an **IPOPI** event

IPIC2019

INTERNATIONAL PRIMARY IMMUNODEFICIENCIES CONGRESS

DIAGNOSIS AND CLINICAL CARE

6-8 NOVEMBER
MADRID, SPAIN

CONGRESS **REPORT**


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INTERNATIONAL PRIMARY IMMUNODEFICIENCIES CONGRESS

BERLIN-GERMANY

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BERLIN,
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ABOUT IPOPI

IPOPI (International Patient Organisation for Primary Immunodeficiencies) is the leading advocate for primary immunodeficiencies' (PIDs) patients worldwide. We work in collaboration with patients, doctors, politicians, regulators, pharmaceutical industry and other relevant stakeholders.

IPOPI is the Association of national patient organisations and our work is dedicated to improving awareness, access to early diagnosis and optimal treatments for primary immunodeficiencies' patients worldwide through global collaboration.

IPOPI has an increasing membership and currently represents 68 National Member Organisations spread across all continents.

IPOPI is an international charity registered in the United Kingdom and under UK Charity Law. IPOPI also has offices in Portugal.

STRATEGIC PLAN 2016-2020

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

1 - To promote early diagnosis & ensure optimal access to care

2 - To develop, strengthen and support National Member Organisations (NMOs)

3 - To raise PID awareness globally

4 - To stimulate stakeholder collaboration

FIND US ONLINE

The best way to learn about IPOPI and our activities and achievements is through our website **www.ipopi.org**. You will find all our statements, events, members' contacts, the IPOPI PID Map, etc.

e-News, our quarterly electronic newsletter, is our main periodic communications' tool. It is released each year in March, June, September and December and features three specific sections: IPOPI's News, Around the world and NMO Focus. Read more: **e-News.ipopi.org**

Watch **TV.IPOPI.org** to find all IPOPI's video contents including patient testimonials, physician interviews and clinical management lectures on primary immunodeficiencies. The videos have been sorted around dedicated sections on Access to care, Diagnosis, Quality of life and Clinical Management.

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

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SUPPORTING ORGANISATIONS

IPIC2019 CONGRESS REPORT (by Dr Lizzy Rivers*)

IPIC2019, the 4th IPOPI International Primary Immunodeficiencies Congress (IPIC), held in Madrid, Spain, saw the joining of 750 clinicians, scientists, patient support and advocacy groups from 70 countries, bringing science and clinical care together with the aim of improving care for patients with primary immunodeficiencies (PIDs). The programme celebrated the incredible work carried out by our global PID network but also highlighted work still needing to be done. Here, a summary is presented of the conference main sessions, where updates in knowledge of disease as well as advances in supportive and definitive therapies for PIDs were discussed.

* ***Dr Lizzy Rivers*** *is a member of the IPOPI Medical Advisory Panel and works at Great Ormond Street Hospital for Children in London. IPOPI wishes to sincerely thank her for the preparation of this congress report.*

KEY MESSAGES:

- Understanding the molecular basis of disease remains key to progressing the field of PID diagnosis and treatments
- Advances in diagnostics bring challenges in evaluation of novel variants of uncertain significance
- Important information on side effects and the potential monitoring needed for novel therapies is emerging but with limited follow-up so far - collaboration is needed to share experiences
- The value of parents and patient organisations in policy making cannot be underestimated

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WELCOME SESSION: PUSHING THE BOUNDARIES OF PIDs TOWARDS NEW HORIZONS

- Functional evaluation of novel variants is essential in determining their significance
- In addition to detecting new inborn errors of immunity, whole genome sequencing is also identifying PID mimics
- With the discovery of targeted therapies for immune dysregulation, we are learning the delicate balance of managing immunosuppression with susceptibility to infection
- Collaboration across disciplines is essential in sharing ideas and understanding for the advancement of PIDs and their mimics
- The 'PID classification' app is a great resource for trainees and experts alike

Prof Stuart Tangye, Chair of the IUIS committee, opened the Welcome Session with a useful update on IUIS classification and highlighted how exploration of the molecular causes of PIDs has done so much for assisting management of patients and medicine beyond PID. This was demonstrated eloquently using the example of XLA. Since its discovery in 1952, dramatic improvement of patients on immunoglobulin (Ig) replacement led to extension of use of Ig to successfully protect other PID patients. It was not for another 40+ years that the BTK gene was found to be the cause of absent B cell development, exploitation of which has now been successfully adapted for treatment of B cell lymphoma using BTK inhibitors.

With the advent of next generation sequencing (NGS), there has been a huge increase in rates of gene discovery for inborn errors of immunity (latest 430 PID genes). This brings its own problems of when to call a variant "pathogenic", with much work needed in functional evaluation and correlation with clinical phenotypes. The committee has a huge task in classifying variants based on their clinical and immunological phenotype. Possible diagnoses can be browsed by predominant immunophenotypes or alternatively, specific clinical and/ or immunophenotypic features can be entered into the search category to return potential diagnoses.

Dr Anne Puel echoed the importance of functional evaluation of novel variants, particularly in determining whether they are predicted to cause loss or gain of function effects. She shared her experience of the drug ruxolitinib (member of the family of JAK (Janus kinase) inhibitors) for STAT 1 gain of function (GOF) patients where, prior to its use at her centre, haematopoietic stem cell transplantation (HSCT) in 15 patients was associated with only 40% overall survival (OS) and significant risk of graft failure. Following its introduction in 2015, ruxolitinib seems to be a game changer with reports of significant improvement in patient symptoms. However, caution was raised about its use in those with invasive fungal disease prior to JAK inhibition, which appears to be associated with significant morbidity and mortality. Dr Puel's experience of 11 patients on ruxolitinib (dose 0.4 to 2mg/kg/day or 15mg/m2 BD) found improvement in cytopaenias, interstitial lung disease and enteropathy. Nonetheless, one patient died from disseminated coccidiomycosis. There also appears to be a significant risk of viral reactivation with CMV, EBV, BKV, JCV, VZV and prophylaxis with aciclovir is recommended.

ESID President, **Prof Isabelle Meyts**, concluded the session by reminding about the importance of considering PID mimics in the management of undefined PIDs. Barrier functions of epithelia play important roles in host defence, with defects resulting in recurrent infections that may phenocopy PID. This was illustrated with two case presentations, the diagnoses of which only came to light after whole genome sequencing; the first, a patient presenting as hyper IgE syndrome (HIES) that turned out to have a variant in a gap junction gene (GJA1) and the second, a patient presenting with an IPEX-like phenotype who was found to have SAM syndrome (Severe dermatitis, multiple Allergies and Metabolic wasting). Conversely, Cystic fibrosis (CF), traditionally considered a PID mimic, has been a condition of particular interest in recent years, with evidence now suggesting that CF neutrophils have higher granule release, with high oxygen consumption, increased reactive oxygen species (ROS) production and neutrophil extracellular trap (NET) formation. With expression of the cystic fibrosis transmembrane receptor (CFTR) found in immune cells, it is possible that CF could well be re-defined as a PID in the not too distant future.


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OPENING SESSION

- Progress in the understanding of PIDs is vital in creating better outcomes for patients
- ERNs are a prime example of how international collaboration can be facilitated for the progression of PIDs' care and benefit of patients

After introductory remarks from Mr Johan Prévot (IPOPI Executive Director) and Mrs Martine Pergent (IPOPI President), the welcome address was given by **Dr Enrique Terol**, European Commission representative for European reference networks (ERNs), highlighting the value of international collaboration in progressing the field of PID and other immunological disorders. Since their launch in 2017, there are now 24 ERNs in 26 countries, involving > 900 healthcare units, which facilitate cooperation between the best specialists from across Europe, offering truly 'cross-border' healthcare. ERNs are meant to be a valuable resource with important roles in education, training and research in the field of rare diseases, ensuring that patients with these pathologies can benefit from expertise from all over Europe, no matter where the patient is based. Healthcare professionals will also be able to exchange safely expertise and clinical data on patients with complex diagnosis and management through virtual remote consultations. IPOPI has been part of ERN RITA since its inception and is present at the Board level as well as in some of the working groups. ERN RITA brings together leading European centres with expertise in diagnosis and treatment of rare immunological disorders, ranging from PIDs to autoinflammatory disorders and autoimmune disease.

The keynote speech was delivered by **Prof Bobby Gaspar**, who highlighted the importance of understanding disease in leading to better treatment outcomes. Since the first hematopoietic stem cell transplantation (HSCT) for severe combined immunodeficiency (SCID) in 1968, the field has evolved enormously over time, with overall survival (OS) now as high as > 80%, thanks to huge international collaborative efforts.

With further understanding of the molecular basis of disease came the onset of gene therapy, which is able to get over the graft versus host disease (GvHD) problem and some SCIDs requiring little or no conditioning. The earlier problems of insertional mutagenesis encountered following gene therapy for X-SCID have been improved by using modified vectors. Outcomes for gene therapy for ADA-SCID are excellent, with 100% event-free and overall survival; much improved outcomes compared with HSCT. Pre-clinical studies in gene editing are on the horizon, with the first likely to be for X-SCID.

When focusing on what can be done to further modify treatment outcomes for SCID, the importance of early diagnosis and newborn screening is highlighted. Following enormous international efforts, all US states are now screening for SCID since December 2018. There is an increasing number of European countries now screening too, but further work is needed.

- BAL WCC can be useful in differentiating interstitial lung disease versus infection
- sIL2R and CO transfer are potential biomarkers for diagnosis and monitoring of disease in ILD
- IFN γ, prolonged courses of antibiotics and early HSCT may be indicated for treatment of patients with susceptibility to mycobacterial disease

SESSION 1: MANAGEMENT OF RESPIRATORY ISSUES IN PID

Prof Klaus Warnatz highlighted important differences in PID-related respiratory disease; airway disease being predominantly linked to innate immune defects, whereas interstitial lung disease (ILD) more commonly seen in immune dysregulation/ adaptive immune disorders.

Recent evidence supports azithromycin prophylaxis (250mg 3x weekly) and targeting a higher IgG plasma trough level in those on Ig replacement therapy to prevent lower respiratory tract infections (LRTIs) in patients with antibody deficiencies. Advances are being made in the development of nebulised Ig, but we are not there yet. Animal studies have demonstrated evidence of Ig at the lung epithelium 1 week post-administration and protection against pneumococcal challenge, but human studies are not in trial yet.

Experience was shared of managing ILD in common variable immune deficiency (CVID) (granulomatous lymphocytic interstitial lung disease, GLILD), which is well documented but still insufficiently defined. It is felt to be part of a lymphoproliferative, multisystem disease. Interestingly, the B cell phenotype in GLILD is different, with a predominance of smB-21lo. Soluble IL2 receptor (sIL2R) appears to be elevated in nearly all ILD patients and is a potential activation marker. Bronchoalveolar lavage (BAL) differential white cell count (WCC) can also be useful; it will typically be lymphocytic (mostly T cells, but also some B cells) in ILD (compared with no B cells in sarcoid). Where neutrophils are the predominant cell type, infection should be considered first. Biopsies can be helpful, particularly where there may be suspicion of

lymphoma. Advice was given to consider cryobiopsy, which results in larger tissue samples and makes the likelihood of finding something much higher.

Radiological evaluation of ILD can be difficult, particularly with post-infectious scars, which may mimic the appearance of ILD. Lung function can be normal, but reduced CO transfer may be a more sensitive and much earlier sign.

Most would agree that the first line of treatment for GLILD would be steroids in achieving disease control, however, maintenance steroids do not appear to be helpful. Second line agents such as rituximab have shown some promise, but there is no certainty and greater collaboration is needed to share experiences. The SAIL study looked at response to abatacept, which did result in some improvement, but not as much as rituximab.

Expanding on this, **Dr John Hurst**, followed with his experience of managing respiratory issues in patients with non-antibody deficiencies. Respiratory disease is often worse in overactivity of immunity rather than immune deficiency, with a vicious cycle of epithelial injury leading to impaired muco-ciliary clearance and inflammation with airway compromise and further ongoing epithelial damage.

When looking at diagnostics for respiratory disease, the presenter reminded that normal lung function doesn't necessarily mean it is optimal, with repeated lung function measurement after therapy sometimes improving to beyond normal on treatment. Effort-independent lung function, e.g. forced oscillation, can be particularly helpful in evaluating airway resistance and cardio-respiratory exercise testing can be helpful in the evaluation of exertional changes. MRI can give complimentary information but cannot replace CT. However, it may have a role in disease monitoring, with functional MRI providing useful information on regional perfusion and ventilation.

Emerging treatments for bronchiectasis include: CFTR modulators, inhaled antibiotics, CXCR2 antagonists and anti-IL-5. Overall, it is important to treat the underlying cause and to use non-pharmacological treatments e.g. pulmonary rehabilitation. Macrolides are the antibiotics of choice for prevention (with no added benefit of 500mg over 250mg zithromycin) – ciprofloxacin is felt to be better kept for treating infective exacerbations. Work looking at the respiratory microbiome highlights trends in health and alterations in disease. With advances in understanding the role of the gut microbiome and faecal transplant in the post-HSCT setting, it is possible that further research could identify a similar benefit of sputum transplant in respiratory disease.

Dr Emilie Catherinot concluded the session with an update on mycobacterial disease in PIDs, with conditions typically associated with higher risk of disease including mendelian susceptibility to mycobacterial disease (MSMD), SCID, GATA2 deficiency and chronic granulomatous disease (CGD). Combined immune deficiencies are generally felt to be low risk.

Susceptibility to mycobacterial disease is usually associated with impaired IFNγ response, either due to lack of production, e.g. STAT1 loss of function (LOF), or IFNγ receptor (IFNγR) defects, or defective response, e.g. IL12, NEMO, ISG15 or IRF8 deficiencies. Interestingly a neutralising anti-IFNγ antibody has now been discovered, phenocopying IFNγ deficiency but presenting later in life. In SCID, higher risk of disseminated disease is seen with T cells < 250 and if vaccinated < 1 month.

Treatment of mycobacterial disease in PIDs involves prolonged courses of antibiotics, with additional IFNγ therapy and early HSCT being recommended in select conditions, but prognosis is poor. IFNγ therapy is currently recommended for IFNγ deficiency, IL12/IL-23 and NEMO deficiencies. HSCT is recommended for SCID, CGD, IFNγ deficiency, GATA2 deficiency and select IL-12/IL-23 deficiency patients but is often associated with immune reconstitution inflammatory syndrome (IRIS), requiring steroid therapy.

SESSION 2: PID TESTING AND SCREENING – A LOOK AT NOVEL PID DIAGNOSTICS

- Low TRECs has been linked to maternal immunosuppression in pregnancy, sepsis and prematurity in addition to primary T cell defects
- The value of obtaining views of parents and patient support groups in policy making for PID management cannot be underestimated
- All PID patients should have access to a diagnosis, regardless of rarity. Physicians need to work together and share ideas on how to achieve diagnosis in resource poor settings.

An update on outcomes for newborn SCID screening in Netherlands and Spain was given by Dr Maartje Blom and Dr Carlos Rodriquez respectively.

A pilot started in April 2018 in the Netherlands, which has now been extended to 2020 with agreement for national implementation afterwards. Screening is currently taking place in 3 provinces. There is also ongoing work looking at opinion on whether newborn screening should be extended for ataxia telangiectasia (AT), which is currently not recommended as there is no treatment. Discussion with parents of affected children, however, revealed 20/35 parents would have wanted earlier diagnosis to prevent a prolonged period of uncertainty, aid family planning and optimise medical care including screening for malignancy. Concern from medical staff about the impact early diagnosis might have on reduction in 'happy years' where diagnosis is unknown was also reported in 15/35 families but, overall, 74% of parents agreed with early diagnosis being preferable. Parents of healthy children were also consulted and the majority felt earlier diagnosis would be preferable. Reporting untreatable incidental findings remains a disputed topic worldwide.

The first pilot for SCID screening in Spain commenced in 2012 and, in 2016, the largest prospective pilot for combined TRECs and KRECs screening was published. Causes of secondary lymphopaenia were identified to be prematurity and low birth weight, which were associated with both low TRECS and KRECs. Maternal immunosuppression was associated with isolated low TRECs. Cut off levels for both have been optimised to TRECS < 6 copies per punch and KRECs < 4 copies/ punch. Results from the Catalonian group (published a few days prior to the conference) found 1 new SCID case in 131,000 children screened, with an additional 11 non-SCID lymphopaenias (partial DiGeorge, chylothorax, Down's syndrome), 4 transient lymphopaenias and 9 false positives. The SCID case identified was transplanted at 2 months of life with good clinical outcome and good immune reconstitution. A separate pilot study in Madrid of 1500 babies used different cut offs of TRECS < 8 copies/ punch and KRECs < 6 copies/ punch. The addition of KRECs clearly aided identification of leaky SCID and XLA, but was associated with a higher rate of false positives.

Next, **Dr Narissa Suratannon** discussed the importance of making a molecular diagnosis in PID patients, where similar clinical presentations may be caused by mutations in several different candidate genes. The pros/ cons and experience of different methods for obtaining genetic diagnosis are discussed in the table below.

METHOD	PROS	CONS
Sanger sequencing	Accessible	Costly, time consuming, limited sensitivity in mosaicism
CGH array/ single nucleotide polymorphisms (SNPs)	Can pick up microdeletions and unbalanced rearrangements	Limited to detection of single nucleotide variants
Next generation sequencing (NGS)	Faster, often less expensive	Limits detection of novel variants
Whole exome sequencing (WES)	High yield	Time intensive, less reliable for copy number variants (CNVs), complicated data interpretation
Whole genome sequencing (WGS)	Ability to detect copy number variants (CNVs) more reliably	Expensive, time intensive, complicated data interpretation


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Bobby Gaspar

However, challenges of reaching a molecular diagnosis in resource poor settings often require novel approaches. In Thailand, they are currently using a genome-wide Illumina® screening array with single nucleotide polymorphisms (SNP) genotyping. This approach is much cheaper than whole exome sequencing (WES)/whole genome sequencing (WGS) and has the additional advantages of being customisable with fewer ethical issues associated with identification of mutations in non-PID genes. Validation of this approach involved evaluation of 95 PID samples that had been diagnosed based on conventional Sanger sequencing. Seventy-five out of 95 were correctly identified using their combined array with SNP genotyping. The cost is only €40 for the array with turnaround time of 1 week. The group proposes starting with the array, with Sanger sequencing for positives and unsolved diagnoses to go to WES/WGS as a second line in resource-poor settings.

The session was concluded with the insightful and brave sharing of personal experience by **Mrs Heather Smith**, mother of two children with X-SCID, the first of whom very sadly died as an infant shortly after diagnosis. Her second child was diagnosed antenatally and the first child in the world to undergo *in utero* haplo-HSCT. He is now 24 years old and has done remarkably well. He graduated from college with a degree in environmental science, has an active life and enjoys playing sports. He had one hospitalisation for suspected Lyme disease and did not reconstitute B cells after HSCT, so remains on Ig replacement therapy. A slow reduction in T cells was picked up recently and after discussion with him about the possibility of severe infection, he enrolled on a gene therapy study. Currently, he is 3 months post gene therapy and doing well. Mrs Smith shared that her experience has taught her the value of being able to meet other families with affected children. Since 2008 she has been involved in 'SCID Angels for Life' charity and now works full time in the SCID community. Amongst other resources, they have an active Facebook group for supporting families affected by SCID, sharing with patients was encouraged.

SESSION 3: THE GOOD, THE BAD AND THE UGLY: MANAGEMENT OF COMPLEX PID CASES

- Analysis of the CEREDIH cohort suggests incidence of malignancy in the PID population is higher than previously thought, which should prompt review of our current protocols for surveillance of all PID patients
- Investigation and management of secondary immunodeficiency requires close collaboration with other specialties
- SCIg may be better than IVIg in maintaining protective Ig levels in protein losing enteropathy
- Management of patients with autoinflammatory disease and associated T/B cell defects can be exceptionally challenging in balancing the control of inflammation and risk of infection; sharing of experiences is vital in determining the best care for patients

Prof Felipe Suarez opened Session 3 with an update on our knowledge of malignancy in the context of PIDs. Although oncogenesis in PID is well known, it is only relatively recently that mechanisms have been explored. Four common mechanisms have been identified:

1) DNA repair defects
2) Altered immunosurveillance
3) Chronic antigenic stimulation
4) Oncoviruses e.g. EBV, HHV8, HPV

Evaluation of the French Reference Centre for Primary Immunodeficiencies (CEREDIH) cohort of 7,500 patients identified 678 cancers in 548 PID patients, most commonly B-CVID/ B-other (45%) and T-CID (22%), including ataxia telangiectasia. Malignancies were predominantly haematological in nature (most commonly B-cell lymphoma), but solid tumours were also seen – particularly skin, gastrointestinal (GI) and breast. There was no difference in sex but age at presentation of malignancy was much older in antibody deficiencies (> 50 yrs) compared with T cell immunodeficiencies (10-25 yrs). Overall, increased risk of malignancy compared with general population was 800x in CID and 1,500x in AT, which provides food for thought for our surveillance protocols.

Dr Stephen Jolles used three case presentations of severe/ recurrent/ unusual infections in complex patients, with important lessons in differentiating primary and secondary immunodeficiency. The first was a case of hypogammaglobulinaemia in an adult male found to have constrictive pericarditis, with subsequent protein losing enteropathy. This case highlighted the importance of considering renal and GI causes of protein loss and how the estimation of total globulin (total protein – albumin) as a surrogate for immunoglobulins can be helpful. Ig replacement in protein losing enteropathy is contentious but his recommendation was to consider replacement where there are ongoing losses and, if doing so, SCIg seems better at providing more sustainable serum levels.

The second case highlighted an important practical tip in interpretation of specific antibody responses in patients who have received/ are receiving Ig replacement. Where specific antibodies are detected, re-vaccinating the patient and checking the increment can still be used to determine functionality of B cell recovery e.g. in patients post Rituximab therapy.

The final case described an adult with systemic lupus erythematosus (SLE) and severe, recurrent and unusual infections with evidence of combined immunodeficiency on immunophenotyping making primary immunodeficiency difficult to exclude. In this scenario, a reduction in immunosuppressive therapy led to improvement in infections, but we were reminded that in other such patients this may be inappropriate and treatment will likely include appropriate surveillance for opportunistic infections, where vulnerable, and treatment/ support with vaccinations, anti-fungal, anti-viral and anti-bacterial medications. More work is likely needed in collaboration with our colleagues in different specialties who use biologics/ immunomodulators, to develop consensus guidelines for how to safely protect these patients from infection.

Dr Benedicte Neven concluded the session with the first of two very popular talks on autoinflammatory disease, starting with a reminder on the difference between autoinflammatory disease (innate immune defects) and autoimmunity (adaptive immune defects).

Components of the innate immune system include epithelial/ chemical barriers, phagocytic cells, complement, pattern recognition receptors (PRRs), Toll-like receptors (TLRs), Nod-like receptors (NLRs), C-type lectin receptors and cytokine pathways. Autoinflammatory syndromes may present with isolated inflammatory features, or with associated B/T cell defects. The molecular basis is being increasingly understood, with increased use of genetic testing, for example mutations leading to deficiencies in *HOIL-1/ HOIP, RIPK1, WDR1, TRNT1, PLAID, APLAID and ADA2*. Autoinflammatory

disease should be suspected in patients with fevers without causative organisms identified, raised inflammatory markers, skin manifestations (e.g. urticaria, livedo, vasculitis, panniculitis) and GI manifestations (abdominal pain, diarrhoea, colitis, ulcers). Autoinflammatory syndromes can generally be separated according to each of the proinflammatory cytokines predominantly responsible:

- IL-1: *NLRP3* GOF (familial cold autoinflammatory syndrome, muckle wells, chronic infantile neurologic-cutaneous syndrome)
- IL-18: *NLRC4* GOF, macrophage activation syndrome (MAS), very early onset inflammatory bowel disease (VEOIBD), systemic onset juvenile idiopathic arthritis (sJIA) and haemophagocytic lymphohistiocytosis (HLH)
- NFkB related-diseases: mainly (but not exclusively) TNF-related
- *ADA2* deficiency is a very polymorphic disease encompassing cytopaenias, immunodeficiency with hypogamma and vasculitis predominant phenotypes, the latter of which may include stroke, skin vasculitis, chilblains, fever, arthralgia/arthritis and IBD.

Experience was shared of difficulty in treating autoinflammation with associated T/B cell defects, where there is susceptibility to infection. This is a rapidly growing field and, for sure, new classifications are to come. With more and more targeted therapies becoming available, the importance of sharing experiences of managing these patients is emphasised.

SESSION 4: REGIONAL CLINICAL PRIORITIES

- Development of cell and gene therapies in some regions is currently hindered by lack of support for molecular diagnostics
- When it comes to policy making, patients often have a stronger voice than doctors. Patient organisations, such as IPOPI, play an essential role in improving access to diagnostics and therapies globally
- In regions where newborn screening for SCID is still far off, the potential to use late pregnancy USS to look for presence of foetal thymus is one example of effective lateral thinking to identify solutions in resource-poor settings

In Session 4 we heard from our regional counterparts about challenges and progress in PID diagnosis and management.

Prof Surjit Singh from the Asia Pacific Society for PIDs (APSID) opened the session with an update on management of CGD. Interestingly, the infection profile in CGD patients in India is not dissimilar to that in other regions, with common pathogens including Staphylococcus aureus, Aspergillus spp, Klebsiella spp, Pseudomonas spp and mycobacteria. Access to diagnostics remains a challenge, for which a collaboration with Hong Kong and Japan has been established through the Asian PID network. Some centres are now able to offer NGS and sanger sequencing, with HSCT available in a limited number of regional centres.

From SEAPID, **Dr Adil Ali** presented their experience of diagnosis and management of SCID. Through involvement of IPOPI, increased awareness of SCID since 2014 led to an increase in SCID diagnoses and the availability of HSCT in major cities. Continuing challenges include funding for HSCT (not fully subsidised) and insufficient resources to implement newborn screening. BCG is part of the routine vaccination schedule, which adds additional difficulties in SCID management. Genetic and functional studies are often unavailable, enzyme replacement therapy (ERT) and intravenous immunoglobulin (IVIg) is limited and GT is not an option. The vision for SCID management in SEA is for increased collaboration with other

regional networks to aid sharing of expertise and support in establishing more centres for HSCT and greater access to diagnostics.

From BGPI, we heard from **Prof Condino Neto** about the challenges in PID management in Brazil, where Ig consumption has been increasing with a decreased supply limiting replacement. Plasma fractionation companies are available, but use is delayed due to predominantly political hurdles, with significant bottlenecks including issues of storage of plasma and stringent laws forbidding the collection of plasma for commercial purposes (categorised as organ donation). However, benefits of being able to use local plasma, including better protection from regional tropical diseases (e.g. Zika virus), continue to drive persistence of pursuing this avenue. Newborn screening pilots have been carried out in Brazil with identification of 50 SCID cases and national screening will be rolled out next year but BCG vaccination remains a problem.

ASID representative, **Prof Tandakha Dieye**, reported the challenges in PID management in Africa, where bacterial infection is a major comorbidity, including susceptibility to mycobacterial disease, often linked to a problem with production or response to IFNγ. MSMD is linked to problems with IL-12/IFNγ pathway, of which CYBB plays a role. Mycobacterial disease was found to be common in their CGD cohort, mostly TB, which raised the suspicion that CGD may be under-diagnosed. Access to NBT/DHR is good, so work is ongoing to improve education in thinking about testing.

Prof Troy Torgerson, CIS representative, presented their challenges in management of immune regulatory disorders. Three big problems:

1) How to diagnose in the context of wide clinical heterogeneity e.g. ADA2, STAT1 GOF
2) How to treat: immunomodulation v HSCT? Targeted therapies are proving effective, but limited experience in the long term to know if these are a suitable long-term solution
3) Does HSCT work? Generally outcomes are poor for immune dysregulatory disorders. There is limited experience in how much chimerism is needed and the effect on quality of life.

Current work is looking at ways to improve outcomes for these patients through collaboration with other regional networks to share experience and work on protocols for clinical trials to compare best available supportive therapy versus HSCT. They are hoping to enrol 500 patients, particularly IPEX and IPEX-like.

From ESID, **Prof Isabelle Meyts** presented challenges in SCID management in Europe, where there is a heterogeneous situation with many places still struggling to include SCID in their newborn screening programmes while other countries already have SCID in their national programmes (i.e. Sweden, Germany or Norway). In countries where screening is not yet happening, increased awareness for SCID has been noticeable, via medical education, awareness raising campaigns etc. Guidelines developed based on the experiences of those countries already screening could be developed to provide guidance on the management of babies between screening and beginning of treatment. Another point that needs consideration would be, in collaboration with the ESID Inborn Errors Working Party, a definition of when to perform a transplantation, with what conditioning (if any), etc.

In terms of challenges ahead of us, Prof Meyts highlighted accessing immunoglobulin therapies, with supply tensions and patients being forced to switch one product to another. There are also great disparities with regards to the price setting of IGs per country, leading to inequalities in availability of the different therapies, the differences in price per gram differing in up to 40% to 50% between countries. Challenges with other treatment options are also experienced, increasing the burden for physicians, patients and family members. There are many opportunities available to improve management of SCID in Europe through work with IPOPI and other patient organisations. ERNs could also play an important role with a shift in focus from national registries to regional registries, which may aid political challenges.


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SESSION 5: PID MANAGEMENT ETHICAL CONSIDERATIONS

- Rights of the child and respect for patient and parent autonomy are vital in managing ethical considerations in complex PID cases
- Parents and patient organisations can be a valuable tool in supporting other parents/ patients and the medical team
- Long discussions following each case highlighted a great need for a forum to discuss complex cases, which might be able to continue through IPOPI and ERNs

Back by popular demand, a session led by **Prof Bobby Gaspar** on the ethical considerations of real complex cases was delivered. A panel of medical and non-medical members (**Prof Alain Fischer, Prof Steve Holland, Dr Nahla Erwa, Mr John Seymour, Mrs Dorothea Grosse-Kreul**) were presented with 3 cases to consider, with final words by ethicist Dr James Taylor, who enlightened and entertained in equal proportions.

[1] Parents of a child with poor outcome following HSCT discovered at 22/40 weeks of pregnancy that their second child had the same condition. Although the chance of having a severely affected child with the particular PID was thought to be very low (~ 5%), the parents considered the experience with their first child too great a risk to continue with the second pregnancy, opting to terminate.

Bottom line: at 22/40, there are no rights of the unborn child. Autonomy is with the parents and ultimately (if in a region where available/ possible) parents may be able to continue to abort as many times as they wish if subsequent pregnancies are also affected. Responsibilities of the medical profession would be to ensure parents are well informed/ provided with support (including from patient organisations) and discuss alternative options for future pregnancies such as the potential for preimplantation diagnosis where possible. Consideration should also be given to the impact of the first child learning that another child with the same condition has been aborted.

[2] A 9 year old boy with cerebral palsy and multiple co-morbidities was discovered to have a true antibody deficiency and immunoglobulin replacement was suggested, but refused by the health insurance company. The parents were considering legal action against the insurance company and the question arose as to whether the medical team should support this.

Bottom line: Rights of the child are key here – the child has the right to access the best care. A legal battle, however, is unlikely to be in the best interests of the patient, parents or doctors and should be avoided where possible. Parents should be provided with enough information to make an informed decision about commencing immunoglobulin replacement, which should be supported by the medical team. It is possible that a compromise might be struck with the insurance company for a trial of treatment for 6 months with clear outcomes to be set.

[3] A 13 month old boy with a clinical phenotype in keeping with severe Wiskott Aldrich syndrome (WAS) had a previously undescribed variant of unknown significance in the WAS gene reported. HSCT was recommended and although agreed by the mother was disputed by the father, who was reportedly struggling to believe the diagnosis was certain in light of the genetic result. In attempt to provide further support to the family that the diagnosis was certain, functional testing was planned but the parents did not attend the appointment.

Bottom line: Rights of the child dictate that the child has the right to access the best care available. Responsibility for consent to treatment lies with the parents but the medical team has a duty to provide appropriate balanced information that allows parents to make an informed decision. Where the decision of the parents clearly puts the child at risk, involving children's services may be necessary to safeguard the child. Caution was raised in the language used to report genetic results to parents.

SESSION 6: LATEST TREATMENT ADVANCES IN IMMUNE DYSREGULATION

- Transplant outcomes for immune dysregulatory conditions are not good
- There have been significant recent advances in diagnostics, understanding of the molecular basis of disease and development of targeted therapies
- Important information on side effects and the potential monitoring needed for novel therapies is emerging but with limited follow-up so far, collaboration is needed to share experiences

Dr Olaf Neth used examples of CTLA-4 deficiency, APDS and STAT1 GOF to highlight the advances but also challenges of treating immune dysregulation.

The Freiburg cohort of 123 pts with CTLA-4 deficiency included 39 patients treated with Abatacept, which showed significant improvement in 16 patients in terms of enteropathy, CNS and lung infiltrates and in some cases also in cytopaenias. Four patients saw worsening of symptoms such as agranulocytosis, viral infections and worsened GI symptoms. However, there is now a clinical trial open which may provide further important information. The cohort also gained insight into side effect profiles of some newer agents, for example development of mouth ulcers with Sirolimus, which appeared to be dose-dependent.

Experience of treatment for APDS found overall a good response to Sirolimus, with favourable HSCT outcomes. It is important to note, however, that there were also some cases where patients did appear to worsen on Sirolimus. Outcomes from an open label trial (CDZ173, Novartis) demonstrated a 40% reduction in lymphoproliferation with normalisation of B and T cell phenotype.

Response to Ruxolitinib for STAT1 GOF demonstrated some promising results but with limited follow-up. Important side effects to watch for include cytopaenias, bruising and altered lipid profiles. There is also a reported potential for thrombosis and discussion was raised about the consideration for whether we should be treating patients with aspirin prophylaxis. Experience of 17 patients on Ruxolitinib (11 STAT1 and 6 STAT3 GOFs) revealed improvement in 14/17 but it is important to note that 4 patients died. Currently, the role of HSCT in STAT1 GOF is not recommended, with 50% overall survival.

Prof Benedicte Neven delivered a useful overview on the investigation and treatment of autoinflammatory conditions was presented. With the increasing discovery/ development of biologics, comes the possibility of truly targeted, precise medicine in the management of autoinflammation. Examples of conditions with success in targeting specific cytokines are highlighted below:

CYTOKINE	CONDITIONS	TREATMENTS
IL-1	NLRP3 GOF mutations	Anakinra, Canakinumab
IL-18	NLRC4 GOF mutations Very early onset inflammatory bowel disease (VEOIBD) HLH phenotypes	Anti-IL-18 (not on the market yet, but in trials for NLRC4 and XIAP deficiency)
Type 1 IFNs	Exaggerated response to viral infections e.g. AGS, SAVI, CANDLE	JAK/STAT inhibitors
TNF	ADA2 deficiency (vasculitis, ischaemic stroke, immunodeficiency with hypogamma, cytopaenias)	Anti-TNF

Like **Dr Neth's** experience of Ruxolitinib for STAT1/3 GOF, **Prof Neven** reported some improvement in skin and lung lesions following Ruxolitinib for 3 children with SAVI. Their group is currently treating another 10 patients but outcomes are pending. Another cohort of 18 patients on Ruxolitinib (10 CANDLE, 4 SAVI, 4 other interferonopathies) saw an improved

interferon signature (in CANDLE but not SAVI) and disease scores with decreased corticosteroid use. Anti-TNF therapy for ADA2 deficiency was also felt to be efficient in preventing ischaemic strokes but probably wouldn't replace the need for HSCT. An increase in infections was seen particularly with JAK/STAT inhibition (including VZV, HSV, BKV, mycobacteria, PCP and toxoplasmosis). Additional adverse effects include pulmonary hypertension, dyslipidaemia, cytopaenias and a withdrawal syndrome if stopped too abruptly.

Overall, there have been some significant advances in the development of therapies for management of immune dysregulatory conditions but further questions are raised, such as: What are the optimal drug dosages and durations to balance risk and benefit? What is necessary to measure to monitor for short and long term effects? Are these treatments likely to be curative or better thought of as a bridge to definitive care? Will efficacy decrease over time/ does tolerance develop? Sharing experiences and collaborating with colleagues in other specialties using some of these newer therapies in different contexts is of increasing importance in gathering information for the benefit of our patients.

The session was concluded by **Prof Kiki van Bilsen** (on behalf of **Prof Martin van Hagen**) who presented some very interesting data on the pharmacology of immunoglobulins, specifically the role of MHC class 1-like protein FcRN, which is used to recycle IgG via endosomes. The discovery of altered FcRN expression in the pathophysiology of non-PID disease has led to some initial data exploring FcRN as a potential therapeutic target. IgG deficiency has been described in myotonic dystrophy (MD), which is felt to be secondary to a hypercatabolic state. In a cohort of 17 MD patients, 12 had total IgG deficiency and 15 IgG1 deficiency, which appeared clinically relevant with increased susceptibility to LRTIs. Altered FcRN expression was also reported in the same cohort. A pilot clinical study inviting those with IgG deficiency to receive SCIg or IVIg replacement showed some promising results. Unfortunately, no correlation has been found between FcRN expression and CVID but a potential role for FcRN in other PIDs has been suggested by gene interaction between FcRN and other PID-associated genes including STAT1. Development of biologics targeting FcRN: anti-FcRN receptor has also shown some promise in ITP and myasthenia gravis.

SESSION 7: 20 YEARS OF GENE THERAPY – THE PAST AND FUTURE

- Outcomes of gene therapy trials have demonstrated proof of principle in safety and efficacy of curing disease
- Accessibility of products, especially following trial closures, remains a problem

Prof Alain Fischer opened the session on advances in gene therapy (GT) for PID by reminding all that the first paper considering GT for human genetic disease was as early as 1972. It is now 20 years since the first patient was treated (X-SCID) and much work has taken place in the development of this field since then. Currently GT is available for 12 genetic diseases, with work ongoing to increase this number (>50 potential candidate genes).

The success in GT for SCID is partly linked to the long life-span of T-cells (memory T-cell lifespan > 50 years), meaning that correction of only a few cells can provide a lifetime cure. In contrast, the half-life of neutrophils and platelets are only a few days, providing challenges for PIDs where lasting corrections in these cell lineages are needed e.g. CGD.

Outcomes for X-SCID 1999-2019: 1st trial (1999-2002) resulted in 90% survival (pooled London and Paris), 85% disease free. Initial problems with T-cell leukaemia secondary to insertional mutagenesis in 6 cases, 1 fatal and the majority are still needing Ig replacement. Development of next generation vectors (self-inactivating retroviruses) progressed and lentiviral vectors are now being used in place of gamma retroviral vectors. Mild myeloablation is now also being used to improve B cell correction. 13 patients have been enrolled using the new vectors and conditioning protocol, with no toxicity and only 1 death from pre-existing infection.

Outcomes for ADA SCID: 2002-2013: A total of 55 patients have now been treated, with median follow-up time of 10.5 years. All are alive and 38 are off enzyme replacement therapy (ERT). Gamma retroviral vectors were used, but no problems with insertional mutagenesis have been encountered. Since 2013, 1 trial using a self-inactivating lentivirus (US/UK) has taken place in > 75 patients. All are alive and > 73 are off ERT.

Outcomes for WAS: 7 patients (London/ Paris) have been treated with self-inactivating lentiviral vectors, using myeloablative conditioning with Busulphan/ Fludarabine and median follow-up of 8 years. No toxicity or clonal dominance has been encountered. Multilineage engraftment has been found in 6/7 patients and reduction in WAS score from 4.7 to 0.3, with resolution of infections, autoimmunity and eczema. Recovery of thrombocytopaenia has proved a little more challenging, with inconsistent results.

Looking to the future, there is ongoing work in developing GT for RAG1/2 and ARTEMIS SCIDs, as well as potential for other PIDs. It is important to remember that advances are simultaneously being made in HSCT and outcomes for GT must


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be reviewed in line with these. There is concern about accessibility to treatments, particularly after trial closures and collaborative effort is needed in ensuring ongoing product availability. Current work is also exploring the use of engineered nucleases for gene repair rather than replacement. One group is currently looking at gene editing for ataxia telangiectasia (AT), which is a very large gene, making vector development for GT challenging. Additional work is needed to manage the risks of malignancy with use of chemotherapy in AT and need for therapies to cross the blood-brain barrier.

Prof Frank Staal added the Netherlands perspective on GT for immune diseases, where work on GT development for RAG-1 deficiency is underway. Ex-vivo lentiviral transduction in a mouse model saw restoration of T and B cells, with production of IgG. Correction of patient cells in a humanised mouse pre-clinical model encouragingly demonstrated T cell development in peripheral blood and a few B cells in the spleen; a clinical trial is planned for next year.

Concerns about regulatory hurdles and pricing, vector development/ production accessibility were echoed. Legal and regulatory challenges are highly complex, with commercial licensing not always possible and difficulty in standardising materials. Estimated cost includes €600-1600k just for the product, not including chemotherapy/ hospital care etc.

Building on the idea of gene editing raised by **Prof Fischer**, thoughts on the appealing nature of targeted integration were shared but challenges identified in creation of stable packaging lines, purification of targeted cells and development of transduction methods by transfection or non-viral means (e.g. nanoparticles) still needed. Editing for GOF mutations is an exciting area of interest, with the idea that endonucleases could be used to induce gene knock-out without the need for integrating a correct copy of the gene.

An important reminder was raised as to the power of the patients in driving research and access to treatments. It seems often the case that patients can influence politicians, policy makers and grant funding agencies much better than doctors.

Finally, an African perspective on the potential of gene therapy in the developing world was provided by **Prof Aziz Bousfiha**. In some respects, the concept of autograft development in places where allografts are not yet possible seemed slightly premature. However, it was pointed out that there should be no reason why the two areas should not be developed simultaneously. A survey conducted of facilities and services available in the 54 African countries found no transplant facilities were available in 21 centres from 7 countries but 47% did report access to transplant facilities, with 67% reporting ability for clinical monitoring post-transplant. 100% of centres reported access to monitoring of FBC, GAM, LSS and BMA. The possibility for developing a GT facility was identified in 5 African countries and 40 countries reported ability to send HSCs for production of corrected cells elsewhere, with 12 of these already having centres set up for appropriate clinical and biological monitoring post GT.

Work is now needed to support centres able to start development of in-house and out-sourced GT where possible. Challenges include the cost of transduction and the need to ensure a molecular diagnosis can be made in patients. Continued work with ASID and IPOPI will be essential in realising this achievement.

SESSION 8: DIAGNOSING AND TREATING PIDs IN ADULTHOOD AND OLD AGE

- Genetic diagnosis can be helpful in management of PIDs in adulthood, e.g. by identifying where novel therapeutics may be indicated, but many adults are still living without a molecular diagnosis
- Monitoring of trough IgG levels is particularly important in adults, where the dose of replacement is not adjusted according to weight; trough of > 10 is associated with reduced incidence of LRTIs
- Prophylactic use of Azithromycin 3x weekly has also been shown to be beneficial
- Rituximab is showing some promise in CVID at reducing cytopaenias and lung disease

Dr Vigil Dalm raised a very interesting topic of the potential role of Ig levels in predicting complications of PIDs, particularly in the context of balancing infections and inflammation in the treatment of immune dysregulation. Evidence suggests high trough IgG is associated with fewer respiratory infections and reduced bronchiectasis. In contrast, low IgA may be associated with granulomatous lymphocytic interstitial lung disease (GLILD). Low IgM may also be associated with hypothyroidism in DiGeorge. Non-autoimmune endocrine dysfunction was found equally distributed in 16/67 patients with CVID, IgG subclass deficiencies (IgGSD) and specific antibody deficiencies (SPAD).

In the older adult population, the normal range of IgG is currently unknown, which has implications on the management of the increasingly ageing population of adults living with PIDs. Work is currently underway in Rotterdam in a study of 15,000 adults > 45 years old. Subjects have undergone clinical, radiological and immunoglobulin level evaluation to better understand the normal ranges for IgG, IgA and IgM and identify potential links between low Ig levels and non-PID diseases including malignancies, infection and cardiac disease.

Prof Charlotte Cunningham-Rundles provided a useful update on the advances in clinical management of CVID.

Recommended criteria for making a diagnosis of CVID include:

- Age > 4yrs
- IgG < 2.5th centile for age
- IgA and IgM below lower limit of normal for age
- lack of antibody response to protein antigens following immunisation in at least 2 assays
- other causes of failure of Ig production must also have been excluded

Genetics may help; in her cohort, a causative mutation was found in 72/277 patients screened. This is comparable to the Swedish (47/129) and Iranian cohorts (112/206). However, many remain without genetic diagnosis (up to 80%) and the genetic diagnosis does not necessarily inform about the disease course.

