those with intravenous (IV) Ig replacement (46.76 vs 55.31 years old, $p < 0.001$). No significant differences were observed in the blood-through levels between both groups. There were more consultations in the IV group ($p < 0.001$), but no statistically significant difference in the number of urgent medical consultations was observed. The adverse effect rate was very low, and did not differ between SC or IV groups. The patients that use SC Ig therapy continued with that administration route after the follow-up period, but those who were treated with IV Ig were more likely to switch to SC administration in our unit ($p < 0.001$).

Conclusions & Future Work: According to the data collected, SC Ig replacement therapy leads to a decrease in the number of lost working days, and shows a better tolerance than IV administration, without documenting a statistically significant increase in the number of infections, or a worse control of blood-through Ig levels. The SC route is preferred among younger patients.

POSTER 98 - SUBCUTANEOUS IMMUNOGLOBULIN REPLACEMENT THERAPY IN SECONDARY HYPOGAMMAGLOBULINEMIA DUE TO NEPHROTIC SYNDROME

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Introduction: Nephrotic Syndrome (NS) is the most common glomerulopathy in children, and is classified according to the age of onset, etiology, histology, glucocorticoid response, and disease evolution. Increased glomerular permeability leads to excessive excretion of plasma proteins resulting in proteinuria, edemas, hypoalbuminemia, and dyslipidemia. Hypogammaglobulinemia is also reported in association with systematic use of glucocorticoids and immunomodulators and predisposes to an increased susceptibility to infections.

Objective: To describe the response of subcutaneous immunoglobulin replacement therapy (SC-IgRT) in patients with hypogammaglobulinemia secondary to NS.

Design: Observational, retrospective, and descriptive, cross-sectional study.

Methods: We reviewed the clinical records of 10 patients attending the immunology and pediatric nephrology consult from 2011 to 2019, in whom hypogammaglobulinemia and a history of recurrent infections, and recurrent relapses of the NS were documented; all patients and were undergoing SC IgRT. We recorded serum Ig, infectious episodes, glucocorticoids, and immunomodulatory therapy before and after SC-IgRT. Data were analyzed using univariate and bivariate statistics.

Results: In this series, 70% of the patients were male and 70% were between 5 to 9 years old with an average age of 3.5 years at clinical diagnosis. Seventy percent of patients had idiopathic NS and 70% had histology suggestive of minimal change disease (MCD). Mutations associated with NS were documented in two patients (FN1 and NPHS-1). All patients had low IgG, (mean IgG 352.2 mg/dl, as well as IgM (116.8 mg/dl and IgA 118.8 mg/dl). Twenty percent were receiving monotherapy with glucocorticoids, 70% glucocorticoids and immunomodulators (dual therapy), and one patient was not on any medication. All patients had recurrent infections (average = 5.7 episodes/patient) with two hospitalizations each, including four at the ICU. After 9 months on SC-IgRT, serum Ig levels increased in all patients (mean IgG 627,6 mg/dl ($p=0,0058$), IgM 120,2 mg/dl and IgA 137,1 mg/dl). In addition, 2 patients in monotherapy with glucocorticoids no longer required it, while there were no changes in patients receiving dual therapy thus 30% of the patients did not require treatment after SC-IgRT. Infections decreased to 1.75 episodes ($p=0.0001$) and patients required fewer hospitalizations (0,6 episodes on average, $p=0.0171$), and none required ICU.

Conclusions: Serum Ig must be assessed periodically in patients with NS. SC-IgRT seems effective in reducing recurrent infections in pediatric patients with hypogammaglobulinemia secondary to nephrotic syndrome with recurrent relapses and infections.

POSTER 99 - LONG-TERM SAFETY OF FACILITATED SUBCUTANEOUS IMMUNOGLOBULIN: FINAL RESULTS FROM A POST-AUTHORIZATION STUDY

AUTHORS

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Objective: Recombinant human hyaluronidase (rHuPH20)-facilitated subcutaneous immunoglobulin (fSCIG) 10% is an immunoglobulin (IG) replacement therapy that utilizes rHuPH20 to depolymerize hyaluronan in the extracellular matrix. This results in enhanced distribution and absorption of IG. fSCIG has a safety profile similar to subcutaneous IG and offers the flexibility to self-infuse at home. The objective of the present study was to obtain data on the long-term safety, immunogenicity, prescribed treatment regimens, and administration of fSCIG in routine clinical practice.

Design and Methods: This prospective, non-interventional, open-label, multicenter study (EUPAS5812) was conducted from July 2014 to February 2020 in Europe and enrolled patients aged 18 years and over who were receiving or were prescribed fSCIG. Treatment regimens were planned by the attending physician in accordance with standard clinical practice. Anti-rHuPH20 antibodies were assessed on a voluntary basis.

Results: Of 111 enrolled patients, 106 had reported data on at least one dose of fSCIG and were included in the safety analysis population (age range: 18–86 years); the majority of patients were prescribed fSCIG for primary immunodeficiency (91.5%), and the median (range) fSCIG exposure was 3.2 (0–5.2) years. The incidences of treatment-emergent non-serious (non-infectious) adverse events (AEs) and treatment-emergent serious AEs were 2.4 events/person-year (PY; 724 events in 84 patients) and 0.3 events/PY (82 events in 36 patients), respectively. Of 74 patients tested for anti-rHuPH20 antibodies, 3 (4.1%) developed positive binding antibodies (defined as titer 160 or greater; maximum titer: 1280) to rHuPH20; no positive titers were reported after 3 years of fSCIG treatment. No relationship between positive titers and incidence of AEs was reported. No neutralizing antibodies were detected. The most common fSCIG treatment interval was every 4 weeks (62.9%), with a total observation time of 114 PYs. Patients used a mean (standard deviation [SD]) of 1.1 (0.4) infusion sites (mean [SD] maximum infusion rate: 238.7 [65.5] mL/h). The proportion of fSCIG infusions administered at home was 92.6% in the first year, 94.8% in the second, 96.8% in the third, and 94.9% after the third year.

Conclusions: This final analysis of prospectively collected data confirms the long-term safety and tolerability of fSCIG in a real-world population.

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POSTER 100 - REAL-WORLD SAFETY AND TOLERABILITY OF FACILITATED SUBCUTANEOUS IMMUNOGLOBULIN IN PEDIATRIC PATIENTS WITH PRIMARY IMMUNODEFICIENCY DISEASES: INTERIM ANALYSIS FROM A POST-AUTHORIZATION STUDY IN EUROPE

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Objective: In a phase 3 trial in primary immunodeficiency diseases (PID; NCT00814320), facilitated subcutaneous immunoglobulin (fSCIG), a dual-vial unit containing immunoglobulin G (IgG) 10% and recombinant human hyaluronidase (rHuPH20), was effective and bioequivalent to intravenous immunoglobulin with fewer systemic adverse events. The objective of this phase 4, prospective, European post-authorization study was to evaluate fSCIG safety, tolerability, and immunogenicity in pediatric patients with PID (NCT03116347).

Design and Methods: Patients aged 2 to < 18 years with PID receiving immunoglobulin therapy from 16 European centers enrolled with informed consent and received fSCIG for up to 3 years (Epoch 2). fSCIG-pretreated and fSCIG-naïve (new starter) patients were included. New starters initiated fSCIG with a ramp-up of up to 6 weeks (Epoch 1). fSCIG safety, immunogenicity, tolerability, use, and IgG trough-level data were collected approximately every 3 months. An interim analysis was preplanned for when 75% of patients completed one year in Epoch 2 (data cut-off: May 14, 2020).

Results: Of 42 patients (81.0% male) enrolled, 23 were fSCIG-naïve and 19 were fSCIG-pretreated (mean age: 10.3 and 11.7 years, respectively). At interim analysis, patients received a mean of 12.5 infusions. In total, 42 treatment-related adverse events (AEs) occurring after first fSCIG dose, excluding infections, were reported in 12 patients; most AEs were mild. Treatment-related AEs occurred more frequently in fSCIG-naïve patients (33 local, 3 systemic treatment-related AEs in 10 patients; 1.7 events/patient-year [PY]) than in fSCIG-pretreated patients (2 local, 4 systemic treatment-related AEs in 2 patients; 0.3 events/PY). No serious treatment-related AEs were reported. No patients developed positive anti-rHuPH20 antibody titers (at least 1:160). Patients received a median of 1.2 infusions/month, with fSCIG-pretreated patients receiving higher median infusion volumes/site than fSCIG-naïve patients (150 vs 80 mL/site) and fewer interrupted/adjusted/stopped infusions (4.9% vs 9.3% of infusions). Mean IgG trough levels at enrollment and 12 months were 9.6 and 8.2 mg/dL, respectively.

Conclusions: This interim analysis supports the long-term safety of fSCIG in pediatric patients with PID, with a safety and tolerability profile consistent with previous clinical studies, and indicates that incidence of local AEs declines with fSCIG treatment duration.

This abstract was previously presented at the Clinical Immunology Society 2021 Annual Meeting. Baxalta US Inc., a Takeda company, funded this study; Takeda Development Center Americas, Inc. funded medical writing support.

POSTER 101 - TRANSITIONING SUBCUTANEOUS IMMUNOGLOBULIN 20% THERAPIES IN PATIENTS WITH PRIMARY AND SECONDARY IMMUNODEFICIENCIES: A CANADIAN REAL-WORLD STUDY

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Objective: Real-world data on transitioning to Immune Globulin Subcutaneous (Human) 20% Solution (Ig20Gly) are limited. This study assessed infusion parameters and experience of patients with primary immunodeficiencies (PID) or secondary immunodeficiencies (SID) transitioning to Ig20Gly in clinical practice in Canada.

Design and Methods: Patients with PID or SID who received subcutaneous immunoglobulin (SCIG) for at least 3 months before transitioning to Ig20Gly were eligible for this multicenter (n=6), phase 4, noninterventional, prospective, single-arm study (NCT03716700). Ig20Gly infusion parameters, dosing and adverse events (AEs) were collected from patient medical records at Ig20Gly initiation and 3, 6 and 12 months post-initiation. Patient satisfaction and quality of life (QoL) were assessed 12 months post-initiation using validated questionnaires.

Results: The study included 125 patients (PID, n=60; SID, n=64; PID+SID, n=1) with a mean age of 62 years (range: 19–83 years). Median volume per infusion was 30 mL at initiation and 40 mL at 6 and 12 months post-initiation. Most patients administered Ig20Gly weekly (at least 70%) and used two infusion sites, primarily the upper and lower abdomen. At each time point, median infusion duration was at least 1 hour, and interrupted or slowed infusions were rare (1.3%). Infusion parameters were generally similar between the PID and SID cohorts, although median infusion duration tended to be slightly longer among those with SID (60 vs 43 minutes at 12 months). Headache and infusion site reactions were the most frequently reported AEs of interest* (4.8% and 4.0% of patients, respectively). Patients expressed overall satisfaction with Ig20Gly at 12 months post-initiation, with all respondents indicating they would like to continue Ig20Gly.

Conclusions: This study provides a detailed description of Ig20Gly infusion parameters, tolerability and QoL in clinical practice among patients with PID or SID switching to Ig20Gly from another SCIG, which are broadly consistent with previous findings from the Ig20Gly PID pivotal trials.

*Included AEs described as warnings and precautions in the product monograph, and those reported in previous trials and observed in post-marketing surveillance.

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POSTER 102 - A NOVEL APPROACH TO CUSTOMIZING THE FLOW PROFILE FOR THE ADMINISTRATION OF SUBCUTANEOUS IMMUNOGLOBULINS FOR INDIVIDUAL INFUSIONS WITH BENEFITS TO MINIMIZE OR ELIMINATE SITE REACTIONS - A CASE STUDY

AUTHORS

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Objective: Ideally every subcutaneous immunoglobulin patient deserves pain free infusions every time an administration is performed. This has been difficult to ensure until the recent development of a novel infusion system to facilitate monitoring and modifying the flow rate during the actual infusion. This system can determine the patency of sites for every infusion and enables real-time flow rate adjustment to minimize any adverse site reactions from occurring – preventing adverse reactions from occurring before they start. The objective of this case study was to confirm the theoretical prediction that such a (breakthrough) system could perform in the clinical environment.

Design: An experienced SCIg patient was selected to deliver 50ml using three 26G needles with the flow rate beginning at the highest settable flow rate. The flow rate was monitored during the infusion and if any decrease in flow rate was noted, the rate was manually and significantly reduced. An assessment of the sites immediately after the infusion was completed was undertaken.

Method: After setting the controller, the patient noted the volume in the syringe, and a stopwatch was started. After 10ml and 20 ml was delivered, the actual initial flow rates were calculated to be 67ml/hr/site and 50ml/hr/site, showing a decrease. Since the system is sensitive to differential pressure (Dynamic Equilibrium), a detectable decrease indicated that the initial flow rate was creating tissue saturation. After infusing 35ml, the flow rate was manually decreased to 25ml/hr/site and continued with no further impairment of flow rate or tissue saturation.

Results: Total time of infusion for 50ml was 24:26 minutes. Patient commented that he could “feel” improvement in the reduced flow rate. At the end of the infusion, when the needles were removed, there was no redness, pain, leaking, or site sequelae.

Conclusion: The theory has long predicted that subcutaneous immunoglobulin administrations can begin at the highest flow rate but may need to be dramatically decreased. This is caused by beginning with empty depots, which may quickly fill with drug under high flow rates, ultimately decreasing tissue perfusion. To deliver the fastest flow rates possible and the minimum time of infusion, the objective is to begin the infusion at the highest possible flow rate and then manually decrease the rate as the sites begin to saturate. This novel approach has the capability to revolutionize subcutaneous immunoglobulin administrations, providing the fastest flow rates for each infusion with little or no adverse site reactions.