Complications associated with CVID include infections (particularly LRTI and sinusitis), autoimmunity, gastrointestinal symptoms (reflux, diarrhoea, inflammatory bowel disease), asthma and chronic lung disease. Interestingly, nodular regenerative hyperplasia in the liver is described in 5-12% patients but, currently, routine liver biopsy is not recommended since it is unclear what to do about it. There is also an increased risk of cancers, particularly haematological, breast and skin. We were reminded to give advice to patients about screening and reducing risk of these (e.g. sunblock).

Supportive treatment for CVID includes low dose Azithromycin prophylaxis three times per week and Ig replacement (usually IVIg 400-600mg/kg every 3 weeks, or weekly SCIg at home). In agreement with the earlier talks, it was reiterated that monitoring of trough IgG levels is important in reducing respiratory infections, with marked reduction in infections where trough IgG > 10. Interestingly, however, trough IgG levels do not correlate with reduction in sinusitis and gastro infections suggesting IgG replacement does not provide sufficient mucosal protection. Autoimmunity remains a problem and does not seem to respond well to IgG replacement. Co-existence of CVID with autoimmunity is associated with a greater risk of lung disease, granulomata, enteropathy and lymphoproliferation. Systemic granulomatous disease is seen in potentially as much as 20%, but use of biopsy is recommended to make the diagnosis. Rituximab has been used in 33 patients in Prof Cunningham-Rundles's cohort, which shows some promise with 71% gaining remission of cytopaenias and lung disease.

Curiously, inflammatory signatures are being increasingly identified in complicated CVIDs, particularly IFNγ. Further exploration is needed to determine if this might present a potential therapeutic target for treatment of CVID-associated inflammatory disease.

Prof Steve Holland described his experience of managing non-antibody deficiencies in adulthood and old age through their comprehensive program for non-malignant immune diseases at the NIH.

New diseases being described in adults include anti-cytokine autoantibody diseases e.g. anti-GM-CSF and anti-IFNγ, which are produced by B cells. Anti-GM-CSF antibodies block stimulation of macrophages, particularly in the lung and are associated with nocardia and cryptococcus in the brain, as well as alveolar proteinosis. Autoantibodies can be treated with Rituximab and inhaled GM-CSF is showing some promise for alveolar proteinosis. JAK inhibitors make good sense for STAT1 GOF, but there is currently no long-term evidence to support this and it is suspected that the effects may wane over time.

Antimicrobial prophylaxis remains of upmost importance in protecting PID patients. Lessons learned from azithromycin prophylaxis in COPD are a warning of a potential for hearing loss in ~5% of patients, though this is felt to be transient and is offset by the reduction in infective exacerbations. With regular use of antimicrobials in prophylaxis it is important to be aware that some resistance will occur but doesn't mean we shouldn't use them.

The session concluded with a humbling patient testimony from **Mrs Laura Miralles**, a CVID patient. She described her journey through diagnosis and treatment, with first signs appearing at 8 years old (frequent infections). Eventually her symptoms progressed to the point that her career as a radio presenter ended, when she had to leave her job at the age of 28 years due to frequent coughing and significantly limited exercise tolerance. After diagnosis, her quality of life has thankfully been completely transformed by Ig replacement. **Mrs Miralles** shared the importance to her of having a diagnosis named but still finds the knowledge that there is no cure somewhat challenging. For now, however, she is greatly enjoying the freedom that comes with her newfound health on Ig replacement.

CLOSING SESSION: PID DIAGNOSIS AND CARE – WHERE WILL WE BE IN 10 YEARS FROM NOW?

An inspiring closure talk was given by **Prof Alain Fischer**. Looking ahead at the next 10 years in PID, **Prof Fischer** focused on developments in the science, medicine and, importantly, society, since advances in science and medicine can be meaningless if societal issues are not taken into account.

In diagnostics of PID the genetics will undoubtably become more complex but the diagnostic tools are likely to also continue to advance, e.g. analysis at a single cell level. If the speed of novel PID mutation identification continues at the current trajectory we will likely be looking at having identified 600 PID genes in the next 10 years. Additionally, diagnoses are predicted to move away from monogenic to composite PID with greater understanding of penetrance and impact of compound mutations that may go some way to explaining the phenotypic variation in affected children from the same families.

There is likely to be an increasing role of pharmacogenomics in development of supportive therapies. Advances in drug discovery have come following greater understanding of the science behind the pathophysiology of disease leading to more precise medicine. We have already had great development in biotherapies in recent years, such as novel use of recombinant proteins and monoclonal antibodies. However, more are on the horizon such as STING and NFkB inhibitors.

In definitive therapies, advances will continue in HSCT, with reduced morbidity and mortality secondary to development of reduced toxicity conditioning agents and improved understanding of which conditions can be transplanted without chemotherapy. Opportunity for early HSCT will come with increasing implementation of newborn screening. Development of in utero HSCT is also likely to advance for those with antenatal diagnoses. We can expect gene therapy development for an increasing number of PIDs and clinical trials to begin using gene editing tools.

We were reminded that we all have a responsibility to advance PID diagnosis and care worldwide (whether doctor, nurse or politician). Priorities should include implementing newborn screening, ensuring Ig supply and making new therapies affordable and, therefore, available to everyone. Additional focus should include investing in social support for the families affected by PID who need it.

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 Cγ2 (PLCγ2)-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 varible 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 thrombocyopaenia
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 immnune 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 junvenile 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

POSTER	PRESENTER	TITLE
1	**L. DEL PINO MOLINA**	EXPLORING NEW MECHANISMS TO UNDERSTAND THE COMPLEX B CELL DYSREGULATION PRESENT IN COMMON VARIABLE IMMUNODEFICIENCY: IMPAIRED CPG DEMETHYLATION ASSOCIATES WITH B CELL PHENOTYPE AND PROLIFERATION RATE.
2	**A. KARIM**	CHRONIC SPONTANEOUS URTICARIA AS AUTO-IMMUNE FEATURE IN COMMON VARIABLE IMMUNODEFICIENCY
3	**M. RAKI SHIRZAD**	NEUTROPENIC PRIMARY IMMUNODEFICIENCY PATIENTS: A REGISTRY-BASED STUDY
4	**L. SOLIS**	SWITCHING OF IMMUNOGLOBULIN THERAPIES: AN INTERNATIONAL SURVEY ON PATIENTS WITH PRIMARY IMMUNODEFICIENCIES
5	**R. SHELLER**	EXPANDING THE REACH OF SEVERE COMBINED IMMUNODEFICIENCY TESTING: THE SCID NEWBORN SCREENING IMPLEMENTATION EXPERIENCE IN THE UNITED STATES
6	**C. SACHSENMAIER**	EPIGENETIC IMMUNE CELL QUANTIFICATION - A NOVEL APPROACH TO EARLY DETECTION OF PRIMARY IMMUNODEFICIENCY FROM DRIED BLOOD SPOTS
7	**T. VAN DER HOUWEN**	ENHANCED TLR5 EXPRESSION IN PATHERGY POSITIVE BEHÇET'S DISEASE PATIENTS INDICATES AN INNATE DRIVEN IMMUNE RESPONSE
8	**D. NEHME - ÁLVAREZ**	A 4 YEARS EXPERIENCE IN PRIMARY IMMUNODEFICIENCIES DIAGNOSIS USING NEXT-GENERATION SEQUENCING IN HOSPITAL 12 OCTUBRE IN MADRID.
9	**L. CASAMAYOR-POLO**	DIAGNOSTIC ALGORITHM FOR AUTOIMMUNE LYMPHOPROLIFERATIVE SÍNDROME
10	**T. ZONDAG**	A RARE RAB27A VARIANT ASSOCIATED WITH A CASE OF HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS ALTERS EFFECTOR PROTEIN BINDING AFFINITIES
11	**K. TOWNSEND**	ANTIBODY RESPONSE TO PREVNAR13 IN IGG SUBCLASS DEFICIENT PATIENTS
12	**G. SOGKAS**	A NOVEL HETEROZYGOUS IKBA MUTATION, REPLACING SERINE AT POSITION 36, RESULTS IN COMBINED IMMUNODEFICIENCY WITHOUT EDA
13	**F. SEIF**	A CASE WITH A NOVEL HOMOZYGOUS MUTATION IN OTULIN ACCOMPANIED BY AUTO-INFLAMMATION
14	**L. RIVERS**	INTERLEUKIN-18 IS A SENSITIVE MARKER OF INFLAMMATION IN WISKOTT ALDRICH SYNDROME
15	**R. PÉREZ DE DIEGO**	DOUBLE-STRAND BREAK REPAIR THROUGH HOMOLOGOUS RECOMBINATION IN AUTOSOMAL RECESSIVE BCL10 DEFICIENCY
16	**B. JOHNSON**	NEXT GENERATION SEQUENCING WITH COPY NUMBER ANALYSIS FOR PRIMARY IMMUNODEFICIENCIES: FINDINGS FROM A COHORT OF OVER 3,900 UNRELATED PATIENTS
17	**C. MESA-NÚÑEZ**	GENE THERAPY FOR LEUKOCYTE ADHESION DEFICIENCY TYPE I (LAD-I): A NEW THERAPEUTIC ALTERNATIVE FOR SEVERE PATIENTS.
18	**C. MILITO**	LOW DOSE AZITROMYCIN PROPHYLAXIS IN PRIMARY ANTIBODY DEFICIENCIES: A MULTICENTER, DOUBLE-BLIND, PLACEBO-CONTROLLED RANDOMIZED CLINICAL TRIAL
19	**E. MALBRAN**	A NEW CYTOTOXIC-T-LYMPHCYTE-ANTIGEN-4 (CTLA4) MUTATION, SEGREGATING WITH OSTOPOROSIS
20	**H. IJSPEERT**	ANTI-INTERFERON GAMMA AND IL-17 AUTOANTIBODIES IN A CHILD WITH ULCERATION AFTER BACILLUS CALMETTE-GUERIN (BCG) VACCINATION AND ONYCHOMYCOSIS

POSTER	PRESENTER	TITLE
21	**A. BONDARENKO**	MUCOSA-ASSOCIATED LYMPHOID TISSUE 1 (MALT1) DEFICIENCY: SEVERE SKIN LESIONS AS AN EARLY DIAGNOSTIC CLUE
22	**R. EL-OWAIDY**	PERFORMANCE OF HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS FEATURES AMONG CHILDREN WITH SEVERE SEPSIS
23	**M.E. PONTES CUNHA DE CASTRO**	CLINICAL AND GENETIC CHARACTERISTICS OF PATIENTS WITH WISKOTT-ALDRICH SYNDROME IN BRAZIL
24	**N. MAHLAOUI**	CHRONIC RHINOSINUSITIS IN AGAMMAGLOBULINEMIA AND HYPER-IGM SYNDROME, SURVEY OF THE FRENCH POPULATION
25	**M. SHABANI**	CONGENITAL CARDIAC DEFECTS IN G6PC3 DEFICIENCY; REPORT OF A NOVEL MUTATION AND A LITERATURE REVIEW
26	**A. YAILIAN**	SECURING IMMUNOGLOBULIN SUPPLY IN PRIMARY IMMUNODEFICIENCY AS A PRIORITY INDICATION: PATIENT'S CARE PATHWAY APPROACH
27	**P. PATRA**	AUTOIMMUNITY IN WISKOTT-ALDRICH SYNDROME; DOES IT MATTER!
28	**S. MESHAAL**	LRBA AND CTLA4 DEFICIENCY AMONG CVID EGYPTIAN PATIENTS
29	**A. KUMAR**	NOVEL MUTATIONS AND CLINICAL EXPERIENCE IN A SINGLE CENTRE COHORT OF PATIENTS WITH HEREDITARY ANGIOEDEMA FROM NORTH INDIA
30	**L. JEDDANE**	INBORN ERRORS OF IMMUNITY: WHAT'S NEW IN LAST IUIS CLASSIFICATION?
31	**M. JAMEE**	CLINICAL AND RADIOLOGICAL FINDINGS IN IRANIAN PATIENTS WITH CHRONIC GRANULOMATOUS DISEASE
32	**I. FADIL**	CLINICAL AND BIOLOGICAL FEATURES OF 26 MOROCCAN PATIENTS WITH HYER-IGE SYNDROME
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POSTER 1 - EXPLORING NEW MECHANISMS TO UNDERSTAND THE COMPLEX B CELL DYSREGULATION PRESENT IN COMMON VARIABLE IMMUNODEFICIENCY: IMPAIRED CPG DEMETHYLATION ASSOCIATES WITH B CELL PHENOTYPE AND PROLIFERATION RATE.

AUTHORS

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O**bjectives:** Common Variable Immunodeficiency (CVID) is characterized by impaired antibody production and poor terminal differentiation of the B cell compartment. Monogenic defects are only present in 10-15% of the cases. The uncommon epidemiology and complex pathogenesis of CVID led us to explore new mechanisms that could impair relevant gene expression for terminal B cell function. In a previous study (Rodríguez Cortez et al, Nature Communications 2015), we reported, for the first time, the existence of aberrant DNA methylation in CVID B cells from a pair of CVID discordant monozygotic twins, and in a cohort of CVID patients. Recent data from whole DNA methylome analysis (Kulis et al. Nature Genetics 2015), throughout different stages of normal B cell differentiation allowed us to design a new experimental approach.

Design and method: Maturation and terminal specialization of B cells require the integration of molecular signals, driven by transcription factors and consolidated by epigenetic marks, which lead to initiation and maintenance of stage-dependent transcriptional programs. The epigenome refers to heritable modifications that influence gene expression but do not change the DNA sequence, such as DNA methylation and histone modifications. The epigenome of B cells is dynamic and it changes during differentiation. CpG sites that displayed significant demethylation in memory B cells compared to naïve B cells from healthy individuals from Kulis et al, were selected for analysis. DNA methylation was analyzed by bisulfite pyrosequencing of specific CpG sites in sorted naïve and memory B cell subsets from CVID patients and controls. In the same samples we analyzed the replication history and the frequency somatic hypermutation by KREC and IgK-REHMA assay.

Results and conclusions: Our study suggests that impaired demethylation in the transition from naïve to memory B cells in CpGs at genes implicated in B cell signalling and survival (STAT3, AKT1, FOXO and NFKB2), and at genes required for the GC reaction (AICDA and BCL6) might contribute to the terminal B cell defect in CVID patients. The intensity of impairment in demethylation is associated with the reduction of memory B cells in CVID patients. The potential implication of altered epigenetic control of terminal B lymphocyte differentiation is only at the dawn of its definition in CVID. Now we present novel insights that point out the possible implication of both passive, due to reduced proliferation rate between naive and switched memory B cells, and active demethylation mechanisms involving AICDA in the pathogenesis of CVID.

POSTER 2 - CHRONIC SPONTANEOUS URTICARIA AS AUTO-IMMUNE FEATURE IN COMMON VARIABLE IMMUNODEFICIENCY

AUTHORS

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Background: Chronic spontaneous urticaria (CSU) is a common and debilitating disease characterized by the presence of urticaria and angioedema for at least six consecutive weeks. It is considered to be an 'auto-allergic' condition and is associated with various auto-immune diseases, including auto-immune thyroiditis and systemic lupus erythematosus. Common variable immunodeficiency (CVID) is one of the most common primary humoral immunodeficiencies among adults. It may also be accompanied by auto-immune phenomena. However, the association between CSU and CVID is rare.

Design: Here, we present two cases of patients with CVID with auto-immune phenomena, granulomatous complications and CSU, followed by a short review of the literature on this association.

Results: patient 1 is a 42-year old male with an unremarkable medical history who presented with severe refractory CSU without a history of recurrent infections, but a total IgE level of <2 kU/L warranted further investigation for humoral immunodeficiencies. CVID was diagnosed based on decreased levels of IgG and IgA, reduction in the absolute number of memory B-cells and an absent response after immunization with polysaccharide pneumococcal vaccine. Furthermore, diffuse lymphadenopathy and multiple pulmonary nodules were observed at CAT scan compatible with a diagnosis of granulomatous-lymphocytic interstitial lung disease (GL-ILD) associated with CVID. Malignant lymphoma was excluded by lymph node excision. The CSU was treated successfully with omalizumab.
Patient 2 is a 52-year old female with a history of thyroiditis, auto-immune hemolytic anemia, thrombocytopenia and recurrent upper and lower respiratory tract infections with bronchiectasis on CAT-scan. Diagnosis of CVID was established based on recurrent infections, low IgG, IgA, IgM, and IgE, and an absent response after immunization with polysaccharide pneumococcal vaccine. In the following years of follow-up, the patient also developed GL-ILD and CSU. For CVID, immunoglobulin replacement therapy was initiated and the GL-ILD was treated with prednisone, mycophenolate mofetil and rituximab. These treatments resulted in improvement of all clinical symptoms, including complete resolution of CSU. After review of the literature, we found 10 previously published cases of patients with CSU and CVID. In most cases, CVID was diagnosed after presentation with CSU. Three patients were treated with omalizumab without effect, but information on the dosages was not provided. Six other patients had remission of the CSU after commencement of immunoglobulin replacement therapy.

Conclusions: CSU may be associated with CVID. In cases of CSU accompanied with recurrent infections or low/absent serum IgE, analysis for CVID should be considered.

POSTER 3 - NEUTROPENIC PRIMARY IMMUNODEFICIENCY PATIENTS: A REGISTRY-BASED STUDY

AUTHORS

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Objective: Neutropenia is a heterologous group of rare hematological disease characterized by impaired maturation of neutrophil and it can be primary due to chronic benign neutropenia, cyclical neutropenia and other congenital and familial neutropenias as primary immunodeficiency disorders (PIDs) or secondary to cytotoxic drugs, aplastic anemia, leukemia, drug reactions, and infections. Neutropenia is associated with an increased risk of recurrent fever and infections such as pneumonia, otitis, gingivitis, skin abscesses, sinusitis and meningitis. The incidence of consanguinity is significantly higher in Middle East countries compare to other countries; correspondingly the rate of PID is greater in this region. Since neutropenia provides a critical condition in patients and early diagnosis is pivotal for the disease management, the current study was performed to evaluate the prevalence and genetically survey of congenital and other kinds of neutropenia in PID patients were referred to immunology and allergy clinic in Al-Zahra university hospital and Isfahan research center.

Design and method: In this study, data from 260 PID registered patients upon signed consent form were reviewed from 1997 to 2019. Within this, PID patient's neutrophil counts and data from neutropenic patients (based on European Society for Immunodeficiencies criteria) were considered. Demographic data, laboratory data and also pedigrees and genetic diagnostic data were evaluated.

Results: 260 PID patients had been registered in our database. Neutropenia in 20% of patients was found and 54% of these neutropenic patients had congenital neutropenia; 31% had phagocyte deficiency, 9% had CID, 4% Chediac-Higashi syndrome and 2% had Hermansky-Pudlak syndrome. 54% of neutropenic patients presented with recurrent fever and infections (pneumonia 31%, fever 28%, otitis 22%, skin infections 20%, sinusitis 11%, gingivitis 8%, meningitis 2% and other infections). Consanguinity rate in PID's families were observed in 60% of cases. 21% of neutropenic patients had genetic diagnosis consist of mutation in ELANE, JAGN1, MSN, STK4, CXCL2 and MFR. Which a few of these variants had been reported as novel genes and most of the variants were not reported as neutropenia caused variants in literature.

Conclusions: The prevalence of neutropenia is varied considerably by ethnicity; our study revealed that 20% of our referred patients have neutropenia which needs additional clinical investigations into pathophysiological mechanisms. The results of our registry reveal that neutropenia is not rare in our PID patients because of high rate of consanguinity; so clinicians should consider primary neutropenia as their differential diagnosis to be able to manage and treat their patients.

POSTER 4 - SWITCHING OF IMMUNOGLOBULIN THERAPIES: AN INTERNATIONAL SURVEY ON PATIENTS WITH PRIMARY IMMUNODEFICIENCIES

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Objective: Develop an understanding of the effects which switching from one immunoglobulin product (IG) to another may have on patients' health and quality of life
Gather patients' opinion on switching of IGs.

Method: IPOPI developed the survey to be filled in electronically by adults living with primary immunodeficiencies (PIDs) or parents of children with PIDs.
The survey was sent to IPOPI's 68 NMOs (National Member Organisations) from May to September 2018.
The inclusion criteria for respondents was to have switched IGs in the past 2 years. Respondents were either adult patients or parents of children with PIDs.

Results: 406 from 35 countries representing the world's regions answered the questionnaire.
Respondents were mainly European & North American.
First international attempt to understand the reasons and describe the process of switching of IGs in patients with PIDs.

Conclusion: The survey provides insights on why switching of IGs may take place and its consequences.
The findings stress the call of patients for a patient-doctor shared decision-making process when considering switching IG therapies, highlighting the need for a personalised treatment plan.

Main findings:

- 40% of respondents have switched more than once in the previous 2 years.
- Main change in the mode of administration is from IVIG to SCIG (63%), from IVIG to SCID is less present (20%).
- 58% of respondents report experiencing side-effects after switching IGs.
- Only 37% of patients that have switched their IG report an improvement in the side effects associated to the therapy.
- 53% of respondents that have experienced increased time between infusions than the one prescribed by their doctor, consider it was due to shortages in IG or other supply problems in their country.
- 85% of respondents consider that IGs are not generic medicines and that they cannot be interchanged freely.
- 96% of respondents believe that a person with a PID should always have the freedom of choice and access the most suitable IG.
- 97% of interviewees respond that the decision to switch IGs should always be based on a joint decision between the patient and their doctor.
- Switches should be understood as both voluntary and not voluntary action (forced). The 3 main reasons for switching IGs:
- Side effects related to previous IG
- Previous IG no longer available
- Interest in receiving home therapy.
- Acknowledgements The authors gratefully acknowledge funding from the Plasma Protein Therapeutics Association and thank all of IPOPI National Member Organisations for encouraging patients in their countries to participate.

POSTER 5 - EXPANDING THE REACH OF SEVERE COMBINED IMMUNODEFICIENCY TESTING: THE SCID NEWBORN SCREENING IMPLEMENTATION EXPERIENCE IN THE UNITED STATES

AUTHORS

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Objective: The Association of Public Health Laboratories (APHL) received funding via a cooperative agreement from the Health Resources and Services Administration (HRSA) to provide technical assistance, educational and financial support to state newborn screening (NBS) programs. The goal of this project was to increase the number of states offering population-wide NBS for Severe Combined Immunodeficiency (SCID).

Design and Method: Needs Assessment: Prior to a request for proposals, APHL utilized the NewSTEPs Data Repository (https://www.data.newsteps.org) to stratify all state programs into a four tier model (Figure 1 attached)). This process enabled an assessment of programs' levels of readiness for performing SCID NBS. Application Process: The program launched a competitive funding process to provide financial and technical assistance to awarded states for advancement of SCID implementation. Eligible applicants were all NBS programs who had not fully implemented SCID screening, and priorities were given to programs in Tier 1 or Tier 2 of screening. Selection: 11 state NBS programs were selected as awardees (Figure 2 attached). Resources available to awardees included financial assistance, consultation with SCID expert advisors and clinical immunologists, and participation in national in-person meetings and webinars.

Results and Conclusions: All 11 state awardees now universally screen for SCID (Figure 2 attached), contributing to the 53 state and US territorial NBS programs offering SCID NBS as of December 2018 (Figure 3 attached).
The addition of SCID to the Recommended Uniform Screening Panel (RUSP) posed challenges and opportunities unique to each awardee. SCID screening required the application of a molecular assay to every NBS specimen for the most efficient screening and the inclusion of a new field of clinical experts and algorithms to NBS. The introduction of new NBS technology coupled with limitations in funding, laboratory space and technical expertise proved to be challenging. Some programs experienced slow and cumbersome legislative processes, while others noted the lag time between approval for SCID NBS and the initiation of testing. While SCID implementation involved continuous changes to each program, it also revealed areas for growth and collaboration. In fact, convening multidisciplinary teams enabled programs to support each other by sharing protocols, advice and expertise.
This work was supported under Cooperative Agreement #UG5MC27837 between the Association of Public Health Laboratories and the Health Resources and Services Administration (HRSA). Its contents are solely the responsibility of the authors and do not necessarily represent the official views of HRSA.

POSTER 6 - EPIGENETIC IMMUNE CELL QUANTIFICATION - A NOVEL APPROACH TO EARLY DETECTION OF PRIMARY IMMUNODEFICIENCY FROM DRIED BLOOD SPOTS

AUTHORS

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Primary Immunodeficiency Diseases (PID) and Primary Immune Regulatory Disorders (PIRD) present with a wide range of unspecific disease symptoms (e.g. recurrent infections, autoimmune symptoms, chronic inflammation). Recent estimates suggest that up to 1% of the population may be affected by a PID or PIRD (Modell et al., Immunol. Res., 2018). Most patients are initially cared for by general practitioners that may not be adequately sensitized to the possibility of an underlying genetic immunodeficiency. As a result, patients may undergo years of symptomatic and undirected therapy, causing unnecessary delays in effective therapy initiation, reduction in quality of life and increase in healthcare expenditure.
Quantification of immune cells from blood is a powerful method for the detection of PID/PIRD. The current standard - flow cytometry - is usually performed when an affected patient is already in specialized care by an immunologist or pediatrician. The test requires fresh blood samples to be analyzed in a well-equipped laboratory and is not being ordered routinely when a patient presents with unspecific symptoms at the primary physician.
We developed a molecular (i.e. epigenetic) method to quantify the most relevant immune cell types from a drop of (dried) blood (Baron et al., Sci Transl Med, 2018). This allows easy blood sample collection (e.g. via finger prick) and shipment of the dried blood spot (DBS) via regular mail. Samples from patients affected by two or more of the 10 Warning Signs for PID (http://www.info4pi.org) can be collected at the primary care office or even at or near home and sent to a testing laboratory.
Current epigenetic test formats are designed for quantification of CD3+/CD4+/CD8+ T-/B-/NK cells, FOXP3+ regulatory T-cells (Treg), monocytes and neutrophils from a single dried blood spot. This allows detection of quantitative dysregulation of the most relevant immune cell types as an early indicator of an underlying PID or PIRD. We successfully identified immune cell dysregulation in patients with T-cell (SCID), B-cell (XLA), Treg (IPEX) and neutrophil (SCN) immune cell disorders. Additional studies are ongoing to demonstrate the broad applicability of the epigenetic method for early detection of patients with PID and PIRD.

POSTER 7 - ENHANCED TLR5 EXPRESSION IN PATHERGY POSITIVE BEHÇET'S DISEASE PATIENTS INDICATES AN INNATE DRIVEN IMMUNE RESPONSE

AUTHORS

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Introduction: Behçet's disease(BD) is an auto-inflammatory vasculitis, characterized by a pathergic reaction, which is an excellent example of excessive innate immune activation. This skin prick test shows exaggerated immune response to tissue damage, suggesting a role for pathogen- or damage-associated molecular pattern recognition receptors, like toll like receptors(TLR).

Methods: To investigate whether the auto-inflammatory nature and the pathergic reaction in BD are driven by a disturbed TLR-response we compared both TLR expression by flow-cytometry and TLR-response by stimulation assay in 18 BD patients (both pathergy positive and negative) with 13 healthy controls.

Results: Expression of TLR1, 2 was significantly elevated in B-lymphocytes of BD patients compared with healthy controls. TLR1, 2 and 4 were significantly higher expressed in both CD4+ and CD8+ T-lymphocytes of BD patients. Granulocytes of BD patients displayed significant higher expression of TLR1, 2, 4 and 6. TLR2, 4 and 5 expression was significantly increased on classical monocytes of BD patients. Intermediate monocytes of BD patients showed an increase in expression of TLR2. Furthermore, TLR2 and 5 were significantly higher expressed in non-classical monocytes of BD patients.
In pathergy positive patients, TLR5 was even higher expressed compared to pathergy negative patients on B-, T-lymphocytes, and granulocytes.
Furthermore, TLR2 and TLR5 showed an elevated TNF-alpha response to stimulation with their cognate ligands.

Conclusion: Immune cells of BD patients overexpress TLR1, 2, 4, 5 and 6. Furthermore, after stimulation of TLR2 and TLR5 of BD patients demonstrate a more potent TNF-alpha response. Strikingly, in pathergy-positive patients, TLR5 expression is even further augmented, suggesting that a microbial (flagellin) danger signal may trigger the exaggerated immune response that is characteristic for the pathergy phenomenon in BD. In conclusion, these result points at an exaggerated TLR-response in the auto-inflammatory nature of BD.

POSTER 8 - A 4 YEARS EXPERIENCE IN PRIMARY IMMUNODEFICIENCIES DIAGNOSIS USING NEXT-GENERATION SEQUENCING IN HOSPITAL 12 OCTUBRE IN MADRID.

AUTHORS

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Objective: The rapid increase of Next Generation Sequencing (NGS) technologies has facilitated the identification of monogenic causes of primary immunodeficiencies (PIDs), and has expanded the prevalence spectrum and our knowledge of the complex clinical phenotypes associated with PIDs. This work reports our experience in molecular diagnosis by using a targeted NGS gene panel and whole exome sequencing (WES) over a period of 4 years in Hospital 12 Octubre.

Design and Method: DNA was extracted from EDTA blood samples using QIAmp DNA Mini Kit. NGS was performed by targeted gene sequencing with an inhouse designed panel of 192 genes involved in PIDs and by WES in 109 patients with clinical history highly suggestive of PID. Patients were selected by clinical and immunological criteria. Mutations detected by NGS were confirmed by Sanger sequencing.

Results: NGS allowed identification of pathogenic variants in 28 of 109 patients (25.7%). Twenty-four patients were identified by targeted NGS, while four were found using WES. Genetic variants were classified into categories based on 2017 IUIS Phenotypic Classification for PIDs. Twelve patients (42.9%) had defects associated with predominantly antibody deficiencies (Group III) [BTK, IKZF1 (2), NFKB1 (3), TACI (5), TCF3], being the largest reported category. In six cases (21.4%), we found variants associated with immunodeficiencies affecting cellular and humoral immunity (Group I) [CD40LG, NHEJ (2), LIG4, MSN, ZAP-70]. In 3 patients (10.7%), we detected variants related to combined immunodeficiencies with syndromic features (Group II) (TBX1, ORAI1, TERT). 3 patients (10.7%) were associated with diseases of immune dysregulation (Group IV) (CTLA4, IL10RB, STAT3 GOF). 3 patients (10.7%) had mutations related to congenital defects of phagocyte number or function (Group V) [GATA2 (2), CYBB]. Finally, we reported a patient (3.6%) with a defect in intrinsic and innate immunity (Group VI) (IFNGR1).

Conclusions: Genetic heterogeneity of PIDs makes a timely and accurate diagnosis a challenge. The use of NGS to test multiple genes simultaneously, allows a rapid, cost-effective, genotype-based approach to molecular diagnosis, allowing, in addition, identification of underlying molecular defects for overlapping clinical phenotypes. In this work, 28.6% of the mutations reported were not described in the databases, and therefore it was necessary to carry out functional studies. Molecular diagnosis not only facilitated the directed evaluation to detect signs or unrecognized clinical presentations, but also allowed a rapid therapeutic intervention, and the management to improve the quality of life in the long term.

POSTER 9 - DIAGNOSTIC ALGORITHM FOR AUTOIMMUNE LYMPHOPROLIFERATIVE SÍNDROME

AUTHORS

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Background and Objective: Autoimmune lymphoproliferative syndrome (ALPS) is characterized by dysregulation of the immune system due to defective lymphocyte Fas mediated-apoptosis. The consequences of this include autoimmune manifestations, lymphoproliferative disease and risk of lymphoma. It has been reported germline mutations in the genes coding for Fas (TNFRSF6), FasL (TNFSF6), caspase 10 (CASP10), caspase 8 (CASP8) and neuroblatoma-RAS (NRAS). In addition, somatic mutations in TNFRSF6 and NRAS have been identified in some patients. The aim of this study is to describe clinical, genetic and immunological features of ALPS patients at the 12 de Octubre Hospital.

Methods: Genes causing ALPS (including TNFRSF6, TNFSF6, CASP10, CASP8 and NRAS) were analyzed from genomic DNA or after DNTs sorted (somatic mutations). Clinical data was collected for each patient. We quantified ALPS biomarkers: circulating DNTs, serum vitamin B12, soluble FAS ligand (sFasL), IL-10 and soluble CD25. FAS-mediated apoptosis assays were also carried out.

Results and Conclusions: Here we report our experience with an ALPS cohort. A total of 19 families were analyzed. Germline heterozygous mutations in the TNFRSF6 gene were the most common cause of ALPS (42%). We found 11 mutations in this gene (5 missense, 2 splicing and 4 nonsense) and most of them affected the death domain. Clinical penetrance was incomplete, the 80% of carriers developed ALPS. Somatic TNFRSF6 mutations were identified in 15% of cases. One patient had a CASP10 germline mutation combined with the somatic event in TNFRSF6 gene. Furthermore, we found 2 missense mutations in TNFSF6 gene from 2 patients affected the extracellular domain of Fas ligand (11%). In this cohort we included 6 patients classified as ALPS-Unknown (in whom mutations in known genes were excluded). Lymphoproliferation features as splenomegaly, hepatomegaly and lymphadenopathy were common in all patients. Among autoimmune manifestations, we observed that neutropenia and thrombocytopenia frequently appeared in our patients; additionally, some cases of lymphoma were noted in this cohort. Laboratory findings in ALPS patients include elevated percentage of circulating DNT lymphocytes, high plasma levels of soluble Fas ligand, IL-10 and vitamin B12. In addition, apoptosis mediated by FAS or AICD were disrupted in some patients with mutations in ALPS genes. The variable penetrance of this syndrome suggests that additional genetic or environmental factors may influence in ALPS. Thus, further studies of ALPS patients are needed to distinguish the particularities of them.

POSTER 10 - A RARE RAB27A VARIANT ASSOCIATED WITH A CASE OF HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS ALTERS EFFECTOR PROTEIN BINDING AFFINITIES

AUTHORS

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Objective: Griscelli syndrome type 2 (GS2) is an autosomal recessive disease associated with partial albinism and development of hemophagocytic lymphohistiocytosis (HLH) and caused by RAB27A gene mutations. The RAB27A protein is cytosolic and required for trafficking of cytolytic granules in lymphocytes and melanosomes in melanocytes. Clinically, GS2 patients typically present HLH in childhood. Here we describe an adult-onset HLH patient with a rare RAB27A c.551G>A (p.184R>Q) variant and study the function of this protein variant.

Design and methods: Functional testing of NK and CD8+ T cells was performed by stimulating PBMCs in vitro and measuring responses by flow cytometry. Interactions of RAB27A with SLP2A and Munc13-4 effector proteins were studied by ectopic expression in cell lines. Cell lysates were co-immunoprecipitated with antibodies against the recombinant, tagged proteins.

Results: A 35-year old male with consanguineous parents presented with recurrent fever and was diagnosed with EBV-driven chronic lymphoproliferation. There was no relevant immunological medical history. A year later, clinical HLH criteria were fulfilled. The patient had grey hair without any skin anomalies. Whole exome sequencing uncovered a homozygous RAB27a c.551G>A (p.R184Q) variant. Western blot showed normal expression of RAB27A. Interestingly, reduced NK cell degranulation was observed, whereas CD8+ T cell degranulation was within normal range. Nonetheless, biochemical evaluation revealed reduced binding to SLP2A when the p.R184Q variant was introduced to both RAB27A wild-type (25% reduction, $p<0,01$) and an active p.Q78L mutant (30% reduction, $p<0,01$). In contrast, the introduction of the p.R184Q variant resulted in greater binding to Munc13-4.

Conclusion: Here we describe a novel RAB27A missense variant identified in a patient with late onset HLH. The mutation results in normal expression of the protein, slightly reduced cytotoxic cell function and altered binding of the effector proteins SLP2A and Munc13-4. Thus, we speculate that this RAB27A c.551G>A variant represents a hypomorphic mutation that impairs protein function, ultimately disrupting immunity and maintenance of immune homeostasis.

POSTER 11 - ANTIBODY RESPONSE TO PREVNAR13 IN IGG SUBCLASS DEFICIENT PATIENTS

AUTHORS

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Objective: Measurement of IgG response to pneumococcal vaccination is a key marker for humoral immunity. However, the relationship between IgG and IgG2, IgA and IgM responses is not firmly understood. Here we investigate this relationship following Prevnar13® vaccination (PCV13) in IgG subclass deficient (IgGScD) patients.

Design and Method: Control (n=10, median 57 years, 27-64) and IgGScD (n=10, median 56 years, 25-65) patients from the Immunodeficiency unit at Karolinska University Hospital were vaccinated with PCV13. Serum samples were collected pre- and 4 weeks post-vaccination. Pneumococcal IgG, IgG2, IgA and IgM responses were measured using VaccZyme™ pneumococcal capsular polysaccharide ELISAs (The Binding Site Group Ltd., Birmingham, UK).

Results: A significant increase in anti-PCV13 IgG, IgG2 and IgA concentrations was observed 4 weeks post vaccination in both IgGScD patients and controls (median, 2.5th-97.5th percentile, p value for IgGScD patients: IgG 83 mg/L, 5-270 mg/L, p=0.002; IgG2 17 mg/L, 1-81 mg/L, p=0.008; IgA 71 U/mL, 10-165 U/mL, p=0.017; for control patients: IgG 215 mg/L, 58-270 mg/L; IgG2 71 mg/L, 14-90 mg/L; IgA 83 U/mL, 26-123 U/mL). However, a significant increase in anti-PCV13 IgM concentration was observed in controls but not in IgGScD patients (median, 2.5th -97.5th percentile: 51 U/mL, 39-256 U/mL, p=0.03, and 38 U/mL, 13-100 U/mL, p=0.065, respectively). In IgGScD patients the pre- to post-vaccination fold change of anti-PCV13 IgM and IgA concentrations were significantly lower compared to controls (IgM 3.2 v 1.5, p=0.04 and IgA 3.0 vs 2.2, p=0.04).
PCP-Ig responders and non-responders were defined from the lower 2.5th percentile of the control population (PCV13 IgG 58 mg/L, IgG2 14.0 mg/L, IgA 26 U/mL and IgM 39 U/mL). Overall, 40% of IgGScD patients were PCV13 IgG non-responders, 40% were IgG2 non-responders, 10% IgA non-responders and 50% IgM non-responders. Positive correlations were observed between PCV13 IgA and IgM in IgGScD patients (Pearson correlation r=0.789, p=0.007) and between PCV13 IgG and IgG2 in controls (Pearson correlation r= 0.921, p=0.001).

Conclusion: In conclusion, IgM and IgA responses to PCV13 may potentially stratify patients further and provide more information to the clinician.

POSTER 12 - A NOVEL HETEROZYGOUS IKBA MUTATION, REPLACING SERINE AT POSITION 36, RESULTS IN COMBINED IMMUNODEFICIENCY WITHOUT EDA

AUTHORS

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Genetic studies have led to identification of an increasing number of monogenic primary immunodeficiency disorders. Heterozygous gain-of-function (GOF) mutations in NFKBIA gene, encoding IkappaBalpha, result in an immunodeficiency disorder typically accompanied by anhidrotic ectodermal dysplasia (EDA). So far, 14 patients with immunodeficiency due to NFKBIA GOF mutations have been reported. Here we present three patients from the same family with combined immunodeficiency presenting with recurrent respiratory tract infections, bronchiectasis and warts due to a novel heterogygous missense NFKBIA mutation replacing serine at position 36 and therefore resulting in gain-of-function as a consequence of reduced IkappaBalpha degradation. Similar to previous presented patients, immunological investigations revealed inadequate antibody responses against vaccine antigens, despite hypergammaglobulinemia. None of the studied patients displayed features of EDA. Considering previous literature we conclude that missense NFKBIA mutations resulting in replacement of the serine residue at position 36, differ from the rest of pathogenic GOF NFKBIA variants in that they cause combined immunodeficiency in the absence of EDA.

POSTER 13 - A CASE WITH A NOVEL HOMOZYGOUS MUTATION IN OTULIN ACCOMPANIED BY AUTO-INFLAMMATION

AUTHORS

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Introduction: OTULIN (Ovarian TUmor domain deubiquitinases with LINear linkage specificity) is a deubiquitinase that plays a critical role in hydrolyzing linear ubiquitins attached to target proteins. OTULIN deficiency due to homozygous mutations leads to an auto-inflammatory syndrome named OTULIN-related auto inflammatory syndrome (ORAS), diagnosed by long-period recurrent fevers, painful erythematous rash with skin nodules swelling of the joints, gastrointestinal inflammation, and lipodystrophy. In the lack of OTULIN, the chain of linear ubiquitin is not regulated; thus the immune system is activated, even in the absence of infection.

Case presentation: Here, we present an Iranian newborn child (gestational age 35 weeks) from consanguineous parents (first cousins). After delivery, she referred to the hospital with abscesses (erythematous nodules) without fever or sepsis and was admitted thereby. The lesions were scattered over the chest and both extremities. We observed leukocytosis, particularly neutrophilia with increased ESR, CRP, and total IgG. Other immunological assessments, such as opsonization, chemotaxis, phagocytosis, and oxidative burst (NBT and DHR) were normal. Blood cultures to find Mycobacterium tuberculosis and of lesion cultures to find Gram negative and positive bacteria were negative. Whole-exome sequencing demonstrated a novel homozygous c.864 + 2 T>C variant in OTULIN (NM_138348). Sanger sequencing confirmed the homozygous OTULIN mutation and revealed a heterozygous mutation in the parents. This variant did not find in the gnomAD and in 1785 Iranian controls. In silico analysis of this variant predicted a change in the wild-type donor site which would likely affect splicing. Therefore, the effect of the variant on splicing of OTULIN mRNA was investigated by reverse transcriptase (RT)-PCR analysis of cDNA derived from fibroblasts of a heterozygous carrier (father) and a healthy control. For detailed analysis of splicing of intron 5–6, we performed a PCR with primers anchored in exon 4 and 7. Interestingly, the expression of OTULIN protein in primary fibroblasts of the father was different to the expression in control fibroblasts.

Conclusion: We detected a novel homozygous mutation in OTULIN that affected splicing. The patient had recurrent erythematous rash, skin nodules, as well as systemic inflammation, leading to fatal pulmonary edema. based on genetic evidence, the diagnosis was made and the presence of multiple alternatively spliced transcripts in the father's RNA sample was established. Although functional experiments would not be conducted, the truncated proteins predicted an inactive product.

POSTER 14 - INTERLEUKIN-18 IS A SENSITIVE MARKER OF INFLAMMATION IN WISKOTT ALDRICH SYNDROME

AUTHORS

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Objective: Wiskott Aldrich syndrome (WAS) is a primary immunodeficiency disorder resulting from actin cytoskeletal dysregulation of haematopoietic cells. An inflammatory phenotype is present in 70-80% of children, with up to 30% experiencing ongoing inflammation post definitive stem cell therapy, particularly when myeloid chimerism is low. Emerging evidence is highlighting the importance of the actin cytoskeleton in autophagy-inflammasome interplay, which is disturbed in WAS. We sought to characterise the inflammatory signature in WAS patients, with a view to identifying potential non-steroid based therapeutic targets.

Methods: Serum samples were obtained from healthy control and WAS patients, before and after definitive therapy in the form of haematopoietic stem cell transplant (HSCT) or gene therapy (GT). Cytokine and chemokine concentrations of IL-1β, IL-18, IL-6, TNF-α, IFN-γ, IP-10 and MCP-1 were measured using ELISA and MSD. These were then correlated to clinical parameters (e.g. presence of inflammatory symptoms or need for anti-inflammatory medication) and laboratory markers (e.g. WASp expression, donor chimerism and vector copy number).

Results: IL-18 is the only inflammatory cytokine found elevated in serum of WAS patients, all of whom had inflammatory symptoms at the time of sample collection. Despite previous evidence of elevated IL-1β following inflammasome stimulation of WAS myeloid cells in vitro, IL-1β was not detected in serum. Elevated IL-18 concentration seems to correlate strongly with inflammatory symptoms and appears particularly high in those with inflammatory bowel disease. Interestingly, IL-18 concentration remains elevated in patients post-HSCT where myeloid chimerism is low (< 50%), but returns to normal in those with myeloid correction, completely reflecting the presence or absence of inflammatory symptoms at the time of sample collection.

Conclusions: IL-18 appears to be a very sensitive and stable marker for inflammation in WAS, in contrast to IL-1β, which has a very short half-life and is difficult to detect in serum. IL-18 is an inflammasome-mediated pro-inflammatory cytokine and elevated serum concentrations in WAS patients provides further evidence to support our previous finding of inflammasome dysregulation in human and murine WAS myeloid cells. Our findings support the targeting of IL-1 family cytokines (e.g. through use of the IL-1 receptor antagonist, Anakinra) as an effective non-steroid based therapeutic approach for managing inflammatory symptoms in WAS.