FRIDAY, APRIL 29, 2022

GUIDED POSTER WALK 4B - DIAGNOSIS & NBS ADVANCES

MODERATOR: Dr Nizar Mahlaoui

POSTER 103 - A FIRST LOOK AT THE NEWBORN SCREENING FOR INBORN ERRORS OF IMMUNITY IN SAO PAULO, BRAZIL

AUTHORS

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Introduction: Since March 2021, the city of São Paulo introduced the expansion of newborn screening (NBS) with the identification of TRECs (T-cell receptor excision circles) and KRECs (kappa-deleting recombination excision circles). According to the American College of Medical Genetics and Genomics (ACMG), detect the SCIDs (Severe Combined Immunodeficiencies) is contemplated in diseases in which NBS must be prioritized; meanwhile agammaglobulinemia stay as second target. At this time few countries implemented TREC/KREC in their routine. The goal of our study was to analyze the first eight months of the program.

Methods: All exams with a cutoff less than 25copies/uL were considered abnormal and referred to a single Immunology Clinic within the city. A retrospective analysis of the charts was conducted. Variables such as prematurity, congenital cardiopathies, TORCHs, maternal and newborn diseases and medications were included.

Results: Were include 72 patients, which correspond to 1:1.666 newborns with an abnormal test (120.000 alive newborns in São Paulo so far). Thirteen babies had TREC<25, 4 with TREC<4. Of these, two SCIDs were diagnosed (both with TREC1), two suspected DGS (awaiting array) with congenital cardiopathies. Regarding to KREC<25, we had 62 infants, reflecting a wider range of possible diagnosis and false positives. Twenty-three had KREC<4, and eight showed CD19<1%. From those last, three recovered CD19, two were born from mother with SLE, two are investigating agammaglobulinemia and one have Down Syndrome with transient myelodysplastic syndrome. Sixteen patients collected the screening before completing 37 weeks of gestation, nonetheless 13 had normal immunophenotyping (IF). Six patients with abnormal TREC/KREC had TORCH, none of them with altered IF. There was one case with normal TREC/KREC that tandem mass spectrometry revealed analytes for suspected ADA-SCID (confirmed with gene sequencing) and one exam with low TREC and elevated KREC, which culminated in the diagnosis of juvenile myelomonocytic leukemia.

Conclusions: NBS is a revolutionary strategy because it can promote a new outcome for treatable diseases. After these few months of screening implementation in Sao Paulo we were able to make three SCIDs diagnosis, have two patients under investigation for DGS, and we were able to transcend frontiers making a leukemia diagnosis. Although we have not an agammaglobulinemia diagnosis yet, few patients with CD19<1% recovered cellularity to normal range. In our sample we could observe a great number of altered KREC false positives, however it may be a new tool to improve the understanding of B-cell development and pathologies related to them.

POSTER 104 - i.MUNE NEO - A NEW TEST FOR EPIGENETIC IMMUNE CELL QUANTIFICATION IN NEWBORNS

AUTHORS

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Epigenetic immune cell quantification allows the determination of various immune cells in dried blood spot samples (DBS) from newborns. Quantitative abnormalities of immune cells can be an early indicator of an underlying Inborn Error of Immunity (IEI).

We describe the design and development of i.Mune NEO, a novel epigenetic test to quantify CD3+, CD4+, CD8+ T-, memCD4+, B- and NK cells from newborn DBS samples. We analyzed a cohort of 50 healthy newborns in order to determine reference values for the individual immune cells. We also show that memCD4+ cells are only detected in adult blood, supporting its usability as a confirmatory marker to identify maternal engraftment of T-cells in newborns. Retrospective case-control studies with comparative TREC and KREC screening results are currently ongoing and data will be presented.

We demonstrate the applicability of epigenetic immune cell quantification to quantify T-, B- and NK lymphocytes in newborn DBS samples. i.Mune NEO can help to identify quantitative immune cell dysregulation at birth that would be followed up by confirmatory diagnosis (e.g. DNA sequencing). The approach also has the potential to be expanded to other IEIs as additional epigenetic immune cell quantification assays are available for test development (e.g. Treg, Th17, Eosinophiles, Neutrophiles).

POSTER 105 - FIRST PROSPECTIVE PILOT STUDY OF SIMULTANEOUS NEONATAL SCREENING FOR SEVERE COMBINED IMMUNODEFICIENCIES AND SPINAL MUSCULAR ATROPHY

AUTHORS

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Objectives: Severe combined immunodeficiencies (SCIDs) and spinal muscular atrophy (SMA) are rare but potentially fatal pathologies. Rapid detection allows prompt and efficient therapy thereby improving the prognosis of patients. In January 2021 we initiated the first pilot study in Spain for using a RT-PCR based TREC/KREC/SMA determination assay from dried blood samples (DBS) of newborns. The objective of this study is to evaluate the potential utility of a technique for the joint detection of SCID and AME.

Methods: RT-PCR (LightMix®KIT, TREC KREC SMA Newborn, Roche-TIB molbiol) from prospectively collected DBS from neonates born in hospitals from Seville, Huelva and Cadiz was performed. Internal and external controls (SCID and AME) were included. TRECS and KRECS were quantified and cut-off points were 6 (copies/punch) for TRECS and 4 (copies/punch) for KRECS. SMA determination was based on positive/negative amplification. Beta-actin was used as sample quality control.

Results: From January to October 2021 a total of 8495 sample were analyzed. No cases of PID or SMA have been prospectively identified. We received two DBS samples (sample 1 and sample 2) of a 3 and 6 months' old neonate with suspected SCID and one DBS sample (sample 3) of a 2 weeks old neonate with suspected SMA. Results obtained are shown in table 1. All included controls (SCID, XLA and SMA) have been correctly identified, repeat rate was 1.5% mainly for KRECS below the cut off (0.8%), values normalized when repeating the same DBS sample. The technique showed pathological results in two neonates with suspected SCID that were confirmed by flow cytometry and genetic analysis (Sample 1, SCID; Sample 2 XLA). Sample 3 did not amplify for SMN1 gene and diagnosis of SMA was confirmed by genetic techniques. All neonates have received curative or supportive therapy with good clinical response.

Conclusion: Neonatal screening of PID is a fast and sensitive technique for early diagnosis of SCID. This is the first prospective neonatal screening study for SCID and SMA in Spain. No cases of SCID or SMA have been diagnosed likely due to the low incidence of these pathologies. The inclusion of SMA does not imply any extra cost whilst providing a great benefit. The study has allowed the rapid diagnosis of three neonates allowing prompt initiation of specific treatment thereby avoiding serious sequelae. The inclusion of this technique in routine neonatal screening will likely be beneficial for the affected children and their families.

POSTER 106 - QUANTITATIVE SERUM IMMUNOGLOBULIN AS AN ASSESSMENT OF ANTIBODIES DEFECT IN A TERTIARY REFERRAL CENTRE IN MALAYSIA

AUTHORS

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Quantitative serum immunoglobulin measurement is utilized to detect abnormal levels of the three major classes of serum immunoglobulin (IgG, IgA and IgM), which primarily used in screening for various primary immunodeficiency diseases that affect the levels of one or more of these immunoglobulin classes.

Objective: This study aims to review the demographic data, indications and clinical profile of pediatric patients investigated with quantitative serum immunoglobulin in our centre.

Design and Method: Profile of pediatric patients (below 12 years) who had performed serum immunoglobulin measurement in Hospital Canselor Tuanku Muhriz UKM (HCTM), Malaysia from January 2018 to December 2020 were reviewed retrospectively.