POSTER 15 - DOUBLE-STRAND BREAK REPAIR THROUGH HOMOLOGOUS RECOMBINATION IN AUTOSOMAL RECESSIVE BCL10 DEFICIENCY

AUTHORS

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Background and Objective: In humans and mice, the CARD-BCL10-MALT1 (CBM) complex mediates NF-κB and MAPK activation in a cell-type-specific and non-redundant manner, after the stimulation of various immune receptors. The only patient reported so far with BCL10 deficiency had autosomal recessive complete form. Recent studies have highlighted the role of the CBM complex in DNA repair. Studies conducted with human cell lines have found that BCL10 can translocate to the nucleus and have shown that BCL10 functions as part of the DNA damage response via homologous recombination (HR).

Methods: To analyze the role of BCL10 in both DNA repair pathways, we treated BCL10-/- SV40 fibroblasts with hydroxyurea (HU) and hydrogen peroxide (H2O2) or γ-irradiated (3 Gy of ionizing radiation) to induce DNA double-strand break (DSB).

Results: The results showed that most of the DSBs induced with genotoxic agents such as HU and H2O2 could be efficiently repaired in the control cells but not in the BCL10-/- patient's cells, which suggests that BCL10 plays an important role in DSB repair via HR. We also studied the complementation of the phenotype in terms of HR repair after treatment with HU and H2O2. The results showed that the DSBs were efficiently repaired by the HR pathway in BCL10-/- cells transfected with WT BCL10.

Conclusions: The evidence makes it abundantly clear that defects in the proteins implicated in the HR repair pathway could cause cancer and are common in cancer cells. In our study, the HR pathway did not properly repair the DSBs in the cells from the patient with BCL10 deficiency. Despite the patient's clinical outcome due to the mutation's severity, this study shows that future patients with new loss-of-function BCL10 mutations will have greater susceptibility to developing cancer because the HR repair pathway would be affected.

Grants: Ramon Areces Foundation, FIS grant PI14/00616, FIS grant PI17/00543, SAF2014-54708-R and B2017/BMD3673.

POSTER 16 - NEXT GENERATION SEQUENCING WITH COPY NUMBER ANALYSIS FOR PRIMARY IMMUNODEFICIENCIES: FINDINGS FROM A COHORT OF OVER 3,900 UNRELATED PATIENTS

AUTHORS

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Objective: Many primary immunodeficiencies (PIDs) share overlapping presentations, complicating clinical diagnosis. Diagnostic next-generation sequencing (NGS) gene panels with simultaneous sequence and intragenic copy number variant (CNV) detection can facilitate rapid diagnosis of patients with PIDs, address differential diagnoses, and in many cases, guide clinical management. We performed a retrospective analysis of nearly 4,000 individuals referred for genetic testing to determine the clinical utility of a 207-gene NGS panel for PID.

Design and Method: A cohort of 3,927 unrelated individuals with suspected PIDs were tested using a 207-gene NGS panel that includes exonic CNV detection. Variants were classified using an evidence-based interpretation system based on ACMG guidelines. A retrospective analysis was conducted to determine the prevalence of CNVs, the diagnostic yield, the clinical utility of the panel, and the outcomes of family member testing.

Results and Conclusions: Among the 3,927 unrelated individuals, 965 (25%) had an aggregate of 577 pathogenic or likely pathogenic (P/LP) variants. CNVs comprised 11% of pathogenic variants identified in our patient cohort. Most CNVs detected in our cohort would likely be missed by chromosomal microarray analysis. The overall diagnostic yield of the PID panel was 6%; XLA, STAT3-conditions, X-linked CGD, and DiGeorge syndrome were the most common diagnoses in our patient cohort. 68 patients were diagnosed with an autosomal dominant condition, 97 with an autosomal recessive condition, and 72 with an X-linked condition. 296 patients had P/LP heterozygous variants in genes with either autosomal recessive or autosomal dominant inheritance patterns, and therefore the positive molecular results required clinical correlation to establish whether they were related to the patient's phenotype. Interestingly, one patient had two distinct molecular genetic diagnoses, suggesting a possible blended phenotype. We received samples for relatives of 210 probands for follow-up testing to resolve variants of uncertain significance or obtain more evidence to change classification for some variants from Likely Pathogenic to definitively Pathogenic. Of these probands, 27% received reports with variant reclassifications compared to 2% of probands who did not have family members tested, highlighting the critical importance of additional family member testing in the context of PIDs. In total, 75% percent of molecular genetic diagnoses were for conditions that are treatable with hematopoietic cell transplantation or enzyme replacement therapy. Together, these results illustrate the utility of broad NGS panels for the diagnosis of patients with PIDs and the importance of including CNV analysis to ensure high clinical sensitivity.

POSTER 17 - GENE THERAPY FOR LEUKOCYTE ADHESION DEFICIENCY TYPE I (LAD-I): A NEW THERAPEUTIC ALTERNATIVE FOR SEVERE PATIENTS.

AUTHORS

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Objective: Leukocyte Adhesion Deficiency Type I (LAD-I) is a primary immunodeficiency characterized by recurrent and life-threatening bacterial infections that, in most cases, cannot be properly resolved. It is caused by mutations in the ITGB2 gene that encodes for CD18, the common subunit of β2 integrins, leading to defective or absent expression of β2 integrins in the leukocytes surface. These heterodimers are required for normal leukocyte trafficking and extravasation to infection sites implying that defects on their expression result in the generation of leukocytes unable to adhere to the endothelium and to extravasate to infection sites. As it is the case with other primary immunodeficiencies, LAD-I is a good candidate for ex vivo gene therapy. The main objective of this study was the development of a gene therapy approach for the treatment of patients with severe LAD-I.

Design and Method: We first developed a lentiviral vector (LV) in which the expression of the therapeutic protein, hCD18, is driven by a Chimeric promoter that resulted from the fusion of the FES and the CTSG gene minimal 5-flanking regions. This promoter presents higher gene expression activity in mature myeloid cells and has proven its efficacy to correct the LAD-I phenotype both in murine and human LAD-I cells. The Chim.hCD18-LV has recently obtained the Orphan Drug Designation by the EMA (EU/3/16/1753) and FDA (DRU-2016-5430) agencies.

Results: Comprehensive safety- and efficacy studies have been performed in LAD-I mouse models harboring hypomorphic and knock-out mutations in the ITGB2 gene. Preclinical studies have been conducted by the infusion of LV-modified HSCs in both LAD-I mouse models, showing stable engraftment of gene corrected LAD-I hematopoietic stem cells (HSCs) and also correction of the leukocyte migration defect. Moreover, safety studies demonstrated the absence of hematotoxic and genotoxic effects in treated animals. Further studies with a GMP-produced Chim.hCD18-LV allowed the optimization of the transduction conditions in human CD34+ cells. The use of specific transduction enhancers facilitated the achievement of very high transduction efficacies, while maintaining the repopulating capacity of transduced cells in NSG mice. Three validation runs have been performed which have demonstrated the robust and reproducible transduction efficiency of CD34+ cells with the therapeutic LAD-I LV.

Conclusions: Our preclinical studies have facilitated the approval of a Phase I Clinical Trial of pediatric patients with severe LAD-I under the sponsorship of Rocket Pharma.

POSTER 18 - LOW DOSE AZITROMYCIN PROPHYLAXIS IN PRIMARY ANTIBODY DEFICIENCIES: A MULTICENTER, DOUBLE-BLIND, PLACEBO-CONTROLLED RANDOMIZED CLINICAL TRIAL

AUTHORS

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Objective: Lacking protective antibodies, patients with Primary Antibody Deficiencies (PAD) suffer from frequent respiratory. Immunoglobulins replacement therapy enhances survival and reduces risk of infections but despite appropriate therapy, patients might develop chronic infection-related pulmonary diseases, including bronchiectasis, Chronic Obstructive Pulmonary Disease (COPD), and asthma. Macrolides prophylaxis has been proven to be effective to successfully manage chronic lung diseases as cystic fibrosis, bronchiectasis, COPD. Based on these observations we conducted a trial to evaluate the efficacy and safety of orally low-dose azithromycin prophylaxis when added to the usual care in PAD patients.

Design and methods: A 3-year, phase II, prospective, multicenter, randomized, double-blind, placebo-controlled trial recruited PAD patients aged 18-74 years with chronic infection-related pulmonary disease. Patients received azithromycin 250 mg or placebo once daily three-times a week for 24 months. The primary endpoint was the decrease of annual episodes of respiratory exacerbations. Secondary endpoints included: time to the first exacerbation, additional doses of antibiotics, number of hospitalizations, Health Related Quality of Life measures and safety.

Results and conclusions: Forty-four patients received azithromycin (n=44) and 45 patients received placebo. The mean number of exacerbations was 3•6 per patient-year (95%CI 2•5-4•7) in the azithromycin arm, and 5•2 (95%CI 4•1-6•4) in the placebo arm (p=0•02). In the azithromycin group the HR for having an acute exacerbation was 0•5 (95%CI 0,3-0•9, p=0,03) and the HR for hospitalization was 0.5 (95%CI 0,2-1•1) (p=0•04). The rate of additional antibiotic treatment per patient-year was 2•3 (95%CI 2•1-3•4) in the intervention and 3•6 (95%CI 2•9-4•3) in placebo groups (p=0•004). Improvement in HRQofL was observed in the intervention group. No serious AEs drug-related or drug-related causes of discontinuation were reported in the intervention group. H. influenzae and S. pneumoniae were the prevalent isolates and they were non-susceptible to macrolides in 25% of patients of both arms. Our study on the efficacy and safety of long-term oral azithromycin prophylaxis reached the main outcome centered in the reduction of exacerbation episodes per patient-year. Moreover, in PAD with respiratory exacerbation, azithromycin prophylaxis led to reduction of additional courses of antibiotics, and of risk of hospitalization. The low azithromycin dosage increased patient adherence and minimize adverse effects. Given the deleterious effects of respiratory diseases, especially on the risk of death, quality of life, and cost of care, adding azithromycin to PAD treatment should be considered as a valuable option.

POSTER 19 - A NEW CYTOTOXIC-T-LYMPHCYTE-ANTIGEN-4 (CTLA4) MUTATION, SEGREGATING WITH OSTOPOROSIS

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Objectives: We describe a new CTLA4 mutation segregating with osteoporosis. Cytotoxic-T-lymphocyte-antigen-4 (CTLA-4) is a negative immune regulator of T cell activation. CTLA-4 haploinsufficiency produces an autosomal dominant immune dysregulation syndrome characterized by hypogammaglobulinemia, recurrent infections, autoimmune cytopenia, hepatosplenomegaly, enteropathy, and lymphocytic infiltrations.

Design and methods: we describe a proband of a CTLA4 haploinsufficiency and the kindred.

Results: A 16 yo white male was referred to our clinic with a diagnosis of CVID. He had a childhood history of recurrent otitis and pharyngitis and a pneumonia at age of 8. At 11 yo, he had recurrent parotitis and a low serum IgG, IgA and IgM was found. A CVID diagnosis was established and he initiated IVIG. He had recurrent diarrhea since age 6. An upper GI endoscopy showed inactive chronic gastritis, unspecific mild duodenitis (marsh 0) and ileitis. A video colonoscopy disclosed a colitis with an increase of mononuclear cells and follicular lymphoid hyperplasia. A CT scan informed maxillary and ethmoid sinusitis, neck adenomegalies, homogeneous splenomegaly (158mm), and no pulmonary complications. The association of CVID, GI disease and lymphoproliferation led to a CTLA4g DNA sequencing. A heterozygous transversion of guanine for thymidine in position c.475, exon 3 was found. This mutation results in the amino acid change D159Y, which is predicted to disrupt the function of CTLA4. CTLA4 expression in activated CD4+ lymphocytes was reduced by 50% (MFI of 2440 in patient vs 4690 in healthy control). CTLA4 functional studies are in progress. Genetic studies were extended to the family. (Figure 1). None of the family members had a history of severe infections. Subject 2.2, who is assumed to be a mutation carrier, died at 52yo of non-Hodgkin lymphoma. Subject 2.4 had a very severe osteoporosis since 40yo, uterine cancer at 50yo and adrenal cortex cancer at 52. Subject 3.4.2 has also severe osteoporosis since 30yo, with 8 vertebral fractures.

Conclusions: We describe a new mutation of the CTLA4 gene. As previously shown, penetrance is incomplete and associated symptoms are variable. CTLA4 mediated Treg cells have been proposed as inhibitors of osteoclasts, and abatacept treatment of rheumatoid arthritis patients leads to osteopenia improvement. So, we propose that osteoporosis could be an unrecognized consequence of CTLA4 haploinsufficiency.

POSTER 20 - ANTI-INTERFERON GAMMA AND IL-17 AUTOANTIBODIES IN A CHILD WITH ULCERATION AFTER BACILLUS CALMETTE-GUERIN (BCG) VACCINATION AND ONYCHOMYCOSIS

AUTHORS

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Objective: Anti-cytokine autoantibodies (ACAAs) neutralize cytokines and are therefore an important mechanism of disease pathogenesis. Neutralizing anti-IFNγ autoantibodies result in susceptibility to mycobacterial and intracellular infections, and high titers of these autoantibodies are associated with adult-onset immunodeficiency in the South-East Asian population. Anti-IL-17A, IL-17-F, IL-22 and IFNα autoantibodies have been associated with chronic mucocutaneous candidiasis, and are found in nearly all patients with autoimmune polyendocrinopathy, candidiasis, ectodermal dystrophy (APECED), while ACAA directed to IFNα among others can also be present in patients with hypomorphic RAG mutations. Here we present an Indonesian boy, born in 2016, with recurrent eczema and onychomycosis, who developed an ulcer of 3cm at the site of the injection 3 weeks after BCG vaccination. The aim of this study is to determine if ACAA are the underlying mechanism causing the onychomycosis and the atypical response to the BCG vaccination.

Design and methods: serum ACAA were measured in the patient using a Luminex based in-house assay and compared to data from the child his parents, APECED patient and healthy control. The neutralizing capacity of the anti-IFNγ autoantibodies was determined by measuring of the level of phosphorylated STAT1 in monocytes after IFNγ stimulation.

Results: The patient was positive for ACAA against IFNγ, -IL-17A and to a lesser extend IL-17F. ACAA against IL-22, IFNα were not detected. The pattern differed from APECED where very high levels of anti-IL17A, IL-17F, IL-22 and IFNα were detected, with low level of positivity for anti-IFNγ autoantibodies. IgG antibodies isolated from serum from the patient inhibited the IFNγ-mediated STAT1 phosphorylation, suggesting that the anti-IFNγ autoantibodies have a neutralizing effect.

Conclusions: To our knowledge this is the first child positive for anti-IFNγ autoantibodies. The anti-IFNγ and anti-IL-17A autoantibodies might explain the clinical phenotype, which we are currently exploring along with exome sequencing to identify a potential genetic defect.

POSTER 21 - MUCOSA-ASSOCIATED LYMPHOID TISSUE 1 (MALT1) DEFICIENCY: SEVERE SKIN LESIONS AS AN EARLY DIAGNOSTIC CLUE

AUTHORS

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Objective: MALT1-deficiency is a combined immunodeficiency characterized by combination of susceptibility to infections and the autoimmune phenomena. It is associated with impaired T cell responses and poor antibody responses, but normal total T cell and B cell numbers which makes the diagnosis quite difficult.

Methods: Clinical and laboratory features of a new patient due to MALT1 compound heterozygous mutations are reported. Sequence analysis and deletion/duplication testing of the 207 PID genes (Invitae Primary Immunodeficiency Panel) revealed de novo mutations in MALT1 gene.

Results: The Ukrainian boy from normal pregnancy and cesarean delivery (4800 g) developed generalized desquamative erytroderma and poor gain weight since 1st month of life. During the second month of life was hospitalized trice for severe atopic dermatitis treated by systemic glucocorticoid therapy with short-term positive effect. Immunologically at the age of 2 months a slight decrease in the number of B-lymphocytes was detected, the T-lymphocytes number was normal, IgG 2.5 g/l. Taking into account the severe widespread desquamative erythroderma without the effect on standard skin care in spite of unconvincing immunological abnormalities, it was decided to perform a genetic test. Panel sequencing revealed heterozygous pathogenic mutation in AT gene, heterozygous variants of uncertain significancy in MEFV, PARN and TCN2, and one pathogenic variant c.571C>T (p.Arg191*) and one variant of uncertain significancy c.1666_1668delGAG (p.Glu556del) in the gene MALT1. None of the parents had these mutations in MALT1, so it remained unclear if these variants were on the same or opposite chromosomes. Additionally, an impared CD45RA/RO ratio, decreased T-regulatory cells and progression of hypogammaglobulinemia (IgG - 1.37 g/l while IgA and IgM were undetectible) were revealed. Prophylaxic IVIG and co-trimoxazol were started. Considering the possible autoimmune mechanism of skin lesions, prednisone was given 2 mg/kg/day with incomplete improvement. Additional infections (recurrent otitis media, pneumonia, pyodermia), deepening of hypogammaglobulinemia, as well as failure to thrive and torpidity of the skin syndrome became an argument in favor of combined immunodeficiency due to MALT1-deficiency. At the age of 6 months, HSCT was successfully conducted from HLA-identical sibling at Tel-Aviv Sourasky Medical Center.

Conclusion: It is important to be aware of skin manifestations in pediatric patients as possible early sign of PID as it helps to prevent associated morbidity and mortality. The early diagnosis of this combined immunodeficiency with minimal laboratory deviations was done due to genetic test and gave a good chance for cure with hematopoietic stem cell transplantation.

POSTER 22 - PERFORMANCE OF HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS FEATURES AMONG CHILDREN WITH SEVERE SEPSIS

AUTHORS

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Objective: Hemophagocytic lymphohisteocytosis (HLH) has common clinical and laboratory features with systemic inflammatory response syndrome (SIRS), sepsis and severe sepsis. All of these disorders have high rates of mortality, yet, the therapeutic options are radically different. For that reason, we sought to investigate the performance of HLH clinical and laboratory features among pediatric patients with severe sepsis in order to draw the attention to the possible association or overlap of features among these 2 disorders, that would necessitate special approach to therapy.

Design and methods: We conducted a retrospective observational study that analyzed the clinical and laboratory data of 70 pediatric patients with severe sepsis. Medical records were revised for the presence of including fever, splenomegaly, pancytopenia, hyperferritinemia, hypertriglyceridemia and hypofibrinogenemia. Soluble CD25 (scD25) was measured in stored samples. Results: Patients' ages ranged between 0.5-11 year with median (IQR): 2 (1-5). All patients had fever and pancytopenia, 58 (82.9%) hepatosplenomegaly, 36 (51.4%) lymphadenopathy, 37 (52.9%) had ferritin >500 ng/ml, 20 (28.6%) had fibrinogen <1.5 mg/ml, 14 (20%) had fasting triglycerides >264 mg/dl while 5 (7.1%) had sCD25 >2400U/ml. Twenty-five (35.7%) patients fulfilled at least 5/6 of the HLH-2004 diagnostic criteria. Multivariate backward binary logistic regression analysis revealed lymphadenopathy as an independent predictor for HLH criteria fulfilment with odds ratio of 23.9. Fibrinogen had the best performance in discriminating HLH fulfilling from non-fulfilling groups (cut-off value:<1.8mg/ml), followed by ferritin/ESR ratio (cut-off value:> 17).

Conclusion: There is a significant clinical and laboratory overlap between HLH and severe sepsis, making the syndromes difficult to distinguish. The use of current HLH-2004 diagnostic criteria should be applied cautiously in those patients.

POSTER 23 - CLINICAL AND GENETIC CHARACTERISTICS OF PATIENTS WITH WISKOTT-ALDRICH SYNDROME IN BRAZIL

AUTHORS

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Introduction: Wiskott-Aldrich Syndrome (WAS) is a rare X-linked primary immunodeficiency characterized by eczema, thrombocytopenia with small sized platelets and recurrent infections1. More than 300 types of mutations associated with the WAS gene have been described, including eight hotspots2,3. The diversity of these mutations can lead to the appearance of great variation in the clinical presentations, which makes it difficult to predict the evolution of the disease based only on the initial symptons4. Furthermore, there is paucity of information on WAS from the Brazilian population.

Objectives: To describe the clinical and molecular characteristics of Brazilian patients with clinical diagnose of WAS. Results: Data from eighteen patients was analyzed (Table 1). Seventeen patients presented first symptoms within first year of age. Mean age for initiating symptoms was 4,5 months and mean time for diagnosis was 31,2 months. Three patients were diagnosed after 10 years of initiating symptoms. Seventeen patients (94.5%) had eczema. The platelet levels ranged from 1,000 to 65,000/mm3 and only nine patients (50%) presented microthrombocytopenia. Two patients (11.1%) had macroplatelets. Sixteen patients (88.9%) had hemorrhagic events throughout their lives, including intestinal, urinary and petechial bleedings. In relation to infectious manifestations, acute media otitis was the most frequent infection, reported by 13 patients (72.2%), followed by skin infections (66.7%). Three patients (16.7%) had autoimmune manifestations including IgA nephropathy, ischemic stroke and vasculitis. Most patients (55.5%) did not present alterations in IgG levels. Twelve patients (70.6%) did not present alterations in IgA levels and elevated levels of IgA was only observed in 4 patients (23.5%). Reduction of IgM levels was observed in 7 patients (38.9%). Patients were classified according to a previously described clinical score5. Most patients presented scores of 3 (33.3%) and 4 (27.8%). Four patients were classified with score 5 due to autoimmune or neoplastic manifestations. Regarding genetic analysis, mutations were found in 10 patients (Table 2). Only three of mutations found in this study were previously described. Conclusion: Clinical characteristics of Brazilian patients are similar to medical features seen in other populations, however genetic analysis showed yet undescribed mutations.

POSTER 24 - CHRONIC RHINOSINUSITIS IN AGAMMAGLOBULINEMIA AND HYPER-IGM SYNDROME, SURVEY OF THE FRENCH POPULATION

AUTHORS

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Background: Chronic rhinosinusitis (CRS) is a common chronic condition in patients with Primary Immunodeficiencies (PID), especially agammaglobulinemia (AG) or Hyper-IgM Syndrome (HIGM). The aim of this study was to (i) better describe CRS in these patients (prevalence, clinical and imaging features, prognostic factors) (ii) discuss medical and surgical management.

Methods: The charts of 100 AG or HIGM patients registered in the French National Reference Centre for PID were retrospectively reviewed.

Results: Forty-four patients (41%) had CRS, which was associated with bronchiectasis and with chronic conjunctivitis in 39% and 21%, respectively. Median age at CRS diagnosis was 9.9 years [6.2-14.7] and delay between PID and CRS diagnosis was 7.4 years [3.2-12.1]. Maxillary sinuses were involved in 59% of cases. Bacteriological analyses were performed in 17 patients, identifying Hæmophilus influenzæ or Streptococcus pneumoniæ in 61 and 32%. All patients with CRS received immunoglobulin replacement therapy, median delay between PID diagnosis and onset of therapy being 28 days. All patients had a mean plasma IgG trough level higher than 8 g/L. Seventy-nine percent of patients received long term prophylactic antibioprophylaxis. No differences in immunological status or therapeutic modalities have been demonstrated between patients with or without CRS. During follow-up (median: 16.7 years), 44% of the patients suffering from CRS showed improvement of their symptoms, possibly due to sinus surgery in 43% of cases. Long term antibioprophylaxis was the only statistically significant factor associated with CRS improvement (p=0.025).

Conclusion: Despite appropriate management of PID, and specific medical and surgical therapeutics, CRS is still a frequent and incapacitating disease in this population. Thorough ENT examination (including nasofibroscopy) and follow-up is paramount. Specific rhinologic quality of life questionnaires should be included.

POSTER 25 - CONGENITAL CARDIAC DEFECTS IN G6PC3 DEFICIENCY; REPORT OF A NOVEL MUTATION AND A LITERATURE REVIEW

AUTHORS

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Background: Glucose-6-phosphatase 3 (G6PC3) deficiency or severe congenital neutropenia type 4 (SCN4), OMIM: 612541, is an allelic heterogeneous inherited immune deficiency causing impaired myeloid differentiation resulting in neutropenia with a defected respiratory burst, chemotaxis, and ROS production. The most frequent non-hematologic manifestation of G6PC3 is congenital cardiac anomaly esp. atrial septal defect. Most cardiac defects are severe enough to undergo surgical repair.

Objective and Design: Herein, we report a case of SCN4 with a novel homozygous frameshift variant in c.911dupC leading to p.Gln305 SerfsTer82. Interestingly, she had developed intermittent neutropenia and the diagnosis of SCN was made long after a repair cardiac surgery for patent ductus arteriosus (PDA). She also had ASD secundum and partial anomalous pulmonary vein connection (PAPVC). To further investigate the importance of immunologic workups for patients with congenital cardiac defects, we provided a literature review on the observed cardiac findings in patients with SCN4.

Results: Among reported patients with SCN4, 80% of males and 76.9% of females developed cardiac defects. 41.5% of patients with cardiac defects were above 10 years old. We found the most frequent cardiac presentations to be ASD (15/39), followed by AI, PDA, PFO, TR and pulmonary hypertension. Overall, 78.3% of reported patients up until now had cardiac defects with more than half of the patients (56%) presenting with ASD. More than half of the patients with ASD required surgical repair, which implies the severity of symptoms. The higher extent of cardiac defects compared to the expected infections covers the immunologic defect underneath. However, a review of mutations found in those presenting with cardiac defects does not reveal any specific genotype-phenotype association.

Conclusion: These findings highlight the importance of performing immunologic workup in children initially manifesting with congenital heart defects. Hopefully, a simple cell-blood-count (CBC) test may prevent future life-threatening disseminated infections in this group of patients, especially in countries with high rates of consanguinity and subsequently higher prevalence of primary immunodeficiencies.

POSTER 26 - SECURING IMMUNOGLOBULIN SUPPLY IN PRIMARY IMMUNODEFICIENCY AS A PRIORITY INDICATION: PATIENT'S CARE PATHWAY APPROACH

AUTHORS

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Introduction:

- Immunoglobulins (IG) regularly subject to recurrent and severe supply shortages all over the world.
- Management: patient dispersion on the territory, diversity of delivery sources, lack of a global approach or reallocation procedures...
- Securing Ig supplies for priority indications as substitutive treatment in primary immunodeficiencies (PID) proposed by French health authorities (PID prevalence is 8.39/100,000 according to CEREDIH, PID reference center).

Objective: to carry out an inventory of patients with PID and their Ig needs to insure that these patients will not experience shortage.

Design:

- A 6-month (from January to June 2018) multicentre retrospective study conducted in 3 French university hospitals.
- Patient inclusion:
  - All in and outpatients with PID who received IG in one of these centers,
  - Dispensations were performed both for inpatients and outpatients (retrocession).
- Data collection for each IG dispensation:
  - Patient characteristics (gender, age, weight),
  - Dispensation context (retrocession, conventional or day hospitalizations), - Indication of IG and prescriber,
  - Brand name and quantity of the medicine dispensed,
  - Reason of switch (if any).

Results are presented as a mean ± standard deviation (quantitative data) or a percentage (qualitative data).

Results:

- 361 patients (See conditions on pic. 1) included: Gender-ratio M/F: 0.8 (204 females, 157 males), Mean age: 45 ± 20 years (34 pediatric patients), Mean weight: 62 ± 19 kg (weight not reported in 31% of dispensations).
- 2,082 dispensations performed by 58 different physicians: 1,124 for outpatients (54%), 860 in day hospitalization (41%), 98 in conventional hospitalization (5%).
- IG medicines dispensed: Overall IG volume: 57 kg (50% IV; 50% SC), 9 different IG medicines dispensed
  - IV: Privigen®: 560 (27%) Clayrig®: 352 (17%) Gammagard®: 42 (2%) Octagam®: 19 (1%) Kiovig®: 7 (<1%) Tegeline®: 1 (<1%)
  - SC: Hizentra® : 655 (31%) Gammanorm® : 323 (16%) Hyqvia® : 122 (6%)
- 108 switches identified (See graphic 2)

Conclusion:

- Innovative patients' pathway approach to allow a review of Ig supplies carried out in 3 University hospitals.
- Situations of supply tensions reported despite PID being one of the highest priority condition.
- Difficulty to obtain an exhaustive vision of patient pathways: dispensation outside university hospitals, outdated list of prescribers, list and data of patients not updated by prescribers....

Perspectives:

- Data analysis of the whole cohort, by including patients who get access to Ig therapy outside of the University hospital pharmacies.
- Multi-stakeholder approach focusing on the patient pathway to ensure patients Ig needs in the perspective of sustainable international supply shortages.

POSTER 27 - AUTOIMMUNITY IN WISKOTT-ALDRICH SYNDROME; DOES IT MATTER!

AUTHORS

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Objective: Wiskott Aldrich syndrome (WAS) is a rare x-linked combined immunodeficiency with an incidence of 1-10 per 100,000 live birth. Patients with WAS are not only prone to recurrent infections but are also at risk of developing autoimmunity and malignancy. In this study, we report the clinical and genetic profile of patients with WAS who developed autoimmune manifestations.

Design and Method: Case records of 46 children with WAS being 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. Their clinical, autoimmune features and outcomes were analysed.

Results: Out of 46 patients diagnosed WAS and followed-up over a period of 12 years, 14 (30.43%) developed autoimmune manifestations (Table 1). Mean age of the children with autoimmune features was 25.53 ± 31.36 months. Family history of death of a sibling was elicited in 3 out of 14 children. At presentation, in majority 8 (57.14%) had recurrent bleeding, 6 (42.85%) had of recurrent pneumonia and eczema was present in all. Leukocytoclastic vasculitis was the most common autoimmune manifestation noted in 8 (57.14%) patients. In 5 (35.71%) had autoimmune hemolytic anemia and direct Coombs test was positive in 5 patients. Antinuclear antibody (ANA) was positive in 5 (35.19%) patients and two had autoimmune hypothyroidism. Primary sclerosing cholangitis, Guillain-Barre syndrome and alopecia were seen in one of each patient. One patient had 3 autoimmune manifestations (primary sclerosing cholangitis, AIHA and vasculitis). Inflammatory bowel disease was diagnosed in 2 (14.28%) children. In one patient there was significant intracranial bleed. One patient developed Non-Hodgkin lymphoma during follow-up. In 7 (50%), mutations were detected in exon whereas in 3 patients intronic mutations were found and novel mutations were detected in 3 (21.42%) patients. Stem cell transplantation was carried out in two children but both patients died during the post-transplant period. Glucocorticoid was used in 9 (64.28%) patients while 12 (85.71%) patients were on intravenous immunoglobulin. The mortality rate in patients with autoimmunity was significant in comparison to WAS without autoimmunity 42.85% vs 21.8% (p 0.001).

Conclusion: One-third of our WAS patients had autoimmune phenomena and leukocytoclastic vasculitis was the commonest. The mortality rate was significant in WAS with autoimmunity. Most patients had mutation in EXON 1 gene.

POSTER 28 - LRBA AND CTLA4 DEFICIENCY AMONG CVID EGYPTIAN PATIENTS

AUTHORS

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Background: In the past few years, many genes and different mechanisms were proved to be implicated in Common Variable Immune Deficiency Disorder (CVID) and yet more to be elucidated. Studying CVID patients originating from highly consanguineous populations with high incidence of autosomal recessive genetic defects would probably help to unravel new mechanisms and add new explanations
The aim of the study is to investigate the role of LRBA/CTLA4 in a cohort of CVID patients.

Methods: This study included 26 patients with CVID based on ESID criteria for diagnosis of CVID. Flow cytometry was used for evaluation of Tregs, differentiation of T and B lymphocytes and expression of LRBA and CTLA4 proteins.

Results: Nine patients were diagnosed with LRBA deficiency, two patients had marked defect in CTLA4 expression following T cell stimulation and the rest of the patients with typical CVID phenotype had normal expression of LRBA and CTLA4 proteins. Profound defect in CD19 B cells and Naïve CD4 T cells were observed in all CVID patients especially in LRBA deficiency. Memory CD4 T cells (CD4+CD45RO+ cells) were significantly increased in CVID and LRBA patients when compared to the control group. Defects in Tregs and CTLA4 were observed in LRBA patients. LRBA expression by flow cytometry was proved reliable as a diagnostic test by the ROC curve.

Conclusions: The LRBA deficiency stands behind around 35% of the CVID among Egyptian patients. The study presents an easy, relatively available and reliable flow cytometric test for diagnosis of LRBA deficiency.

POSTER 29 - NOVEL MUTATIONS AND CLINICAL EXPERIENCE IN A SINGLE CENTRE COHORT OF PATIENTS WITH HEREDITARY ANGIOEDEMA FROM NORTH INDIA

AUTHORS

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Objective: Hereditary angioedema (HAE) is an uncommon primary immunodeficiency disorder. There is paucity of literature on long term follow-up of patients with HAE from developing countries. This study was carried out to analyse the clinical and laboratory features of patients diagnosed with HAE at our centre between January 1996 and December June 2019.

Design and method: Data were retrieved from medical records of the Pediatric Immunodeficiency Clinic, Post Graduate Institute of Medical Education and Research, Chandigarh, India.

Results: 27 patients were diagnosed to have HAE. Median age at onset of symptoms was 4 years (range 1-16 years) and a median delay in diagnosis was 5 years (0-23 years). Clinical presentation included swelling over lips, eye lids (figure 1), hands and feet; abdominal pain and laryngeal edema. Erythema marginatum was also noted in 2 patients (figure 2). Blunt trauma was identified as a trigger in 2 patients. A suggestive family history was present in 17/27 (63% patients). Serum complement C4 level was found to be decreased in 22/27 patients while it was normal in 5. C1- esterase inhibitor (C1-INH) quantitative or functional levels were found to be low in 24/27 (89%) patients (type I or type II HAE) while C1-INH levels were normal in 3 patients (type III HAE). Sanger sequencing of SERPING1 gene (all 8 exons) was performed in 17 patients from 14 different families. Four novel pathogenic variants (3 missense and 1 nonsense mutation) were identified in 4 families (Table 1). Six families were found to have previously reported mutation while 4 families had no mutation in SERPING1 gene. Because of lack of availability of recombinant or plasma derived C1-INH therapies in India, all patients were managed with prophylactic attenuated androgens or tranexamic acid. Acute attacks of life threatening laryngeal angioedema were managed with plasma infusions. Total patient month of follow-up is 1452 patient months with a mean follow-up of 54 months. One patient suffered recurrent first trimester abortions while she was taking tranexamic acid. Her next pregnancy progressed without any complications when tranexamic acid was discontinued. Side effects related to the use of attenuated androgens such as weight gain, hirsuitism, acne and hoarseness of voice were seen in majority. No disease related mortality was seen.

Conclusion: This is the largest single centre cohort of patients with HAE from India. Attenuated androgens and fibrinolytic agents may be effectively used for management of HAE in resource limited settings.

POSTER 30 - INBORN ERRORS OF IMMUNITY: WHAT'S NEW IN LAST IUIS CLASSIFICATION?

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In the era of Next-Generation sequencing, "primary immunodeficiencies" (PID) is an ever-growing field, now comprising more than 350 diseases. In the last classification, this term was replaced by "inborn errors of immunity" (IEI), as more and more phenotypes are associated to immune defects, and susceptibility to infections is just a part of them.
In this work, we'll review all new disorders in last IUIS classifications, not necessarily known to the community, as sometimes only one or a few kindreds are diagnosed (eg, GINS1 deficiency), or old disorders not associated to "primary immunodeficiencies" to date and now included in the IEI classification (eg, cystic fibrosis, Kabuki syndrome).
In the last published classification by the IUIS expert committee, 80 new disorders have been added to the catalog, with a majority associated with T-cell defects (28 disorders) or innate immunity (19 disorders).
Inborn errors of immunity are expanding each year and don't concern only immunologists, but is a pluridisciplinary field. Keeping updated with the classification is essential to not miss out on patient diagnosis and management.

POSTER 31 - CLINICAL AND RADIOLOGICAL FINDINGS IN IRANIAN PATIENTS WITH CHRONIC GRANULOMATOUS DISEASE

AUTHORS

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Objective: Chronic granulomatous disease (CGD) is a rare primary immunodeficiency caused by mutations in the genes encoding NADPH oxidase enzyme complex responsible for the initiation of phagocytic respiratory burst. As a result, phagocytes are unable to produce reactive oxygen species required for the killing of ingested microorganisms which in turn predispose patients to recurrent infections and a hyper-inflammatory state. The lung is the most frequently affected organ which can represent both infectious and granulomatous complications. Thus, we aimed to identify the pattern of clinical and paraclinical pulmonary involvement in patients with CGD.

Design and method: Thirty-eight patients (30 males and 8 females) with confirmed diagnosis of CGD were enrolled in the study and appropriate questionnaire on demographic and clinical manifestations were completed for all of them. Pulmonary function test (PFT) including FEV1, FVC, FEV1/FVC and maximal mid-expiratory flow (MMEF 25-75%) were recorded for each patient. We retrospectively evaluated the chest X-ray and high-resolution computed tomography (HRCT) scans. All statistical analyses were performed using the SPSS software (v. 25.0, Chicago, IL).

Results: The median (IQR) age of patients at the time of study was 12.0 (6.5-19.0) years. The median (IQR) age of onset and diagnosis was 1.8 (0.6-3.5) and 7.9 (5.0-14.0) years, respectively. Positive family history of early death was reported in 14 (34.2%) CGD patients. First and second degree consanguinity was reported in 20(52.6%) and 4 (10.5%) patients, respectively. The most common organs involved in CGD patients included lung (mostly at the age of presentation), lymphatic system and skin (mostly at the age of onset), and gastrointestinal system (mostly at the age of diagnosis). Thirty (78.9%) patients were complicated with fungal [9 (23.7%)] or bacterial [17 (44.7%)] pneumonia or a combination of microorganisms [4 (10.5%)]. Restrictive pattern was the most common pattern in PFT. In HRCT, the most common finding was consolidation [in 17 (44.7%) patients] followed by bronchiectasis [11 (28.9%)] and nodular infiltration [11 (28.9%)] and all of them were mainly observed in the right upper lobe of the lung. Other common findings included mediastinal adenopathy [9 (23.7%)], hilar adenopathy [9 (23.7%)], scar [8 (21.1%)], and ground glass opacity [8 (21.1%)].

Conclusions: The pulmonary CT scans of the patients with CGD demonstrated a variety of respiratory abnormalities. As respiratory manifestations are major complications of CGD, early diagnosis and precise monitoring of the respiratory system are needed to prevent further pulmonary complications

POSTER 32 - CLINICAL AND BIOLOGICAL FEATURES OF 26 MOROCCAN PATIENTS WITH HYER-IGE SYNDROME

AUTHORS

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Objective: Hyper-immunoglobulin E syndrome (HIES) are rare and complex primary immunodeficiencies disorder, characterized by high serum concentration of IgE, eczema, cold staphylococcal skin abscess and recurrent lung Infections. To date, there are many molecularly defined subgroups: autosomal dominant form (AD-HIES) associated with heterozygotes mutations in STAT3, and autosomal recessive forms (AR-HIES) associated with DOCK8 mutation, PGM3, SPINK5, ZNF341 and IL6ST mutation.
This work aims to establish the epidemiological, clinical-biological and genetic profile of hyper-IgE patients.

Methods: Analysis of 26 cases, presented at our Clinical Immunology Unit Abderrahmane Harouchi between 2010 and 2017, with suspected HIES was done retrospectively. All cases were studied for their presentations and associations and were investigated accordingly for the same. Score for HIES was counted as per National Institutes of Health (NIH) scoring system.

Results: Sex ratio is 1, 6 predominantly male, mean age of first symptoms was 11 moth, mean age at diagnosis was 5,7 years inbreeding rate is 46,15%, mean total NIH score was 30 points.
IgE level was higher than 2000 IU/ml in all patients, ranging from 2000 to 30,000 IU/ml. The most commonly occurring manifestations were eczema and dermatitis, pneumonia, upper respiratory tract infections, cutaneous abscesses, xerosis cutaneous, cold abscesses, and mucocutaneous candidiasis. Other less frequent manifestations were sinusitis, Molluscum contagiosum, conjunctivitis and diarrhea.
Genetic confirmation was done for only 8 patients, ARPC1B mutation in a single patient, 4 patients with DOCK8 mutation, one V637M mutation in STAT3 gene and two patients with ZNF341 mutations.
Genetic analysis was not done because of no availability of testing in our state and poor financial conditions of patients.

Conclusion: Hyper IgE syndrome is a rare immune disorder responsible for recurrent infections especially skin and lung associated with high serum IgE. The prognosis depends on the severity of lung and skin infections, which deserves further evaluation for detecting the syndrome.

POSTER 33 - X-LINKED CHRONIC GRANULOMATOSIS: MOLECULAR AND CELLULAR MECHANISMS UNDERLYING INTESTINAL INFLAMMATION

AUTHORS

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Background: Chronic Granulomatous Disease (CGD) is a primary immune deficiency of phagocytes caused by defects in one of genes encoding any of the NADPH-oxidase components responsible for the respiratory burst. The most frequent form is X-linked and is caused by mutation in CYBB encoding for the gp91phox protein. Patients suffering from this disease are susceptible to severe life-threatening bacterial and fungal infections and excessive inflammation characterized by granuloma formation in any organ. The inflammatory and autoimmune manifestations in CGD patients involved mainly the intestine and about half of XCGD patients develop IBD-like disease.

Objective: To investigate the mechanisms underlying the abnormal response of the intestinal immune system in KO-XCGD mouse and human gut samples.

Methods: Biochemical and functional studies performed on cells collected from KO-XCG and WT mice, and human XCGD patients and Healthy Donor.

Results and conclusion: mice data: Gut inflammation in the gp91phox-/- mice was evidenced by high tissue expression of IL-17, IL-6 and IL-1beta. Treg cell frequency in the mesenteric lymph nodes was reduced in knock out mice as well as the percentage of CD103+ dendritic cells, endowed with tolerogenic functions. Consistently, in vivo Treg generation and induction of oral tolerance was impaired in gp91phox-/- mice. Furthermore, gp91phox-/- Tregs co-transferred with wt naïve T cells failed to control intestinal disease progression in immune-deficient hosts. Intestinal IgA were similarly defective in mutant mice and analysis of in vivo IgA-class switching indicated a possible defect of gp91phox-/- DCs in mediating plasma cell differentiation. Human data: Preliminary analysis of gut biopsies from X-CGD patients showed increased frequencies of INFgand TNFa-producing T cells, both in the large and small intestinal mucosa, as well as of colonic Tregs. Percentages of intestinal B cells were tendentially reduced in patients, correlating with defective fecal IgA content. Microbiota of X-CGD patients had a significantly less diversity compared to controls, with a higher relative abundance of inflammatory Proteobacteria and Bacteroides species. Consistently, fecal content of succinate, a metabolite considered a signal for inflammation, was markedly elevated in X-CGD, while propionate was found reduced respect to controls.

POSTER 34 - SEVERE CMV RETINITIS IN AN ADULT PATIENT WITH CARMIL2 (RLTPR) DEFICIENCY

AUTHORS

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Objective: CARMIL2/RLPTR is involved in cytoskeletal organization, cell migration, TCR co-signaling. Defect results in a primary immunodeficiency (PID) with recurrent respiratory/urinary tract infections, persistant viral infections, viral skin infections, inflammatory bowel diseases, inflammatory and fungal dermatitis, growth restriction and tumors.

Design and Methods: A patient admitted in adulthood with severe CMV retinitis, onychomycosis and genital HPV infection was evaluated with PID next-generation panel screening.

Results: A 28 year old woman presented with visual dysfunction. It resolved within a month with intravenous (IV) gancyclovir, however, recurred 1 months later. She was again given first i.v. gancyclovir, CMV specific immunoglobulin (IG) and then prophylactic valacyclovir therapy. Symptoms due to exacerbations continued for 5-6 months and as the patient had no symptom for 8 years, she lost follow-up. In her past history, she has a history of taking steroid therapy for 9 months with the diagnosis of nephritic syndrome in the first decade. On admission at 28 years old, physical examination showed loss of visual acuity, onychomycosis, and genital condyloma accuminata lesions. Her parents were consanguineous, and similar disease was not present in the family. AntiHIV, antiCMV IgM antibodies were negative, antiCMV IgG was positive. However, CMV PCR was positive during the second exacerbation 8 years later. In addition to antiviral therapy including gancyclovir and foscarnet, she was given monthly IVIG, and CMV specific IG. Immunological findings at first and last (8 years later) evaluation during the exacerbations are given in Table 1. The molecular genetic study done showed a homozygous defect in RLTPR gene (c.311_325delITGAACAGCTGGCCC, p. Ala103_Leu107del). Immunophenotype showed low switch memory, marginal zone and active B cells, central memory T cells. T cell activation was normal. CMV specific T cell therapy and hematopoietic stem cell transplantation from HLA matched sibling was planned, however the patient refused the therapy.

Discussion: Primary CMV infections cause significant morbidity/mortality in patients with primary and secondary immunodeficiencies. In patients with RLTPR gene defect, viral skin infections and persistant CMV and EBV infections were reported. This autosomal recessive PID may associate with immunodysregulation. Migration experiments shows that T cell lymphoblasts are less capable of chemokine-directed movement. T cell immunophenotype shows increased naive T cells and decreased regulatory T cells. Primary immunodeficiency diseases may present with obscure findings in the childhood, and may complicate in adulthood with severe morbidity. Thus, follow-up of patients and molecular genetic study is important.

POSTER 35 - PID PRINCIPLES OF CARE - GLOBAL STATUS OF IMPLEMENTATION

AUTHORS

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Objective: In 2014, the International Patient Organisation for Primary Immunodeficiencies (IPOPI), together with international experts, established six principles of care providing a gold standard framework for PID care worldwide. Based on these IPOPI has conducted a survey, prepared in collaboration with its Medical Advisory Panel, with the objective to identify the global status of implementation of the principles.

Method: The survey was sent to all 63 of IPOPI's national member organisations (NMOs) and to health care professionals in the immunology field in 29 countries. Out of 63 NMOs, 58 countries replied to the questionnaire. Out of 29 additional contacts, 10 country replies were received. The overall number of participating countries was 68. The respondents were asked to reply to the questionnaire according to their records and best knowledge, with the help of their medical advisers and national PID experts.

Results: The study shows great discrepancies regarding the global status of these principles, both from continent to continent and between countries within the same continent. Pressing issues include lack of national registries, complicating the mapping of data needed to compare the progress in different countries.
Discrepancies regarding access to diagnosis is due to lack of facilities, including genetic diagnosis. Treatment varies greatly depending on the country and many patients also face partial or complete lack of reimbursement, leading to patients not being able to access life-saving treatment available in their countries. A majority of the respondents have a national PID reference center, but geographical accessibility issues remain. Adult care is available in over 50% of the responding countries. Transition care is rarely addressed at all.
The biggest concerns for the national PID patient organisation's relate to diagnosis, access or continuity of immunoglobulin treatment and lack of recognition of PID as a life impairing condition.

Conclusions: The survey shows the extent to which access to diagnosis and treatment remains a sound problem in many countries. Better knowledge on these rare diseases can be achieved through an increased number of national registries for epidemiology, clinical and research purposes.
The survey has proven to be a good tool to assess the implementation of the principles of care. Its outcomes can also serve as a basis to facilitate awareness and advocacy campaigns to improve access to PID diagnosis and care. IPOPI is committed to produce similar surveys in the future to monitor the status of the principles of care' implementation.

POSTER 37 - ADOLESCENTS AND YOUNG ADULTS (AYAS) WITH PIDS: ORGANIZE THE TRANSITION FROM AN ADULT DEPARTMENT PERSPECTIVE

AUTHORS

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Objectives: Clinical Immunology department of Strasbourg wanted to improve the transition from Adolescent Young Adults (AYAs) with PID. Adolescence, time of physical, psychological and social changes, is also time to gain in autonomy. For AYAs with chronic disease, it is time to be followed in an adult unit which could be a source of trouble and conflicting feelings.

In conjunction with paediatricians we wanted to:

- promote exchange between professionals,
- offer AYAs and their family a continuous and personalised support,
- encourage autonomy,
- promote adherence to treatment and care.

Design and Methods: Our transitioning program is centered on AYAs (16-24 years-old).
First, we developed a transition shared-document to follow the different steps of the process of transitioning from paediatrics to adults.

2- Through a questionnaire, we identified 3 main needs expressed from AYAs: share experiences with other people, find appropriate information to answer their questions and have their own place.

3- We devoted a dedicated place for AYAs and their family in our adults' department.

4- We developed a family-counselling consultation so that AYAs could meet at the same place a paediatrician and an adult physician during a single consultation.

5- We developed a patient educational program addressing transition issues: autonomy, treatment, transmission and heredity, and plan for the future.

Results: Our department, have an active-file about 130 adult patients and 60 children with PID. Since the beginning of our project in 2017, we followed 75 AYAs and performed 40 consultations of transition family councils each year. Our ambulatory area is also the place for genetic council and investigations such as NGS-panel. We set up a working group (paediatricians, internists, nurses, social worker and psychologist) and followed a training to mount an educational program and we plan to realize 3 to 4 sessions (group of 5 to 10 AYAs) by year. The transformation of our department is actually in progress with 3 dedicated beds for AYAs and this place will also be dedicated to the educational program.

Conclusion: Transition is a continuous process and having a dedicate plan and place for this is important. Digital tools would help improving physicians' practice but a close and coordinate effort of all professionals is helpful and needed to integrate AYAs in hospital and healthcare system, and we have shown that it is possible even in a mild-size tertiary center. This program also shows common issues among AYAs with different pathologies that could be shared widely.

POSTER 38 - ALTERATIONS IN THE IL-12/IFN-GAMMA AXIS AS A MECHANISM OF SUSCEPTIBILITY TO INTRAMACROPHAGIC INFECTIONS

AUTHORS

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Objective: Genetic defects in IFN-gamma axis (known as MSMD, OMIM: 209950) confer increased susceptibility to intramacrophagic pathogens, most commonly to non-pathogenic mycobacteria. Although tuberculosis (TB) infection is a global problem, extrapulmonary TB during primoinfection in otherwise healthy children is uncommon; similarly, in areas of Leishmania spp. endemicity only a small number of exposed individuals develop visceral leishmaniasis (VL); both conditions may underlie an increased susceptibility to intramacrophagic infections. Our aim was to define the mechanisms underlying susceptibility to extrapulmonary TB or VL in previously healthy pediatric patients.

Design and Methods: We performed an ambispective cohort study of patients with VL (n=23; median age: 7.4 years), extrapulmonary TB (n=24, 7.3 years), and 23 family-related and 18 unrelated controls. After discarding common primary immunodeficiencies, specific tests were performed (at least one month after infection resolution): 1) cytometric determination of IFN-gamma and IL-12 receptors; 2) STAT1 phosphorylation in response to IFN-gamma; 3) cytokine production in whole-blood culture in the presence of BCG with or without IL-12p70 or IFN-gamma co-stimulation; and 4) genetic study with a panel of 33 genes related to the IFN-gamma axis.

Results: No complete defects of the IFN-gamma axis were detected; Yet, patients with VL and extrapulmonary TB showed functional alterations. VL patients showed a reduced IFN-gamma production (p=<0.0001) and extrapulmonary TB patients showed a reduced IFN-gamma response assessed by IL-12p70 (p=0.008), TNF-a (p=0.021) and IL-1B (p=0.016) production when compared to unrelated controls. Interestingly, differences in IFN-gamma response disappeared when compared to family-related controls: IL-12p70 (p=0.45), TNF-a (p=0.9) and IL-1B (p=0.9). Genetic evaluation showed a total of 105 variants in exons causing aminoacidic changes, 6 of which in known MSMD-causing genes with a pathogenic prediction in silico. Segregation studies and functional validation are ongoing.

Conclusions: Pediatric extrapulmonary TB and VL in our setting do not seem to be a warning sign for MSMD complete defects. However, cytokine production and genetic studies results suggest that alterations in the IFN-gamma axis may be a mechanism of susceptibility for intramacrophagic infections in these children.
Study supported by PI15/01094, PFIS0200 (AC16/00025) and PI18/00223 to LA, integrated in the Plan Nacional de I+D+I and cofinanced by the ISCIII – Subdirección General de Evaluación y Formento de la Investigación Sanitaria – and the FEDER, by “Subvencions per a la Intensificació Facultatius Especialistes” del Departament de Salut de la Generalitat de Catalunya: PERIS 2016-2020 (SLT006/17/00199).

POSTER 39 - SCREENING FOR SEVERE T AND B CELL LYMPHOPENIAS IN ANDALUCIA USING 3 TECHNIQUES

AUTHORS

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Objective: Andalusia is leading in number of births in Spain with 80,000 per year. In 2014 we initiated a prospective, observational and longitudinal pilot study of neonatal screening for severe immunodeficiencies using a RT-PCR based TREC/(KREC)/b-actin determination assay. Since then we have tested the original technique and two commercial kits. Here we provide an overview of our experience with these three methods in our setting. Design and Methods: Determination of TRECs (all methods) and KRECs (in the original technique and Roche-TIB) using dried blood spots (DBS) from neonates in three public hospitals in Seville, Spain. Internal and external controls (provided by the CDC) were included. Results: From 2012 to 2017 a total of 12.212 DBS samples were analysed with either one of the three techniques: original, manual (n=8.582), Perkin-Elmer, automated (n=1.026) and Roche-TIB, partially automated (n=2.604). All three tested kits correctly identified the samples derived from patients with T and/or B cell deficiencies. Whilst specificity (>98%) was similar in all methods, sensitivity was variable (51-74%). All tests correctly distinguished between healthy subjects, internal and external controls (Figure 1a-c). The original and Roche-TIB method allow to quantify TRECS and KRECS, whereas the Perkin-Elmer kit provides TREC values. Conclusion: T- (and B-) cell lymphopenias were correctly identified by three (two) methods tested.

POSTER 40 - TRANSIENT VERSUS PERSISTENT HYPOGAMMAGLOBULINEMIA: CAN WE PREDICT THE OUTCOME?

AUTHORS

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Objective: Hypogammaglobulinemia represents a diagnostic challenge for Paediatric Immunologist. Low immunoglobulin in infancy may represent the first sign of Primary Immunodeficiency (PID) or just a delayed development of the immune system. Despite the evolution in the field of PIDs, there are no diagnostic tools that can exactly separate patients that will resolve the hypogammaglobulinemia spontaneously from the ones that will persist or get worse.
The aim of our study is the clinical and immunological characterization of children presenting with hypogammaglobuinemia. We focused our attention on observations at the beginning of follow up to identify prognostic signs to orient early diagnosis.

Design and method: We retrospectively revised data of children sent to our Institute since January 2006 to June 2018. One hundred and three patients were selected according to the criteria showed in table 1.
On the base of outcome presented during the follow up patients were divided according to ESID criteria: 67 Transient Hypogammaglobulinemia of Infancy (THI), 20 Unclassified Hypogammaglobulinemia (UH), 16 Common Variable Immunodeficiency (CVID).
Data about patient history and clinical symptoms at the first examination were collected as well as extensive immunological evaluation (full blood count, immunoglobulin(Ig), vaccine response, lymphocyte subpopulation and immunophenotype).
Since Ig level rapidly changes in the first years of life we created an age independent score (Ig score), to compare Ig values, as shown in figure 1.

Results and conclusions: Clinical characterization is summed in table 2. Age of onset was significantly lower in THI group (median: 0,42 yrs; IQR 0,17-0,77) than UH (3 yrs; IQR 2-6) and CVID (12 yrs; IQR 4-14). UH onset was lower than CVID group ($p<0.0001$).
In the immunological evaluation (table 3), IgG, IgA and IgM score were significantly lower in CVID patient compared to THI and UH (figure 2). Immunophenotyping shown a reduction of switched-memory B cells and an increase of CD21low B cells in CVID compared with UH. Vaccine response data, although incomplete, where coherent with literature showing a greater response in THI.
To find a predictor of normalization, we compared Ig scores and age of onset with a multivariate analysis in two groups (THI vs UH+CVID). The analysis pointed out age of onset as the most powerful predictor, confirmed by ROC curve analysis in figure 3 (AUC=0,95). This parameter should be considered in the follow up of patients with hypogammaglobulinemia, especially for children with onset between 2 and 4 years whose deficit will more likely persist.

POSTER 42 - APPLICATION OF TARGETED PROTEOMICS USING IMMUNO-SRM FOR POTENTIAL NEWBORN SCREENING OF PRIMARY IMMUNODEFICIENCY DISORDERS (PIDD)

AUTHORS

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Objectives: Tandem mass spectrometry (MS/MS) became a primary platform for many clinical and newborn screening (NBS) laboratories in the world. Unfortunately, many disorders in which early detection can lead to a much better outcome do not have detectable biomarkers and therefore, would benefit from the direct quantification of intracellular target proteins in dried blood spots (DBS). The extremely low (e.g., pmol/L range) protein concentrations in blood cells, however, limit their detection via standard MS/MS. Recently, our lab has demonstrated that immuno-SRM methods are able to reliably distinguish affected patients from the normal controls for Wilson disease (WD), Wiskott-Aldrich Syndrome (WAS), severe combined immunodeficiency (SCID), and X-linked agammaglobulinemia (XLA) (J. Proteome Res., 2017 and Front. Immunol., 2018) opening the feasibility of NBS.

Designs: We further explored the peptide immunoaffinity enrichment coupled to selected reaction monitoring (immuno-SRM) for the quantification of low abundance proteins in DBS for potential NBS for several primary immunodeficiency disorders.

Methods: Several candidate peptides for each protein were selected based on uniqueness and LC-MS/MS response. Monoclonal antibodies (mAbs) were then generated for peptide enrichment from DBS. Blood from normal controls and patients was spotted onto filter paper, dried, and stored at -20 °C. Proteins were extracted from DBS, digested with trypsin, and enriched using mAbs bound to magnetic beads. The enriched peptides were then analyzed using SRM mode with a Waters Xevo TQ-XS.

Results/Conclusions: To date, immuno-SRM methods have been reported for WAS, SCID, XLA, and WD. Preliminary data shows immuno-SRM methods are able to reliably quantify signature peptides and distinguish patients from normal controls (NCs). Analysis of signature peptides found statistically significant reduction or absence of peptides in affected patients compared to controls (WAS and BTK: $p = 0.0001$, SCID: $p = 0.05$). In a blinded sample set of 42 PIDD patients and 40 NCs, immuno-SRM-predicted diagnoses showed excellent agreement with clinical or genetic diagnoses. Every molecularly-confirmed case of WAS and BTK was identified by immuno-SRM. Signature peptide biomarkers and associated mAbs are available for Cystinosis, ADA Deficiency, Dock8 Deficiency, AT, and cell markers CD42 and CD56. These markers are readily quantified from DBS. Antibody production is under way targeting FHL2 (PRF-1), XLP1 (SAP), and CGD (CYBB). Current assays can quantify 12-14 disease-associated peptides within a single run that has been shortened to less than 3 minutes. Data herein provides proof-of-concept that immuno-SRM workflow may have utility for many PIDD as a potential multiplexed newborn screening method.

POSTER 43 - VARIABLE CLINICAL PHENOTYPE OF PATIENTS WITH TFRC GENE MUTATION

AUTHORS

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Background and Aims: Combined immunodeficiency (CID) due to a TFRC gene mutation that encodes the transferrin receptors (TFR1) is rare. This study describes the different clinical phenotypes of seven patients with the same TFRC gene mutations treated in one center.

Methods: A comprehensive review of clinical and immunological features of patients diagnosed with a TFRC gene mutation between 2015 and 2019 in one tertiary center.

Results: Seven patients from five unrelated families, including two not transplanted adults, were enrolled. All patients presented with recurrent sinopulmonary infections, chronic diarrhea and failure to thrive in early life. Less common features were skin abscesses and conjunctivitis with novel presentations of global developmental delay, milestone regression with optic nerves atrophy, vitiligo, multinodular goiter and HLH like symptoms. All patients had intermittent neutropenia, microcytic anemia with more than 50% had severe recurrent thrombocytopenia. There were no reported viral infections apart of two with hepatitis B infection. The same homozygous missense mutation in P.58T>C: PY20H encoded by TFRC gene was detected in all patients. Lymphocytic surface markers were normal apart of low CD19 and NK cell marker in four patients. All had impaired function of T and B cells with pan hypogammaglobulinemia, except one had a persistent high IgM level. Stem cell transplantation from matched donors was successful in two patients. Five patients not transplanted and received prophylactic treatment, two adults and three pediatric. All alive except one pediatric patient died due to severe sepsis and neurological complications.

Conclusions: TFRC gene mutation has a variable clinical phenotype and needs to be considered as a differential diagnosis of WAS and HIGM syndrome. Stem cell transplantation warrants the correction of immunodeficiency and better overall survival.

POSTER 44 - A NOVEL CARMIL2 MUTATION RESULTING IN COMBINED IMMUNODEFICIENCY MANIFESTING WITH DERMATITIS, FUNGAL AND VIRAL SKIN INFECTIONS AS WELL AS SELECTIVE ANTIBODY DEFICIENCY

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So far, more than 350 monogenic inborn errors of immunity have been reported, resulting in a wide range of clinical conditions, including increased susceptibility to severe infections, autoimmunity, and malignancy.
In order to identify the genetic basis of 100 patients diagnosed with common variable immunodeficiency (CVID) or combined immunodeficiency (CID), we used a targeted, next generation sequencing (NGS)-based method.
Here we identified a novel germline homozygous splice acceptor site mutation in the invariant AG sequence of the intron 6 of the CARMIL2 gene g.1587G>A [c.795-1 G>A] in three CID patients born to consanguineous parents, which segregated with their phenotype.
Sequencing of the CARMIL2 cDNA, produced by reverse transcription of total RNA from patients' PBMCs, revealed skipping of the second nucleotide in exon 7, which causes a reading frame shift with a subsequent premature stop codon (M227*).
CARMIL2 expression was absent in PHA-blasts, PBMCs, and naïve CD4+ T cells of all three patients but not of wild type controls and heterozygous mutation carriers. Similar to previously reported CARMIL2-deficient patients, all here presented patients suffered from viral skin infections such as molluscum contagiosum and verruca vulgaris as well as eczematous dermatitis. One patient suffered from recurrent respiratory tract infections since early childhood, which associated with selective antibody deficiency with normal immunoglobulins (SADNI). This patient displayed inadequate responses to vaccinations against diphtheria, tetanus, and pneumococcal infections and was therefore treated with immunoglobulin replacement therapy. Clinical heterogeneity among patients with CARMIL2 deficiency, and especially among those harboring the same deleterious mutation, such as the coexistence of antibody deficiency in some patients or marked differences in age of disease onset, suggests the pathogenic relevance of additional genetic and/or epigenetic modifying factors.
In conclusion, we report on three patients with a recently described combined immunodeficiency disorder, CARMIL2- deficiency, bearing a novel homozygous mutation on splice acceptor site region on CARMIL2-gene. These cases underline the role of CARMIL2 in immunity and suggest that CARMIL2 mutations should be considered in patients presenting disseminated and/or persistent warts or other virus-related skin conditions. Furthermore, differences in clinical and immunological phenotypes among our patients highlight the variable clinical presentations of CARMIL2-deficiency, which cannot be explained by an additional rare variant of another PID-related gene, included in current panel.

This study was supported by DZIF TTU 07.801 (German Centre for Infection Research)

POSTER 45 - DISEASE BURDEN FOR PATIENTS WITH PRIMARY IMMUNODEFICIENCY DISEASES - EVIDENCE FROM SOUTH INDIA

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

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

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

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

POSTER 46 - EVALUATION OF POLYSACCHARIDE TYPHIM VI ANTIBODY RESPONSE AS A PREDICTOR OF HUMORAL IMMUNODEFICIENCY IN HAEMATOLOGICAL MALIGNANCIES

AUTHORS

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An increasing healthcare challenge in the management of haematological malignancy (HM) is secondary immunodeficiency. From January 2019, the EMA included the evaluation of specific antibody (Ab) responses to better select patients for IgRT. We evaluated Ab responses to pneumococcal and Salmonella typhi pure polysaccharide immunization in a cohort of 42 HM patients and 24 healthy controls. Pre-post specific Ab concentrations were measured by ELISA at 4 weeks. Globally, significantly lower TV seroprevalence (9%) compared to PPV (76%) ($p<0.001$) was observed. TV non-responders (88%) were higher than PPV non-responders (62%) ($p<0.0001$) and correlated better to infectious history. By ROC analysis, pre-post 5-fold TV increase was the best cut-off to discriminate HM with recurrent infections and controls (sensitivity 91%, specificity 100%). TV Ab responses were superior to PPV to identify SID and defective primary responses, notably in patients with high PPV baseline titers in the conjugate vaccine era.

POSTER 47 - DEFICIENCY OF INTERLEUKIN-1 RECEPTOR ANTAGONIST; A CASE WITH LATE ONSET SEVERE INFLAMMATORY ARTHRITIS, NAIL PSORIASIS WITH ONYCHOMYCOSIS AND WELL RESPONSIVE TO ADALIMUMAB NOT TO CANAKINUMAB THERAPY

AUTHORS

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DIRA (deficiency of the IL-1Ra) is a rare condition that usually presents in the neonatal period. Patients with DIRA present with systemic inflammation, respiratory distress, joint swelling, pustular rash, multi-focal osteomyelitis and periostitis.

Previously, we reported a patient with a novel mutation in IL1RN with a healthy neonatal period and a late-onset of pustular dermatosis and inflammatory arthritis and excellent response to canakinumab treatment. We are herein presenting a new case of late-onset DIRA syndrome, carrying a different mutation and showing different clinical findings. This patient is the first one in the literature with the inflammatory arthritis, nail psoriasis and onychomycosis and with her remarkable response to monoclonal antibodies. The case responded well and fully recovered after treatment with adalimumab, but not with canakinumab.

The DIRA disease can lead to death from multiple organ failures and if recognized early, the treatment with replacement of the deficient protein with biologic agents induces rapid and complete remission. Therefore, clinical symptoms should be learned exactly by the pediatricians and pediatric rheumatologists and molecular analysis targeting this defect must be performed as early as possible.

POSTER 48 - SKIN DISORDERS ARE PROMINENT FEATURES IN CAUCASIAN PATIENTS WITH PRIMARY IMMUNODEFICIENCY DISEASES: A QUESTIONNAIRE-BASED STUDY IN PEDIATRIC AND ADULT PATIENTS

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Objective: Previous studies reported skin disorders as prominent clinical features in primary immunodeficiency disease (PID) patients, which may be among the presenting manifestations. However, most data originated from Middle-Eastern countries. Prevalence of PID-associated skin disorders in Caucasian patients remains largely unknown. Therefore, we evaluated the prevalence of skin disorders in pediatric and adult patients in a tertiary referral center in the Netherlands.

Design and method: A retrospective partner-controlled questionnaire-based study on skin disorders in PIDs was conducted among 79 pediatric and 360 adult PID patients and their partners of the Pediatric Immunology and Clinical Immunology departments, Erasmus MC University Medical Center between October 2017 and May 2019. Presence of 70 well-defined skin disorders was evaluated. We assessed the diagnostic delay, i.e. time between onset of first symptom and diagnosis of PID, from both the first classical PID symptom and first skin disorder.

Results: Forty-five children and 207 adults (response rate 57.4%) completed the questionnaire. Patients had a median (IQR) age of 46.3 (23.5-61.2) years, 120 (46.9%) patients were male and 98.4% were of Caucasian race. According to the International Union of Immunological Societies, 86.6% of the patients were diagnosed with a predominant antibody deficiency. Median age at time of diagnosis of PID was 37.0 (12.8-55.0) years; a median of 6.0 (1.0-20.0) years after the first classical PID symptom. Classical symptoms were present at a median age of 10.0 (1.0-40.3) years and included mainly upper and lower airway infections (n=140, 55.6%). Sixty controls with comparable demographic characteristics completed the questionnaire. A history of skin disorder was reported by 198 (78.6%) patients and 23 (41.1%) controls. Dermatitis (n=72, 28.6%), oral ulcers (n=63, 25.0%), warts (n=55, 21.8%), perleche (n=46, 18.3%), and oral candidiasis (n=45, 17.9%) were most commonly reported in patients. In controls, dermatitis (n=13, 23.2%) and seborrheic dermatitis (n=10, 17.9%) were most prevalent. Patients reported their first skin disorder at a median age of 8.0 (0.0-25.0) years; a median of 11.5 (2.0-30.0) years before the PID diagnoses. Controls reported their first skin disorders at a median age of 35.0 (1.0-63.0) years. In participants reporting a history of skin disorder, dermatitis was the most prevalent presenting skin disorder (48 patients (24.2%) and 12 controls (52.2%)).

Conclusions: Skin disorders are prominent features in PIDs when compared to partner controls and may precede the classical PID symptoms. Earlier diagnosis of PIDs could be facilitated by recognition of specific skin conditions as signal function of PIDs.

POSTER 49 - NOVEL PRETRANSPLANT IMMUNESUPPRESSION TO PREVENT GRAFT REJECTION IN PRIMARY IMMUNE DEFICIENCY DISORDERS

AUTHORS

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Graft rejection poses a significant challenge in children with some primary immune deficiency disorders associated with immune dysregulation. This is especially pronounced in haploidentical stem cell transplantation. We present here a case series performed using a novel and cost efficient strategy to overcome graft rejection in these children prior to haematopoietic stem cell transplantation.

Case 1
A five-year-old male child had presented with three episodes of glandular tuberculosis since early infancy requiring prolonged anti-tubercular therapy. IL12RB1 deficiency was confirmed and haematopoietic stem cell transplantation from the fully matched sibling donor was planned. Graft rejection is high in these children as high levels of interferon gamma prevents engraftment. The use of plasma exchange and rituximab have been documented to reduce gamma interfron levels. There was no active infection he received two cycles of pretransplant immunosuppression (PTIS) with fludarabine (40mg/m2 for 5 days and dexamethasone 25mg/m2 for 5 days) 3 weekly intervals. He underwent a myeloablative conditioning with thiotepa (8mg/kg/day), treosulfan (14 mg/m2/day for 3 days) and fludarabine (40mg/m2 for 4 days) he is now one year post transplantation with complete chimerism and no infections.
A one year old girl with XIAP deficiency had presented in the newborn period with very early onset inflammatory bowel disease. There was a history of sibling death due to a similar condition. The child was treated with two cycles of PTIS prior to haploidentical transplantation from her father with myeloablative conditioning and TCR alpha beta and CD19 depleted stem cell graft. The post transplant period was uneventful with CMV reactivation which settled with ganciclovir. The child is over four months post transplantation with 100% donor chimerism, no active viral infections or bowel inflammation and able to eat normal weaning food.
Fludarabine and dexamethasone are cost effective medications which help overcome the barrier of graft rejection and do not increase the risk of infections even in children with primary immune deficiency disorders.

POSTER 50 - LEUKOCYTE ADHESION DEFICIENCY TYPE III – THE FIRST CASES IN EASTERN EUROPE

AUTHORS

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Objective: Leukocyte adhesion deficiency type III (LAD-III) is an autosomal recessive disorder (FERMT3 gene) characterized by immune disorders similar to LAD-I and a Glanzmann thrombasthenia-like bleeding disorder. 3 children from 2 families of Ukrainian origin shared a similar clinical presentation - severe bacterial infections and a severe bleeding disorder.

Design and method: Immunological examinations included the study of subpopulation of lymphocytes and adhesion markers by flow cytometry. The diagnosis was verified genetically by the NGS method.

Results: The two boys from Kyiv, prematurely-born fraternal twins, were presented with a hemorrhagic birth syndrome (intrahepatic hemorrhage, petechiae) and persistent leukocytosis, considered as neonatal sepsis. Both patients displayed infectious syndrome (paraproctitis, recurrent purulent otitis media with perforation, pneumonia, and sinusitis), as well as residual neurological symptomatology and macrocephaly, disturbance of the autistic spectrum, hepatosplenomegaly and calculous cholecystitis. Laboratory examination revealed leukocytosis due to neutrocytosis, monocytosis (> 3000 cells / µl), B-lymphocytosis (> 12,000 cells / µl). More than 95% of patient neutrophils expressed CD18 and CD11b integrins, ruling out a LAD-I syndrome.
The third patient - a 4-year-old boy from the Donetsk region presented with severe nasal bleeding from birth due to the lack of platelet aggregation (thrombocytopathy), including hemophthalmia, invasive infections (5 episodes of pneumonia, brain abscess, skin necrosis) and pneumosclerosis. In all hemograms, leukocytosis (20-40 000 cells /µl, up to 99 000 cells / µl during invasive infection) due to absolute neutrocytosis and moderate B cell lymphocytosis (65.2% / 8040 cells / µl) was revealed.
Genetic analysis revealed FERMT3 mutations in all patients (table 1).

Conclusions: We presented the first 3 cases of LAD-III in Eastern Europe. In 3 children from 2 families, 4 different mutations in the FERMT3 gene were detected. Notably, in all patients, leukocytosis is noted not only due to neutrophilosis, but also due to the B-cells lymphocytosis.

POSTER 51 - IDENTIFICATION OF A NOVEL MUTATION IN TICAM1 IN A PATIENT WITH HERPES SIMPLEX ENCEPHALITIS.

AUTHORS

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Introduction: Herpes simplex encephalitis (HSE) is a severe viral infection of the central nervous system (CNS). Replication of this DNA virus involves the production and accumulation of RNA species which are recognized by the intracellular TLR3 signaling pathway. The susceptibility to HSV appears to result from impaired TLR3-dependent interferon production by nonhematopoietic cells that reside within the CNS.

Objective: Identify genetic variants involved in the susceptibility to infection induced encephalopathy.

Design and method: The proband in this study was a young male who initially presented herpetic meningoencephalitis when he was 5 years old. At age of 21 he developed acute retinal necrosis with retinal detachment due to herpes virus. The microbiological analysis revealed the presence of herpes virus type 1, which lead to begin treatment with foscarnet. A next generation sequencing (NGS) was performed with a TICAM1 variant detected (c.700C>T).
Genomic DNA was isolated from the peripheral whole blood of the patient using a genomic DNA kit (Inmunodeficiencias-GeneSGKit-CE; Sistemas Genómicos. Valencia, Spain) following the manufacturer's protocol. Whole coding exons and in exon-intron boundaries of genes involved in immune responses to viral infections, including those related to the susceptibility to infection- induced acute encephalopathy (UNC93B1, TLR3, TRAF3, TICAM1 y TBK1) were amplified and then sequenced on Illumina sequencing system. Low quality reads of which the read depth was less than 20× were discarded, and qualified sequences were mapped to human reference genome GRCh38/hg38. The variants of the genes were annotated using online software “G-Viewer” (v.3.0.0, GeneSystems). The missense variants were considered to be possibly related with Encephalopathy, Acute, Infection-Induced, 6, susceptibility on the basis of the following criteria: 1) The minor allele frequency is < 1% or unknown. 2) The variants are in coding or splicing zones. Specific primers were applied to amplify the fragments of genomic DNA containing identified candidate variation.

Results: Our patient has a heterozygous variant p.Pro234Ser which is a missense change that affects a conserved amino acid in a proline rich region. The variant has been predicted as deleterious and disease causing using in silico tools and has a minor allele frequency (MAF) of 0.068 (Gnom). All this suggest a pathogenic role for this variant.

Conclusions: Our study is the first report to identify the novel heterozygous variant c.700C>T in the TICAM1 gene, involved in the TLR3 pathway, which might be a cause of susceptibility to herpetic encephalitis.

POSTER 52 - NEWBORN SCREENING FOR SEVERE COMBINED IMMUNODEFICIENCY BY QUANTIFICATION OF T-CELL EXCISION CIRCLES AND KAPPA DELETING RECOMBINATION EXCISION CIRCLES IN GUTHRIE CARD: FIRST PILOT STUDY IN MADRID

AUTHORS

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Introduction and Objective: Severe combined immunodeficiency (SCID) is the most severe form of primary immunodeficiency (PID). This disorder is characterized by lack of T cell-mediated immunity and impaired B cell function.
Early diagnosis by newborn screening (NBS) of SCID using T-cell receptor-excision circles (TRECs) and kappa deleting recombination excision circles (KRECs) in dried blood spots (DBS) improves outcome of affected children and identify neonates with severe T- and/or B-lymphopenia. The curative treatment of SCID consists mainly in hematopoietic stem cell transplantation (HSCT) or gene therapy in selected cases, whose success depends largely on the age of diagnosis and lack of active infection.
Systematic NBS for SCID have been established in all United States of America, Taiwan, Israel and Norway (and Germany, Switzerland and Sweden from summer 2019).
The objective of this study is the development of the first pilot NBS program for SCID in the community of Madrid, Spain.

Methods: Quantification of TRECs and KRECs by multiplex qPCR (TRECs, KRECs, βactin) from neonates born in Hospital 12 de Octubre in the Community of Madrid. Ten patients previously diagnosed with SCID (5 IL2RG, 3 ADA, 1 RAG2, 1 DCLRE1C) and three patients with X-linked agammaglobulinemia (BTK) were included in the study as positive controls.

Results: A total of 1500 neonates were tested. TRECs/KRECs were analyzed in DBS samples. Patients previously diagnosed samples were also included. After reassessment, cut-off levels were readjusted from 10 copies/punch to 8 for TRECs and 6 for KRECs. With these confirmatory cut-off levels the retest rate was 0.1% for TRECs and 1.4% for KRECs.

Conclusion: Newborn screening for SCID has shown to reliably identify patients with T and/or B-cell lymphopenia in the asymptomatic phase. Our experience lends insight to the logistics, testing algorithms, results of the TREC/KREC test and healthcare flowchart as applied to NBS for SCID.

POSTER 53 - A LITERATURE REVIEW ON SHARED DECISION-MAKING TO INFORM THE DEVELOPMENT OF AN SDM TOOL IN PRIMARY IMMUNODEFICIENCY DISEASES

AUTHORS

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Objective: Shared decision-making (SDM) allows patients and physicians to align treatments with patients' preferences. For patients with primary immunodeficiency diseases (PID) who require immunoglobulin replacement therapy (IGRT), SDM may help tailor IGRT to clinical needs and lifestyles. The objective was to summarize results of a targeted literature review on SDM models and their impact on clinical outcomes and to introduce a new SDM tool for PID.

Design and Method: Focused searches for articles in English were conducted in EMBASE and MEDLINE (range: January 1, 1999-August 15, 2018). The search targeted key elements of SDM and impact of SDM on clinical outcomes. Relevant literature was examined for the state of SDM in PID and used to inform the development of a novel SDM tool.

Results: The search found 4730 records with SDM in the title or abstract. A range of therapeutic areas was represented, and publication frequency increased with time. Focused searches found 159 articles that discussed key elements of SDM. Common elements of SDM were: recognizing the decision, 2-way knowledge sharing between physician and patient, expression of patient values/preferences, weighing options, and making and implementing the decision. The impacts of SDM on clinical outcomes were discussed in 59 studies; 15 were reviewed in detail in acute (n=7), chronic (n=5), and general/other (n=3) conditions. Two studies suggested that SDM may improve clinical outcomes in chronic diseases. In 4 studies, patients who participated in SDM used fewer/less intensive diagnostic tests and treatments for acute illness. Positive effects of SDM were reported in mental health settings, chronic illness, longer-term decisions, and for SDM interventions with multiple sessions. No studies of SDM in PID were found. In a survey of US immunologists (n=15), participants recognized the value of SDM; however, in another survey, patient preferences for IGRT were not the same as what physicians perceived of patients' preferences, underscoring a need for SDM in PID.

Conclusions: SDM has been widely studied and increasingly implemented in health care decisions; however, its effects on key patient outcomes are not well understood. There are no known SDM applications in PID. Key findings from this review support the applicability of SDM in PID and highlight the need for a new tool to help patients recognize their own priorities and needs, and to ensure these guide important clinical decisions such as IGRT selection. Based on these findings, an SDM tool is being developed to facilitate SDM in PID.

POSTER 54 - INTERIM ANALYSIS OF A POSTAUTHORIZATION SAFETY STUDY ON THE LONG-TERM SAFETY OF HYALURONIDASE-FACILITATED SUBCUTANEOUS IMMUNOGLOBULIN 10% IN PATIENTS WITH PRIMARY IMMUNODEFICIENCY DISEASES IN EUROPE

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Objective: fSCIG (HyQvia®) is a recombinant human hyaluronidase (rHuPH20)-facilitated subcutaneous immunoglobulin 10% replacement therapy approved in Europe for patients with primary immunodeficiency diseases (PID). This study is acquiring additional data on the long-term safety of fSCIG and assessing the prescribed treatment regimens and administration in routine clinical practice.

Design and Methods: This ongoing prospective, noninterventional, open-label, uncontrolled, multicenter study initiated in July 2014 in Europe, includes patients aged =>18 years with PID currently receiving or prescribed fSCIG (EUPAS5812). The treatment regimens are prescribed at the discretion of the attending physician in accordance with standard clinical practice. Assessments of anti-rHuPH20 antibodies are performed on a voluntary basis.

Results: As of January 10, 2019, out of 111 enrolled patients, 103 patients had received =>1 dose of fSCIG and were included in the safety analysis population; the mean (SD) fSCIG exposure duration was 2.26 (1.19) years. Incidence of treatment emergent nonserious (noninfectious) adverse events/treatment emergent serious adverse events in the safety population (n=103) was 2.37/0.24 events per person-year; 553/57 events were observed in 83/28 patients. Two of 78 patients with immunogenicity data developed positive binding antibodies (defined as titer =>160) to rHuPH20. There were no neutralizing antibodies to rHuPH20. The average annualized per-patient rates for both hospitalizations and emergency room visits were <0.25. Most treatments were administered at home during the first (91.2%), second (93.2%), third (93.2%), and fourth year (85.2%).

Conclusions: This interim analysis of prospectively collected data of fSCIG use suggests that fSCIG is well tolerated in a real-world study population.

POSTER 55 - MANIFESTATIONS OF IMMUNODEFICIENCY IN AN IRANIAN PATIENT WITH HERMANSKY-PUDLAK SYNDROME TYPE 2, A NOVEL VARIANT IN AP3B1 GENE

AUTHORS

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Introduction: Hermansky-Pudlak syndrome (HPS) is a rare autosomal recessive disease described in ten types. All types showed oculocutaneous hypopigmentation and platelet dysfunction. However, immunodeficiency is a substantial element of two types of HPS, i.e. type 2 and type 10. Both innate and adaptive immunities are affected by mutation in the AP3B1 gene, which is responsible for pathogenesis of HPS-2. Decrease in cytotoxicity of NK cells, perforin level, and intracellular elastase content in neutrophils are among the innate immunity involvement. This syndrome can adversely affect the function of cytotoxic T-lymphocyte (CTL) as well. Expression of CD63 is increased in adaptor protein 3 (AP-3)-deficient CTLs. It is mislocalized to the plasma membrane and cytotoxic granules of CTLs become hypertrophied and cannot be secreted toward the target cells.

Case presentation: A 47 year-old female conceived from consanguineous marriage, who was a known case of arthritis rheumatoid and psoriasis was referred to our clinic with the history of abscess, skin lesions, ecchymosis, nose bleeding, poor vision, anemia, meningitis and sever coughs, led to multiple hospital admissions since her childhood. In the laboratory tests, she had decreased leukocyte counts and neutropenia before receiving treatment; WBC, 2170 /microl; percentage of neutrophils, 21.6%. The flow cytometry analysis was compatible with NK cell deficiency; CD3, 77.1%; CD4, 53%; CD8, 24.1%, CD19, 13%; and CD16-56, 3%. Neutrophil chemotaxis test was also impaired, 65 and 82 (normal range, 77-125). She had also increased levels of IgE (17249, 26800, and 17320). Whole exome sequencing showed homozygous splice donor variant (end of exone 19) in AP3B1 (LRG_170t1: c.2249+2T> A) which was confirmed by Sanger sequencing. Treatment of neutropenia was performed by application of granulocyte-colony stimulating factor (G-CSF).

Discussion: Mutations in the b subunit of cytosolic AP-3, encoded by AP3B1 gene, causes HPS2. Lack of this protein leads to lysosomal dysfunction and immunodeficiency. The variant reported in our patient was not previously described; however, variants in AP3B1 gene are responsible for HSP. Her clinical sign and symptoms were compatible with the diagnosis as well. She had dental deformity due to recurrent periodontal infections, lung fibrosis, severe cough and recurrent respiratory tract infections, one episode of meningitis, cutaneous and ocular albinism, ecchymosis and epistaxis. In order to prevent progress of the symptoms of HSP, assessment of various systems affected by this disease and their management is vital.

POSTER 56 - EBV NEGATIVE LYMPHOMA IN A PATIENT WITH MAGT1 DEFICIENCY

AUTHORS

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Childhood lymphoreticular malignancies have been the only reason for some patients with primary immunodeficieny diseases to come to medical attention. Loss-of-function mutations in the gene encoding MAGT1 cause XMEN (X-linked immunodeficiency with magnesium defect, Epstein–Barr virus infection (EBV), and neoplasia) disease, a mild form of combined immune deficiency. The hallmark of X-MEN disease is uncontrolled EBVinfection, causing a strong susceptibility to B cell lymphoma.

A 14-year-old boy was referred to our hospital to be investigated for primary immunodeficiency disorders after the diagnosis of nodular sclerosing Hodgkin lymphoma (NSHL). He was born to non-consanguineous healthy parents. Developmental milestones were normal. There were no frequent infections except upper respiratory tract infections 2-3 times in the winter months. He was admitted to another hospital with the complaint of neck swelling and enlargement in cervical lymph nodes and was diagnosed as NSHL (EBV negative) 14 months ago. It was learned that laboratory investigations showed hypogammaglobulinemia (IgG 623 mg/dl, IgM 23 mg/dl, IgA: 23 mg/dl). After chemotherapy, the patient was admitted to our hospital for further investigation. Physical examination was normal except submandibular lymphadenopathies <1 cm in diameter. Complete blood cell count, acute phase reactants and biochemical parameters were normal. His immunoglobulin levels and lymphocyte subsets were as follows; IgG: 671 mg/dl, IgM: 18 mg/dl, IgA: 22 mg/dl, CD3+ T cells: 57%, CD19+ B cells:34%, CD3+CD4+ T helper cells: 22%, CD3+CD8+ T cells: 22%, CD3-CD16/56+ NK cells: 5.5%, CD1+IgM-CD27+ class-switched memory B cells: 1.2%). Repeated serologic tests for EBV-DNA were negative. The targeted next generation sequencing (TNGS) of a comprehensive Ion AmpliSeq™ Primary Immune Deficiency Research Panel detected a hemizygous MAGT1 mutation (c.340C>T, p. Gln114Ter).

MAGT1 is a critical regulator of intracellular free Mg2+ in the immune system. Loss-of-function mutations in MAGT1 abolish the transient TCR-induced Mg2+ flux that is essential for optimal T and NK cell activation. The major clinical features of XMEN disease include persistent elevation in EBV-viral load, EBV-associated lymphoproliferative disorders, often with splenomegaly, dysgammaglobulinemia, and decreased CD4/CD8 ratio.
To our knowledge this is the first MAGT1 deficient case reported who developed lymphoma in the absence of detectable EBV or other common viruses.

POSTER 57 - A VERSATILE MULTIPLEX QPCR ASSAY FOR THE SCREENING OF SEVERE COMBINED IMMUNODEFICIENCY, X-LINKED AGAMMAGLOBULINEMIA AND SPINAL MUSCULAR ATROPHY IN NEWBORNS

AUTHORS

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We have developed a four-plex, real-time PCR assay to screen for Severe Combined Immunodeficiency (SCID), X-linked agammaglobulinemia (XLA) and Spinal Muscular Atrophy (SMA) in DNA extracted from a 3.2mm punch of a newborn dried blood spot (DBS). The assay identifies the homozygous deletion of exon 7 in the SMN1 gene and simultaneously quantitate the number of T-cell receptor excision circles (TREC) and Kappa-deleting recombination excision circles (KREC), which are widely-accepted biomarkers of SMA, SCID and XLA in newborn screening. The amplification of a reference gene, RPP30, is also included in the assay as a quality/quantity indicator of the DNA isolated from the DBS.
The assay consists of a simple buffer DNA extraction done in a 96-well plate format followed by a 96 or a 384-well plate PCR that can be supported by multiple thermalcyclers. The workflow can be manual or semi-automated so it is useful for both, low and high-throughput laboratories. The semi-automated high-throughput system uses liquid handlers and has the capacity of processing more than 1,500 DBS samples from sample to result in less than 8 hours with minimal hands-on time.
The system was tested with 3000 putative normal newborn DBS samples as well as contrived samples to study population distribution and pre-determine cut off values. Additionally, a comparison was made between the manual process and two semi-automated processes using two different liquid handlers for automated DNA extraction and PCR setup, the PerkinElmer's JANUS® G3 Automated Workstations and a Tecan FREEDOM EVO® 150 platform.
The results confirm the viability and flexibility of this testing system and demonstrate its upcoming benefits to newborn screening programs.