Results: Fifty-six cases, mean age of 27.2 months (2.27 years) with majority were male (62.5%, n=35), were reviewed. Nearly half of the patients (42.50%) had recurrent infections including recurrent upper respiratory tract infections (20%), multiple recurrent skin and deep abscesses (12.50%), skin and gastrointestinal infections (10%), 4 patients (10%) had underlying haematological malignancy. Three patients (7.50%) had polymorphonuclear defects while one patient (2.50%) had underlying Down Syndrome. From this cohort of cases, five patients had abnormally low IgG level, with two of the patients having concurrent low IgA and IgM levels, and a single patient had isolated IgA deficiency. To date, none of the five patients with abnormally low IgG level had a definitive molecular diagnosis for their antibodies defect either by targeted gene sequencing or whole exome analysis.

Conclusion: All the 56 patients were referral cases for assessment of possible primary immunodeficiencies, with initial screening of their immune system had shown to be largely normal or indeterminate. Most cases were complex pediatric cases presented with clinical possibility of primary immunodeficiencies yet with diagnosis dilemma, thus explaining the lack of classical primary antibody deficiencies diagnosis such as X-linked agammaglobulinemia, or HyperIgM syndrome within this cohort of patients.

POSTER 107 - SCREEN4RARE: ADVOCATING FOR IMPROVED EU COOPERATION IN THE FIELD OF NEONATAL SCREENING

AUTHORS

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Objective: Screen4Rare is a multi-stakeholder initiative launched by the International Patient Organisation for Primary Immunodeficiencies (IPOPI), the International Society for Neonatal Screening (ISNS) and the European Society for Immunodeficiencies (ESID). The initiative aims to exchange knowledge and share best practices on newborn screening (NBS) for rare diseases. Its ultimate objective is to ensure all babies born in the EU can have equal access to NBS which can be a life-saving tool for conditions such as severe combined immunodeficiency (SCID).

Design and method: Screen4Rare is building strong relations with European partners: many of the European Reference Networks (ERN), individual Public Health representatives of member states and the European Commission, and international patient organizations. Screen4Rare is actively collaborating with its political supporters who are Members of the European Parliament to achieve the initiative's objectives.

Results and conclusions: In 2020, Screen4Rare launched a political "Call to action" to 1) Find common ground for generally accepted overarching guidelines on NBS, 2) Build a platform for stakeholders and 3) Cooperate to position the EU as the central point for data collection and information on rare diseases NBS practices. The call to action was endorsed by more than 30 members of the European Parliament and currently, Screen4Rare is working towards its implementation together with its European partners.

In 2021, Screen4Rare, European Commission and ERN representatives agreed that ERN Expert Platform on Newborn Screening for Rare Diseases, coordinated by MetabERN and ERN Rita with the assistance of the ERN Secretariat and Screen4Rare, would be initiated and could coordinate future ERN action on the topic. The platform was launched in September with three working streams – (1) Identifying gaps and differences between NBS programs in EU Member States; (2) Proposing clear case definitions for NBS and establishing consistent approaches to confirmatory testing; (3) Developing interoperable disease registries to support the provision of outcome data for patients identified by screening. At international level, Screen4Rare was also instrumental in the organization and establishment of International Neonatal Screening Day (28 June). This initiative offers opportunity to celebrate the vision of those who have pioneered and expanded neonatal screening programmes and will, in turn, encourage a new generation of doctors, scientists and policy makers to extend these benefits to more children suffering from a wider range of disorders.

FRIDAY, APRIL 29, 2022

GUIDED POSTER WALK 5 - COVID-19

MODERATOR: Prof Fabio Candotti

POSTER 108 - NURSES MANAGEMENT OF PATIENTS WITH INBORN ERROR OF IMMUNITY DURING COVID-19 PANDEMIC IN MILAN, ITALY

AUTHORS

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On February 2020, in Lombardy, started the outbreak of the COVID-19 pandemic that dramatically hit Italy's Northern part. The Rare Diseases Unit had to rapid reorganize the patients' management and the strategies timely adopted to ensure the best possible care, while mitigating the risk of infection. We report the experience of nurses highly specialized for PID and other Rare Diseases working at a referral Centre.

During the COVID-19 outbreak, the rapidly evolving situation left a short time to manage the increasing surge need for intensive care units (ICUs) beds and our Hospital became the coordinating hub for COVID-19 ICUs in Lombardy. This dramatically affected the Rare Diseases Center and its PID center. The building of the Centre was allocated to COVID-19 ICU, and the Rare Diseases Unit with its 1800 adult patients transferred elsewhere twice in 2 days.

According to the hospital general reorganization, two of six nurses of our Centre were reassigned to COVID-19 care wards since March to July 2020, and in January 2021 another one was reassigned to the anti-SARS-CoV2 vaccination Centre. Nurses started a phone call triage to identify potential positive cases and encouraged patients to notify spontaneously any symptom or concern. A dedicated fast-track was available for molecular nasopharyngeal swab in symptomatic cases. Only in November 2020 it was possible to adopt the systematic use of the antigenic-rapid-test-swab-kit in the Centre rooms.

The Igs-replacement therapy for the 80 patients with PAD was guaranteed. Both IVIG and SCIG products have been available. Since IVIG cannot be administered at home in Italy, one third of IVIG patients were rapidly shifted to SCIG. Three patients discontinued the therapy. All the new diagnosis started with SCIG. Since transportation outside the regions was prohibited, two patients temporarily infused IVIG in hospitals close to their homes; SCIG were delivered via a dedicated hospital-delivery-service.

The PID patients' perception of being more fragile increased the fear of falling sick and eventually dying in case of SARS-CoV2 infection. Hence, the psychologist started remote assistance, which involved 32 PID patients. Group discussions and individual psychological support was provided.

None of the PID patients got COVID-19 during the first wave, because they stay at home. Thirteen PID patients got COVID-19 during the second and third waves, they are all alive.

Resilience applied by health-care-professionals in either personal and working life demonstrated that despite COVID-19 pandemic it is possible to guarantee a high-level care to these rare, complex, and fragile patients.

POSTER 109 - UNDERSTANDING ATTITUDES AND OBSTACLES TO VACCINATION AGAINST COVID-19 IN PATIENTS WITH PRIMARY IMMUNODEFICIENCY

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Background: Patients with primary immunodeficiency (PID) are at increased risk for infections such as SARS-CoV-2 (COVID-19), due to the nature of their diseases and being immunocompromised. At this time, four vaccines against COVID-19 (Pfizer-BioNtech's Comirnaty®, Moderna's Spikevax®, AstraZeneca's Vaxzevria®, Johnson & Johnson's Janssen®) have been approved for use by Health Canada. Due to the novelty of these vaccines, clinical studies in patients with PID are ongoing. Despite limited evidence, Canada's National Advisory Committee on Immunization (NACI) recommend that patients with PID without any contraindications should be vaccinated with any of the approved vaccines as the potential benefits of being immunized against the virus likely outweigh the risks of contracting a severe infection. The aim of this study was to understand the perceptions regarding COVID-19 vaccination among patients with PID and to identify specific factors related to vaccine hesitancy.

Methods: The Canadian Immunodeficiencies Patient Organization (CIPO) conducted an online survey of its members to evaluate uptake of the COVID-19 vaccines by patients with PID. Data was collected using a self-administered online questionnaire. The survey was conducted between March and April 2021.

Results: At the time of survey, among 370 respondents who had not received the COVID-19 vaccine, 302 respondents (81.6%) indicated they were very or somewhat likely to get vaccinated against COVID-19; and 68 respondents (18.4%) indicated they were somewhat or very unlikely, undecided, or not planning to get vaccinated. A large majority of respondents indicated they had a diagnosis of PID (67.8%) and/or specified their type of PID (27.7%). The most common reason for vaccine hesitancy was primarily due to uncertainty about immune response given an underlying immunodeficiency. Other concerns included unknown long-term side effects of COVID-19 vaccination, pre-existing history of allergic reactions, limited amount of data, lack of investigation of safety and effectiveness of COVID-19 vaccines in those with medical conditions, and skepticism of the underlying science and/or the medical system.

Conclusions: The results point to the importance of ongoing patient outreach, education, and up-to-date information on the rapidly evolving scientific knowledge and evidence on COVID-19 relevant to the PID community, from clinical trials to real-world evidence and observational studies.

POSTER 110 - THE IMPACT OF SARS-COV-2 INFECTION IN PATIENTS WITH INBORN ERRORS OF IMMUNITY: THE EXPERIENCE OF THE ITALIAN NETWORK FOR PRIMARY IMMUNODEFICIENCY (IPINET).

AUTHORS

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COVID-19 manifestations range from completely asymptomatic to life-threatening infections. The outcome in different inborn errors of immunity (IEI) is still matter of debate. In this paper, we describe the experience of the Italian Network for Primary Immunodeficiency (IPINET). Data were collected retrospectively through a survey sent to 16 Italian Reference Centers for adult or pediatric IEI. 114 patients were enrolled into the study including 35 pediatric and 79 adult patients. Median age was 32 years and male-to-female ratio was 1.5:1. The most common IEI were 22q11.2 deletion syndrome in the pediatric cohort (26%) and common variable immunodeficiency (CVID) in the adult cohort (65%). Ninety-one patients did not require hospital admission and among these 33 patients were asymptomatic. Hospitalization rate was 20.17%. Older age (p 0.004) and chronic lung disease (p 0.0008) represented a risk factor for hospitalization. Hospitalized patients were more often under immunoglobulin replacement therapy and had lower B cell counts. However, patients in this group were mainly adults suffering from humoral immunodeficiencies. The highest hospitalization rate was observed in Good's syndrome (66%), agammaglobulinemia (55%) and CVID (22%). 47.36% of the hospitalized patients required non-invasive ventilation and 4 required invasive ventilation (mean age 53 ± 7.61 years; male-to-female ratio 3:1). All the patients requiring intensive care unit admission suffered from CVID. Infection fatality rate in the whole cohort was 6.14%. The highest infection fatality rate was observed in Good's syndrome (66.6%) and in unclassified antibody deficiency (12.5%). In conclusion, similarly to general population risk factor for hospital admission included older age and chronic lung disease. The fatality rate observed in IEI was slightly higher compared to the general population, even if this difference was not statistically significant. Moreover, the age of the patients who did not survive was lower compared to the general population. We hypothesize that this is due to the fact that comorbidities in IEI patients are very common and usually appear early in life.

POSTER 111 - SARS-COV-2 PNEUMONIA IN PATIENTS WITH COMMON VARIABLE IMMUNODEFICIENCY: CLINICAL EXPERIENCE WITH CONVALESCENT PLASMA

AUTHORS

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Objective: Describe the outcome of 4 patients with common variable immunodeficiency (CVID) hospitalized for SARS-CoV-2 pneumonia in a tertiary hospital who were treated with convalescent plasma. Their clinical features, laboratory findings, radiological findings, and clinical response are described.

Design And Method: Case series study. 4 cases of COVID-19 are presented in patients with CVID, all presenting good evolution after the administration of convalescent plasma. The epidemiological and clinical characteristics of the patients were studied by consulting the clinical history, previously informed consent had been obtained.

Results: We herein report the case of 4 patients diagnosed with CVID that required hospitalization with respiratory insufficiency due to COVID-19 infection. All of them were treated periodically with immunoglobulin (subcutaneous/intravenous) and had optimal levels of IgG in the last 6 months. All had a positive SARS-CoV-2 diagnostic test upon admission (PCR in nasopharyngeal exudate) and presented radiological signs of pneumonia. All patients received treatment with immunoglobulins, broad-spectrum antibiotic therapy, anti-inflammatory drugs (corticosteroids in all cases, tocilizumab in one of them). Convalescent plasma (300cc with antibody titers > 1/320) was administered for compassionate use. In addition, one received antivirals (lopinavir/ritonavir). Three of them had a torpid evolution, with persistent fever, but none of them required intensive care.

Conclusion: In our experience, although limited due to the reduced number of patients, we found a good safety and efficacy of convalescent plasma in 4 immuno-deficient subjects. Our findings may have implications for clinical decision-making for immunodeficient patients. Further data are needed in order to assess whether this subtype of patients may particularly benefit from passive immunization.

POSTER 112 - HUMORAL RESPONSE TO ANTI-SARS-COV-2 VACCINATION IN PRIMARY ANTIBODY DEFICIENCIES PATIENTS

AUTHORS

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After December 2020, the first two vaccines based on mRNA technology (BNT162b2, Pfizer-BioNTech and mRNA-1273, Moderna) were available and received emergency use authorization to contain the global SARS-CoV-2 pandemic infection.

Inborn errors of immunity (IEI) patients have been included in the plans for mass-immunization campaigns and have often been prioritized for receiving these mRNA vaccines, despite they have not been involved in the trials for validation study neither it was known the efficacy and immunogenicity of these vaccines in this population.

Data from patients with primary antibodies deficiency (PAD), and in particular CVID and XLA patients are still needed, especially for monitoring of long-term maintenance of response.

This study aims to measure the response after both Moderna and Pfizer-BioNTech vaccines, among 79 PAD patients.

We present here an interim analysis of antibody responses 4 weeks after the second dose of vaccine. We measured a quantitative detection of serum IgG against the SARS-CoV-2 Spike (S) protein receptor binding domain with Elecsys R Anti-SARS-CoV-2 immunoassay (Roche Diagnostics, Monza, Italy). A result ≥ 0.8 U/mL was considered positive.

We analysed 60 CVID, 7 XLA and 12 UnPAD patients who underwent vaccination, 20 with Pfizer-BioNTech (14 CVID, 3 XLA, 3 UnPAD) and 59 with Moderna vaccines (46 CVID, 4 XLA, 3 UnPAD). Two CVID and one XLA patients refused vaccination.

All the CVID and XLA patients were under Igs replacement therapy. All the products used had undetectable levels of IgG anti-S.

We found that after 4 weeks since the vaccine second dose, CVID patients had a median anti-S serum level of 629 U/mL (range 0.2 to >7500), XLA patients 193 U/mL (range 0.2 to >7500), and UnPAD 2689.5 U/mL (0.2 to > 7500).