Disclaimer: For Research Use Only. Not for use in diagnostic procedures.

POSTER 58 - CLINICAL AND GENETIC SPECTRUM OF PATIENTS WITH GATA2 MUTATIONS

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Introduction: Mutations in human gene GATA2 are associated with different conditions such as MonoMAC syndrome, DMCL deficiency, haematological disorders, congenital neutropenia, and opportunistic or viral severe infections. The wide range of clinical manifestations and genetic alterations poses a major diagnostic challenge.

Objective: To describe the genotype-phenotype correlations in four patients carrying different GATA2 mutations in order to understand the pathogenesis of this entity.

Design and method: Genomic DNA from patients' peripheral blood was isolated and GATA2 was amplified by PCR method. Sanger sequencing analysis (Applied Biosystems) was performed and sequences were compared to the consensus sequence of GATA2 in NCBI database (access: NC_000003.12) with BLAST tool.

Results:

CASE 1: 41 year old male patient was diagnosed with myelodysplastic syndrome (MDS) at the age of 26, carrying a chromosome 8 trisomy. Medical history of lymphopenia, herpetic conjunctivitis, skin abscesses and respiratory infections. After genetic analysis, it was identify an heterozygous mutation in GATA2 gene, p.R396W. This mutations has been previously described and affects the second Zinc-Finger domain, disturbing DNA-GATA2 binding.

CASE 2: 46 year old male with lymphopenia, absence of monocytes and neutropenia for more than 10 years. He has also suffered from multiple viral infections. Bone marrow study suggested MDS at early stage. Patient was heterozygous for a mutation in GATA2, p.R396Q, also previously described.

CASE 3: 60 year old female whose symptoms began at the age of 59 with fever of unknown origin. Blood count test revealed complete absence of monocytes and mild cytopenias. After this, she had multiple opportunistic infections and type A influenza virus infection. MDS diagnosis was determined after bone marrow study along with identification of a SRSF2 mutation. Furthermore, DNA analysis from peripheral blood showed an heterozygous mutation, p.L305V, in GATA2, which affects Zinc-Finger domain 1.

CASE 4: 7 year old infant with lymphopenia from its birth, especially B lymphocytes, and hipogammaglobulinemia together with severe infections and chronic neutropenia for two years. Eventually, he was diagnosed with severe MDS and cytogenetic analysis of bone marrow revealed monosomy of chromosome 7. Molecular analysis from peripheral blood allowed to identify an heterozygous deletion of two nucleotides in GATA2 gene, which leads to a change in the reading frame (p.V296Qfs).

Conclusions: This series of cases shows the heterogeneity of the clinical spectrum regarding the age of onset, initial clinical manifestations and subsequent clinical course. These differences correlate with the variety of GATA2 mutations and cytogenetic alterations.

POSTER 59 - RAPID PUSH INFUSION - A WELL-TOLERATED METHOD FOR SUBCUTANEOUS SELF-INJECTIONS OF GAMMANORM®: A RANDOMIZED NON-INFERIORITY CROSS-OVER TRIAL IN ADULT PATIENTS WITH PRIMARY IMMUNODEFICIENCIES

AUTHORS

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Objective: Many primary immunodeficiencies (PIDs) require lifelong immunoglobulin replacement therapy (IgRT) to prevent infections. Administration via the subcutaneous route (SCIg) allows patients to safely self-administer immunoglobulins at home, thereby giving the patient flexibility and independence. SCIg may be administered either weekly by pump or by Rapid Push using smaller volumes given more frequently with the flow rate adapted by the patient to his/her own comfort. Study GAN-06 (NCT02503293) compared the impact of pump vs. Rapid Push administration on patients' quality of life.

Design and Method: GAN-06 was a randomized, cross-over, non-inferiority study in PID patients accustomed to weekly SCIg infusions (gammanorm® 16.5%) by pump at home. Patients used either pump or Rapid Push for 3 months before switching to the alternate modality for further 3 months. Primary endpoint was PID-Life Quality Index: treatment interference (PID-LQI factor I). The non-inferiority threshold for the ratio LQI Isyringe / LQI Ipump was set at 90% (lower bound of the two-sided 95% CI).

Results: Of 30 adult patients randomized, 28 completed the two cross-over periods. There was a high level of patient satisfaction with both delivery devices in general. While the defined primary non-inferiority endpoint was statistically not met (ratio LQI Isyringe/LQI Ipump was 93.5 [87.6-99.8]), QoL was similar between delivery devices assessed by additional tests (LQI II and III, TSQM, SF36-v2, PRISM test). Indeed, the majority of patients rated their satisfaction with Rapid Push as rather good, good, or extremely good and 34.5% of patients reported a preference for using Rapid Push over the pump.

Conclusions: Since IgRT is a lifelong treatment for many PID patients, individualization of treatment to optimally address the patients' different needs is essential. Rapid push complements the available therapeutic options offering an additional mode of IgG administration chosen by some patients for its simplicity and flexibility.

POSTER 60 - CHARACTERISTICS OF VIRAL INFECTIONS AMONG PRIMARY IMMUNODEFICIENT CHILDREN

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Objective: To present the frequency and spectrum of viral infections in primary immunodeficient children

Methods: The data was obtained from the Kuwait National Primary Immunodeficiency Disorders Registry during the period of 2004-2018.

Results: A total of 274 PID children were registered in KNPIDR during the study with a predominance of patients diagnosed with immunodeficiencies affecting cellular and humoral immunity (35.4%) followed by combined immunodeficiencies with associated syndromic features (24.5%), predominantly antibody deficiencies (12.4%), diseases of immune dysregulation (17.2%), congenital defects of phagocyte number or function (6.2%); autoinflammatory disorders (0.3%) and complement deficiencies (4%). Overall infectious complications affected 82.4% of the patients, and viral infections affected 31.7% of the registered patients. Forty-five patients (16.4%) developed viral infections caused by at least 2 organisms, among those 20 patients were affected by 3 or more viral infections. There was a statistically significant association between viral infections and PID category. However, there was no statistically significant association between viral infections and gender or the patients' onset age. There was a total of 170 viral infections during the study period and the causes of these infections were predominated by CMV (22.2%), adenovirus (11.7%), EBV (11.1%), and enteroviruses (7.4%). CMV and parainfluenza infections were more common in the group of immunodeficiencies affecting cellular and humoral immunity while EBV and HPV were more common in the immune dysregulation group and combined immunodeficiencies with associated syndromic features, respectively. The most common presentation was viremia (28.8%) followed by pneumonia (28.2%) and skin infections (17.6%). The most common presentation was viremia (28.8%) followed by pneumonia (28.2%) and skin infections (17.6%) (Table 3). The most common causes of viremia were CMV followed by adenovirus and EBV, while the most common organisms causing pneumonia were CMV followed by rhinovirus and parainfluenza. There were 80 deaths among the registered patients, 10% were caused by viral infections.

Conclusions: Viral infections are common in PIDs and result into a wide-range of clinical manifestations causing significant morbidity and mortality.

POSTER 61 - SINGLETON-MERTEN SYNDROME; A RARE SYNDROMIC TYPE I INTERFERONOPATHY WITH AN EVOLVING AUTOIMMUNE DOMAIN (CASE REPORT)

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Background: Type I interferonopathies represent discrete examples of a defective homeostatic regulation of this system with a striking phenotypic overlap. These disorders can present with a classic autoinflammatory phenotype with or without an adding autoimmune spill over.

Objective: To define & correlate the underlying genetic paradigm of a multisystem phenotype associated with an early progressive autoinflammatory & evolving autoimmune manifestations.

Methods: A 9 years male patient,1st sibling of 1st degree cousin marriage, presented with a life long history of recurrent episodes of fever, multiorgan involvement, developmental delay &pathological short stature. A family history of a 2 years old younger brother with recurrent otitis media & Failure to thrive

Results: Patient was referred at the age of 4 years with history of mucoid diarrhea & failure to thrive since birth misdiagnosed as cow milk allergy. Throughout the first two years he suffered recurrent attacks of infections with an irrelevant assay for an immunodeficient status. At the age of three left ankle monoarthritis with periodic attacks of high grade fever, abdominal pain was reported, ESR(85mm/1sthr). Familial Mediterranean Fever genetic studies showed no abnormality. On examination, patient<5thcentile for weight & height with peculiar facial features (high anterior hairline, broad forehead, smooth philtrum, thin upper vermillion, destroying caries), joint laxity, dry skin & multiple lentigines. Skeletal radiological survey revealed marked generalized demineralization. Echo study & Ophthalmological examination were free. Immunological survey for an autoimmune status was negative. The unique features, prominent autoinflammatory state & lack of consistent autoantibody production raised the clinical suspicion of a pathology related to enhanced type I IFN signaling. Singleton-Merten syndrome was confirmed by genetic Studies. Patient showed marked clinical improvement on oral colchicines & full dose oral prednisone. While on therapy, patient developed pancreatitis(resolved on Pulse methylprednisolone for 5 days).Six months ago, patient was diagnosed clinically &pathologically as Crohn's disease. I nfliximab course was added with a non significant response. An interferon score & a trial of a targeted therapy are planned.

Conclusions: Autoinflammatory disorders are an enigmatic diagnostic challenges for clinicians. Singleton-Merten is an uncommon multifactorial autosomal dominant genetic disorder with variable expression & diverse symptoms. It constitutes part of type I interfernopathy disease spectrum. Autoinflammation was prominent but with recent evolution of multisystem autoimmune involvement. Steroid dependence & limited efficacy of anti-TNF drove to a more complicated situation.

POSTER 62 - THERAPEUTIC APPROACH BY SIROLIMUS FOR ENTEROPATHY TREATMENT IN LRBA DEFICIENCY

AUTHORS

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LRBA deficiency is a rare genetic disorder caused by biallelic loss-of-function mutations in the LRBA gene. This disorder is characterized by early-onset hypogammaglobulinemia, autoimmunity and chronic diarrhea.
the purpose of this study was to report the successful use of sirolimus for management of enteropathy in four patients with LRBA deficiency.
For all patients colonoscopy was performed and the diagnosis of enteropathy and acute colitis were confirmed. As prior therapy including infliximab, cotrimoxazole, clarithromycin and gluten free diet had failed to control the disease process, sirolimus therapy with the dosage of 1 mg/day for three months was started for all patients. This treatment led to a complete improvement of their symptoms including decrease in frequency and severity of diarrhea and improvement in the patients' weight. Evidence of a response trend is further documented by normal serum level of albumin, calcium and potassium. No signs of abdominal cramps and anorexia were also detected during the follow up period after treatment. In conclusion, sirolimus with its potential efficacy and immunomodulatory properties may be recommended for the treatment of severe enteropathy refractory to conventional therapy in patients with LRBA deficiency.

POSTER 63 - PROACTIVE: PROPHYLAXIS OF RECURRENT RESPIRATORY TRACT INFECTIONS BY MUCOSAL IMMUNISATION IN COMMON VARIABLE IMMUNODEFICIENCY (PRELIMINARY RESULTS).

AUTHORS

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Objective: The main objective of the study was to demonstrate the clinical benefit of mucosal vaccines for patients with common variable immunodeficiency (CVID) and recurrent respiratory tract infections despite adequate IgG trough levels and antibiotics' use.

Design and Method: Single-institution retrospective study of 17 adults CVID patients on IgG replacement therapy (IgRT) with adequate trough IgG levels (between 80-100 g/dl)*.They were divided into two groups according to the presence or not of recurrent respiratory tract infections (RRTIs). RRTI-Group was given a combined polybacterial mucosal vaccine Bactek® for 3-months, (inactivated whole bacteria implicated in respiratory infections, 90% Gram-positive as Staphylococcus spp., Streptococcus pneumoniae, and 10% Gram-negative as Klebsiella pneumoniae, Branhamella catarrhalis, Haemophilus influenzae). Patients were assessed at 6 and 12 months as a routine follow-up. CVID patients on IgRT without infections (Non- RRTIs) were recruited as control group.
The primary endpoint was the reduction of infections rate: >70% complete response; by 25-69% partial response; <25% no response at 6 and 12 months. Quality-of-life (QoL) was measured by a Short Form designed in our center, at baseline, 6 and 12 months.

Results: The RRTI-Group (n=10) started the immunization with Bactek®. NonRRTI-Group shaped by 7 CVID. Eighty percent (n= 8) of RRTI-Group presented with bronchiectasis, whereas only 14% (n=1) of the NonRRTI-Group. At 6 months post-immunization, 30% (n=3) of patients reported a respiratory infection, coinciding with the period of use of the vaccine. Nevertheless, all patients who received mucosal immunization presented a complete response at 12 months post-vaccine. No patient has adverse effects related to the treatment. The QoL forms referred a reduced of antibiotic cycles (median 5 (3-7) to 1 (0-4); reduced frequency of visits to Emergency Dept. (from median 5 (2-6) to 0 (0-3) reduced days of work loss (from median 2 (0-3) to 0 (0-2) after 1-year follow-up.

Conclusions: Our preliminary data in a small cohort of CVID patients with recurrent RRTI show a beneficial and safety strategy with mucosal vaccines in reducing infections. The advantages this therapeutical approach might represent a key element for the improved control of subclinical infection in CVID patients with improve in QoL and positive economic consequences. Studies with larger sample size are needed to warrant these results.

POSTER 64 - SPUR TB TO? WHAT IS ON THE MENU?

AUTHORS

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Severe infections in the absence of secondary immunodeficiency can alert to single gene in-born errors of immunity, underlying susceptibility to specific infections. Mendelian Susceptibility to Mycobacterial Disease (MSMD) is a primary immunodeficiency (PID) characterized by errors in the IL12-IFN-y pathway. MSMD is defined by selective susceptibility to weakly virulent mycobacteria, as well as mycobacterium tuberculosis complex (MTBC). These patients are often missed under the justification of an environment of hyperendemic tuberculosis (TB) exposure and poor treatment compliance but also due to lack of laboratory and clinical awareness. Severe, persistent, unusual or recurrent (SPUR) infections have been applied as clinical warning signs for PID and are proposed in the context of MSMD.
Between 2013-2018 paediatric patients 5-15 years with SPUR TB infections were recruited through the Immunology Unit at Tygerberg Hospital (TBH). Severe TB was defined as poor host control of infection or complicated disease manifestation, persistent as infection not responding to treatment despite appropriate regimen and compliance, unusual site or infection and recurrent TB as more than one episode. Basic immunological screening then, focused immuno-phenotyping and whole exome sequencing (WES) was performed on each of the cases.
A total of 22 patients (4.4 per year) were entered on the South African PID registry with a diagnosis of MSMD. Presentation with MTBC predominated (73%), 14% (3) with non-tuberculous mycobacteria (NTM) and 14% (3) with disseminated bacillus calmette-guerin (BCG). All presented with severe TB. Unusual infection (BCG or NTM) had a pathogenic variant in all cases. Functional work on the IFN-y IL-12 pathway was done on 45% (10) and all showed abnormal function with a varied phenotype. 40% of SPUR TB infections were identified with a known MSMD variant and 60% with a true variant requiring further functional validation. Treatment regimen was documented in 54% of cases and all required a longer duration of treatment than normal for disease.
In the paediatric population SPUR TB infections in the absence of secondary immunodeficiency should alert to further screening for PID. More than one episode of TB can signify MSMD as should poorly pathogenic mycobacteria, in the absence of secondary immunodeficiency. Baseline immunological screening is usually normal and disease could be missed without focused immuno-phenotyping and molecular diagnosis. These patients often require longer duration or expert initiated individualized treatment to clear disease. The phenotypic presentation is wide and severe infection with abnormal presentation should alert further investigation.

POSTER 65 - UNPRECEDED INFLUX OF HLH IN A TERTIARY REFERENCE CENTER

AUTHORS

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Introduction: Hemophagocytic lymphohistiocytosis (HLH) is a rare, potentially fatal condition in which a certain trigger can induce a cytokine storm in a subset of apparently susceptible patient subgroups. Perforine related variants are the major cause of primary HLH in children, whereas in adults multiple factors such as malignancies (M-HLH), viruses (VAHS), autoimmune/ autoinflammatory diseases (MAS-HLH) can be related. In 2018/2019 an unusual high number of patients with new and full blown HLH were admitted to a large academic referral center in the Netherlands.

Methods: We retrospectively describe the clinical course, underlying factors and outcome of 17 newly diagnosed HLH patients admitted between March 2018 and June 2019. If a clear underlying disorder was not directly evident, a whole exome sequencing with a gene panel analysis including more than 350 PID related genes was initiated.

Results: All patients met the HLH-04 criteria set by the Histiocyte Society. Mean age was 43.6 years (SD 15.9) and 11/17 were male. The most prevalent underlying disorders of the patients admitted with a clinical picture of HLH were hematological malignancies (9, predominantly T-NHL). Both MAS-HLH and primary HLH (PRF-1, RAB-27A and PIK3CD variants) were diagnosed/ suspected in 3 patients and 2 patients had VAHS due to systemic HSV infection. Treatment included high dose steroids in all patients, IVIG in 11, etoposide in 9 and anakinra in 3 patients. Other treatment modalities were tailored disease-directed (chemo)-immunotherapy and/ or salvage therapy. Clinical parameters such as ferritin and sIL-2R were significantly elevated (mean value 55963µg/L and 69842gm/mL, respectively) in all patients. Overall mortality was 58%, with the highest mortality rate of 89% (8/9) in M-HLH. Most prevalent triggers included EBV in 5, HSV and CMV both in 2 patients.

Conclusion: A remarkable number of patients with HLH have been admitted in a relatively short period of time. More than half of those eventually were diagnosed with a hematological malignancy in which HLH heralds a poor prognosis. Remarkably, the HLH in 3 adult patients could be related to genetic alterations that are related with primary HLH. Therefore we underscore the relevance of sequencing in the case of unexplained HLH also in adult patients.

POSTER 66 - DIVERSE IMMUNOLOGICAL FINDINGS IN TWO SIBLINGS DIAGNOSED WITH ITCH DEFICIENCY

AUTHORS

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Introduction: Ubiquitin ligases play an important role in the regulation of the immune system and also in cell trafficking, functional activation, proteosomal degradation, and programmed cell death. Itch E3 ubiquitin ligase deficiency has been linked with severe autoimmune disease in mice. Recently, ITCH deficiency has been reported in humans resulting in a complex phenotype characterized by syndromic features, growth retardation, and autoimmune manifestations.

Case report: We report on two siblings of a consanguineous family diagnosed with ITCH deficiency. The second child of the family, a 7-month-old girl, was born after an uneventful pregnancy and was admitted to NICU because of SGA, where craniofacial abnormalities were noticed. Several admissions were reported during infancy due to respiratory infections and growth retardation. Extended laboratory control was conducted at the age of seven months. Ground glass opacity was shown in HRCT and pulmonary fibrosis was found in biopsy. Additional, Intestinal Pseudo-obstruction and liver failure on possible basis of autoimmune hepatitis were noticed. The girl was also suffered by multiple infections and hypotonia. Laboratory investigation of the immune system shown normal lymphocyte counts and immunoglobulins levels. Abnormal lymphocyte proliferation with anti-CD3 stimulation was found once but was normal after two years. The older child of the family, a 5-years-old boy, was evaluated because of growth delay, taking also into consideration his sister medical history. At the time, interstitial lung disease and pseudo-obstruction were found. His past medical history was remarkable for an admission during infancy due to respiratory infection whereas dysmorphic features were described. Immune investigation revealed low immunoglobulins levels and low memory switched B-cells with normal specific antibody response. Autoantibodies were negative. Recently, the whole exome sequencing revealed a novel pathogenic homozygous mutation in ITCH: c.2077G>T. The children are followed systematically; the boy is under reinvestigation for the purpose of receiving the most appropriate immune intervention, whereas the girl already receives supportive care.

Conclusion: ITCH deficiency is a rare disorder with variant clinical manifestations. We described two siblings with the same mutation, but different clinical phenotype and disease course since infancy. Further study of ITCH pathophysiology is needed in order to clarify the immune pathogenetic mechanisms of the disease.

POSTER 67 - REAL WORLD INFECTION RATES BETWEEN INTRAVENOUS IMMUNOGLOBULINS IN PATIENTS WITH PRIMARY IMMUNODEFICIENCY DISEASE

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Introduction: Primary immunodeficiency diseases (PIDD) are a group of genetic disorders that lead to immune system dysfunction, leaving patients at higher risk for chronic infections. Multiple brands of intravenous immunoglobulin (IVIg) therapies are used to treat PIDD. While the products are all human immunoglobulin, there remain differences in manufacturing processes, which may have different outcomes. This study's objective was to assess real-world PIDD infection rates between IVIg therapies in a US claims database over a one-year period.

Methods: The Pharmetrics Plus commercial claims database was used to identify PIDD patients starting IVIg therapy from 1/2012-6/2017. Patients were indexed on their first IVIg claim, and the analysis included a 6-month pre- and a 12-month follow-up period. Only adults with no previous history of any transplant and IVIg compliance for at least 10 out of the 12 follow-up months (83%) were included. Rates and time to infections (defined as pneumonia, acute sinusitis, acute bronchitis, and acute upper respiratory infection) were compared between Gamunex-C (GX), Gammagard (GD), and Privigen (PN) using t-tests and Wilcoxin-rank sum for continuous variables, chi-squares for categorical variables, logistic regression providing odds ratios for binary events, and cox proportional hazard models analyzing time to event. In all comparisons, GX was defined as the reference group.

Results: 795 individuals were included in this analysis (GX:278, GD:360, PN:157). Mean age was highest in PN (GX:50, GD:51 [p=0.22], PN:53 [p=0.03]). All groups were predominantly female. Charlson Comorbidity Index (CCI) score was significantly higher in PN (p<0.01), but not GD. The percentage of patients with at least 1 infection was highest in PN (GX:38%;GD:45% [p=0.09], PN:48% [p=0.04]). Both GD and PN had higher rates of pneumonia, and PN had higher rates of acute bronchitis. GD had higher rates of patients with an infection leading to an ER or inpatient visit (GD:8.6% vs GX:3.2%; p<0.01). After adjusting for age, sex, and significantly different Elixhauser comorbidities between groups, the odds of having an infection were 70% higher for PN (OR:1.7; p=0.04), but not significant for GD. The odds of having an infection leading to an ER or inpatient visit were 160% higher for the GD group (OR:2.6; p=0.04), but not significant for PN. The hazard of having an infection were higher for PN (HR: 1.4; p=0.02).

Conclusion: This study has illustrated several instances where Gamunex-C had lower rates of infections in addition to significant odds and hazard ratios within a one-year follow-up period.

POSTER 68 - OUR EXPERIENCE WITH SEVERE COMBINED IMMUNODEFICIENCY IN NORTH INDIA

AUTHORS

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Background: Severe Combined Immunodeficiency (SCID) is a medical emergency often characterised by life-threatening infections in early infancy. Hematopoietic stem cell transplant (HSCT) or gene therapy is the definitive management for SCID. Early diagnosis and management are essential for successful outcomes.

Methodology: Case records of patients diagnosed with SCID at our Institute from 2001-2019 were analysed. Diagnosis of SCID was based on the European Society for Immunodeficiencies (ESID) criteria.

Results: Eighty-nine (89) cases of SCID have been diagnosed to date. Genetic diagnoses have been established in 57 cases (Fig. 1). Mean age of onset of clinical manifestations and age at diagnosis were 2.3 and 9 months, respectively. Only 7 cases were identified between 2001 and 2010. We witnessed a steady increase in the number of cases over the next eight years. The number of cases diagnosed in the years 2011, 2012, 2013, 2014, 2015, 2016, 2017, and 2018 was 2, 3, 5, 5, 7, 11, 19, and 22 respectively. Eight (8) new cases have been diagnosed in the year 2019, until June. The increase in the number of cases paralleled with the increase in awareness of paediatricians through various academic activities, improvement in laboratory services, and initiation of a separate pediatric immunology sub-speciality course at our Institute. Septicemia due to unusual organisms- Alkaligens faecalis, and Pichia fermentans were seen in our series. Hemophagocytic lymphohistiocytosis, graft-versus-host disease (GVHD), Omenn syndrome, and autoimmune hemolytic anemia were noted in 3, 11, 12, and 3 patients, respectively. We documented 4 novel variants in IL2RG, 3 in ADA, 2 in RAG1, 1 in JAK3 and STK4 each. Four (4) cases with SCID underwent HSCT and three were successful. Eighty (80) patients (89.9%) expired due to uncontrolled infections.

Conclusions: We envisage that the community prevalence of SCID would also be high in India. Newborn screening for SCID and availability of easy access to HSCT services are the needs of the hour to estimate the actual incidence, and also for successful early diagnosis and management.

POSTER 69 - CLINICAL AND MOLECULAR FEATURES OF CHRONIC GRANULOMATOUS DISEASE: A 26 YEARS' EXPERIENCE FROM A TERTIARY-CARE CENTRE IN NORTH INDIA

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Background: Chronic granulomatous disease (CGD) is an inherited phagocytic disorder characterised by recurrent infections with usually catalase-positive organisms. The pattern of infections and microbiological profile in CGD from developing countries is expected to be different from developed nations.

Methodology: Case records of 69 patients diagnosed with CGD at Pediatric Immunodeficiency Clinic, Advanced Pediatrics Centre, Postgraduate Institute of Medical Education and Research, Chandigarh, India from February 1993- May 2019 were analysed. Diagnosis of CGD was based on the nitroblue tetrazolium test (NBT) alone in eight, dihydrorhodamine (DHR) testing alone in two, and by both in 56 cases.

Results: Median age of onset of clinical manifestations and age at diagnosis was five months (range: 10 days- 20 years) and 24 months (range: 1 month- 21 years), respectively. Male to female ratio was 52:17. The ratio of cases with X-linked (XL) and autosomal recessive CGD was 28:31. Mutations in CYBB, NCF1, and NCF2 were noted in 27, 16, and 12 patients, respectively. Pneumonia (42%) was the commonest initial manifestation followed by lymphadenitis (24%), skin infections (15%), and colitis (11%). Liver abscesses were noted in 6 patients. Commonly isolated bacteria were Staphylococcus aureus (n=17), Klebsiella pneumoniae (n=10), and Pseudomonas spp. (n=7). Lymphadenitis due to Burkholderia spp. was seen in 3 children. Aspergillus was the most common fungus isolated (n=22, 3-brain abscess, 19-pneumonia). Localised BCGitis was noted in 3 children. Mycobacterium tuberculosis was isolated in 5 children. Children with XL-CGD presented earlier and had a greater number of infections. Non-infective complications noted were lung granulomas (n=12), colitis (n=8), hemophagocytic lymphohistiocytosis (n=2), liver granuloma (n=2), intestinal obstruction (n=2), and atopiform dermatitis (n=1). Eight (8) out of the 12 patients with NCF2 defect had a common single mutation c.835_836delAC, and they all hail from a particular state (Punjab) in North India, suggesting a founder effect of this mutation. Mortality was observed in 31 (46.9%) patients.

Conclusions: Various socioeconomic and environmental factors coupled with lack of awareness for primary immunodeficiencies, accounted for a late clinical presentation with severe infections and increased mortality in our cohort. Incidence of infections and mortality were significantly lower after initiation of antibacterial and antifungal prophylaxis.

POSTER 70 - REFRACTORY/RELAPSED AUTOIMMUNE CYTOPENIAS AS CLINICAL MANIFESTATION OF PRIMARY IMMUNODEFICIENCY

AUTHORS

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Primary immunodeficiencies (PIDs) are characterized by increased susceptibility to infections and immunedysregulation phenomena, including allergy, autoimmunity and lymphoproliferation. Autoimmune cytopenias (AIC) are widespread among pediatric population and their pathogenesis is often unknown. The most common autoimmune manifestation (AM) reported in PIDs is AIC, often refractory to conventional therapy. AIC can sometimes mark the onset of PIDs.

Objective: To describe clinical, immunological and genetic characteristics of patients presenting with refractory AIC as clinical manifestation of PID, aiming to look for prognostic markers and personalized therapies.

Design and method: We report clinical, immunological and genetic features of 12 patients with AIC as clinical manifestation of PID. Flow-cytometric and principal component analysis (PCA) were used to evaluate different T, B and NK subset. Genetic analysis was made by ION Torrent/Haloplex panel on NGS platform.

Results: Nine out thirteen patients manifested a refractory/relapsed isolated immune thrombocytopenia (ITP) whereas three cases presented with a combination of autoimmune hemolytic anemia (AHA) and ITP (Fisher-Evans Syndrome). All patients are alive except for one, affected by Omenn Syndrome, who died for multi-organ-failure. All the patients showed variable immunological alterations affecting the antibody and/or cellular compartment. We observed decreased percentage in T cell naïve compartment associated to decreased Treg cells frequency. AIC patients had decreased class-switched memory B cells, increased naïve and CD21low B cells. A positive correlation between pTfh/ CD21low was noted. Two patients were diagnosed of severe combined immunodeficiency (SCID), the first one due to homozygous IL7R mutation and the second one due to homozygous RAG1 mutation. Two patients resulted affected by Wiskott-Aldrich syndrome (WAS) and in one case a diagnosis of Del22 syndrome was made.
In four patients heterozygous mutations known to be involved in PIDs were detected in the following genes: RAG1, RAG2, CTLA4, PTEN, PIK3CD, LIG4. Among these patients, in one case a diagnosis of Noonan syndrome due to SOS1 mutation was made. In the other three patients genetic analysis is still ongoing.
Three patients underwent hematopoietic stem cell transplant (HSCT), other two patients are awaiting it.

Conclusions: PIDs should be ruled out in early onset and/or severe relapsing/refractory autoimmune cytopenias.
Early immunological investigations and molecular diagnosis will help to clarify the pathogenesis and may lead the specific choice of a targeted therapy.

POSTER 71 - MALIGNANCY AMONG PATIENTS WITH COMMON VARIABLE IMMUNODEFICIENCY: A SINGLE-CENTER EXPERIENCE

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Objective: Common variable immunodeficiency (CVID) is the heterogeneous disease with increased risk of malignancy.

Design and method: This is a retrospective study analyzing the clinical and immunological data of 39 patients with diagnosis of CVID established according to European Society of Immunodeficiency criteria. Patients were treated in Clinic of Allergy and Immunology, Belgrade, Serbia during ten years, from 2009 to 2019.

Results: Four patients from our group (10.26%) had malignant disease. Three of them were diagnosed with B cell lymphoma as follows: diffuse large B cell lymphoma (DLBCL), extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT) and follicular lymphoma. Patient with DLBCL also had multiple malignancies (basal cell carcinoma, uterine and colorectal adenocarcinoma). Fourth patient had gastric adenocarcinoma. The median age of onset of symptoms in this group of patients was 36±3.56 years and diagnostic delay was 5.5±5.32 years. There were no differences between malignant and non-malignant group of patients concerning demographic data, levels of immunoglobulins at the diagnosis and the number of CD3+, CD4+, CD8+, NK lymphocytes and CD4/CD8 ratio. The most common comorbities in patients with malignancy were splenomegaly (75%), chronic lung disease (75%), hepatomegaly (50%), lymphoid nodular hyperplasia (50%) and gluten-sensitive enteropathy (50%). Mortality in this group of patients was 50%. Statistical analysis showed that patients with malignancy had significantly higher incidence of lymphoid nodular hyperplasia (2/4 vs. 3/35; $X2= 5.51$; $p<0.05$) and gluten-sensitive enteropathy (2/4 vs. 3/35; $X2= 5.51$; $p<0.05$) and also higher mortality (2/4 vs. 4/35; $X2= 4.1$; $p<0.05$) comparing to non-malignant group.

Conclusions: B cell lymphomas are the most common type of malignancy in our group of patients with CVID. Lymphoid nodular hyperplasia, gluten-sensitive enteropathy and high mortality rate are the common features of this group of patients.

POSTER 72 - PHENOTYPIC ANALYSIS OF DERMATITIS CAN DISTINGUISH HYPER IGE SYNDROME FROM ATOPIC DERMATITIS

AUTHORS

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Introduction: Hyper-IgE syndrome (HIES) belongs to a group of primary immunodeficiency disorders caused by monogenic defects mainly in DOCK8 and STAT3; exhibiting persistent eczema, recurrent skin and pulmonary infections, markedly elevated eosinophilia and IgE levels. Although, HIES patients can share many phenotypic features of dermatitis that observed in atopic dermatitis (AD), some distinctive localizations could be suggestive for HIES. We aimed to validate new diagnostic criteria for atypical localizations of dermatitis that can distinguish HIES from AD.

Methods: HIES and AD patients were included. Clinical and laboratory features were evaluated. Categorical variables were compared by chi-square. Receiver operating characteristic test was used to determine the sensitivity and specificity.

Results: There was 34 patients (DOCK8: 13, STAT3: 10, AD: 11). When HIES patients were compared to AD for atypical cutaneous localizations; nuchal (p=0.016), retroauricular (p=0.002), sacral (p=0.024), inguinal and/or genital (p=0.026) regions involvement were found significantly higher in HIES. A dermatitis score (DS) was created by giving one point to each of these featured regions and this score in HIES was significantly higher than AD (p<0.001). In HIES, =>2DS had sensitivity of 95.7% and specificity of 63.6% in the diagnosis and a positive predictive index (PPI) of 84.6% and a negative predictive index (NPI) of 87.5% compared to AD. Next, the cutaneous localizations, clinical and laboratory findings were evaluated to differentiate DOCK8 and STAT3 from AD. When DOCK8 patients were compared to AD, the sensitivity of =>2DS was 92.3% and the specificity was 63.6%, PPI and NPI were 75%, 87.5%; respectively. In patients with DOCK8, CD3+T (p<0.001), CD4+T (p<0.001), CSB (p=0.024) cells were detected significantly lower than AD patients. A laboratory score (LS) was generated by giving one point for each of the low levels of CD3+T, CD4+T and CSB cells. The LS=>2 had a sensitivity of 90.9% and 100% specificity for DOCK8 compared to AD. In STAT3, DS=>2 had sensitivity of 100% and specificity of 63.6% (p=0.001) in the diagnosis and a PPI of 71.4%, NPI of 100%, compared to AD. A clinical score (CS) was formed by giving one point to each of featured manifestations that are statistically significant for STAT3 (newborn rash (p=0.005), pneumotocele (p=0.026), characteristic facial appearance (p<0.001), skin abscess (p<0.001) and =>2CS had sensitivity/specificity of 100% in the diagnosis of STAT3 and a PPI/NPI of 100% compared to AD (p<0.001).

Conclusion: New diagnostic criteria including atypical cutaneous localizations is helpful to differentiate HIES from AD.

POSTER 73 - NOVEL MUTATIONS IN ADENOSINE DEAMINASE DEFICIENT SEVERE COMBINED IMMUNODEFICIENCY: OUR EXPERIENCE AT CHANDIGARH, NORTH INDIA

AUTHORS

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Introduction & Objective: Variants in the adenosine deaminase(ADA) gene deficiency result in severe combined immunodeficiency(ADA-SCID) with T-B-NK-immunophenotype and severe lymphopenia. Early diagnosis must be made before severe life-threatening infections occur so that therapy with enzyme replacement, hematopoietic stem cell transplantation(HSCT)and gene therapy can be initiated. Here, we report the clinical, immunological, and molecular findings in 7 patients with ADA-SCID from North-west India.This is the largest series from our country so far.

Material and methods: Review of records was carried out to describe the profile of ADA-SCID in our cohort of 84 children with SCID diagnosed at Pediatric Immunodeficiency Clinic, Advanced Pediatrics Centre,Postgraduate Institute of Medical Education and Research, Chandigarh, India.The diagnosis of ADA-SCID was based on lymphopenia, lymphocyte subset analysis, ADA activity and molecular studies.Results:Six of the 7 patients presented within 3 months of age. One case had a late onset illness and presented at 4 years of age. Male to female ratio was 5:2. There was history of consanguinity in 2/7 patients and significant family history with sibling deaths in 4/7 cases.The most common clinical manifestations were pneumonia (7/7), failure to thrive (6/7) and diarrhea (4/7).Rash was present in 2 cases with Omenn syndrome and BCG site abscess in 1.One child had ascites and nephrotic range proteinuria-this association has never previously been reported. Blood cultures revealed Acinetobacter baumanii, Methicillin resistant Staphylococcus aureus (MRSA) in 1 each.Bone changes(squaring of scapula)were characteristically seen in 3 cases.All patients had lymphopenia(absolute lymphocyte counts/microlitre< 1000) ranging from 53 to 722 cells/microL.Flow cytometry revealed of T-B-NK-SCID with hypogammaglobulinemia.CD4/CG8 reversal was documented in 3 cases.Molecular diagnosis was carried out in 5 cases. There were 3 novel variants(Table) in ADA gene which were confirmed by functional studies with low ADA activity. All patients had low ADA activity ranging from 0 to 0.3 nmol/h/mg. Six patients succumbed to their illness (86%) as HSCT could not be arranged because of logistic/financial reasons. One child (Patient 3 in table) has undergone HSCT and is currently well.

Conclusion: We describe the first largest series of ADA-SCID from India. We have documented compound heterozygous mutations in 2 patients and 3 had novel variants. Delayed diagnosis due to lack of awareness of SCID among the pediatricians, lack of easy access to HSCT and financial constraints and lack of a suitable donor are the reasons for poor survival rate observed in our cohort.

POSTER 74 - X-LINKED CARRIERS OF CHRONIC GRANULOMATOUS DISEASE: AN UNEXPLORED VISTA

AUTHORS

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Objective, Design, Methods: In our cohort of 69 patients with chronic granulomatous disease(CGD),25 X-linked cases and 35 X-linked carriers have been identified. We describe 3 symptomatic X- linked carriers with varied manifestations.

CASE 1:A 6-year-old-girl developed suppurative anterior cervical adenitis requiring incision and drainage.Two maternal uncles had died at first year due to infective illness.Her younger brother was diagnosed as CGD with a novel homozygous mutation in CYBB(c.675-1G>T) at 4 months age and succumbed at the age of 4 years.Dihydrorhodamine 123 assay(DHR) of the index case showed only 9.38% right shift of PMA-stimulated neutrophils and the stimulation index,B558 expression were markedly low.She was started on cotrimoxazole, iitraconazole prophylaxis and remained well. The index case, however was noted to have only a small carrier peak in the DNA electropherogram. Karyotyping showed 47 XXX.Short tandem repeats analysis revealed that she had inherited both X chromosomes from mother and one X chromosome from father and X inactivation study using HUMARA assay confirmed absence of X inactivation in sister.

CASE 2: The mother of the case 1 was identified to be a heterozygous carrier for the same mutation in CYBB as her daughter (c.675-1G>T).She had been symptomatic from the age of 25 years with arthralgia and malar rash, diagnosed as systemic lupus erythematosus(SLE). At 32-years, she developed diplopia, bilateral lower limb weakness, loss of sensation over both lower limbs, hypotonia, power 0/5,loss of touch, pain, vibration sense, joint position. ANA was 4 + speckled, antids DNA positive; lupus anticoagulant positive. Nerve conduction velocities revealed axonal neuropathy. MRI/MRA brain showed findings consistent with transverse myelitis. She was given pulse-intravenous-methylprednisolone and cyclophosphamide but succumbed to illness.

CASE 3: A 28-year-female, symptomatic since 23 years of age with persistent sinopulmonary infections. Systemic examination revealed bilateral crepitations. In view of recurrent pneumonia, requiring prolonged antimicrobials with poor response, PIDs were considered upfront. Basic laboratory investigations were normal. Work up for tuberculosis was non-contributory. HIV serology was non-reactive. CECT chest showed right upper lobe bronchectasis. Immunoglobulin profile showed hypergammaglobinemia. DHR assay showed markedly reduced oxidative and a low stimulation index. he was started on trimethoprim- sulphamethaxazole and itraconazole phrophylaxis, following which her symptoms gradually improved. She was found to be a CGD carrier with a mutation in CYBB(c.442C>T p. Gln148Ter).

Conclusion: We describe the first series of X-linked carriers in CGD from India. Our series highlights the varied clinical spectrum of X- linked CGD carriers.

POSTER 75 - LYMFOPENIA AS A PREDICTOR OF SARCOIDOSIS IN PATIENTS WITH A FIRST EPISODE OF UVEITIS

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Objective: To study the value of lymphopenia as a diagnostic biomarker for sarcoidosis-associated uveitis.

Design and methods: A study was conducted of 191 patients with a first episode of uveitis, who visited the ophthalmology department of the Erasmus Medical Center (Rotterdam, The Netherlands) between January 2011 and July 2017 and in whom the lymphocyte counts were determined within a month after onset of the first uveitis attack. Receiver operating characteristics (ROC) analysis was performed to evaluate test performance and compared to known ROC values from literature of diverse diagnostic tests used for sarcoidosis-associated uveitis. An ideal cut-off with optimal test characteristics was determined for lymphopenia by calculation of the highest Youden-index for different cut-offs.

Results: Out of all patients with first uveitis attack, 32/191; 17% were subsequently diagnosed with biopsy-proven or clinical and radiological diagnosis of sarcoidosis. The optimal cut-off for lymphopenia for diagnosing sarcoidosis-associated uveitis is 1.47 x10^9/L, which similar to the general cut-off for lymphopenia (<1.5 x 10A69/L). Low lymphocyte counts (<1.5 x10^9/L) were significantly more often observed in sarcoidosis-associated uveitis patients when compared to non-sarcoidosis-associated uveitis patients (P<0.05). The sensitivity and specificity of lymphopenia (1.5 x10^9/L) was 75% and 77%, respectively. The corresponding Youden Index was 0.54. Lymphopenia (cut-off 1.5x10^9/L) resulted in a 12.0 (95% confidence interval (CI); 4.7-30.5) fold risk for having sarcoidosis, corrected for sex, race and age at onset of uveitis in patients with a first uveitis attack.

Conclusions: Lymphopenia is a non-invasive and useful marker for diagnosing sarcoidosis associated uveitis, and when using the 1.5 x10^9/L cut-off, has better diagnostic qualities than angiotensin converting enzyme and the soluble interleukin-2 receptor.

POSTER 76 - DIHYDRORHODAMINE FLOW CYTOMETRIC TEST - APPLICATION IN TOLL-IL1R DEFICIENCIES

AUTHORS

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Objective: Evaluation of phagocyte respiratory oxidative burst using dihydrorhodamine test (DHR-test) allows a fast diagnosis of Chronic Granulomatous Disease(CGD). DHR-test often employs phorbol myristate acetate (PMA) and E.coli as standard stimuli of NF-kB signaling pathway. PMA signals through Protein Kinase C (PKC), whereas E.coli triggeres Toll-like Receptors (TLRs)-mediated activation and probably other pattern recognition receptors. Patients with Toll-IL-1R(TIR) deficiencies and CGD usually suffer pyogenic infections. However, the specific functional tests for TIR deficiencies are usually available only in specialized laboratories. Herein we aimed to assess the capacity of DHR test to screen forTIR deficiencies in a diagnostic setting.

Design and Methods: Four patients with a definitive diagnosis of TIR deficiency (two IRAK-4- and two MyD88-deficient), 3 healthy family members with heterozygous IRAK-4 genotypes (HFM), and 10 healthy control subjects (HC) were analyzed by DHR-test with PMA and E.coli.

Results: Gating on neutrophils, the Stimulation Index (SI) = (MFI-DHRstimulus/MFI-DHRnegative control) was calculated. All enrolled individuals showed normal results (SIPMA>30) in DHR-test with PMA.
TIR-deficient patients showed a marked reduction of DHR-test responses upon E. coli stimulation (mean SIE.coli:45.3) compared with healthy controls (mean SIE.coli: 100.56) and HFM (mean SIE.coli:59.8). When the ratio between SIE.Coli/SIPMA was calculated, all TIR-deficient patients showed ratios <0.5 while 9/10 controls and all the heterozygous relatives displayed ratios >0.5

Conclusions: TIR-deficient patients show a specific impairment of E. coli DHR-test responses as opposed to PMA responses. This dissociation is not observed in CGD patients (both responses equally affected), nor in HFM. Therefore, DHR test using both PMA and E. coli could reveal TIR deficiency.