Among these patients, 13 got COVID-19 (11 CVID, 1 XLA, 1 UnPAD) before the vaccination, seven had anti-S levels detectable before the first dose.

Sixteen patients (13 CVID and 3 XLA) had no anti-S detectable 4 weeks after vaccination.

We compared anti-S levels of patients receiving Moderna vs Pfizer and we found no significant difference, despite the patients receiving Moderna had a median levels twice higher than the ones receiving Pfizer (840.0 vs 366.0 U/mL).

These findings suggest that CVID and XLA patients have a considerable heterogeneity of immune response to SARS-CoV-2 vaccination. This has profound implications to identify an optimal immunization regimen for the safety of these patients, given the current guidance relaxing masking restrictions for vaccinated patients.

POSTER 113 - HYPERIMMUNE IMMUNOGLOBULIN TO SARS-COV-2 HAS HIGH CAPACITY TO NEUTRALIZE WUHAN ORIGINAL WILD-TYPE VIRUS AND VIRUS VARIANTS OF CONCERN

AUTHORS

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Objective: Patients with primary antibody deficiencies (PAD) have a higher risk for suboptimal response to SARS-CoV-2 vaccination. Therefore, PAD patients may benefit from passive immunization with anti-SARS-CoV-2 hyperimmune globulin (hIG). The hIG is an IgG product enriched with anti-SARS-CoV-2 antibodies prepared from convalescent plasma. In this study, we have functionally characterized an anti-SARS-CoV-2 hIG by evaluating its neutralization capacity for four different SARS-CoV-2 isolates, assessed by four different methodologies.

Design and method: SARS-CoV-2 virus neutralization was evaluated by plaque reduction, virus induced cytotoxicity, TCID50 reduction and immunofluorimetry-based methodologies. Assays were performed at four different laboratories and using four geographically different SARS-CoV-2 isolates (one each from USA and Italy; two from Spain). Two of the isolates contained the D614G mutation (second wave). Stock viruses were prepared by collecting the supernatant from Vero cells. SARS-CoV-2.Sctδ19 Wuhan, B.1.1.7 (Alpha), B.1.351 (Beta), P.1 (Gamma), and B.1.617.2 (Delta) variants were generated (GeneArt) from the protein sequence of the respective spike sequences. Neutralization capacity against variants was evaluated using a pseudovirus platform expressing the spike (S) protein.

Results: All the SARS-CoV-2 isolates tested were effectively neutralized by hIG solutions (ID50: CBIFA: 483.5±173.5; CCLA: 1075±277.5; PFU: 4924±2430; TCID50: 1872±610.3). This was confirmed by all four methodologies employed. Our data showed that Wild-type SARS-CoV-2 and the VOC evaluated were effectively neutralized using the pseudovirus platform (hyperimmune IG [half-maximal inhibitory dilution, ID50]: the neutralization range varied among the variants).

Conclusions: These results showed that hIG solutions have strong neutralization capacity against SARS-CoV-2, which was not only present against viruses that plasma donors were exposed to, but also against the new SARS-CoV-2 emerging variants. The fact that similar results were obtained with multiple experimental approaches suggests that hIG treatment is a promising therapeutic option for SARS-CoV-2.

POSTER 114 - ANTIBODIES AGAINST COMMON HUMAN CORONAVIRUSES IN PLASMA AND IGG IMMUNOGLOBULIN MEDICINAL PRODUCTS

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Objective: Patients with primary antibody immunodeficiency (PAD) experience frequent respiratory tract infections that are typically managed with antibiotics and immunoglobulin (IgG) replacement therapy. Although coronaviruses are responsible for a number of respiratory tract infections, there has been little research on the presence of antibodies against coronaviruses in IgG products. In this study, IgG products formulated for different routes of administration (IV, IM, SC) and prepared from geographically diverse plasma pools were tested for activity against common human coronaviruses (HCoV).

Design and method: IgG products (Grifols, Barcelona, Spain and Research Triangle Park, NC, USA) included IV solutions (Flebogamma® DIF 5% and 10%; Gamunex®-C 10%), IM solutions (Gamastan® 15-18%; Igamplia® 16%) and a SC solution (Xembify® 20%). Source plasma was obtained from Germany, Czech Republic, Slovak Republic, USA and Spain. IgG products were tested at different concentrations by ELISA for antibodies to four human HCoV: 229E, OC43, NL63 and HKU1. Since IgG products are manufactured from pooled plasma from thousands of donors, the antibodies therein are a representation of the HCoV exposure of the population at large. The antibody potency was calculated multiplying positivity ratio for the inverse of the most diluted sample. In addition, neutralization assays were conducted using HCoV-229E expressed in MRC5 cells. Complete concentration-neutralization curves were calculated.

Results: When expressed as specific activity (anti-HCoV activity/mg IgG), similar activity against the four common HCoV was seen across the IgG products regardless of concentration or geographic origin. Highest anti-HCoV activity was seen against HCoV-229E, followed by HCoV-OC43 and then HCoV-NL63 and HCoV-HKU1. A similar profile was observed when the data from all the products were combined: greatest activity against the HCoV-229E (885±267 units anti-HCoV activity/mg IgG) virus followed by the HCoV-OC43 virus (633±76 units) with similar lower levels of activity against the HCoV-NL63 (306±53 units) and HCoV-HKU1 viruses (301±32 units). These antibodies had infectivity neutralization capacity (HCoV-229E used as an example) showing similar potency for two preparations of IgG prepared by different processes.

Conclusions: These studies are the most complete demonstration of the presence of functional antibodies to common HCoV in IgG products to date. The level of activity was similar regardless of the geographic origin of the plasma pool. These antibodies demonstrated neutralization activity against HCoV-229E in MRC5 cells. In the light of the known cross-reactivity seen with pre-pandemic IgG products and SARS-CoV-2, the possible impact of IgG products in PAD patients is highlighted.

POSTER 115 - CELLULAR AND HUMORAL RESPONSES TO SARS-COV-2 VACCINE IN PATIENTS WITH COMMON VARIABLE IMMUNODEFICIENCY

AUTHORS

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Objective: The aim of this study was to evaluate cellular and humoral responses in patients with common variable immunodeficiency (CVID) who were vaccinated against SARS-CoV-2.

Design and methods: We studied 20 patients with CVID according to ESID criteria for specific anti-SARS-CoV-2 interferon-gamma (IFN-g) production before vaccination and between three and six months after the second dose of SARS-CoV-2 vaccine. As a control group, 20 healthy age-matched donors (HD) vaccinated or recovered from the infection were assessed. In addition, anti-Spike IgG antibody titers were measured.

Results: Cellular response before vaccine administration was measured in 10 CVID patients, showing positive anti-SARS-CoV-2 IFN-g levels in 4 out of 5 patients who had passed the infection prior to vaccination. Post-vaccine results displayed positive T cellular immune response in 18 out of 20 (90%) CVID patients (1,296±703 mUI/ml) and in 19/20 (95%) HD (1,600±665 mUI/ml). There was no statistically significant differences between CVID patients and HD control group with respect to SARS-CoV-2 T cell responses (p=0.157). 2 CVID patients and 1 HD showed borderline SARS-CoV-2 IFN-g levels (100-200 mUI/ml). Whereas all HD mounted a specific humoral immune response, only 42% of CVID patients showed positive anti-SARS-CoV-2 IgG, with significantly lower titers than those of HD (p = 0.044).

Conclusions: Our preliminary data show that 90% of CVID patients were able to mount an adequate specific cellular response after SARS-CoV-2 vaccination, emphasizing the relevance of vaccination in this group. In those CVID patients with prior infection, the vaccine enhanced T cell responses. However, detectable specific antibody responses anti-SARS-CoV-2 vaccination was attained in 42% of CVID patients, with significantly lower levels than HD. Our data might support the relevance of these immunological studies to personalize preventive and treatment decisions.

POSTER 116 - NEUTRALIZING ANTIBODIES AFTER MRNA-1273 VACCINATION IN A COHORT OF PATIENTS WITH INBORN ERRORS OF IMMUNITY.

AUTHORS

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Background: Although the efficacy of RNA-based COVID-19 vaccines has been evaluated in the general population, very few information is available about their efficacy in patients with inborn errors of immunity (IEI). A better correlation with clinical protection has been suggested between titers of neutralizing antibodies and clinical outcomes in other models of immunodeficiency.

Objective: Our objective was to evaluate the neutralizing ability by inhibition of receptor-binding domain-angiotensin-converting enzyme 2 binding after immunization with mRNA-1273 vaccine in a cohort of IEI patients.

Methods: A total of 17 adult patients with IEI (10 female, 7 male; mean age 50 years; 13 CVID, 4 other IEI) were enrolled and serum was collected and frozen following the second dose of mRNA-1273 COVID-19 vaccine. Humoral response was evaluated by testing neutralizing ability by inhibition of receptor-binding domain-angiotensin-converting enzyme 2 binding (competitive ELISA). We correlated this response with routine information of our center of anti-SARS-CoV-2 spike (S) antibody titers (CLIA). All patients were receiving immunoglobulin replacement therapy.

Results: Of the 17 patients, 58.8% developed specific neutralizing antibody response (Median 73.8%, IQR 9.64-95.02%). Median titer of CLIA assessed anti-spike COVID19 antibodies was 3315.30, IQR 1164.30-10679.50 UA/mL. There was a good correlation between both determinations, Spearman Correlation 0.80, p=0.015. Interestingly neutralizing activity and anti-spike antibody levels were lower in CVID patients (47 vs 84%, p=0.016; 2426 vs 11584 UA/mL, p=0.061, respectively) as compared with other IEI. Mean levels of neutralizing activity in 3 patients who had previous COVID-19 infection was higher after vaccination (95% vs 47%, p=0.001) than in patients without previous COVID19.

Conclusion: Around 60% of patients with IEI were able to develop vaccine-specific neutralizing antibody response. Neutralizing antibodies correlated well with anti-spike titers in IEI patients.

POSTER 117 - "DE NOVO" DETECTION OF TOTAL IGM AFTER A SARS COV2 INFECTION IN A PATIENT WITH COMMON VARIABLE IMMUNODEFICIENCY

AUTHORS

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Objective: We describe a common variable immunodeficiency in a 43-years old male patient with undetectable IgM levels during the entire follow-up of his disease and presented "de novo" production of IgM in the context of a SARS CoV2 infection.

Design And Method: Clinical and laboratorial follow-up of a patient with common variable immunodeficiency from diagnosis to date is performed.

It was observed that undetectable levels of IgM were maintained during the entire follow-up of his disease, a "de novo" production of IgM was seen in the course of a SARS-CoV-2 infection with a subsequent decrease to its basal levels, coinciding with the recovery of the infection.

Results: A 43-year-old male patient with a history of common variable immunodeficiency for 25 years, in substitutive treatment with immunoglobulins, with undetectable IgM levels during the whole follow-up of his disease.

No history of severe or recurrent infections during early childhood. During adolescence he presented repeated otitis and pneumonia. A familial history of a brother with common variable immunodeficiency.

On March 23, 2020, started fever peaks between 37.7 and 38.2°C, and on March 27, SARS-COV-2 infection was diagnosed. The initial approach was as an outpatient basis with azithromycin and hydroxychloroquine.

On April 2 he was hospitalized due to COVID-19 bilateral pneumonia. During admission, specific IgM antibodies against COVID 19 were detected, coinciding with the "de novo" detection of IgM in a transient manner, having maximum IgM values of 137 mg /dl.

After 18 days of hospitalization the patient was discharged on 04/20/2020. With clinical improvement of the pneumonia, although abnormal radiological infiltration persisted.

Subsequent analytical controls showed a progressive reduction of IgM levels to baseline levels. Laboratory tests in October 2020: IgM <10 mg/dl, IgA <2 mg/dl, IgG 1271 mg/dl. (under treatment with immunoglobulins).

One and a half year after infection the patient is clinically stable, with no respiratory sequelae following SARS COV2 infection.

Interestingly after the vaccination he developed again a low increased of total IgM (17 mg/dL)

Conclusions: Despite suffering from a common variable immunodeficiency with undetectable IgM levels (<10 mg/dl in all follow-up controls during 25 previous years) the patient generated IgM antibodies against SARS-CoV-2 virus but not IgG, thus elevating total IgM values transiently and subsequent decrease to their basal levels after COVID-19 infection recovery.

POSTER 118 - SURVEILLANCE OF ANTI-SARS-COV-2 ANTIBODIES IN HEALTHY DONORS PLASMA POOLS AND INTRAVENOUS IMMUNOGLOBULIN PRODUCTS. A CONTINUOUS PROGRAM FROM MAY 2020

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Objective: The current COVID-19 pandemic demands research not only into treatment/prophylaxis options, but also on reliable epidemiological surveillance. Concentrated immunoglobulins (IgG) used as replacement therapy for immunodeficiency diseases are obtained from plasma pools of thousands of donors. However, there has been limited study of the seroprevalence of anti-SARS-CoV-2 antibodies in the general population. In May 2020, Grifols established a program for continuous monitoring the evolution of anti-SARS-CoV-2 antibodies in pooled plasma of different geographical origins plus the derived intravenous IgG (IVIG) products and studies of the neutralizing activity of these antibodies that include the latest variants of concern (VOC).

Design and method: Plasma pools (collected in Spain, Germany, Czechia, Slovakia, and the U.S.) and the resulting batches of IVIG have been followed from May 2020. Plasma and products from Hungary and Italy have been included since May 2021. Antibody against SARS-CoV-2 were analyzed by ELISA. Neutralization studies in IVIG final products (ID50 = dilution producing 50% neutralization) were conducted with original Wuhan SARS-CoV-2 virus and pseudoviruses representing the native strain and several VOC.