POSTER 77 - CLINICAL AND LABORATORY FEATURES OF PATIENTS WITH HYPERIMMUNOGLOBULIN M SYNDROME

AUTHORS

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Hyperimmunoglobulin M syndrome (HIGMS) is a primary immunodeficiency (PID) associated with the defect in isotype switching and/or somatic hypermutation mechanisms. Patients with have predisposition to autoimmune diseases and infections.
The aim was to investigate the correlation of clinical/laboratory parameters with the genetic mutations. 49 patients who had been diagnosed as HIGMS between June 1985-June 2017 were included this study. AID defect was found in 18 patients, CD40L defect in 13 patients, CD40 defect in 2 patients, HIGM type 4 in 1 patient, and other defects (ATM, Artemis and Cernunnos gene mutations) in 3 patients. At the time of admission, IgM levels were high in 63% of the patients, normalin 30.4%, and low in 6.5%. The complaints on admission were frequent (69.4%) and severe infections (16.3%), presence of similar sibling illnesses (14.3%). The most common infection was pneumonia, and Candida subtypes and H.influenza were the most common microorganisms that could be isolated. The most common non-infectious finding was arthritis. Eosinophilia was the most common hematological finding. Neutropenia, thrombocytopenia and lymphopenia were also observed for each in 12% of the patients. All patients were given intravenous immunoglobulin therapy. Hematopoietic stem cell transplantation was performed in 1 patient, and planned in 2 patients. During the follow-up period, 10 patients (%20) died because of infectious (14%), autoimmune (2%) and malignant (2%) causes. It has been observed that eosinophilia (26,5%) is an important finding in our patients and rheumatic findings (16 %) are one of the manifestations of HIGMS. IgM levels in the patients with CD40L deficiency were low, suggesting that the diagnostic criteria of the disease should be reevaluated.

POSTER 78 - CLINICAL EFFICACY, SAFETY AND TOLERABILITY OF A 16.5% SUBCUTANEOUS IMMUNOGLOBULIN (SCIG) PREPARATION IN PEDIATRIC PRIMARY IMMUNE DEFICIENCY (PID) PATIENTS

AUTHORS

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Objectives: In this study (NCT 01888484) the efficacy, safety and tolerability of a 16.5% IgG preparation for subcutaneous administration (cutaquig®, Octapharma/Switzerland) were evaluated in adult and pediatric PID patients. The results of the pediatric subgroup are presented here. Primary outcome was to assess efficacy in preventing serious bacterial infections. Secondary endpoints included tolerability, safety and rate of other infections.

Design and Methods: Prospective, open-label, single-arm phase 3 study conducted in North America and Europe. PID patients stable on IVIG treatment for at least six infusions (with IgG trough levels equal to or higher than 5.0 g/L) underwent a 12-week wash-in/wash-out period, followed by a 52-week efficacy period. In both periods patients received weekly SCIG doses.

Results: Twenty-four children (age: 2-16 years; 25% female) received a total of 1,350 SCIG infusions. No serious bacterial infections were recorded. A total of 77 other infections were reported in 19 patients during the efficacy period. The majority of these infections were either mild (86%) or moderate (13%) in intensity. Only one infection (RSV bronchiolitis) was graded as severe. Infection rate per person-year was 3.6. One patient was hospitalized on 2 occasions.
Of the 115 reported adverse events, 5 were assessed as being related to the study drug (all non-serious). Rate of related adverse events per infusion was 0.0037. The majority of infusions (82%) did not trigger an infusion site reaction. Serum IgG trough levels were relatively constant and higher at the end of the study than after IVIG treatment.

Conclusions: Results demonstrate that treatment with the subcutaneous 16.5% human normal immunoglobulin preparation (cutaquig®) in pediatric patients with PID is effective, safe, and well tolerated.

POSTER 79 - INCLUSION OF PRIMARY IMMUNODEFICIENCIES IN WHO LIST OF ESSENTIAL DIAGNOSTICS

AUTHORS

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Objective: In 2018, the World Health Organisation (WHO) published the 1st Model List of Essential in Vitro Diagnostics (EDL), concentrating on a limited number of priority diseases – HIV, malaria, tuberculosis, and hepatitis. WHO announced that the 2nd EDL would be expanded to include more noncommunicable and communicable diseases. IPOPI embarked on a joint effort with the International Union of Immunological Societies (IUIS), to request the inclusion of primary immunodeficiency essential diagnostics. Early diagnosis of PID is crucial to fasten access to life-saving treatments. Yet, it is estimated that 70-90% of people with PID are still undiagnosed worldwide.

Method: A task force made up of experts in the field was put together. Through the expertise of the involved experts and literature searches, data were collected to provide the necessary evidence requested to WHO. IPOPI coordinated the communications between the task force and the WHO EDL secretariat and prepared the applications with input from the experts. Separate applications were submitted to the WHO within the requested timelines and specific format. A number of societies and associations kindly accepted to support the IPOPI-IUIS applications.

Results: In July 2019, the 2nd WHO Model List of Essential In Vitro Diagnostics was published. It includes total and differential counts of white blood cells in the previously existing IVD for Complete Blood Count and a mention of primary immune disorders. A new disease-specific section on primary immunodeficiencies has been included in section IIb “Disease Specific IVDs for use in clinical laboratories”. It comprises:

- HIV 1/2 antibody (anti HIV Ab) “for the differential diagnosis of PID”
- Immunoglobulin plasma levels (IgG, IgA and IgM) “to identify patients with low Ig levels and monitor replacement”
- Lymphocyte subtype enumeration to “aid the diagnosis of PIDs and SIDs”

Conclusions: A joint stakeholder approach was taken to prepare these applications and led to a successful outcome. Essential PID tests are now included in the WHO EDL. Additional evidence will need to be submitted to maintain some of these tests and IPOPI is considering applying for additional new tests (i.e. vaccine response test). The EDL is a great tool for patient groups and stakeholders particularly in developing countries to advocate for increased PID diagnostic resources, together with the WHO Essential Medicines Lists. Visit www.ipopi.org for more information and the list of supporting experts and organisations.

POSTER 80 - COMMON VARIABLE IMMUNODEFICIENCY AND LYMPHOMA, A CHICKEN AND EGG SITUATION

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Objectives: Lymphomas account for two-thirds of all malignancies reported in primary immunodeficiency disease patients, with antibody deficiencies predominating as the underlying immune defect. The majority of lymphomas reported in primary immunodeficiency disorders are B cell lymphomas. patients affected by B cell malignancies are prone to antibody production deficits associated with bacterial infections that might benefit from immunoglobulin replacement therapy.
In secondary antibody deficiency, mature B-cell lymphomas are associated with low IgG concentrations. IgG concentrations before and after treatment should be monitored to predict hypogammaglobulinemia.

Design and methods: Here we present two cases of lymphoma and hypogammaglobulinemia.

CASE1: A 49 years old man with chronic diarrhea who underwent chemotherapy with a diagnosis of intestinal B cell lymphoma which was cured thereafter. He had history of recurrent complicated respiratory infections since 25 years ago. The patient was pan hypogammaglobulinemia and had impaired antibody response to pneumococcal polysaccharide antigen with normal lymphocyte profile. He was diagnosed as having lymphoma secondary to common variable immunodeficiency and intravenous immunoglobulin was started.

CASE2: A 21 years old woman with a history of recurrent complicated respiratory infections and splenomegaly since childhood. She had hypogammaglobulinemia and poor antibody response to vaccine antigens, intravenous immunoglobulin was started with a diagnosis of common variable immunodeficiency. After four years she presented with B cell lymphoma which was cured after chemotherapy.

Results and conclusion: It is not straightforward to determine if either lymphoma or primary immunodeficiency is responsible for hypogammaglobulinemia. When a patient first presents with hypogammaglobulinemia, it is more obvious that lymphoma is the consequence. But when lymphoma is the inciting manifestation, determination of chronologically is more complicated. In the latter condition as in case1, some clues may help determine the priority: first, history of prior medical conditions which lead towards of immunodeficiency as a risk factor for lymphoma. second, a genetic study could reveal a mutation which implies a primary immunodeficiency. Unfortunately, the past history is not always convincing, On the other hand, genetic study in common variable immunodeficiency is not always definite, as only ten Percent of these patients have a known mutation. it is important to clarify if there is a primary immunodeficiency disease, as the prognosis, medical care, follow-up plan and genetic consult would be different. More focused studies are needed to find a way to determine if it is egg or hen.

POSTER 81 - PRENATAL DIAGNOSIS AND CARRIER SCREENING FOR PRIMARY IMMUNODEFICIENCY DISEASES

AUTHORS

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Introduction: Primary Immunodeficiency Diseases (PIDs) are a heterogeneous group of genetic defects in the innate or adaptive components of the immune system. PIDs are grossly unrecognized and undiagnosed in India due to lack of awareness and dearth of laboratory amenities. This is especially true regarding facilities for a molecular diagnosis of these disorders. Prenatal diagnosis and carrier detection forms an essential component of management in families with children afflicted with PIDs.

Objectives: Prenatal diagnosis, carrier screening and genetic counselling in families with known mutations in different PID genes

Materials and methods: Chorionic villous sampling (CVS) was performed at 10 weeks of gestation. Maternal tissue was removed from the CVS sample under a dissecting microscope and DNA was extracted. Cordocentesis was performed in 6 patients and amniocentesis was done in three patients. Maternal contamination was ruled out by variable number of tandem repeat (VNTR) analysis and an amelogenin PCR was carried out for sex determination using X and Y chromosome specific primers. Amplification PCR was done for specified exons of the gene and the amplified PCR product was purified and subjected to sequencing to verify the presence or absence of the known mutation. The sequencing reads were analyzed using the CLC genomics workbench and codon code aligner software.

Results: Prenatal diagnosis was made in thirty five families with a child affected with PID. Seven cases were of Wiskott-Aldrich syndrome, 9 of Chronic granulomatous disease and severe combined immunodeficiency, four cases of X-linked agammaglobulinemia and one each of Hemophagocytic Lymphohistiocytosis, Congenital Neutropenia, Deficiency of Interleukin-1 receptor Antagonist, Syntaxin11 and Griselli syndrome. Out of these thirty-five, twenty-one were affected and fourteen were not affected. The parents were counselled and all parents with affected foetuses opted for a medical termination. Carrier screening was done for all the patients, and mothers were detected to be the carriers in x-linked cases.

Conclusion: Prenatal diagnosis, genetic counselling and detection of carriers are an indispensable part of patient care in genetic diseases and need to be integrated into overall patient management of PIDs.

POSTER 82 - FATAL HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS AS THE PRESENTING MANIFESTATION OF WISKOTT ALDRICH SYNDROME: A CASE REPORT

AUTHORS

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Introduction: Wiskott Aldrich syndrome is an X-linked primary immunodeficiency characterized by a clinical triad of ezcema, thrombocytopenia and recurrent infections. It has a wide spectrum of presentation, ranging from intermittent thrombocytopenia to classic WAS. Patients with WAS may also develop autoimmune and inflammatory manifestations. However, hemophagocytic lymphohistiocytosis as the presenting manifestation of WAS is distinctly unusual.

Case: A 9 year old boy, born of non-consanguineous marriage presented with 1 month history of high-grade fever, swelling of left testis and left side of neck, progressive pallor and arthralgia. On examination, boy was underweight, pale, discrete LN was palpable in B/L cervical and inguinal regions.
Laboratory investigations revealed anemia (Hemoglobin 7.9), leucopenia (TLC: 600, DLC: were undetectable, Platelet: 10,000 per ml) elevated C-reactive protein (530, 610 unit) and elevetaed ferritin (1224 ng/mL). 2-D echocardiography showed enlarged RA/RV. Immunoglobulin profile showed hypogammaglobulinemia {IgG 452(673-1734); IgA 72(70-250); IgM 141(50- 180) mg/dL}. CD3 (T lymphocytes): 92.9%, reduced CD19 (B lymphocytes): 0.36%. A clinical possibility of primary immunodeficiency was considered and he was initiated on intravenous antimicrobials cefoperazone+sulbactam and amikacin were started worsening tachypnea, for which antimicrobials were changed to piperacillin+tazobacatm and vancomysin along with amphotericin. He had worsening cytopenia and respiratory distress for which he had to be ventilated. However, he succumbed due to persistent respiratory failure. A full body autopsy was carried out that revealed disseminated hemophagocytosis thymic hypoplasia, pulmonary fungal abscesses (Aspergillus species), diffuse alveolar damage with patchy bronchopneumonia, Candia in gastrointestinal tract and, secondary hemosiderosis of liver and spleen. In view of persistent thrombocytopenia, a possibility of Wiskott Aldrich Syndrome was considered and genetic mutation analysis revealed WAS gene mutation (c.91G>A, p.E31K).

Conclusion: Wiskott Aldrich syndrome can have a variable clinical presentation. However, HLH like presentation is distinctly unusual. Persistent thrombocytopenia with recurrent infections in a male child should be evaluated for WAS.

POSTER 83 - QUANTITATIVE DETERMINATION OF TREC AND KREC DNA MOLECULES FOR SCREENING OF PRIMARY IMMUNODEFICIENCIES IN ST. PETERSBURG NEWBORNS.

AUTHORS

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Objective: According to statistics, the most common among primary immunodeficiencies are defects in antibody production (61%) and combined immunodeficiencies (18%). These groups of immunodeficiencies are characterized by the absence or lack of T- and / or B-lymphocytes, or the weakening of the functions of these cells. In this connection, of particular interest is the study of the content in humans of T-receptor excision rings - TREC (T-cell receptor excision circles) and B-cell excision rings - KREC (kappa-deleting recombination excision circles). TREC and KREC remain in one of the daughter cells during lymphocyte proliferation, which allows their definition to be used as a marker of the normal development of the adaptive immune system and used for early diagnosis of immunodeficiency diseases. The goals of our research are:

1. Testing the most convenient method for screening DNA extraction from donor samples and validating the TREC and KREC quantitative methods for the quantitative determination of DNA molecules using real-time PCR;
2. Population analysis of TREC and KREC concentrations in the blood of conditionally healthy newborns.

Design and method: In the present study it has been used umbilical blood of healthy newborn infants. Highlighted in DNA from blood cells was performed on a set manual method for isolating DNA/RNA «Ribo-Prep» (InterLabService, Russia) according to the manufacturer's instructions. To determine the number of TREC and KREC, the Russian test system provided by the Institute of Chemical Biology and Fundamental Medicine. Interpretation of the results was performed according to the recommendations of the developer. Statistical analysis was performed using the program GraphPad Prizm 5.0.

Results and conclusions: We analyzed samples of umbilical cord blood of newborn 157 - 79 girls and 78 boys. TREC concentrations ranged from 10,762 to 121,068 copies/105 lymphocytes. The concentration of KREC ranged from 10,550 to 89,533 copies/105 lymphocytes. There were no significant intersex differences between the TREC and KREC concentrations, which coincides with the literature data. The possibility of determining the number of TREC and KREC for the diagnosis of defects of the immune system is shown in a number of foreign and domestic studies. Further experiments are required to determine a more accurate range of reference values and formulate recommendations for using this method in the broad practice of the national newborn screening program.

POSTER 84 - EFFICACY, TOLERABILITY AND SAFETY OF CUTAQUIG®, SUBCUTANEOUS HUMAN IMMUNGLOBULIN 16.5%, IN ADULT PATIENTS WITH PRIMARY IMMUNODEFICIENCIES

AUTHORS

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Objectives: The majority of patients with primary immunodeficiencies (PID) require life-long replacement therapy with immunoglobulins (IgG) to prevent severe infections and irreversible complications. A 16.5% IgG preparation, octanorm (Octapharma, Switzerland; recently approved as cutaquig®in North America and Europe) has been developed for sub-cutaneous administration (SCIG) derived from the established manufacturing process of Octapharma's intravenous IgG (IVIG) brand octagam®. Primary endpoint of the presented study was rate of serious bacterial infections (SBI). Main secondary endpoints included (among others) evaluation of tolerability and safety of octanorm, number and rate of other infections, number of days missed at work.

Design and methods: Prospective, open-label, non-controlled, single-arm phase 3 study in adult patients with PID conducted at 5 Russian centers. Patients treated with at least 4 infusions of IVIG prior to enrollment and with IgG trough levels of at least 5.0 g/L underwent an 8-week wash-in/wash-out period followed by a 24- week efficacy period. After training, patients self-infused octanorm on a weekly basis (at the same monthly dose as during previous IVIG treatment divided by 4 for weekly dosing).

Results: Twenty-five patients were enrolled and twenty-four patients completed the study. One patient terminated early (for personal reasons). Mean age was 35.24 years (range 18-64 years; 60% female). No serious bacterial infections were recorded. During the efficacy period 26 non-serious infections were observed in 14 patients, of these 17 (65%) were mild and 9 (35%) moderate in intensity. The infection rate per person-year was 2.37.
During the study a total of 775 infusions of study drug were administered. Average dose of cutaquig® was 0.11 g/kg/week. During the entire study, 59 systemic adverse events were reported, three were rated as related to study drug, all three were non-serious. Infusion site reactions occurred during 15% of infusions. Serum IgG trough levels were nearly constant during the efficacy period. Median IgG trough levels were 8.15 g/L at Screening, 9.52 g/L at the end of wash-in/wash-out period and 10.71 g/L at the Termination Visit. During the efficacy period 10 patients (41.7%) used antibiotics in 19 treatment episodes (total of 229 treatment days; range 5-76 days) and 3 patients had 4 absences from work or school due to infections (total of 14 days of absence).

Conclusion: This study demonstrated that the new subcutaneous human normal immunoglobulin 16.5% is well tolerated, safe and effective in adult patients with PID.

POSTER 85 - EFFECTIVENESS OF IMMUNOMODULANT INTRAVENOUS IMMUNOGLOBULIN THERAPY IN A PATIENT WITH X-LINKED LYMPHOPROLIFERATIVE SYNDROME TYPE 2 (XLP-2)

AUTHORS

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Background: XIAP deficiency has been described in patients suffering from IBD (Inflammatory Bowel Disease) and very early onset-IBD (VEOIBD). The therapeutic response of these patients represent a challenge.

Methods: Molecular and functional studies to investigate XIAP gene, apoptosis and TNF-alfa expression.

Results: We describe a 44th yo man, characterized by pancytopenia, recurrent infections, fever episodes and chronic diarrhoea since childhood. Hepatosplenomegaly with hypertransaminasemia, hyper-ferritinemia and pancytopenia worsening were detected and he developed HLH episodes triggered by primary CMV infection. Immunomodulant (corticosteroids) therapy with intravenous immunoglobulin was started with good response. The patient actually has long symptom-free intervals in which there is a remission of IBD clinical manifestations.
Immunological investigations revealed hypogammaglobulinemia and reduced NK cell frequency. We found a pathogenic mutation c.664C>T (p.Arg222Ter) in XIAP gene. In vitro apoptosis assay in CD4+ and CD8+ T cells from the patient's PBMC unstimulated and stimulated with OKT3/CD28, or muramyl dipeptide (L18-MDP) showed propensity to apoptosis compared with a healthy control. TNF-alfa production by monocytes in response to NOD2 stimulation by L18-MDP was severely abrogated in vitro.

Conclusion: Further investigation will be required to clarify the role of this mutation and its pathogenic effect. Moreover, immunomodulant treatment with IVIG has never been described in patients with XIAP deficiency, however our case suggests its effectiveness in this disease.

POSTER 86 - TWINS WITH NOVEL X-LINKED VARIANT IN IL2RG GENE SUSPECTED TO EARLY ONSET INFLAMMATORY BOWEL DISEASE

AUTHORS

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Objective: X-linked severe combined immunodeficiency is caused by the IL2RG gene which encodes a protein called the common gamma chain. Several variations have been identified in the IL2RG gene, which potentially are able to prevent the production of proteins or lead to producing nonfunctional versions. Herein, a case of novel X-linked variant in IL2RG gene in twin brothers with inflammatory bowel symptoms has been reported.

Case Presentation: Two-year-old twin brothers born to non-consanguineous parents were referred to Children's Medical Center following chronic non-bloody diarrhea which was started at the age of 12 months. Also, their first hospital admission was at the age of 2 months following pneumonia. Pancolitis revealed after performing upper and lower endoscopy for one of the brothers with more severe gastrointestinal symptoms. Furthermore, polymerase chain reaction confirmed cytomegalovirus colitis and the patient underwent intravenous Gancyclovir. Further investigations confirmed positive Epstein–Barr virus serology as well. However, the other brother's tests were negative for the mentioned viral infections, both had experienced recurrent respiratory symptoms and two episodes of otitis media. They had failure to thrive and several admissions due to severe watery diarrhea. Moreover, complementary investigations demonstrated G6PD deficiency in the twins, that was in accordance with episodes of jaundice and hemolytic anemia.
The family history was positive for the death of their paternal grandparents' daughters due to unknown reasons during infancy. Their older 7-year-old brother and both parents were apparently healthy.

Results: Immunologic laboratory tests showed very low levels of CD4+ cells in both patients. Next generation Sequencing-based gene panel tests proved a novel missense X-linked IL2RG gene variant (70330011 A>G) in one of the patients, which soon after was confirmed by Sanger segregation in his twin brother. Both parents were wild type and never had experienced similar symptoms.

Conclusions: In this report, twins with a novel IL2RG gene variant has been described. Based on genetic analysis both parents were wild type and symptom-free. While the bowel inflammatory symptoms were the very early disease manifestations, X-linked severe combined immunodeficiency was established as the final diagnosis. In conclusion, various severe combined immunodeficiency manifestations could be a result of different mutation sites, even in the same gene defect

POSTER 87 - RECURRENT INFECTIONS IN AN ETHIOPIAN INFANT WITH A CONGENITAL T-CELL IMMUNODEFICIENCY - DIGEORGE SYNDROME

AUTHORS

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Objective: DiGeorge syndrome is a rare form of congenital T-cell deficiency. The disorder is characterized by hypoplastic or aplastic thymus, hypocalcemia, recurrent infections and other associated congenital defects. We describe the first case diagnosed in Ethiopia.

Case presentation: We report an eleven month old male infant from Addis Ababa, Ethiopia presenting with recurrent chest and diarrheal infections, failure to thrive, lymphopenia, hypocalcemia and hypoplastic thymus on imaging. A diagnosis of DiGeorge syndrome was confirmed after determination of low CD3 and CD4 counts. The infant had a normal Echocardiograph. Further testing was not possible due to constraint of resources in our hospital.

Conclusion: We report the first Ethiopian child suffering from DiGeorge syndrome. A timely diagnosis is needed for adminstering prophylaxis against recurrent infections and appropriate management.

POSTER 88 - CLINICAL EVALUATION RESPIRATORY IMPAIRMENT AND IMMUNOLOGICAL MANAGEMENT OF COMMON VARIABLE IMMUNODEFICIENCY DISORDERS

AUTHORS

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Objective: To study and analyze clinical course of respiratory diseases and immunological approach to the common variable immunodeficiency disorders

Design and methods: The study involved 42 patients aged 17-68 treated at the 1st Republic Immunological Clinical Centre between 2015-2017. All patients were examined, including physical methods, clinical and biochemical analyzes of blood and urine, immunological tests, radiography and computed tomography of the chest and paranasal sinuses, ECG, respiratory function.

Results: The study showed that broncho-pulmonary system was accompanied by the development of complications such as bronchial obstruction in 12 patients (28.5%), bronchiectasis in 14 (33.4%), pulmonary fibrosis 10 (24%), chronic pulmonary heart disease in 4 patients (14.0 %); in 2.8 % of cases performed lobectomy. Deafness developed in 13 patients (31%) due to repeated purulent perforated otitis. In 34.8 % of patients, respiratory infections were associated with gastrointestinal lesions (enterocolitis, recurrent diarrhea, malabsorption syndrome). Thus, the involvement of the gastrointestinal tract pathology in adults occurs more often than in children, in whom these manifestations are observed in 25% of cases. In 21% - autoimmune diseases (hemocytopenia, nephritis, hepatitis, scleroderma), including in the debut of the disease. In 7 patients (16.6%) of malignant tumors: cancer of the stomach, intestines, breast, ovaries, T-cell lymphoma, multiple myeloma, chronic lymphocytic leukemia. Viral and fungal infections were also observed, reflecting a cellular disorder of immunity in patients with CVID: recurrent herpetic infection - 34.3%, mucosal candidiasis - 15%, viral hepatitis B and / or C - 12%. An individual patient was given with a starting dose of 0.4 to 0.5 g/kg/month for both intravenous immunoglobulin (IVIG) at 3- or 4-week intervals and 0.4 to 0.6 g/kg/month for subcutaneous immunoglobulin (SCIG). If there is pre-existing bronchiectasis unless there was evidence for using 0.6 g/kg/month. There were significant decreases in the LRI and gastroenteritis frequencies in the first year of IVIG treatment

Conclusion: Bronchiectasis was the most common finding, and the other findings included enlarged hilar lymph nodes, nodules, and a mosaic pattern. An early diagnosis and treatment initiation are protective against CVID lung complications. Thus, the relatively low prevalence of primary immunodeficiencies in the population, the diversity of their clinical forms, the lack of awareness of practitioners about this pathology, the inability in some cases to conduct an immunological examination lead to the fact that patients do not receive pathogenetic therapy for a long time.

POSTER 89 - RAPID RESPONSE OF CVID SKIN GRANULOMATOUS DISEASE TO INFLIXIMAB

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Objective: Comment a case of CVID associated necrotizing granulomatous disease with good response to Infliximab.

Design: Retrospective chart review from July 1992 to may 2019.

Method: We here describe a 26yo white male referred for monthly IVIG in august 2016. At age 1, he developed large areas of erythematous polymorphic plaques in his cheeks, arms and legs. A skin biopsy showed tuberculoid granulomas negative for bacteria, BAAR and fungi, with infiltrating CD4+ lymphocytes. A prolonged course of steroids did not improve his skin. He also had multiple pneumonias and bronchiectasis, and oral candidiasis. He received all vaccines, including BCG with no complications. With low immunoglobulins and a poor response to pneumococcal polysaccharides and tetanus toxoid he was diagnosed as CVID and placed on IVIG at 7yo with excellent infectious control since then. At age 8, his skin lesions persisted and deepened to the bone on his left leg. Broad spectrum antibiotics for 3 months were unsuccessful. At 16yo to 18yo, skin grafts were performed on his arms, legs and both cheeks. Two ulcers persisted on his left leg until August 2018 that increased in size, deepened and became erythematous and extremely painful (Fig. 1). RAG 1 and RAG 2 genes sequencing was normal. In September, two new ulcers appeared on his right cheek and right gluteus, respectively. One week later a third ulcer was found on his left calf. On September 28th, Infliximab 5mg/kg (300mg) was administered.

Results: On the second Infliximab dose, October 12th, the pain was completely gone and all ulcers were shrinking, and those ones in the cheek, gluteus and calf almost completely resolved. By the third dose, on November 23rd the ulcers in his right leg were almost closed (Fig. 2). Infliximab 300mg treatment continues every 4 weeks, but after de fifth dose he had a relapsed with multiple new ulcers on his left leg. Addition of meprednisone 40mg led to rapid ulcers healing.

Conclusions: Granulomatous disease in CVID is a challenge. Both B and T cell directed therapies are encouraged. We add a new case of an Infliximab responsive patient to others already reported.

POSTER 90 - CASE REPORT OF HYPER IGM SYNDROME IN DOWN SYNDROME CHILD

AUTHORS

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Introduction: Down syndrome is the most common genetic disease that often presents with a high frequency of infections especially upper airway infections in their early years, characterized by increased severity and prolonged course of disease. Individuals with Down syndrome are known to have abnormal function of the B-cell function, which might present with high IgG and low IgM serum levels.

Case Description: A one-year-old known Down syndrome child presented with persistent nasal congestion, fever, noisy breathing, and daily cough for 8 months. He had several outpatient consults and treatment with antibiotics but with poor relief of symptoms. Due to persistent symptoms, he was referred to the Ear, Nose and Throat surgeon. His paranasal radiographs revealed sinusitis. He was then referred to pediatric infectious specialist for further management. Examination revealed a sick-looking, syndromic child who was having marked nasal congestion, global hypotonia and generalized erythematous rash. He was otherwise well nourished (BMI 25th centile on Down syndrome growth chart). Serum immunoglobulin test show marked elevated Ig M with low Ig G and Ig A levels. Rheumatologist and Pulmonologist review was done. Rheumatologist agreed with the possible diagnosis of primary immunodeficiency. Pulmonologist confirmed no underlying congenital lung pathology from the chest CT scan. The echocardiogram was unremarkable. He received intravenous immunoglobulin (IVIG) as part of the therapy and his symptoms improved markedly. An impression of Hyper Ig M syndrome was made. He received two other courses of IVIG after discharge. Currently, the mother reports good improvement of symptoms.

Discussion: Hyper IgM syndrome is a primary immunodeficiency syndrome characterized by defective CD 40 signaling, which lead to defect in Ig class switching recombination. It is manifested as elevated Ig M with a deficiency in other class of Ig which leads to increase susceptibility to infections.
The association of Down syndrome with primary immunodeficiency is not clearly demonstrated. In our case, elevated Ig M was an incidental finding. Warning signs present in children with Down syndrome warrants a detailed immunology investigation to exclude primary immunodeficiency. Diagnosing primary immunodeficiency imposed a great challenge to doctors especially due to the co-existing condition. A delay in diagnosis is common and associated with increased morbidity and parental distress.

Conclusion: There is an urgent need to create awareness amongst the healthcare workers concerning primary immunodeficiency especially in children with co-existing disease. We need to assure earliest diagnosis, appropriate treatment, and proper care management are provided to the affected children.

POSTER 91 - CASE SERIES REPORT OF COMMON VARIABLE IMMUNE DEFICIENCY: A SINGLE – INSTITUTION STUDY AT THE CHILDREN'S HOSPITAL 1, HO CHI MINH, VIETNAM

AUTHORS

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Objective: Describe clinical manifestations, laboratory findings, genetic analysis and outcome of four cases with CVID.

Design and Method: We performed complete blood count, quantitative serum immunoglobulin test and lymphocyte subset analysis to identify possible diagosis of CVID in all patients suspected of having PIDs subsequently confirmed by genetic testing.

Result: Three boys and one girl aged 6 to 14 years had CVID. The onset age was 2 to 11 years for all patients, of whom 1 boy first presented at more than 10 years of age. Two boys had family history with brothers' death. All patients had recurrent respiratory infections. One patient had persistent diarrhea, chickenbox, measle and another had sepsis. One of the 3 patients with lymphoid hyperplasia had cutaneous granulomatous. The remaining patient progressed to B cell lymphoma. Serum IgG levels reduced by more than 2 SDs below the mean and IgA levels remarkably decreased in 4/4 patients, IgM levels was normal in 2/4 patients and remarkably decreased in the others. Lymphocyte immunophenotyping showed normal B cells in 2/4 patients, a mild decrease in one patient and absence in one patient, an increase of CD4-CD8- T cells more than 2.5% in 2/4 patients, an inverted CD4/CD8 ratio in 2/4 patients.
Next generation sequencing and sanger sequencing were performed to verify segregation of the mutation among the family members. Novel compound heterozygous stop gain mutations c.1933C >T, p.R645X and c.949C > T, p.R317X of the LRBA gene were found in a boy whose parents were heterozygous carriers. A de novo stop gain mutation c.2557C >T: p.R853X of the NFKB2 gene (autosomal dominant inheritance) was found in a girl whose parents were normal. Interestingly, a nonsense mutation c.654C>A: p. C218X of the CD40LG gene which causes X-linked hyper IgM syndrome was found in a boy whose mother was heterozygous carrier. All patients had IVIG prophylaxis, 400-600 mg/kg every 4-5 weeks, except the boy who progressed to lymphoma had anaphylactic reactions to IVIG. Three out of 4 patients did not acquire severe infection after 4 to 36-months follow-up. The patient who progressed to lymphoma was lost follow-up after chemotherapy.

Conclusion: Clinical phenotyes of CVID are heterogeneous and may overlap with agammaglobulinemia or hyper IgM syndromes. Genetic analysis should be performed in all patients with CVID especially those who have family history to confirm diagnosis, outcome and genetic consultation. IVIG prophylaxis should be given early for prevention of recurrent infections.

POSTER 92 - THE EFFECT OF HOME-BASED TREATMENT WITH IMMUNOGLOBULIN ON PSYCHIATRIC ASPECTS IN PATIENTS WITH PRIMARY IMMUNODEFICIENCIES

AUTHORS

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Objective: Immunoglobulin is administered by intravenous route in the hospital every 3-4 weeks or subcutaneously every 1-2 weeks to prevent infections, complications and improve quality of life in patients with primary immunodeficiency. It was aimed to determine the effect of home-based treatment with immunoglobulin on the psychiatric aspects in patients with primary immunodeficiency and in their parents.

Design and method: The patient population consisted of 34 patients who were receiving subcutaneous immunoglobulin (SCIG). Three patients were excluded and nine patients returned to intravenous route in follow-up. During intravenous immunoglobulin (IVIG) and SCIG therapy phases child Depression Inventory (CDI) was implemented to both patients and their parents, Beck Depression Inventory (BDI) and Beck Anxiety Inventory were implemented only to parents of the twenty-two patients who continued with SCIG treatment.

Results: Fourteen boys and 8 girls, with a mean age of 150.0 ± 59.5 months completed the study. The most common diagnosis (50%) was common variable immunodeficiency. The depression inventory child form values were significantly lower in SCIG phase than in IVIG period (4.3±4.3 vs 7.0±5.4, p=0,038). Although the depression inventory parent form values were also lower in SCIG phase the difference was not statistically significant (5,3±4,1 vs 8,4±6,3, p=0.092). According to Beck Depression and Anxiety inventories, it was seen that the anxiety inventory scores of the parents were significantly lower in SCIG period (p=0.009).

Conclusions: The subcutaneous route allows self-administration at home and therefore enables a more independent lifestyle than with IVIG therapy. Therefore the home-based SCIG treatment option reduces the psychological problems in patients with PID and in their parents.

POSTER 93 - NEONATAL DIARRHEA AND ECZEMA: FIRST PERUVIAN REPORTED CASE OF IMMUNE DYSREGULATION, POLYENDOCRINOPATHY, ENTEROPATHY, X-LINKED (IPEX) SYNDROME

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Objectives: To present and share the first peruvian diagnosed case of dysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX) syndrome. To understand the importance of genetic analysis for a precise diagnosis.

Design and Method: Case report study

Results: Presenting the case of a 6-month-old child hospitalized at the age of 2 months with chronic diarrhea, malnutrition and evidence of sepsis. Patient had no family history of primary immunodeficiency. Parents and sister looked healthy. Patient was born apparently healthy. However, since the first weeks of life showed chronic diarrhea of up to 20 episodes per day. Concomitantly, he was fed with elemental formula due to insufficient mother milk production.
Initially, gastrointestinal sepsis was suspected. As a consequence, he received several antibiotics regimens. However, the patient's symptoms exacerbated. At that time, patient showed erythematosus rash at face and back, and eczema (picture 1). After a period without antibiotics, milk allergy was suspected due to IgE high levels and positive specific IgE for milk protein. Lymphocyte population showed mild B cells diminished but normal rest of immunoglobulins levels. Patient received amino-acid milk without improvement, so he turned to parenteral nutrition. Antibiotics course started again due to Staphylococcus aureus sepsis. No major physical signs were presented.
Other causes of chronic diarrhea were ruled out (including drug-induced, infectious, hypothyroidism and parasitosis). Primary immunodeficiency was suspected. Endo-Colonoscopy showed architecture distortion, glandular atrophy with fibrosis and presence of eosinophils. Blood samples were sent to the USA, where flow cytometry report absence of FOXP3 expression in T cells. Sanger sequencing for FOXP3 gen showed a hemizygous mutation. IPEX syndrome was confirmed.
Patient started with Tacrolimus and corticosteroids with stationary evolution. He has travelled to Roma for Hematopoietic progenitor-cell transplantation (HPCT), he and his sister are fully matched. Currently, we are waiting for engrafment after HPCT.

Conclusions: IPEX syndrome is characterized by early onset of enteropathy. It can be associated with food allergy, sometimes this leading to diagnosis delay. Doctor awareness of PID, teamwork and international support will allow us to do an early diagnosis benefiting patients with a timely treatment.

POSTER 94 - IMPLEMENTATION OF THE MODEL OF COMBINING PHYSICIAN EDUCATION AND PUBLIC AWARENESS WITH THE INFRASTRUCTURE TO DIAGNOSE PRIMARY IMMUNODEFICIENCY DISEASES IN CHILDREN

AUTHORS

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Background: The issue of early diagnosis, timely and effective treatment, prevention of complications and improved prognosis remains extremely relevant for of primary immunodeficiency diseases (PID).
Objective of this study was to evaluate the efficacy of the model of combining physician education, public awareness with the infrastructure to diagnose PID.

Methods: Integration of three strategies has been following from February 2017 till now in Ternopil region of Ukraine. The first of them concerns the education of primary-care physicians (pediatricians, GP doctors) and other specialists (rheumatologists, otolaryngologists, pulmonologists, surgeons, etc.) in early PID symptoms and detection using workshops, trainings, and targeted publications. The second one deals with organization of public events, media appearance to raise awareness of PID. The third one is to build the structure of testing for patients with suspected PID.

Results: Workshops and trainings for primary care physicians on early PID detection were organized in every district of the region (in total 15 districts were covered). In total 540 physicians and nurses have attended lectures and worhshops, including pediatricians, general practitioners and other specialists. We also visited the outpatient departments, talking to doctors, patients and their parents about the warning signs of primary immunodeficiencies.
During the visits an examination of the children at risk for PID was conducted. We developed examination cards for children with suspected PID. These children were referred to the regional children's hospital for further examination.
We have translated into Ukrainian and published educational materials: warning signs, stages of testing. We also created some educational materials about PID. These materials were disseminated among physicians.
By the beginning of project, there were 11 children with PID in our region. We created a local register of patients with PID. Now there are 38 patients with PID in local registry, 17 of them were diagnosed during last 2 years: Nijmegen breakage syndrome (3), ataxia-teleangiectasia (1), Di George syndrome (3), hypogammaglobulinaemia (2), common variable immunodeficiency (1), selective IgA deficiency (3), congenital neutropenia, unspecified (2), cartilage-hair hypoplasia (1), deficiency of IgG subclasses (1). We also follow 12 patients with suspected PID that need repeat examinations to finalize the diagnosis.

Conclusion: Implementation of the model of combining physician education, public awareness with the infrastructure to diagnose these diseases is effective strategy to increase PID diagnosis.

POSTER 95 - PROSPECTIVE OPEN-LABEL SINGLE-ARM PHASE 3 STUDY OF THE SAFETY OF PRIVIGEN® IN JAPANESE PATIENTS WITH PRIMARY IMMUNODEFICIENCY

AUTHORS

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Objective: Primary immunodeficiencies (PID) can be effectively treated with immunoglobulin G (IgG) replacement therapy. Intravenous (IVIG) and subcutaneous IgG are equally effective. However, an early peak of IgG immediately after IVIG infusion is beneficial for highly symptomatic patients. Also, IVIG requires less frequent infusions and the clinic setting for IVIG infusion may be favorable for patients with reduced manual dexterity, lack of self-reliance or aversion to self-administration. This study assessed the safety of Privigen® (IgPro10, CSL Behring, King of Prussia, PA, USA) in Japanese patients with PID.

Design and method: This was a prospective Phase 3, open-label, single-arm study in Japanese patients with PID. Privigen® was administered at doses of 138–556 mg/kg body weight per dosing cycle (3- or 4-weekly) for up to 4 months including a 12-week wash-in/wash-out period. Frequency and intensity, as well as relationship to study drug, of adverse events (AEs) were assessed. AE rate per infusion (AERI) was also evaluated.

Results: Ten of eleven patients completed the study. Treatment adherence was high, with an overall dose compliance ranging from 98.5% to 100.9%. The median (range) total duration of exposure was 16.14 (4.1–16.3) weeks. A total of 19 AEs, most of which mild, were reported in 8 patients, resulting in an AERI of 0.442. One AE was deemed related to Privigen® treatment (mild infusion site discomfort, resolved) and 3 patients experienced temporally associated AEs (within 72 h post-infusion). No serious AEs or deaths were reported. No changes in clinical laboratory parameters were considered clinically significant or reported as AEs. Nine out of ten patients (90%) tolerated a flow rate of 8 mg/kg/min or higher and five patients (50%) tolerated 12 mg/kg/min (7.2 mL/kg/h). This translated into a 3-fold decrease in mean (SD) infusion time throughout the study, from 173.4 (53.65) min for the first infusion to 58.5 (14.24) min during fourth infusion (Figure).

Conclusions: Privigen® was safe and well tolerated at flow rates of up to 12 mg/kg/min.

POSTER 96 - A CASE REPORT OF SEVERE CONGENITAL NEUTROPENIA, A NOVEL HAX1 MUTATION

AUTHORS

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Introduction: Severe congenital neutropenia is a disease which causes extreme susceptibility to recurrent infections. The patients have a low number of neutrophils that leads to having problems with inflicting proper inflammation. This disease is mostly diagnosed at birth and infancy or soon after that. It causes recurrent infections of sinuses and lungs and liver. Patients also have gingivitis and skin infections. In some cases it can cause osteopenia and osteoporosis which prone them to have multiple fractures due to brittle bones.
This disease can also cause neurologic problems such as seizures, abnormalities of the heart or the genitalia. Developmental delay has been reported too.

Case presentation: A 4 months old girl was referred to us with a history of 11 times hospitalization mainly due to chronic diarrhea, lymphadenopathy, chronic fever, bleeding tendency, oral ulcers and thrush. Delayed degree of maturation according bone age. The onset of her disease was with fever, neutropenia, chronic diarrhea and congenital kidney abnormality.
There was a consanguineous (second cousins) marriage, several unknown death in paternal side resulted from relative marriages.
Lab results was as followed:
WBC range (2800- 5000), Neutrophil % range (1-5), Lymphocyte % range (40-60), Monocyte % range (30-40), Hb rage (9.5-11), Plt range (250000-350000)
Immunoglobulin levels were as mentioned below:
IgG:845 mg/dl, IgA:304 mg/dl, IgM: 116 mg/dl
Flow cytometry also showed the following results:
CD5:19%, CD7:5%, CD10:1%, CD14:17%, CD13:29%, CD33:24%, CD34:11
She was under treatment with Ceftazidime and Vancomycin when referred to us. Due to neutropenia granulocyte colony-stimulating factor (GCSF) was started for the patient. After receiving GCSF the neutrophil count increased to 8% (410/ul). However the patient withdrew the treatment for six months which resulted in the declining of the neutrophil count to 1% (40/ul).
Genetic results identified the patient with homozygous unstart variant in HAX1 (LRG_64t1: c.2T> C; p.Met1?).

Discussion: HAX1 is the gene responsible for the mitochondrial protein HAX1, which is accounted for functions in signal transduction and cytoskeletal control. HAX1 is critically important for maintaining the inner mitochondrial membrane potential and protecting against apoptosis in myeloid cells. Researches suggest that HAX1 plays a very important role in neutrophil development. It is the main regulator of myeloid homeostasis and showed substantial function in genetic control of apoptosis.
This particular mutation of HAX1 observed in our patient was not described before and as it affects the start codon, a damaging effect is what we see in this patient.

POSTER 97 - EFFICACY AND SAFETY OF A NEW 16% SUBCUTANEOUS IMMUNOGLOBULIN PREPARATION IN A COHORT OF ADULT PRIMARY ANTIBODY DEFICIENCY PATIENTS

AUTHORS

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Objective: Immunoglobulin preparations, administered via the intravenous (IVIG) or the subcutaneous (SCIG) route, represent the mainstay of treatment of primary antibody deficiency (PAD). Due to the home self-administration and the lower rate of systemic adverse events, SCIG has increasingly gained interest among patients and physicians. Here we present the results of a retrospective/perspective study assessing efficacy and safety of a new 16% SCIG product (Kedrion S.p.A.) when administered in PAD adult patients who had been previously treated with intravenous immunoglobulin (IVIG).

Design and method: Eight PAD adult patients (6 females, 2 males) undergoing IVIG (5% or 10%) were shifted to 16% SCIG (Kedrion) with similar cumulative doses and at an interval of 10 days between the infusions. Demographic characteristics, laboratory data and IgG doses during the IVIG treatment, were retrospectively collected from medical charts. Tolerability information, infectious events and IgG pre-infusional levels were recorded, in a perspective way, before and 3, 6 and 12 months after the initiation of SCIG therapy.

Results: Mean age was 32.8±12 years, mean weight was 56.7±6.3 Kg. Although normalized IgG dose of SCIG (389±48 mg/Kg/4 weeks) was significantly lower (p = 0.03) compared to the previous intravenous treatment (434±70 mg/Kg/4 weeks), no significant difference was observed in IgG pre-infusional level depending on the administration route (Fig. 1 A-B). Interestingly, a trend towards higher IgG levels was observed during the subcutaneous treatment (904±211 mg/dl vs 800±235 mg/dl), despite the lower average administered dose (Fig. 2 and 3). No systemic adverse reaction was observed during the 12 months of subcutaneous treatment. No difference in the annualized bacterial infection rate was observed between the two treatment regimen (3±1.5 in IVIG versus 2.8±2.4 in SCIG; p = 0.98).