Results: Plasma pools collected in Spain and US from July to early September 2020 tested positive for the presence of anti-SARS-CoV-2 antibodies. From mid-September up to November 2020, most pools were positive for anti-SARS-CoV-2 antibodies with increased titers. Conversely, the first positive plasma pool in central Europe countries was collected in mid-November 2020. From that point, anti-SARS-CoV-2 antibodies have dramatically increased (10 to 50-fold) in all plasma pools and IVIG products regardless of geographic origin. Highest titers and largest increases in anti-SARS-CoV-2 antibody titers were seen in the regions where antibodies first appeared (Spain and U.S.). Titers of anti-SARS-CoV-2 antibodies in the final products showed similar evolution over time as those seen in pooled plasma. All products showed upwards trends in their titers except those from Slovakia. Neutralization studies evidenced the neutralization potency of Gamunex®-C and Flebogamma® DIF from plasma of different origins. IVIG products showed neutralization activity against pseudoviruses of the wild type, second wave and variant viruses (alpha, beta, gamma, and delta).

Conclusions: This study provides strong evidence that anti-SARS-CoV-2 antibodies in pooled plasma and IVIG products mirror exposure to the virus in the general population. Although the clinically protective dose of anti-SARS-CoV-2 antibodies remains to be established, these data are encouraging for patients with immunodeficiencies. Continued monitoring of these antibodies is recommended.

POSTER 119 - HIGH DOSE IVIG IN SELECTED HIGH RISK PATIENTS WITH SEVERE COVID19 NEUMONIA

AUTHORS

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Objective: COVID-19 disease is associated with high mortality among high-risk patients. No definitive treatment is available. Up today the only widely accepted interventions for hospitalized patients are enoxaparin, dexamethasone, Tocilizumab and Remdesivir. Immune-based therapies are under investigation in clinical trials but patients with risk factors are not included in these trials.

We report a case serie of 4 high risk patients admitted in our hospital with COVID-19 bilateral pneumonia who were selected for therapy with high-dose intravenous immunoglobulin.

Design and method: Retrospective review of clinical charts.

Results and conclusion: Patient 1, male 40 years, with previous history of lymphoma, severe secondary IgG hypogammaglobulinemia and persistence of SARS-Cov2 viremia (more than 3 months). Previous therapy included corticosteroids, Tocilizumab, Anakinra, Lopinavir/Ritonavir, Remdesivir and 2 sessions of convalescent plasma. Low and transitory maintenance of SARS-Cov2 IgG antibodies was observed after plasma infusions. He received high-dose intravenous immunoglobulin, 0.5 grams/kilograms for 5 days (total 150 grams).

Patient 2, male 60 years, obesity (120 kilograms), hypertension and diabetes as risk factors. Previous therapy included Azithromycin, Hydroxychloroquine and Lopinavir/Ritonavir. Due to severe bacterial infection corticosteroids and Tocilizumab were not added. He was treated with intravenous immunoglobulin 0.4 g/kg for 3 days (total 150 grams).

Patient 3, male 31 years, Common variable immunodeficiency with IgG hypercatabolism that evolved to bad radiological image of pneumonia and need of supplementary oxygen soon after admission. He received therapy with 1 grams/kilograms of intravenous immunoglobulin.

Patient 4, male 91 year, Common variable immunodeficiency with obesity, dyslipemia, hypertension, diabetes, chronic obstructive pulmonary disease and Granulomatous-lymphocytic interstitial lung disease as risk factors.

Biomarkers associated with bad prognosis were observed in all cases. High-dose intravenous immunoglobulin prevented deterioration of clinical symptoms and progression to mechanical ventilation in all cases. After high-dose intravenous immunoglobulin was completed all were discharged from the hospital with a stable clinical condition in a few days. 6 months follow-up revealed stable clinic. Infusions were tolerated well. Deep Vein Thrombosis was observed in patient 2.

High-dose intravenous immunoglobulin can improve clinical condition and prevent progression to Intensive Care Unit admission in selected high risk COVID-19 patients with severe symptoms and comorbidities.

FRIDAY, APRIL 29, 2022

GUIDED POSTER WALK 5B - PID ENVIRONMENT & QOL

MODERATOR: Dr Nahla Erwa

POSTER 120 - PID LIFE INDEX: THE TOOL MEASURING THE GLOBAL PID ENVIRONMENT

AUTHORS

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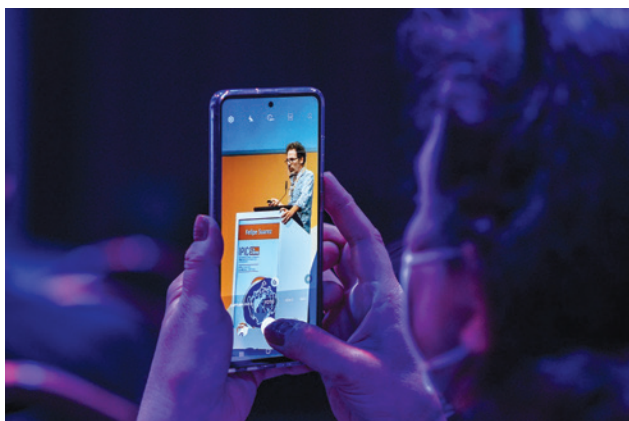
Objective: A global gold standard framework for primary immunodeficiency (PID) care, structured around six principles, was published in 2014 by IPOPI, together with international experts. Since then, IPOPI has been working to bring these principles closer to the day-to-day life of people with PIDs. To reach this objective IPOPI developed the PID Life Index in 2020, an interactive tool aggregating national PID data, facilitating the task of measuring the implementation of these principles. This index allows for handling large amounts of data on key indicators and for describing or comparing life with a PID in a given country or region.

Design and method: To start, the six PID Principles of Care were reviewed to consider advances in the field, as well as political developments that had occurred after their initial publication in 2014. Based on this revision the list was updated, and a new principle was added. The six established principles were: diagnosis, treatment, universal health coverage, specialised centres, national patient organisations and registries.

Each principle is measured through a series of criteria and has been given the same weight, as they are considered equally important. Specific weights were attributed to the criteria depending on their relevance and importance to quantify the principle. The index was translated into a survey for data collection: initially including data from selected countries for a pilot, followed by integration of data from IPOPI's members and key countries.

Results: The PID Life Index offers a holistic overview of the PID environment in different countries and regions. The data is displayed through a map or through a data visualisation system ranking countries according to their index score. The system provides three different options to view the countries: in a horizontal list from high to low, in a vertical list from highest scores to the lowest or by alphabetical order. The shape of the visuals allows for the display of the overall score of a country as well as the score of the 6 individual principles. In November 2021 the Index hosted data from 62 countries. The index is envisaged to be enlarged over time.

Conclusions: The PID Life Index is the first attempt to provide a global harmonised educational approach to the gold-standard principles of care for PIDs. It provides measurable information on key PID indicators, allowing worldwide country-to-country comparisons to empower PID stakeholders to make informed choices, and support advocacy initiatives nationally, regionally, and globally.





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“

“Super meeting all around and so wonderful to see everyone again - high level talks aimed just right - it was pretty much a triumph! Best organized meeting I have ever gone to as well! “

“

“Seriously the best congress I have ever been to!”

“

“I just went back to the ipic5app and all the videos of the sessions were up and running. I'm definitely going to go over each session and absorb as much as I can. I can't thank the committee enough for organizing such a good congress. “

“

“I am very grateful to the perfect organization that put the participants in the best condition to be able to capitalize on the contents during the exhibitions and in the Poster Room.”

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“Best aspect of IPIC5th was sharing the newest information/knowledge in curing and caring PID patients”



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