Conclusions: This is the first study assessing clinical effectiveness and tolerability of this 16% immunoglobulin preparation in a cohort of adult PAD patients. Although larger cohort studies are required to confirm these results, this preliminary data indicates that Kedrion 16% SCIG is a safe and effective option for PAD patients previously on intravenous treatment, without the need for dose adjustment.

POSTER 98 - PRIMARY IMMUNE DEFICIENCIES IN BOLIVIA: CASE SERIES

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Introduction: Primary immune deficiencies (PIDs) are a heterogeneous group of genetic disorders in development and maturation of the immune system. Even though the estimated incidence is around 1:10000 of newborns, PIDs are poorly known and usually under diagnosed. In Bolivia there's no published data about PIDs. We present for the first time a case series of pediatric patients with diagnose of PID in two main children hospitals from two important cities in Bolivia: Hospital del Niño "Manuel Ascencio Villarroel" in Cochabamba city and Hospital del Niño "Dr. Ovidio Aliaga Uria" in La Paz city.

Case presentation: We present a case series of 12 patients, including: 2 cases of X-linked agammaglobulinemia, 1 case of Isolated IgG subclass deficiency, 1 case of Common Variable Immune Deficiency, 3 cases of Severe Combined Immune Deficiency, 1 case of Chronic munocutaneous candidiasis, 2 cases of Di George Syndrome, 1 case of Wiskott-Aldrich syndrome, 1 case of Hyper-IgE syndrome. Four of them have been confirmed by molecular diagnosis thanks to Immunology Unit from Hospital de Niños "Juan P. Garrahan" in Buenos Aires-Argentina. Patients receiving intravenous immunoglobulin (IVIG) have lots of difficulties to get access to the treatment, and patients in need of hematopoietic stem cell transplant (HSCT) or gene therapy have the need to migrate to other countries.

Discussion: Even though we lack of published data regarding PID in Bolivia, it doesn't mean this group of diseases is not present in our country, but they are under diagnosed. We started to registry our cases in the last 2 years, and for the first time bolivian PID patients appear in LASID registry. In Bolivia we have a lot of difficulties to diagnose and treat PIDs since we don't have access in the public health system to diagnose tests, replacement therapy with IVIG or HSCT. The registry and publication of our cases is very important to demand for an adequate diagnose and treatment of PID patients in Bolivia.

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De Vries E. et al. Patient-centered screening for primary immune deficiencies, a multistage protocol designed for non-immunologists: 2011 update. Clinical Immunology 2012; 167: 108-119

POSTER 99 - PERIPHERAL IMMUNE CELL MARKERS IN CHILDREN WITH RECURRENT RESPIRATORY INFECTIONS IN THE ABSENCE OF PRIMARY IMMUNODEFICIENCY

AUTHORS

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Objective: Recurrent respiratory infections (RRIs) represent a high percentage of general infantile pathology under the conditions of an immune system with no apparent major defects. Because they may be associated with a modified cellular immune response, the aim of the study was to identify possible immunological changes with an impact on the RRIs pathogenesis by quantifying the T and B lymphocyte subpopulations.

Design and method: The casuistry comprises two groups of children (1-7 years), as follows: i) RRIs group (30) - children with minimum 6 episodes of respiratory infections/year; ii) control group (10) - clinically healthy children. Blood samples were taken for serum immunoglobulin (IgG, IgA, IgM) dosing by nephelometry and for lymphocyte immunophenotyping (LI) by flow cytometry (BD FACSCanto II). There were quantified different subpopulations: T-helper (CD4+) and T-suppressor/cytotoxic (CD8+), T-double negative cells (CD4-CD8-CD1d-), NKT cells (CD19+CD20+), NK cells (CD16/56+) and B-total cells (CD19+CD20+) with mature/naive B subpopulations (CD27-IgD+), B memory (CD27+) and plasmocytes CD38bright).

Results: Serum Ig values were normal in 70% of cases. The most important changes observed in T-lymphocytes were the decrease of T-CD8+ (p=0.009) percentages and the increase in T-CD4+/T-CD8+ ratio (p=0.002). Although the values obtained for NK cells in the RRIs group are higher (p=0.003) than controls, they fall within the normal range. 86% of cases had decreases in B lymphocytes with low mean values (p=4.5x10-5). Lymphocyte subclass B analysis revealed a decrease in mature/naive B lymphocytes and an increase in memory B lymphocytes (p=0.027). No statistically significant differences were observed between the test groups for the other cell subpopulations analyzed.

Conclusions: Investigation of cellular immunological parameters may complete clinical diagnosis, especially in cases where humoral parameters are within normal limits. Given that RRIs can cause developmental disorders, detection of the causes and prophylaxis of these infections are major elements for improving the living conditions of the affected infant population.
This work was carried out through the Nucleus Program, with the support of ANCSI, the projects PN19.29.01.01; PN19.29.02.03, Grant PN-III-P1-1.2-PCCDI-2017-0341/2018 and 7PFE/16.10.2018.

POSTER 100 - REPORT OF PRIMARY IMMUNODEFICIENCY DISORDERS FROM A TERTIARY CARE HOSPITAL IN SUB- HIMALAYAN REGION IN NORTH WEST INDIA

AUTHORS

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Objectives: To describe a cohort of children with Primary Immunodeficiency Disorders(PIDs) from a tertiary care resource-limited setting in North-West India

Method: Retrospective case review of all children suspected to have PID at Dr Rajendra Prasad Government Medical College,Tanda, India

Results: A total of 13 children (12 boys) with suspected PIDs were identified. Presence of PID was suspected on the basis of clinical features like recurrent infection(Table1). Median age of symptom onset was 2.7years(range: 1 month-5years). Definitive diagnosis could be arrived at in 9 cases. We diagnosed 4 cases of Leukocyte Adhesion Defect(LAD) in one year and 1 case each of X-linked Severe Combined Immunodeficiency(SCID), Chronic Granulomatous Disease(CGD), Common Variable Immunodeficiency disease(CVID), X-linked Agammaglobulinemia(XLA) and Hyper IgM Syndrome. Laboratory Investigation: Common investigation has been shown (Table 2). Specific investigation were done based on suspected disease: Btk protein expression was reduced in XLA. BAFF, CTLA and TACI mutations were performed in suspected CVID, but were not detected. CD18 expression, as assessed by flow cytometry was reduced in LAD patients and CD40 ligand expression was reduced in child with Hyper IgM syndrome who also had Lymphoid Interstitial pneumonia as revealed by Lung biopsy and HRCT thorax. DHR assay was consistent with CGD in one patient. All LAD patients were found to have mutation in ITGB2 gene:c.2077C>T;p.Arg693Ter. Interestingly all had a common mutation even though they were a product of non-consanguineous marriage and came from different parts of the state.At present, infants diagnosed with LAD and SCID have succumbed and others are on follow-up. Child with CGD has developed hypothyroidism and growth hormone deficiency with chronic kidney disease Stage1 which is unusual. Children with XLA, CVID, and Hyper IgM syndrome are on Cotrimoxazole prophylaxis and regular IVIG replacement therapy . Child with CGD is receiving Eltroxin and Itraconazole apart from Cotrimoxazole prophylaxis. XLA in addition has developed Subacute Sclerosing Panencephalitis and is on anti-epileptic drugs.

Conclusion: We suspected a total of 13 patients with PIDs with a male preponderance and most common manifestation was recurrent pneumonia. PIDs must be considered in differential diagnosis in children presenting with recurrent pneumonia and recurrent infection after ruling out HIV infection which mimics PIDs. All the 4 cases of LAD were easily diagnosed based on clinical examination and complete hemogram whereas four cases of suspected PIDs posed diagnostic challenge in a resource- limited setting. This is the first report of Pediatric PIDs from this part of India.

POSTER 101 - DEPRESSIVE MOOD DISORDERS IN RELATION TO T CELL ABNORMALITIES IN A COHORT OF COMMON VARIABLE IMMUNE DEFICIENCY PATIENTS

AUTHORS

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Objective: Depressive mood disorders belong to the leading causes of disability and high burden of disease worldwide. While our knowledge of the diverse clinical manifestations of Common Variable Immune Deficiency (CVID) increases, not much is known on the association between CVID and mental illness. Recently, it was shown in 304 CVID patients that 46% were at risk for anxiety and depressive mood disorders. It is hypothesized that mental illness results from the psychological burden of chronic illness. However, extending evidence supports that inborn immune defects, especially in the T lymphocyte compartment, could contribute to the development of mood disorders. This study investigated the prevalence of depressive disorders in patients with CVID. Additionally, we aimed to examine the frequency and nature of T cell aberrancies and to correlate depressive mood disorders to T cell subset aberrancies.

Design and Method: Patients with CVID from the department of clinical immunology were enrolled and screened for depressive symptoms using the Patient Health Questionnaire-9 (PHQ-9). When a patient scored 6 points or higher, structural diagnostic interview was performed using the Schedule for Affective Disorders and Schizophrenia (SADS) and the Hamilton Depression Rating Scale (HAMD). Blood samples were collected for B/T cell counts and material was stored for additional T cell subset analyses.

Results and conclusions: Forty patients were evaluated, 21 showed a PHQ-9 score of 6 or higher, suggesting a depressive mood disorder. Upon further examination, 10 patients had a depressive disorder (HAMD > 7 with depressed mood and/or anhedonia), including 5 patients with severe depression. Preliminary data reveal that out of 33 patients from whom current T cell counts were available, total T cells, CD4+ and CD8+ T cells were increased in 2 patients and decreased in 4 patients. Total T cells and CD8+ T cells were increased in 4 patients. Total T cells and CD4+ T cells were decreased in 2 patients. Four of 33 patients had both a depressive mood disorder and abnormal T cell counts (decreased in 1 patient and increased in 3 patients). Further analyses will be performed to evaluate whether potential abnormalities in regulatory T cell and/or helper T cell numbers are associated with depressive mood disorders in CVID. Altogether, current study confirms that depressive mood disorders are common in CVID patients. Further in depth studies are required to evaluate whether T cell abnormalities are associated with these depressive mood disorders. Mental health assessment should be considered in CVID patients.

POSTER 102 - PERSISTENT SEVERE CONGENITAL NEUTROPENIA: A NOVEL HETEROZYGOUS VARIANT IN ELANE

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Introduction: Severe congenital neutropenias are amongst rare haematological diseases which can be in charge of recurrent, often serious infections in first months of life. These are caused most commonly by autosomal dominant mutations in the ELANE, a gene encoding neutrophil elastase and autosomal recessive mutations in HAX1. Clinical manifestations, bone marrow aspiration and biopsy, blood neutrophil count, genetic and immunological tests are commonly used for the diagnosis. Subcutaneous G-CSF is administered on a daily basis as the treatment of choice which can lead into a considerable increase in blood neutrophil count. Also, haematopoietic stem cell transplantation is considered as an alternative treatment.

Case Report: This case report describes a girl born in 2006 with sustained severe congenital neutropenia with parental consanguinity but no familial history for similar symptoms or any death in infancy due to unknown/related diseases. When she referred, she was 8 years old with history of multiple episodes of pneumonia, recurrent non-malignant cervical lymphadenopathies and recurrent gingivitis. Also, hypocellular bone marrow was detected in the bone marrow examination. She was on filgrastim (G-CSF) and the absolute neutrophil counts (ANCs) after injection ranged from 1000-1500. A Whole Exam Sequencing was performed for the patient using Agilent V6+UTR library preparation and an Illumina Next-Seq 500 sequencing platform. Subsequently, Sanger sequencing was used to confirm the genetic variant in the patient and her family. For the patient, a de novo heterozygous frame-shift variant in ELANE was identified and the parents and sister were wildtype.

Discussion: Although frame-shift variants in the ELANE gene have been previously described that can lead to the autosomal dominant neutropenia explaining the phenotype in the patient, our tests demonstrate a novel frame-shift variant in this gene.

Conclusion: To our knowledge, the specific de novo frame-shift variant in ELANE found in our patient has never been previously reported. We reviewed and compared the clinical and genetic results of our patient in order to characterize this novel variant.

POSTER 103 - COST ANALYSIS OF IV AND SC IMMUNOGLOBULINS USED IN THE TREATMENT OF PRIMARY IMMUNODEFICIENCY DISEASES IN SPAIN

AUTHORS

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Objective: Patients with primary immunodeficiency diseases (PID) who require immunoglobulin (IG) replacement (IGRT) receive either intravenous IG (IVIG) or subcutaneous IG (SCIG), which provides equivalent efficacy. Using the Spanish National Health system and societal perspectives, this study developed a cost-minimization analysis to evaluate costs of SCIG versus IVIG.

Design and Methods: The base case modeled the annual cost per patient (weighted average of pediatric and adult patients) of IVIG and SCIG for the mean doses (established by clinical consensus) over a 1-year time horizon in terms of direct (drug and administration) and indirect (lost productivity for adults [45% assumed working] and parents of pediatric patients [64% assumed working]) costs. Adults (=>19 years) comprised 52.5% of the model population. IVIG was assumed to be administered in a day hospital, whereas SCIG was predominantly (95%) administered at home. Drug costs were calculated from ex-factory prices obtained from local databases minus the mandatory deduction. Costs were valued on 2018 euros.

Results: The annual modeled costs were €4,266 lower for patients with PID who received SCIG (total: €14,466) compared with those who received IVIG (total: €18,732). Annual modeled costs were lower for both adult (–€1,744) and pediatric (–€2,522) patients. The two largest contributors were differences in annual immunoglobulin costs and dosage (–€1,927) and annual hospital administration costs (–€2,688). However, SCIG incurred training costs for home administration (€695). Costs of premedication, dispensing, and indirect costs were also included in the model.

Conclusion: Our model suggests that SCIG may represent a cost-saving alternative to IVIG for patients with PID in Spain.

POSTER 104 - FACILITATED IMMUNOGLOBULIN ADMINISTRATION REGISTRY AND OUTCOMES STUDY: INTERIM RESULTS

AUTHORS

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Objective: HyQvia (facilitated subcutaneous immunoglobulin [fSCIG]) is a dual-vial unit of recombinant human hyaluronidase (rHuPH20) and 10% normal immunoglobulin (IgG) solution. In the registration study, fSCIG was effective, safe, and bioequivalent to intravenous IgG at the same administration intervals, with fewer systemic reactions. FIGARO will provide real-world data about fSCIG usage in routine administration.

Design and Methods: In this multicenter, prospective, observational study in Europe under the auspices of ESID (NCT03054181), patients are eligible for documentation if they receive treatment for primary or secondary immunodeficiency diseases and provide informed consent. Planned enrollment is 100 patients. The cutoff for this interim analysis was February 18, 2019.

Results: Patient characteristics (n=85) are shown in the Table. For most patients, average time between infusions was every 4 (68.3%) or every 3 (22.0%) weeks. Median dose of the last fSCIG infusion was 30 g (interquartile range: 20–35 g), median maximum infusion rate was 300 mL/hr, and thus, median volume infused was 300 mL; most patients used one application site (91.9%; most commonly abdomen) and an infusion pump (97.4%). The most recent fSCIG administration was most commonly given at home (80.5%), followed by doctor's office (12.2%) and hospital (7.3%) by self-administration (84.0%) or by nurse/physician (16.0%). Technical problems occurred twice. In all cases, the full planned dose of fSCIG was administered.

Conclusions: fSCIG offers the flexibility of infusions performed at home by the patient or in the hospital. Dosing schedule allows variability; however, most infusions are administered every 4 weeks into 1 site. The study is recruiting, and patient observation continues.

POSTER 105 - INFUSION PARAMETERS AND KEY CHARACTERISTICS BY AGE GROUP OF PATIENTS WITH PRIMARY IMMUNODEFICIENCY DISEASES INITIATED ON IG20GLY IN A PATIENT PROGRAM

AUTHORS

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Objective: HCUVP is a patient product-introduction program that provides Cuvitru® (immune globulin subcutaneous [human], 20% solution [Ig20Gly]) free of charge for the first 4 infusions to eligible patients with primary immunodeficiency diseases (PID). Using patient data from this ongoing program, our analysis described the clinical characteristics and infusion parameters of pediatric and adolescent patients who were initiated on Ig20Gly through HCUVP.

Design and method: HCUVP eligibility criteria were: patients aged =>2 years old, with a primary ICD-10-CM code verifying diagnosis of PID, and no current or prior use of Ig20Gly at program initiation. Data from patients who received the first Ig20Gly infusion between January 1, 2017, and September 1, 2017 were included. Data from patients receiving infusions after October 31, 2017 were censored. Descriptive statistics were calculated for patients' demographic and clinical characteristics and prescribed and actual infusion characteristics by age group (2–5, 6–11, 12–17, and =>18 years).

Results: In total, 817 patients who completed all 4 infusions were included in the analysis, of whom 97 were aged <18 years. Among those who previously received immunoglobulin (IG) therapy, a greater percentage of patients aged <18 years were treated with intravenous IG therapy (n=46; 73%) compared with adult patients (n=222; 62%) before initiating Ig20Gly. Nine patients aged <18 years were treatment naïve. The median (IQR) infusion volume per site was lower among patients aged <18 years (2–5 years: 20 [15–25] mL; 6–11 years: 29.2 [17.5–30] mL; and 12–17 years: 34.2 [26.3–40] mL) than among patients aged =>18 years (40 [30–50] mL). However, the median (IQR) infusion rate per site was similar between patients aged 6–17 years (6–11 years: 47 [47–60] mL/h; and 12–17 years: 47 [27.5–55] mL/h) and patients aged =>18 years (47 [42.5–50] mL/h), but higher for patients aged 2–5 years (60 [31–60] mL/h). In addition, by the final infusion, fewer patients aged <18 years were infused weekly (n=18 [19%] patients) compared with patients aged =>18 years (n=232 [32%] patients). Conversely, a greater percentage of patients aged <18 years were infused biweekly (n=35 [36%] patients) compared with patients =>18 years (n=168 [23%] patients).

Conclusion: The results provide insights into the clinical and infusion characteristics of pediatric and adolescent patients who have received Ig20Gly and clinical use of Ig20Gly outside of a controlled clinical trial setting.

POSTER 106 - IMMUNE GLOBULIN SUBCUTANEOUS (HUMAN) 20% SOLUTION TOLERABILITY AND INFUSION CHARACTERISTICS IN PEDIATRIC AND ADVANCED-AGE PATIENTS WITH PRIMARY IMMUNODEFICIENCY

AUTHORS

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Objective: Immune globulin subcutaneous (human) 20% solution (Ig20Gly/Cuvitru) was well tolerated in the phase 2/3 North American study in patients with primary immunodeficiency diseases (PID). Here, we analyze the tolerability and onboarding experience with Ig20Gly infused at high rates and volumes in pediatric and advanced-age patients (2–<16 y and >60 y).

Design and Methods: Patients aged >2 years with PID received weekly Ig20Gly infusions at volumes =<60 mL/site and rates =<60 mL/h/site for ~1.3 years in the North American study (NCT01218438). Adverse events (AEs), tolerability, and infusion parameters were assessed in pediatric (n = 21) and advanced-age patients (n = 14).

Results: Median maximum infusion rates and volumes/site were higher in advanced-age patients (60 mL/h/site; 47.5 mL/site) versus pediatric patients (30 mL/h/site; 26.75 mL/site). Five (23.8%) pediatric patients and 9 (64.3%) advanced-age patients used infusion rates =>60 mL/h/ site for =>2 infusions. Maximum infusion rates were not tried in the majority of pediatric patients given the smaller-dose volumes used in these patients. Percentages of infusions associated with causally related AEs were low among pediatric patients (all [2.8%], local [2.7%], systemic [0.4%]) and in advanced-age patients (all [1.3 %], local [0.4%], systemic [0.9%]); no causally related AEs were serious or severe in either age group. Larger infusion volumes and faster infusion rates were not associated with an increase in causally related local AEs in either age group.

Conclusions: Ig20Gly infused at relatively high rates and volumes was well tolerated in both pediatric and advanced-age patients with PID.

POSTER 107 - MEASLES VIRUS NEUTRALIZING ANTIBODIES IN IMMUNOGLOBULIN LOTS PRODUCED FROM PLASMA COLLECTED IN EUROPE OR THE UNITED STATES

AUTHORS

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Objective: Widespread vaccination against the measles virus (MV) has reduced disease incidence and led to a progressive decline of MV antibody (MVAb) levels in human plasma, thereby decreasing MVAb levels in individual lots of immunoglobulin (IG). Although IG lot release from the United States (US) requires a minimum MVAb titer, equivalent information is unavailable for other geographies. This analysis assessed regional differences in MVAb titers in IG preparations prepared from plasma collected from the US and European Union (EU).

Design and Methods: MVAb titers were determined in 1739 IG lots fractionated from US (n=1466) and EU (Austria, Germany, and the Czech Republic; n=273) plasma between 2013-2018. Plasma was collected by plasmapheresis (source plasma) or by whole blood donations (recovered plasma). Titers were determined as the reciprocal dilution resulting in 50% MV neutralization (NT50[1:X]) using a fully validated neutralization assay.

Results: Mean [±SEM] neutralizing MVAb titers were significantly higher in IG lots from the EU than from the US (1521 [33] vs 1373 [13]; P<0.0001). MVAb titers for IG fractionated from recovered plasma were significantly higher than titers from source plasma (2000 [29] vs 1245 [10]; P<0.0001); this difference was evident in IG from the US and the EU (Figure).

Conclusions: Neutralizing MVAb titer levels in IG lots from the EU are functionally similar but slightly higher than levels in IG lots from the US, supportive of equivalent protection against MV infection. Thus, dosage in the EU could be aligned with US Food and Drug Administration recommendations for IG use as postexposure MV prophylaxis.

POSTER 109 - A CASE REPORT OF GRISCELLI SYNDROME TYPE 2; MUTATION, PROGNOSIS AND TREATMENT

AUTHORS

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Introduction: Griscelli syndrome type 2 (GSII) is an autosomal recessive disease, which affects the immune system and pigmentation of hair and skin. This disease is a rare syndrome with three subtypes, among which the type 2 is more common and important to be diagnosed. The relationship between genetic alterations and the body immune function is of great importance in process of treatment of this disease. Differential diagnosis such as GSI, GSIII, and Chediak-Higashi syndrome (CHS), are substantial to be ruled out.

Case presentation: The patient was a six-year-old boy referred to the clinic with silvery-gray hair, history of G6PD deficiency and increased level of fibrinogen (403 mg/dl), cholesterol (159 mg/dl) and ESR (23 mm/hrs). Count of white blood cells (WBC) was 6400 /microliter including 45.8% neutrophils, 49.7% lymphocytes, 3.5% monocytes, 0.9% eosinophils and 0.1% basophils. Hemoglobin (Hgb) was 11.6 g/dl with mean corpuscular volume (MCV) of 84 fl. The level of IgE was 148. The patient had no history of hospital admission or recurrent infections. He was gave birth from a consanguineous marriage. The parents were cousins, free of clinical symptoms who had another healthy boy and history of an abortion.
Microscopic view of the hair shafts and peripheral blood smear (PBS) were analyzed. The PBS was normal. Hair shafts showed a large clumps of pigment, compatible with GS. Whole exome sequencing and direct Sanger sequencing were done to detect and confirm mutations. Mutation was reported in the gene RAB27 (NM_183236: exon3: c.T137G). Parent both had heterozygote mutation and the child had homozygous mutation. The patient undergone bone marrow transplantation (BMT).

Discussion: Signs and clinical manifestations play an important role in making the differential diagnosis of genetic diseases. Paraclinical tests then are essential to assess and confirm the possible diagnosis. In a patient with GS, symptoms such as hypopigmented skin and silvery-gray hair are key findings. Although other diseases such as CHS share these manifestations, PBS can help to differentiate these diseases. Despite CHS, polymorphonuclear WBCs are normal and no giant granuloma are present in GS. Findings in analyzing hair shaft is also helpful to make the diagnosis. Both tests were performed for the patient, which were compatible with GS. Genetic report with homozygous RAB27A mutation approved the GSII.
Patients with GSII survive about one to four years. However, allogeneic BMT is a therapeutic approach for these patients. For the presented patient, allogeneic transplantation was performed which was successful.

POSTER 110 - CUTANEOUS MANIFESTATIONS OF PRIMARY IMMUNODEFICIENCIES IN SENEGALESE CHILDREN: ABOUT 4 CASES

AUTHORS

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Objective: The aim was to contribute to the documentation of these affections in our regions, more specifically to describe clinical pattern especially cutaneous pattern, to describe the immunological profile and propose a treatement.

Design and method: Multicentric study from 2014 to date: children (from 0 to 15 years) with HIV(-), who present two or more signs of 10 warnings signs of PI; or children who present signs described on the ASID 10 recommendations for PI diagnosis were explored.

Results and conclusions: cutaneous manifestations represent the 3rd most frequent sign. We report 4 cases.

OBSERVATION 1
8-year-old girl received in dermatological consultation for flat whart. The personal history contained 3 hospitalizations for infections, one of which occurred during neonatal periods. There was second-degree parental consanguinity. The dermatological examination found flat wharts, with eczema like lesions and ptyriasis-versicolor like lesions (image 1, 2, 3). Cutaneous Biopsy confirmed the verruciform Epidermodysplasia.

OBSERVATION 2
16-month-old infant who present severe eczematous dermatitis at dermatological consultation. Family and personal history reveals 2 deaths in the sibship and repeated ENT infections. The dermatological examination finds hypochromic spots, as well as plates with hemorrhagic crusts. (image 4, 5). The biology and the genetic study allowed to hold the diagnosis of wiskott-aldrich syndrome.

OBSERVATION 3
9-month-old infant received in pediatric dermatology consultation for a swelling of the lower lip (image 7) evolving by thrusts and remissions, appeared since the 3rd day of life (image 6). Their was a absence of associated signs and no similar case in the family. The diagnosis of hereditary angioedema has been made; however the quantitative and functional rate of the C1 inhibitor, at the age of 13 months, in remission period returned normal.

Observation 4
The last case is a BCGitis revealing a combined primary immunodeficiency. Gadio is a 5 month infant, with 2nd degre of parental consanguinity, 5 death in the sibship.
She present BCGitis, with repeated thrush, and chronic diarrhea. Blood cell count shows Lymphopenia, and immunophénotyping reveal low CD3, CD4, CD8, CD16, CD59 but normal rate of CD19. She has been hospitalized in April 2019 at the age of 6 months for acute gastroenteritis and appearance of an axillary ganglion, at the bacteriology of ganglionic cyto-puncture fluid: presence of acid-fast bacillus. The diagnosis of ganglionic tuberculosis post BCGitis was retained (image 8, 9).She is currently under rifampicin, isoniasid,ethambutol treatement and sulfametoxazol-trimétroprim prophylaxis.
Diagnosis of PI can be facilited by recognition of specific skin disorders.

POSTER 111 - SAFETY AND TOLERABILITY DATA ON KEDRION 5% IVIG - A PHARMACOVIGILANCE DATABASE ANALYSIS

AUTHORS

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Objective: Intravenous immunoglobulins (IVIg) are used to treat a variety of immune disorders; the most relevant of them are primary and secondary immunodeficiency and several autoimmune diseases.
This work is aimed to describe tolerability and safety of Kedrion 5% IVIg in a real world setting, with a particular focus on potential serious complications. Although IVIg products have had a generally good safety record, laboratory assessments, case reports, and prior observational studies have suggested a potential causal link between IVIg products and an increased risk of thromboembolic adverse events (TEEs) with incidence rates reported in literature ranging from 0.5% to 17%. Other rare but potentially severe complications of high-dose IVIG therapy are haemolysis, which can result in severe haemolytic anemia, and the development of acute renal failure or renal insufficiency associated with the sugars present in immunoglobulin preparations. Aseptic meningitis has been reported too.

Methods: The source data on Kedrion 5% IVIg refer to the period January 2001 - December 2018, and are retrieved from the Kedrion Pharmacovigilance Database (ARGUS Oracle Health Science, Redwood Shore, CA US). Due to the use of different posologies depending on the pathology for which Kedrion 5% IVIg is administered, only a rough estimation of the total number of doses distributed in the reference period can be made. Nevertheless, an estimate of patient exposure can be calculated starting from worldwide product distribution volume in grams of active substance, assuming an average dosage of 0,4 grams/Kg of Kedrion 5% IVIg and an average patient body weight of 70 kg.

Results: Out of 2,151,781 estimated doses distributed worldwide, a total of 1,067 ADRs were received by Kedrion (a reporting rate of 4.96 ADRs/10,000 infusions) of which 49% (515/1,067) non-serious and 51% (549/1,067) serious. The most frequent ADRs (out of 1,067) were: headache (n=95), pyrexia (n=76), vomiting (n=54), chills (n=44), nausea (n=38), dyspnoea (n=31), erythema (n=29), urticaria (n=29) and rash (n=23).
With regards to the rare but potentially severe complications, the ADRs are reported in Table 1.

Conclusions: Based on spontaneous and literature reporting safety rate the benefit-risk balance of Kedrion 5% IVIG is to be considered favourable.

POSTER 112 - MARSHALL SYNDROME AS A MULTIDISCIPLINARY PROBLEM OF CHILDHOOD

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Introduction: Marshall Syndrome was first described in 1987 by a group of scientists together with G.S. Marshall. The true prevalence of this disease in the pediatric population is unknown for two reasons: there is no statistical reporting and low awareness of the first-contact physicians about the clinical manifestations of this nosology.

Objective: the analysis of knowledge level about Marshall syndrome among medical interns and medical specialists.

Materials and methods: We have compiled a questionnaire containing five questions about Marshall Syndrome (MS), its correct diagnosis and basics of treatment. It was proposed to choose one correct answer among the five options. 34 tertiary specialists in the provision of medical care (8 were pediatricians, 6 - dentists, 8 - otolaryngologist, 6 - neurologists, 2 - nephrologists, 2 - hematologists, 2 - pulmonologists) and 26 interns (pediatrics - 10 and family medicine - 16) were interviewed anonymously.

Results: Only 14 (41.2%) of specialist doctors identified MS by the symptoms. The results obtained from the interns of family medicine were close to these results: 5 (31.2%). All pediatric interns have recognized the MS.
Among the priority examinations, the immunogram and complete blood count were most often prescribed by 12 (35.3%) of the respondents. 8 (23.5%) wanted to get the result of bacteriological seeding from the mucous membrane of the oropharynx. 70.5% (24) of specialists consider it necessary to refer a patient to immunologist, in 6 (17.6%) cases - to infectious diseases specialist and in 4 (11.8%) - to otolaryngologist.
Medical interns in only 2 (7.7%) questionnaires were defined with a consultant, an immunologist. Among the proposed drugs, the prescription of prednisolone was considered by 8 interviewed doctors with experience, and the same number choose ibuprofen or interferon as a treatment.
Among the proposed preventive measures in the recommendations of experienced doctors, the rehabilitation of chronic foci of infection (18) and immune correction (10) prevailed and only 4 suggested extended immunization (calendar + recommended vaccinations by the immunologist). The answers of the interns were correct only in 7 questionnaires (26.9%).

Conclusion: The survey revealed a lack of knowledge of the diagnostic criteria for Marshall syndrome among medical specialists. Therefore, the program of continuing education should include training in the basic position of the diagnosis of autoimmune diseases and familiarization with the observation algorithm in the outpatient practice of a doctor, regardless of his specialization.

POSTER 113 - PHENOTYPIC HETEROGENEITY IN THREE PATIENTS WITH NF-<KAPPA>B1 DEFICIENCY

AUTHORS

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Objective: To compare the clinical and immunological phenotype of three patients with different mutations in NFκB1 gene.

Design and Methods: Nuclear factor kappa-light-chain-enhancer of activated B cell 1 (NF-κB1) is a key factor in both canonical and non-canonical NF-κB signaling. This pathway participates both acquired and innate responses. The NFκB1 loss-of-function mutations have initially been associated with common variable immunodeficiency (CVID). Of contrast, we have observed an expansion of the clinical phenotype in patients with this condition.
Circulating T, B, dendritic cells (DCs), mucosal- associated invariant T (MAIT) cells and follicular helper T cells (cTFH) subsets were quantified. Molecular characterization by next generation sequencing (NGS) was also performed.

Results: We report three patients carrying different NFκB1 loss-of-function mutations which resulted in haploinsufficiency of the NF-κB1 subunit p50. Sequencing of genomic DNA identified two nonsense mutations, c.1597 C>T (p.Q533X) and c.250C>T (p.Q84X) in Patient 1 (P1) and Patient 2 (P2), respectively. Patient 3 (P3) showed a synonymous mutation, c.705G>A (p.V235V) which finally resulted in exon 8 skipping. In P1 and P2 the onset of the first manifestation of the disease was at the age of 42 and 3 years, respectively. In P3 the age of onset was 5 years with features of combined immunodeficiency and disseminated Mycobacterium genavense infection. All patients showed a low proportion of switched memory B-cells. Decreased naive and increased effector phenotype in T cell subsets were observed in P1 and P3 while P2 showed a normal proportion of T cell subsets. Of contrast, cTFH subset was severely decreased in P3 with a Th1-skewed profile like P1 and P2 which presented normal proportion of cTFH. DCs were absent in P3 and normal in P1 and P2. MAIT cells were absent in all patients.

Conclusion: NF-κB1 could be critical for development of acquired and innate immunity as described for cTfh, DC and/or MAIT cells.

POSTER 114 - A PHASED PROGRAM FOR THE INITIATION OF SCREENING FOR PRIMARY IMMUNE DEFICIENCIES IN SURINAME

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Objective: Primary immune deficiencies (PID) comprise a diverse clinical spectrum of diseases and, although rare, taken together can be present in up 1 in 1200 live births. Both diagnostic tests and treatment for PID are costly and therefore not optimal available in most LMIC countries such as Suriname, situated at the North coast of South America. Local awareness, knowledge and vigilance of PID are the first tools in the assessment of disease and may pave the way for efficient diagnostic and treatment plans on a national and regional level. Establishing a screening program of PID in Suriname will be a first step to identify patients and offer them appropriate therapy accordingly.

Design: Two year phased strategic approach designed to establish the prevalence of PID in Suriname and to improve diagnostics and treatment modalities with the help of identified national and international partners.

Methods:

Phase 1: Improve awareness and referral

- National symposium on “Frequent Infections” with lectures from experts in the field of pediatrics, pulmonology, ENT, dermatology, infectious diseases, clinical genetics, clinical immunology and patient experiences
- Develop and distribute e-flyers on warning signs of possible PID and stimulate early referral

Phase 2: Clinical screening

- Second line (ENT, pulmonology, dermatology, pediatrics and internal medicine) and final third line screening (pediatrics, infectious diseases, clinical genetics and clinical immunology)

Phase 3: Perform diagnostic tests

- Strife for strengthened, efficient and achievable national laboratory analysis
- Collaboration with PID referral center for ancillary laboratory analysis (including flow cytometry and genetic analysis)

Phase 4: Treatment assessment

- Prophylaxis overview
- Immunoglobulin substitution assessment
- Collaboration with PID referral center, partners and support groups i.e. Hemophilia support groups

Phase 5: Epilogue - Achievable goals for Suriname

- Overview of prevalence of PID
- Improved and cost-effective overview of diagnostic options for PID
- Improved and cost-effective overview of treatment options for PID
- Evaluation for newborn screening
- Improved collaboration which will benefit medical specialist and patients

Conclusions: Establish a solid foundation for the future for PID in Suriname through a one-time, yet timely, assessment. In the end be able to offer a helping hand.

POSTER 115 - COMPARISON OF CLINICAL AND IMMUNOLOGICAL FEATURES AND MORTALITY IN COMMON VARIABLE IMMUNODEFICIENCY AND AGAMMAGLOBULINEMIA PATIENTS FOR PATIENTS MANAGEMENT

AUTHORS

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Objective: Common Variable Immunodeficiency (CVID) and agammaglobulinemia are two of the main types of symptomatic primary antibody deficiencies. The pathogenic origins of these two diseases are different; agammaglobulinemia is a group of inherited disorders that usually are caused by mutations in the gene encoding Bruton Tyrosine Kinase (BTK) protein while CVID is a heterogeneous disorder mainly without monogenic cause. However, both diseases share a characteristic of frequent bacterial infections, a decline in serum immunoglobulin levels, and abnormality in antibody responses.

Design and method: The demographics and immunologic parameters, clinical manifestation, and mortality statistics from 297 patients with CVID and agammaglobulinemia followed up over 2 decades in the Children's Medical Center of Iran.

Results and conclusions: Age at onset of symptom in agammaglobulinemia was earlier than CVID but the course of disease in CVID patients was longer than agammaglobulinemia patients. Pulmonary infections were the most prevalent clinical manifestations in both groups of patients. Lymphadenopathy, hepatomegaly, and splenomegaly were significantly higher in CVID patients than agammaglobulinemia patients and there was a significant association between these complications and mortality in CVID patients. Among 297 patients, 128 patients (88 CVID and 40 agammaglobulinemia) deceased. The predominant causes of death in CVID patients were infections, chronic lung disease, and malignancy while in agammaglobulinemia patients were infections and respiratory failure.
Infections, especially respiratory infections were the most common complication and cause of death in both CVID and agammaglobulinemia groups and recent treatment advances even Immunoglobulin replacement cannot completely control these complications. Thus prompt recognition and specific management of these complications are worthwhile.

POSTER 116 - DOCTORS' AWARENESS OF PRIMARY IMMUNODEFICIENCIES AT A REFERRAL CENTER, LIMA - PERU

AUTHORS

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Objective: To assess the awareness of Primary immunodeficiencies (PID) of health care professionals working at a reference center for paediatric diseases.

Design and Method: Cross-sectional study at the Instituto Nacional de Salud del Niño (INSN). We included all physicians, fellows and specialists. that worked at the INSN during 2017-2019. Physicians that worked at the Allergy, Asthma and Immunology's National Referral Center (CERNAAI) and those who worked on a surgical specialty were excluded. Convenience sampling was performed.

We developed an ad hoc instrument that included sociodemographic characteristics and questions regarding their education on PID, general knowledge and diagnostic suspicion of PID and how they act on suspicion of a PID. Absolute and relative frequencies were used to describe categorical variables while central tendency and dispersion measures were used for quantitative variables. The analyses were performed using a level of significance of 5%, with the software Stata v14. This study was approved by the Institutional Committee on Research Ethics of the INSN.

Results: 86 physicians were included. Median age was of 33 years (IR: 29 - 50) and most of them were women (71.1%). 51.8% were currently in the residency program.
Regarding the education of PID during their undergraduate studies, 43.1% referred they had taken courses about PID. Within the residency program, 60.3% had attended dissertations about PID. While after the residency program for those who were already specialists, 50.0% referred they had taken courses about PID, 53.1% had attended dissertations about PID, and only 3.1% had performed a fellowship in a specialized center. Concerning to the most important barrier to diagnose a child with a PID, physicians considered the lack laboratory tests as the main reason (57.7%). Related to general knowledge related to PID, half of the physicians (51.2%) considered that treatment existed for only some of the PID, and most of them (43.2%) considered that some PID were severe diseases. 44.2% referred that they knew the Jeffrey Modell Foundation's 10 warnings signs. Finally, 95.3% evaluated patients who had recurrent infections, but only 61.6% discarded PID.

Conclusions: It is still necessary to improve educational efforts for increasing PID awareness, which may lead to earlier diagnosis and less morbidity and mortality.

POSTER 117 - CHRONIC MUCOCUTANEOUS CANDIDIASIS COMPLICATED BY ENDOFTALMITE - CASE REPORT

AUTHORS

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Chronic Mucocutaneous Candidiasis (CMC) is a primary immunodeficiency characterized by recurrent or persistent infections affecting nails, skin, and oral and genital mucosa caused by Candida spp., mainly C. albicans.
CMC is one of the infectious phenotypes in patients with inherited or acquired T cell deficiency. Autosomal dominant, involving a mutation in STAT1 gene or autosomal recessive, when it involves AIRE gene mutation.
Mutations can also occur in genes encoding proteins involved in the innate immune response to fungi, such as PTPN22, Dectin-1 and CARD9 (protein 9 containing a caspase-associated recruitment domain). CARD9 is an important adapter molecule in the production of IL- 17 and protection against fungal invasion.
This report describes a patient diagnosed with chronic mucocutaneous candidiasis with a mutation in CARD9 that evolved with visual impairment - endophthalmitis, an uncommon presentation.
Female patient, 32 years old, white, with history of scintillating scotoma in right vision. With suspected toxoplasmosis, she was treated with acyclovir and sulfamethoxazole-trimethoprim. After 3 days of treatment, the condition evolved with worsening of visual acuity and blindness. She was, then, referred to ophthalmology evaluation at the State University of Campinas (UNICAMP) hospital, where the presence of candidiasis was identified through culture of secretion and ocular scaling.
She was hospitalizated at UNICAMP Hospital, assisted by Ophthalmology service. Received fluconazole, 450mg per day, during a month, associated with anphotericin B and three intraocular anphotericin B punctions. After five days, still injured, a surgery was performed with scrapping and intraocular punction of silicon oil. She unfortunatelly became blind of the right vision.
This patient is beeing followed now at the clinical immunology discipline, UNICAMP, CARD9 mutation was confirm by a CMC genetic panel.
We recommend molecular diagnosis, when possible, of suspected cases of chronic mucocutaneous candidiasis due to possible association with endocrinopathies, other autoimmune diseases, other recurrent infections, and complications, even rares, as in the case described, endophthalmitis.

POSTER 118 - PHARMACOKINETIC ANALYSIS OF 3-WEEKLY OR 4-WEEKLY INFUSIONS OF IGPRO10 IN JAPANESE PATIENTS WITH PRIMARY IMMUNODEFICIENCY

AUTHORS

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Objective: Immunoglobulin G (IgG) replacement therapy is the first-line treatment for patients with primary immunodeficiency (PID). IgPro10 (Privigen®, CSL Behring, King of Prussia, PA, USA) is a 10% liquid with proline stabilization administered intravenously (IVIG). The pharmacokinetic (PK) properties of IgPro10 are well-established in non-Japanese patients with PID. This study evaluated IgPro10 PK parameters following 3- or 4-weekly administration in Japanese patients with PID.

Design/methods: This study was a prospective Phase 3, open-label, single-arm study of IgPro10 in Japanese patients with PID. IgPro10 doses of 138–556 mg/kg body weight (selected as per the patient's last steady-state dose recorded for the previous IVIG product) were administered at 3- or 4-weekly intervals for up to 4 months. Serum samples for PK analysis were collected during the last IgPro10 dosing cycle (starting at Week 13). Sampling time points in the 3-weekly dosing regimen included -60 min and -1 min prior to infusion and 3–20 min, 24±2 h and 3±1, 7±1, 10±1, 14±1 and 21±1 days post infusion. For the 4-weekly dosing regimen, sampling points included an additional time point of 28±2 days post infusion. PK analysis included all patients who received at least one or a partial dose of IgPro10 and had at least one post dose blood sample. PK parameters including area under the concentration-time curve from time point zero to the last quantifiable time point (AUC0–last), dose-adjusted AUC0–last (dAUC), lowest and highest observed immunoglobulin G levels (Cmin, Cmax), time to reach Cmax (Tmax), and total clearance (CL) were analyzed for both dosing regimens.

Results: Ten patients were included in this analysis (3-weekly/4-weekly: n=2/n=8); median (range) age of 30 (9–67) years, 1:4 female:male ratio. Most patients were diagnosed with common variable immunodeficiency or congenital agammaglobulinemia. All PK parameters were similar between dosing regimens, although the small number of patients in the 3-weekly regimen limits interpretation. Cmax was observed approximately 1 h after the start infusion in both groups. Mean (SD [not applicable for 3-weekly infusion parameters]) PK parameters were: Cmax, 16.60 and 14.20 (5.53) g/L; Cmin, 10.60 and 8.53 (3.89) g/L; AUC0–last, 5971 and 6591 (2633) g*h/L; dAUC, 0.41 and 0.46 (0.19) g*h/L/mg; CL, 2.53 and 2.53 (0.99) mL/h; and median Tmax was 1.19 and 1.14 h, for 3-weekly/4-weekly dosing regimens, respectively.

Conclusions: There were no noticeable differences in PK parameters of IgPro10 in Japanese patients between 3-/4-weekly dosing regimens, which might offer improved flexibility of IVIG IgPro10 administration.

POSTER 119 - LEUKOCYTE ADHESION DEFICIENCY DIAGNOSED ON THE BASIS OF CLINICAL FEATURES AND COMPLETE HEMOGRAM FROM A RESOURCE LIMITED SETTING IN SUB-HIMALAYAN REGION OF NORTH-WEST INDIATITLE:LEUKOCYTE ADHESI

AUTHORS

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Objective: To describe infants with Leukocyte Adhesion Deficiency(LAD) from a resource limited tertiary care center in North West India.

Method: Retrospective case review of all infants diagnosed as LAD from January-December 2018 at Dr. Rajendra Prasad Government Medical College was done. Presumptive diagnosis was based on clinical features and complete hemogram report.

Results:

CASE 1: I month girl, delivered at term, presented with swelling and redness around umbilicus and around umbilicus with no discharge.(fig1a ,1b)

CASE 2: 1 month old boy, born to primigravida presented with history of vesicles around neck from 1 week of life followed by formation of necrotising black patch over neck and redness around umbilicus. Delayed shedding of cord was present(fig1c)

Case 3: 3 month old, well thriving boy presented with history of fever for 10 days and multiple vesicular eruptions 15 days back which healed leaving black coloured lesions .History of delayed cord fall present. On examination eschar was present on forehead and fluid filled vesicles present in groin. Periumbilical redness with mucoid discharge was also present (fig 1d)

CASE 4:5 month old girl, third in birth order presented with fluid filled vesicles over legs and face for 5 days followed by development of non-healing ulcer. Delayed shedding of cord was present.

All the four cases were born at term having normal birthweight with no postnatal complication. In all 4 cases, systemic examination was unremarkable and complete hemogram revealed neutrophilic leucocytosis. Flow cytometry for CD18 was performed and was markedly reduced in all(Table). All patients were found to have mutation in ITGB2 gene: c.2077C>T,pArg693Ter. Interestingly all had common mutation, even though they were born of non-consanguineous marriage and came from different parts of the state. Acute infections were managed in all patients. Though not available in our setting, Hematopoietic Stem Cell transplant(HSCT) was planned and discussed with the family. However none of them could undergo HSCT as all cases succumbed within a year .

Conclusion: LAD may not be unusual in the Sub-Himalayan part of North India. We were able to diagnose 4 cases within a short period of 1 year, based on history of delayed cord fall with examination suggestive of omphalitis, necrotising fasciitis and investigations revealing neutrophilic leucocytosis. Hence it can be concluded that it is not always difficult to diagnose Primary Immunodeficiency Disorders like LAD based on history and basic investigation like complete Hemogram in a resource-limited setting.

POSTER 120 - COMBINED IMMUNODEFICIENCY DISORDER DUE TO ZAP-70 DEFICIENCY: REPORT ON TWO CASES.

AUTHORS

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Background: ZAP-70 is a rare autosomal recessive form of combined immunodeficiency caused due to mutations in CD3-ZAP70 gene and leads to the defect in T-cell activation. The zeta chain-associated protein kinase (ZAP-70) is of 70 kD. It is involved in T cell receptor (TCR) signaling and is critical for T cell differentiation as well as function.

Methods: Patients were evaluated for lymphocyte subsets analysis (LSSA), double negative T cells (DNTs), memory and naïve T cell analysis, serum immunoglobulin levels, T cell proliferation assay and T cell receptor excision circle (TREC) followed by molecular confirmation of ZAP-70 gene by Sanger sequencing.

Results: A complete blood count revealed a high total leukocyte count (TLC) with elevated absolute lymphocyte count (ALC) and serum immunoglobulin levels was normal. Of the two patients, only one patient showed characteristic results of LSSA i.e normal total T, B, NK cells with elevated CD4 count with significant CD8 lymphopenia whereas other had normal CD8 count with low naïve CD8. In vitro, T-cell proliferation induced by phytohemagglutinin, CD3 and CD28 antibody was impaired in both the patients as compared to control. TREC copy numbers were found to be borderline low as compared to the age matched control. Molecular analysis of ZAP-70 gene revealed novel homozygous mutation at c.183 T>A in one patient and other patient revealed reported homozygous mutation at c.847 C>T ZAP70 gene.

Conclusion: ZAP-70 deficient patients present with recurrent infections like severe combined immunodeficiency (SCID) during infancy or at an early age. However, in contrast to SCID patient; these patients have normal TLC and ALC. Thus, characteristic laboratory findings of these patients like LSSA reveals significant low CD8+ T cells with normal CD3+ and CD4+ T-cell counts, abnormal lymphocyte function and low TREC values provide clue for ZAP-70 however molecular analysis is needed for confirm diagnosis

POSTER 121 - DIAGNOSIS OF CONGENITAL NEUTROPENIA

AUTHORS

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Congenital neutropenia is a family of genetic diseases associated with three main features: low neutrophil count and susceptibility to infection, various organ dysfunctions, and an extraordinarily high risk of leukemic transformation. Neutropenia is divided into three degrees of severity based on the absolute neutrophil counts (ANC), mild when ANC level is between 1000-1500 /UL, moderate between 500-1000/UL and severe when below 500/UL.
When neutropenia is detected, an attempt should be made to establish the etiology, distinguishing between acquired forms and congenital forms that may either be isolated or part of a complex genetic disease.
The interview and physical examination may reveal a particular etiology, such as a viral infection or malignant hemopathy, an iatrogenic cause, or an immune deficiency, warranting further specific investigations. The permanent or intermittent nature of the neutropenia should be established by monitoring the ANC during period of a few weeks, in which the number of infections and any changes in buccal disorders should be noted, as they can help guide patient management. Bone marrow examination is often necessary to rule out malignant hemopathies, determine cellularity, assess myeloid maturation and detect signs of a precise etiology. Several other investigations are of interest, especially anti-neutrophil antibody assay, immunoglobulin assay, lymphocyte immunophenotyping and pancreatic markers.
The therapeutic possibilities depend on the nosological setting and the occurrence or not of infectious complications. Granulocyte growth factors, in particular G-CSF, are the main therapeutic weapon, posing the problem of their long-term safety.

POSTER 122 - HYPER IGE SYNDROME ASSOCIATED WITH NOVEL DOCK8 HETEROZYGOUS MUTATION

AUTHORS

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Objective: Dedicator of cytokinesis 8 (DOCK8) deficiency is an autosomal recessive, combined immunodeficiency within the spectrum of hyper-IgE syndromes. Previous reports demonstrate compound heterozygosity and heterozygosity defects within the DOCK8 gene, as well as that different mutation in the DOCK8 gene, can lead to variable severity of the disease.

Design and method: Genetic sequencing evaluation of DOCK8 was performed by INVITAE

Results: The patient presented with severe atopic dermatitis from birth, allergic rhinitis and bronchial asthma was developed during the 2-nd year of life. Also, the patient suffered from recurrent otitis and lymphadenopathy of the inguinal lymph nodes. Family history was not burdened. From 3,5 years, joint pain, limitation of physical activity and morning stiffness was noted. The immune evaluation showed normal lymphocytes subpopulation and increased serum IgE - 32,131 kU/L. Genetic sequencing revealed a heterozygous defect c.5266A>T (p.Ile1756Phe)a variant of uncertain significance in the DOCK8 gene.
Therapy with omalizumab (150 mg / 1 time in 2 weeks) was started. The first efficacy evaluation (after 4 injections) revealed the improved general condition of the child as well as amelioration of skin manifestations. The inguinal lymph nodes were decreased in the size, exacerbation of bronchial asthma and allergic rhinitis did not observe.
Second assessment of effectiveness (after 12 injections) revealed residual lesions of the skin of the lower extremities. No exacerbation of bronchial asthma (without therapy for 3 months) and allergic rhinitis (without baseline therapy 4 months) were noted.

Conclusions: The c.5266A>T variant is a previously unreported mutation that is likely responsible for the findings in this patient. Our data and therapeutical approach may be clinically useful in the diagnosis and treatment of severe atopic dermatitis that does not fit the established criteria for previously reported hyper-IgE syndromes.

POSTER 123 - NOVEL COMPOUND HETEROZYGOUS MUTATIONS IN IL-7 RECEPTOR ALPHA GENE IN A 15 MONTHS OLD GIRL PRESENTING WITH THROMBOCYTOPENIA AND NORMAL T CELL COUNT

AUTHORS

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Patients with severe combined immunodeficiency (SCID) exhibit T lymphopenia and profound impairments in cellular and humoral immunity. IL-7 receptor alpha (IL-7Ra) deficiency is a rare form of SCID usually presenting in the first months of life with severe and opportunistic infections, failure to thrive and high risk of mortality unless treated. Here, we report an atypical and delayed onset of IL7Ra-SCID in a 15-months old girl presenting with isolated thrombocytopenia. She had a previous history of EBV infection without seroconversion and thrombocytopenia successfully treated with IVIG. At the admission she performed a chest TC revealing multiple bilateral nodules and diffuse ground glass opacity. High level of EBV replication was detected on peripheral blood and on bronchoalveolar lavage (BAL).
Immunological investigations revealed a normal count of total lymphocytes, low CD4+ with absent naïve T cells, reduction of T cell proliferation to OKT-3 and marked polyclonal hypergammaglobulinemia. Abnormal distribution of T lymphocyte subsets and evidence of a high proportion of cells expressing maternal HLA antigens on both peripheral blood and skin biopsy suggested a diagnosis of SCID with maternal T-cell engraftment. Targeted NGS, (Ion Torrent), revealed two novel compound heterozygous mutations in IL-7Ra gene: c.160T>C (p.S54P) and c.245G>T (p.C82F) predicted damaging and confirmed by Sanger sequencing. The IL-7Ra expression was reduced in total CD3+ T cells with a bimodal pattern and markedly reduced in CD3+CD4- T cells. In line with these results, STAT5 phosphorylation in response to IL-7 stimulation was reduced in total CD3+ and almost absent on CD3+CD4- T lymphocytes compared to her parents. The patient successfully received four courses of Rituximab and iv corticosteroids with a full recovery in lung parenchima and skin and control of EBV replication.
Regular intravenous immunoglobulin and prophylactic antimicrobial therapy were administered from the time of the diagnosis. The patient was listed for bone marrow transplantation and she has just concluded the pre transplantation workup. The atypical onset and the unusual immunological phenotype expressed by our patient highlights the diagnostic challenge in the field of primary immunodeficiencies (PID) and in particular in SCID patients where prompt diagnosis and therapy greatly affects the survival.

POSTER 124 - IMPACT OF IMMUNOGLOBULIN REPLACEMENT THERAPY SUPPLY INTERRUPTION: A SINGLE CENTRE PERSPECTIVE

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Objective: The interruption to the international and national supply of immunoglobulin replacement products necessitated a change in prescribing and administration practices. We aimed to evaluate the impact of these supply issues on patient and nursing staff experience.

Design: Patients and Nursing Staff perspectives were recorded regarding the impact of the Immunoglobulin supply shortages

Method: Patients and nurses at the Royal Free Hospital NHS Trust (RFH) Immunodeficiency Unit in London, UK were surveyed regarding their perspectives on the effects of treatment modifications arising from product supply issues. Responses were collated and analysed.

Results: Several issues were identified to have arisen as a direct impact of national and international shortages of immunoglobulin products. This included an increased number of hospital outpatient encounters to attend for test doses of new products. In some cases patients had to attend again due to adverse reactions causing more uncertainty. This resulted in an increased financial burden to the patient due to time off work and additional travel costs. Some patients had an increased length of stay in the infusion unit, as it was necessary to use a more dilute product. Patients reported concerns and anxiety regarding their current and future treatment. From the nursing staff perspective, for a period of time, the shortage affected the teams' ability to offer some treatment options. There was a marked increase in workload arising from managing associated changes, and queries from patients infusing at RFH, home and satellite infusion centres as well as home care providers.

Conclusion: The national and international shortage of immunoglobulin replacement therapy products had a significant impact upon patient experience, and delivery of nursing care in an immunodeficiency centre.

POSTER 125 - OSTEOMYELITIS A DREADED COMPLICATION OF CHRONIC GRANULOMATOUS DISEASE: EXPERIENCE FROM A TERTIARY CARE CENTER IN NORTH-WEST INDIA

AUTHORS

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Introduction and Objective: Chronic granulomatous disease (CGD) is an inherited phagocytic defect associated with inability to clear catalase positive organisms. Infections in patients with CGD are severe and recalcitrant. Commonest infections are pulmonary followed by soft tissue infections and suppurative lymphadenitis. Osteomyelitis is an uncommon infection in patients with CGD. It poses several diagnostic and therapeutic dilemmas. We herein report our experience of osteomyelitis in CGD over the last 10 years.

Design and methods: Review of records was carried out to describe the profile of osteomyelitis in a cohort of patients with CGD at Pediatric Immunodeficiency Clinic, Advanced Pediatrics Centre, Postgraduate Institute of Medical Education and Research, Chandigarh, India. The diagnosis of CGD was based on Nitroblue tetrazolium dye reduction test (NBT) and Dihydrorhodamine reduction (DHR) assay.

Results: Of the 69 patients with CGD in our cohort, 7 (10%) had osteomyelitis (5 males and 2 females; age range 1- 10 years). Most patients had their first episode of serious infection in early childhood (mean age: 1.5 years). Stimulation index (SI) of DHR assay ranged from 1 to 4.58. Mutational analysis was done in 4/7 patients (2 X-linked; 2 autosomal recessive). Site of involvement was variable: lower extremities (tibia)- 2; ribs- 2; vertebrae- 1; radius- 1; skull- 1. All patients had concurrent pneumonia when they had osteomyelitis except one patient who had skull osteomyelitis. Aspergillus fumigatus was isolated from 4 patients (57%; 4/7); Aspergillus nidulans, Aspergillus terreus and Serratia spp. was isolated in 1 patient each. Antifungals (intravenous amphotericin B and voriconazole) were given for a duration of 4-6 weeks and were followed by oral voriconazole in therapeutic doses for 3 to 6 months. Debridement and resection of ribs was required in 1 patient, while other patients were managed conservatively. Two of the seven patients succumbed to their illness.

Conclusion: Osteomyelitis in the context of CGD is a difficult infection to treat and requires debridement in addition to a prolonged course of antimicrobials. Long term prognosis remains guarded.

POSTER 126 - INTERPRETING NOVEL VARIANTS ON NEXT GENERATION SEQUENCING IN PRIMARY IMMUNODEFICIENCY DISORDERS: OUR TRIALS AND TRIBULATIONS AT CHANDIGARH, NORTH INDIA

AUTHORS

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Introduction: More than 400 genetic defects have been recognized to result in Primary Immunodeficiency Disorders (PIDs). This number, however, continues to increase. Next Generation Sequencing (NGS)is a powerful new technology to rapidly screen for multiple genes. This has revolutionised the diagnosis of PIDs. However, reporting a novel variant is still contentious. With advancement in our understanding of the human genome, several variant prediction tools have been developed to facilitate clinical reporting. A clear understanding of these prediction tools is of utmost importance for clinical reporting.

Objective: To interpret novel variants in PIDs using In silico tools and validating it by functional assays at the Pediatrics Immunology Laboratory, Advanced Pediatrics Centre, Post Graduate Institute of Medical Education Research, Chandigarh, North India.

Method: The variants were initially run on Ion Torrent S5 instrument analysed on Ion-Reporter Software and viewed over Integrative Genome Viewer. All variants were checked on gnomAD, Human gene mutation database and on disease-specific databases (e.g.BTKbase, WASbase, CYBBbase) to confirm if these were novel or previously reported. SIFT, Polyphen-2, PANTHER, CONDEL, GDI and CADD scores were then calculated to check the pathogenicity of the novel variants. Sanger sequencing was subsequently used to validate the results. The carrier status of parents and siblings was subsequently checked to assess inheritance and study family segregation patterns.

Result: Fifty-seven patients with PIDs were run on targeted NGS and analysed during the period July 2018 to March 2019. Variants in different genes were identified in 40/57 (70%) patients. Seventeen (42%) of these were identified to be novel variants based on aforementioned prediction tools. These were subsequently validated by Sanger Sequencing. We identified 3 novel variants each in XLA, SCID, CGD and TypeI LAD; 2 in Hyper-IgE syndrome and one each in MSMD, DOCK8 deficiency and GATA2 deficiency. Functional assays were carried out to confirm the effect of variant on protein expression for 14 of the 17 novel variants. (Table1)

Conclusion: Validating a novel variant to establish genotype and phenotype correlation is important. In our experience CADD, SIFT, POLYPHEN-2, CONDEL scores are useful variant prediction tools in the realm of PIDs. Functional validation is, however, necessary to confirm pathogenicity.

POSTER 127 - SIIGNAL TRANSDUCER AND ACTIVATOR OF TRANSCRIPTION 3(STAT3) LOSS OF FUNCTION RELATED AUTOSOMAL DOMINANT HYPER IGE SYNDROME AND OSTEOCLASTOGENESIS: STUDY OF THE OSTEO-IMMUNOLOGICAL CROSSTALK

AUTHORS

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Objective: To elucidate the role of STAT3 c, p.T714I and c.1552 C>T, P.R518X mutation in the generation and function of monocyte derived osteoclasts in Autosomal Dominant Hyper IgE Syndrome (AD-HIES).

Design and Method: Two HIES kindreds with mutation in the transactivation domain (c.2141 C>T) and linker domain (c.1552 C>T) of STAT3 were the subjects of the study. NIH scoring, th17 cells, memory B cells and pSTAT3 were assessed for the patients along with 5 healthy controls. The subjects did not have significant skeletal manifestations. Monocyte derived osteoclasts were generated after 21 days culture in presence of 2.5µg/mL human mCSF and 5µg/mL human RANKL in alpha MEM medium with 5% FBS maintained at 37°C in 5% CO2 and 95% humidity. DAPI staining to assess the nuclei, αVβ3 integrin with fluorescence staining and Tartarate resistant acid phosphatase (TRAP) assay were performed. The cells were functionally characterized using pit resorption assay. Osteoclasts from the HIES subjects were compared with control osteoclasts on the basis of its area, number and total number of nuclei per osteoclast.

Results: TRAP and Phalloidin positive osteoclasts were assessed under microscope and analyzed. Average area of osteoclasts observed was 18587.13/mM² ± 3232.059 in patients and 15440.66/mM² ± 2895.053 in controls, while total number of osteoclasts was 5.066667± 2.314 in patients and 4.393333± 0.9044 in controls. DAPI stained nuclei were calculated to be 4.4± 1.94 in HIES osteoclast and 3.6± 0.54 in controls. Toluidine Blue O positive pits were observed on bone matrix plates for both patients and controls.

Conclusion: Osteoclasts were generated successfully from the monocytes isolated from peripheral blood. STAT3 c.2141 C>T, p.T714I and c.1552 C>T, P.R518X mutant monocytes were capable of generating morphologically and functionally active osteoclasts. There was no significant difference in the number of osteoclasts per mM², area covered by each osteoclast and the number of nuclei per osteoclast and similar pit resorption in control and patients. The data suggests that the c.2141 C>T mutation in transactivation domain of STAT3 and c.1552 C>T mutation in linker domain of STAT3 does not contribute to osteoclast function thus explaining the lack of significant facial/skeletal anomalies in these patients. This is the first ever study studying the role of STAT3 in osteoclastogenesis in AD-HIES patients.

POSTER 128 - PRENATAL DIAGNOSIS OF HYPER IMMUNOGLOBULIN E SYNDROME IN A FAMILY WITH DOCK8 DEFICIENCY HISTORY

AUTHORS

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Introduction: Primary Immunodeficiency Diseases (PIDs) are a heterogeneous group of genetic defects of the immune system. DOCK8 deficiency is a rare disease and a subgroup of recessive Hyper IgE Syndrome (HIES) with a high mortality rate. Prenatal diagnosis facilities in families with previous affected children could manage next pregnancies.
This study reported for the first time, the application of a multiplex Polymerase Chain Reaction (PCR)-based protocol for rapid and timely detection of a large deletion in prenatal diagnosis of DOCK8 deficiency; using Chorionic Villus Sampling (CVS).

Objective: To report the first prenatal diagnosis in DOCK8 large deletion by multiplex PCR in a family with an affected child in Iran.

Design and method: CVS was performed at 12 weeks of gestation by the transcervical method. Maternal Cell Contamination (MCC) testing was used to rule out the presence of maternal DNA within the CVS sample by a variable number of tandem repeat (VNTR) analyses. PCR was done for specified exons' pairs of the gene and the amplified PCR product was subjected to gel electrophoresis to verify the presence or absence of the known disease causing mutation in CVS, parents and control samples (affected child as positive and healthy sample as negative specimen). The electrophoresis bands patterns documentation was analyzed beside the appropriate DNA ladder; using the known disease causing mutation.

Results: Prenatal diagnosis with CVS was made on the second child of a family with a first child being affected with DOCK8 large deletion. The results of multiplex PCR of the fetus demonstrated the same mutation as the first affected child, resulting in medical termination after respective counseling and legal process before the 18 weeks of pregnancy.

Conclusions: Prenatal diagnosis by multiplex PCR and detection of affected fetus could be a rapid and timely manner in PID genetic diseases management with known disease causing mutations.

POSTER 129 - SEVERE CRYPTOCOCCAL INFECTION DUE TO ANTI-GRANULOCYTE-MACROPHAGE COLONY- STIMULATING FACTOR AUTOANTIBODIES

AUTHORS

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Objective: To understand phenocopies of primary immunodeficiencies due to anti-cytokine autoantibodies.

Design and Method: Case report Study

Results: I present a case, 58 year-old man presented after experiencing at least 1 year of cough. He had progressive headache, nausea, vomiting for four days. He does not have a family history of primary immunodeficiency, personal history of previous severe infections, neoplasms or autoimmunity.
His chest X-ray and Computed Tomography (CT) showed an approximately 10-cm mass in the right upper lobe lung. Lumbar puncture revealed an opening pressure of 40 cm H2O, 220 WBCs/mm3, polymorphonuclear predominance, glucose of 29 mg/dl, and protein of 107 mg/dl. Cerebrospinal fluid and serum cryptococcal antigens were positive. Chest CT-guided aspiration and bronchoscopic biopsy also demonstrated encapsulated yeasts consistent with Cryptococcus.
Common predisposing diseases, such as AIDS or contiguous infections, were ruled out.
Testing for anticytokine autoantibodies (NIH-USA) revealed the presence of high levels of neutralizing autoantibodies against GM-CSF.
He received amphotericin B treatment two months followed by fluconazole. No recurrence of disease was reported during follow-up period.

Conclusions: Anti-GM-CSF Autoantibodies increase susceptibility to severe brain and pulmonary infections in adults.
This case highlights the importance of clinical suspicion for Phenocopies of immunodeficiency in patients with severe disseminated cryptococcal infection without known congenital or acquired immunodeficiency.

POSTER 130 - SEVERE PULMONARY DISEASE IN TWO SIBLINGS WITH X LINKED AGAMMAGLOBULINEMIA: POSSIBLE CONTRIBUTION OF MUTATIONS IN TUMOR GROWTH FACTOR BETA 1 AND TUMOR NECROSIS FACTOR SIGNALING PATHWAY.

AUTHORS

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Here we describe two siblings with X linked Agammaglobulinemia (XLA) and bronchiolitis obliterans in whom mutations in Btk and in genes related with TGFβ1 and TNF pathway were identified. Both patients have a history of recurrent pneumonia and sepsis. The diagnosis of XLA was established at 11 months (patient 1) and 2y5m (patient 2) of age. They were kept on monthly infusion of human immunoglobulin and prophylaxis with azithromycin after the diagnosis, and no severe bacterial infections have been observed since then. At the time of the diagnosis, image suggesting bronchiolitis obliterans was observed in the thorax tomography of both. They evolved with recurrent respiratory viral infections, severe bronchospasm and the need of several hospitalizations. Patient 1 is currently 6 years old and has a partial control of the bronchospasm, even with high doses of LABA and inhaled corticosteroids. Patient 2 evolved with a severe pulmonary disease and was kept on high doses of LABA associated with inhaled corticosteroid, oral cyclosporine, as well as oral corticosteroid. No response was observed with hydroxychloroquine. He died with respiratory insufficiency at 6 years of age. Whole Exome-Sequencing analysis of both siblings revealed, besides a pathogenic mutation in Btk gene, a GOF mutation in the TGFβ1 and two variants with unknown significance in TRAF1 and TRAF2 gene. After literature review, we suggest that the mutations described here could contribute to an increase in fibrosis and in inflammatory response, contributing to the severity of pulmonary disease observed in both patients.

POSTER 131 - AUTOIMMUNITY IN WISKOTT-ALDRICH SYNDROME: AN UNDEREXPLORED AREA

AUTHORS

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Objective: Wiskott Aldrich syndrome (WAS) is a rare X-linked combined immunodeficiency with an incidence of 1-10 / 100,000 live births. Patients with WAS are not only prone to recurrent infections but are also at risk of developing autoimmunity and malignancy. In this study, we report the clinical and genetic profile of patients with WAS who developed autoimmune manifestations.

Design and Method: Case records of 46 boys with WAS being followed-up in Pediatric Immunodeficiency Clinic, Advanced Pediatrics Center, Post Graduate Institute of Medical Education and Research, Chandigarh, India were reviewed. The clinical profile (including autoimmune features), laboratory findings and outcomes in the cohort were analysed.

Results: Over a follow-up of 12 years during the period January 2006 to December 2018, forty six patients were diagnosed to have WAS. Fourteen (30.43%) developed significant autoimmune manifestations (Table 1). Mean age of children with autoimmune features was 25.53 ± 31.36 months. Family history of death of a sibling was found in 3. At presentation, 8 (57.14%) had recurrent bleeding, 6 (42.85%) had recurrent pneumonia and eczema was present in all. Leukocytoclastic vasculitis was the most common autoimmune manifestation and was noted in 8 (57.14%) patients. Five (35.71%) had autoimmune hemolytic anemia and direct Coombs test was positive. Antinuclear antibody (ANA) was positive in 5 (35.19%) patients and 2 had autoimmune hypothyroidism. Primary sclerosing cholangitis, Guillain-Barre syndrome and alopecia were seen in one patient each. One patient had 3 autoimmune manifestations - primary sclerosing cholangitis, AIHA and vasculitis. Inflammatory bowel disease was diagnosed in 2 (14.28%) children. In 1 patient there was significant intracranial bleed. Non-Hodgkin lymphoma during follow-up was noted in 1. Eight patients (57.1%) had exonic mutations; 3 had intronic and novel mutations were detected in 3 (21.42%) patients. Prednisolone was used in 9 (64.28%) patients while 12 (85.71%) patients were on intravenous immunoglobulin for therapy of autoimmune features. Stem cell transplantation was carried out in 2 children, both patients however, succumbed to infections at 45 and 100 days respectively during the post transplant period. Mortality rate in patients with autoimmunity was significantly higher in comparison to WAS without autoimmunity (42.85% vs 21.8%; p 0.001).

Conclusion: One-third of patients with WAS in our cohort had autoimmune phenomena and leukocytoclastic vasculitis was the commonest finding. Mortality rate was significantly high in patients with autoimmunity. Most patients with autoimmunity had mutations in exon 1 of WAS gene.

POSTER 132 - CLINICAL CHARACTERISTICS IN ADULT PATIENTS WITH X-LINKED AGAMMAGLOBULINEMIA

AUTHORS

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Introduction: The X-linked agammaglobulinemia (XLA) is a primary immunodeficiency(PID) is caused by a B cell defect with differentiation arrest, associated with mutations in the BTK gene that is encoded in the long arm of the X chromosome. The most common manifestation of these PID are recurrent sino pulmonary infections, mainly caused for encapsulated bacterias like H. influenzae, S. pneumonia. The most common age of presentation is at childhood, only few patients begun at elder age.
The objective of these study was to present the clinical characteristics of a group of adults patients with XLA.

Methods: we conducted a cross sectional observational study at the Department of Allergy and Clinical Immunology of the Hospital Especialidades XXI Medical Center in Mexico. Included all the patients with XLA diagnosis, according with ESID criteria and with mutations confirmed at the BTK gene. All patients filled a poll that included demographic and clinical data. Also we performed high resolution chest tomography, spyrometry, laboratory tests.

Results: we studied 6 adults patients, the average actual age was 28.5 years. 50% of the patients were diagnosed at teen age. Of them just one reported only trivial infections of pulmonary upper tract. 4 patients had familiar history, in fact 3 of them were related.
83% of the patients with bronchiectasis as a pulmonary complication and one of them requires oxigen supplement. 50% with obstructive pattern at the spirometry.
Only 2 with chronic diarrea.
None with autoimmune diseases. 5 with treatment of subcutaneous immunolglobulin and one with intravenous. All of them with levels of IgG above 900 mg without recurrent infections

Conclusions: we found that 50% of our patients begun al teen age, and it's not a common feacture reported; none of them with autoinmune diseases and 2 with apparently novo mutations. It's important to look for these diseases even at teenage if the clinical history is suggestive.

POSTER 133 - MOROCCAN CLASSIFICATION OF THE COMMON VARIABLE IMMUNODEFICIENCY

AUTHORS

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Introduction: The heterogeneity of the common variable immunodeficiency called for a clinical classification as well as the biological relevance of B lymphocytes. A European multicentre trial was launched to develop a classification scheme based on B-cell phenotyping by flow cytometry and the clinical manifestations indicated in these patients.

Objective: Establish a clinical and immunophenotic classification of Moroccan cases with a CVID.
Design and method: 20 patients with CVID in this study who met ESID/PAGID inclusion criteria.
Phenotyping of B-cell sub-populations is performed by flow cytometry.

Results: A reduction in switched memory B lymphocytes has been confirmed in most patients, associated with an increased risk of splenomegaly and granulomatous disease. An expansion of CD21low B lymphocytes has marked patients with splenomegaly. Adenopathy was significantly related to transient B cell expansion.

Conclusion: Based on these findings and the pathogenic consideration of B cell differentiation, we suggest an improved classification for CVID (EUROclass / MAGHclass), separating patients with almost absent B cells, and those who are significantly reduced to switched memory B cells.

POSTER 134 - DOCK8 MUTATION, A CASE REPORT ON APPLICATION OF GENETICS IN MEDICINE

AUTHORS

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Introduction: Hyper-Immunoglobulinemia E Syndromes (HIES) are rare hereditary immunodeficiency diseases mostly characterized by lung and skin manifestations adjacent with elevated serum IgE. HIES is known to be either autosomal dominant -caused by mutation in STAT3 - or autosomal recessive (DOCK8 mutation). The AR form of the disease bares the risk of severe cutaneous viral infections and the promise of higher chances for developing malignancy in a younger age. Thus, the conventional treatment of these diseases fails to address the unique manifestations among varied genetic etiologies. Understanding the genetic basis of this disease is destined for better therapeutic outcomes. A more comprehensive description of this diseases' pathogenesis can also open new windows in understanding diseases with unknown causes that are showing part of this multifaceted disease manifestations.

Case presentation: A 9-years-old girl of a consanguineous marriage was referred to our center by a dermatologist showing signs of recurrent sinopulmonary infection and skin manifestations such as warts and molluscum, with elevated IgE. A WBC of 8790 with 25% Eosinophilia was detected. The patients IgE level was 878 IU/ml. Parents were free of symptoms however, pedigree assessment revealed a cousin of the index patients with the history of immunodeficiency manifestations who was a 9-years-old boy.
A PCR for DOCK8 exons 24 to exon 31 was performed. Compared to the DNA of a normal donor there were no products for exon 24 to exon 30 for both index patients and her cousin. Exon 31 was present for the cousin, but absent for the index patient.

Conclusive remarks: The genetic basis of HIES was unclear until late into 2006. Until then patients were treated symptomatically and regardless of distinctive features of the disease. The presentation of the disease is undistinguishable through the early years due to similar sings as symptoms, such as skin manifestation and sino-pulmonary infections. Patients with AR-HIES are highly prone to developing cancers at an early age. The viral infection of the skin in these patients (distinctively in patients with DOCK8 mutations) is recurrent and resistant to treatment. Due to life threatening nature of this condition, early detection of this mutation is crucial. Prior to identifying DOCK8 mutations patients would have been neglected and later identified with malignancies however now actions like Bone Marrow Transplantation would be considered as the course of treatment to reduce mortality drastically.

POSTER 135 - NOVEL SAMD9 GENE MUTATION IN A PATIENT WITH SKELETAL SYSTEM COMPLICATION AFTER HSCT: A CASE OF MIRAGE SYNDROME?

AUTHORS

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Background: MIRAGE (myelodysplasia, infection, restriction of growth, adrenal hypoplasia, genital phenotypes, and enteropathy) syndrome is a recently described form of syndromic adrenal hypoplasia due to pathogenic SAMD9 variants.

Objective: Clinical-immunological follow-up, molecular and cellular characterization of a female patient at first described as an early-onset severe combined immunodeficiency characterized by agammaglobulinemia, absence of B, NK and monocyte precursors, and altered T cell function, who developed skeletal system complication after hematopoietic stem cell transplant (HSCT).

Methods: Next-generation Sequencing (NGS), cell culture and functional studies (FACS, WB)

Results: Clinical/immunological follow-up after HSCT: a) at eighteen months after HSCT, the patient showed a good engraftment with an improvement in growth charts and in pulmonary imaging; b) in the next years the patient developed unexpected complications involving the skeletal system apparently not correlated with previous corticosteroid therapy and conditioning regimen and post transplant immunosuppressive therapy. Five years after HSCT she developed a bilateral osteonecrosis of the femoral heads, a severe genu valgum and a severe scoliosis. Molecular NGS data: we identified a rare heterozygous missense variant (c.4067A>G p.E1356G) in SAMD9 gene predicted damaging. Functional investigations: The level of SAMD9 protein evaluated in fibroblast from patient resulted normally expressed and up-regulated after TNFa stimulation compared to HD. Moreover increased p-ERK1 expression level in fibroblasts from patient was found although both p-ERK1/2 proteins resulted normally regulated.

Conclusion: We described a female patient who developed skeletal system complications after hematopoietic stem cell transplant (HSCT) in which we found a variant in SAMD9 gene suggesting a MIRAGE syndrome diagnosis. Preliminary functional tests were performed to corroborate this suspicion. On the other hand, the variant in SAMD9 could be the cause of the unexpected complications faced by our patient who only restored the immunological abnormalities after HSCT.

POSTER 136 - SPEEDY DIAGNOSIS OF ANTIBODY DEFICIENCIES WITH THE MEASUREMENT OF SERUM-FREE LIGHT CHAINS

AUTHORS

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Objective: Low concentrations of Serum free light chains(FLC) were found in some antibody deficiencies like Common Variable Immunodeficiency Syndromes(CVID). Moreover, a pattern for CVID consisting of low free kappa(<3.3mg/L), low free lambda(<5.7mg/L) or both low has recently been proposed by some groups as a new diagnostic tool which could help to discriminate between CVID and plasma cell dyscrasias related hypogammaglobulinemia. In addition, we would like to propose another tool, the sum of serum-free kappa and free lambda or total serum FLC(tsFLC) as an interesting biomarker to identify CVID patients and other patients with abnormal vaccine responses in whom immunoglobulin replacement therapy could be considered.

Design and method: Serum FLC were determined in 65 healthy donors,29 CVID patients and 76 other patients studied for vaccine responses. Patients were obtained from 2 centers from Madrid. Patients under four years and altered serum creatinine, glomerular filtration rate or monoclonal gammapathies were excluded.

Results: CVID patients displayed a median value for tsFLC of 9.5mg/L. Other primary antibody immunodeficiencies including specific antibody deficiencies, IgG subclass deficiencies and unclassified hypogammaglobulinemia had a median value of tsFLC of 22.46mg/L. Agammaglobulinemia and thymoma patients showed even lower values than most CVID patients with a median of 2.1mg/. Other primary immunodeficiencies showed values of tsFLC of 13.8.
The CVID pattern showed a sensitivity of 55.17%, a specificity of 89.4% and a +LR:5,21. With ROC-curves we calculated the performance of different cutoffs for CVID diagnosis.Percentile 99th had a sensitivity of 79.31% and specificity of 83.53%.
We then calculated the performance of our population-defined cutoff among patients with abnormal production of specific IgG and IgG-2 to pneumococcal polysaccharide antigens vaccine. Abnormal vaccination was defined as patients who could not reach a three-fold increase in serum levels of specific antibodies after 3 or 4 weeks from vaccination. In this setting, our population-defined cutoff performed with a sensitivity of 50% and a specificity of 91.4%, with a positive likelihood ratio of 5.87. We also defined a more restrictive cut-off established at 11.56mg/L with a sensitivity of 39.6%, a specificity of 100%, +LR:18.6, and an odds ratio of 60.2 with a p-value of 0.0046.

Conclusions: Our results favor tsFLC determination over CVID pattern and help to identify patients unable to mount a valid response to vaccination. As tsFLC measurement could be performed in less than an hour, restrictive cutoffs could help to identify candidate patients for immunoglobulin replacement therapy at the same day of patient evaluation.

POSTER 137 - NOVEL ELANE GENE MUTATION IN A VIETNAMESE BOY WITH SEVERE CONGENITAL NEUTROPENIA

AUTHORS

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Severe chronic neutropenia is a congenital condition defined as an absolute neutrophil count of less than 500/μL for at least three months. There are three categories according to the onset time or pattern of variation of neutrophil levels: congenital, cyclic, and idiopathic. Among them, severe congenital neutropenia is an inborn disorder with maturation arrest of the early stage of granulopoiesis associated with various genetic abnormalities that has been classified with 26 genes. We here report a 4 year-old boy was admitted due to fever, sepsis, skin abscesses and gingivitis. He had a past history of febrile illnesses including septic shock, pulmonary tuberculosis, recurrent pneumonia, cutaneous abscesses, oral thrush and isolated neutropenia from birth (0. 1 – 0.4 x 109/ L) . Family history was nonspecific and he had no siblings. Initial laboratory revealed severe neutropenia (white blood cells, neutrophils, lymphocytes, monocytes was 4.73 x 109/ L; 0.17 x 109/ L; 3.68 x 109/ L, 0.68 x 109/ L, respectively) and increasing of erythrocyte sedimentation rate (112 mm/hr) and C-reactive protein (121 mg/L). A gram-stain and culture of blood showed Ralstonia pickettii and culture of abscess fluid showed negative. Bone marrow findings showed normal myeloid cells, reduced granulocyte cell line and no malignant cells. Test of HIV and TB profile were negative. Immunoglobulin quantification results showed normal range of IgG, IgA and IgM. Lymphocyte immuno-phenotyping showed normal count of T lymphocytes, TCD4, TCD8, TCD4, B lymphocytes and natural killer cells. No duplication or deletion in the CGH. Of note, novel mutation of the ELANE gene encoding human neutrophil elastase is found via whole exome sequencing and validated by Sanger sequencing. Functional motif Patient were managed with prompt administration of combination intravenous antibiotic therapy in two week without granulocyte colony stimulating factor. When he discharged from hospital, white blood cells and neutrophils was 9.94 x 109/ L and 0.43 x 109/ L, respectively. He received antimicrobial prophylaxis with trimethoprim-sulfamethoxazole and did not accept high cost of G-CSF prophylaxis in 6- month follow- up. During the follow-up observation period, he suffered from two times of skin abscesses.

POSTER 138 - THE CLINICAL AND SOCIO-ECONOMICAL IMPACT OF IMMUNOGLOBULIN CRISIS – A SINGLE ROMANIAN CENTER REPORT

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Introduction: Immunoglobulin substitution is essential for infection prevention and is lifesaving in immunodeficiencies with antibody deficiencies. Romania experienced in 2017-2018 a severe crisis of immunoglobulin because all immunoglobulin companies retired from the Romanian market due to claw-back taxes and the prices.

Objective: To highlight the clinical and socio-economical impact of discontinuation of the immunoglobulin administration in the patients with antibody deficiencies.

Material and method: 24 patients 1-60 years old (15 children and 9 adults) with variable immunodeficiencies needing immunoglobulin substitution were included in the study.

Results: Discontinuation of the immunoglobulin administration for 4 months was registered in 8 patients, for 2 months in 4 patients, decreasing the dose with 75% in 9 patients and with 25% in 3 patients. The patients who still receive immunoglobulin bought it from abroad with own resources or moved for 1 month in that center which still had immunoglobulin. The clinical consequence was severe: all patients experienced infections: sepsis in 1 patient, pneumonia in 10 patients, sinusitis in 14 patients, reactivation of chronic viral infection in 3 patients. Relapsing of the autoimmune diseases was found in 7 patients: inflammatory bowel disease in 6 cases, cerebral vasculitis in one case, arthritis in 4 cases, immune urticaria in 2 cases, hemolytic anemia in 1 case. 3 patients needing bone marrow transplantation (BMT) went abroad. 1 patient from them died before bone marrow transplantation. 1 patient who experienced reactivation of viral infection and of hemophagocytic lymphohistiocytosis underwent BMT in our center but died soon after it. The patient with cerebral vasculitis lost his hearing. 2 patients have emigrated (one with all the family) due to lack of immunoglobulin in a western country.

Conclusion: The discontinuation of immunoglobulin administration in patients with antibody deficiencies has not only a severe impact on the patient's health status, going up to death, and patient's quality of life but also affect the patient and his family from an economic and social point of view due to a lot of days missing from the school or work.

POSTER 139 - A RARE AUTOSOMAL RECESSIVE AGAMMAGLOBULINEMIA: IGLL1 (LAMBDA 5) GENE MUTATION

AUTHORS

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Objective: Autosomal recessive agammaglobulinemia (ARA) is a rare form of primary immunodeficiency characterized by severe reduction of all groups of immunoglobulins and the absence of peripheral B cells, in the absence of BTK mutations. To date, ARA has been linked to mutations in genes involved in B cell development including IGHM, CD79A, CD79B, IGLL1, BLNK, PIK3R1 and SLC39A7. Here we present a case with IGLL1 (lambda 5) gene mutation, H. pylori gastritis and growth hormone deficiency.

Design and Method: We used flow cytometry to characterize defects in peripheral lymphocyte subsets. Genetic analysis was performed by whole exome sequencing and further confirmed bySanger sequencing.

Results: A four-year-old Turkish girl born to consanguineous parents, was referred to our hospital with hypogammaglobulinemia and short stature. The patient had a history of recurrent upper and lower repiratory tract infections. Height and weight at first presentation were 84 cm (-3.75 SDS, <3rd percentile for age) and 11 kg (-2.68 SDS, <3rd percentile for age), respectively. Physical examination revealed no tonsillar tissue. Serum IgG levels were low (IgG: 677 mg/dl, N: 722-1,037 mg/dl). Serum IgA and IgM levels were lower than the detection limits (IgA: <6.67 mg/dl, N: 46-91 mg/dl, IgM: <4.4 mg/dl, N: 50-121mg/dl). Isohemagglutinin, anti-HBs, rubella IgG and polio antibody titers were negative. Immunephenotyping revealed lack of B cells, whereby T cell counts and activation responses were normal. Chronic fibrotic changes were detected with lung HRCT. The patient was diagnosed with agammaglobulinemia and commenced on IVIG replacement and TMP/SMX prophylaxis. Duodenal biopsy revealed H. pylori gastritis which could be eradicated which three courses of antibiotics. The patient was diagnosed with growth hormone deficiency at the age of six and started growth hormone therapy. Genetic analysis showed homozygous mutation p.G86fs in IGLL1 (lambda 5) gene. In the nine-year follow-up, there has been no infectious disease except intermittent sinusitis.

Conclusions: IGLL1 mutation is very rare and only three cases have been reported to date. H. pylori gastritis is common and difficult to eradicate in diseases such as agammaglobulinemia. We recommend to screen these patients for H. pylori, as well as growth hormone deficiency if they have short stature.

POSTER 140 - HEREDITARY ANGIOEDEMA WITH C1 INHIBITOR DEFICIENCY AND SYSTEMIC AUTOIMMUNE DISEASES: A SINGLE CENTRE SERBIAN STUDY ON EIGHTY-TWO PATIENTS

AUTHORS

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Objective: Hereditary angioedema (HAE) is an autosomal dominant disease due to mutations in the SERPING1 gene, resulting in the deficiency of C1 inhibitor (C1-INH) that plays a regulatory role in the complement system, the contact system and the intrinsic coagulation cascade. Occasional reports and few studies link HAE with autoimmune conditions with controversial results. Although several autoimmune disorders have been reported, the prevalence of defined autoimmune diseases still remains unknown.

Design and method: Serbian database included 82 patients (47.6% female) with C1-INH-HAE from 39 unrelated families. The majority of patients (90.2%) had C1-INH-HAE type I. Mutational analysis of the SERPING1 gene was performed for 59 patients from 32 unrelated families. We reviewed the medical records, laboratory findings and perform physical examination of patients with C1-INH-HAE for manifestations of autoimmune disorders.

Results: Autoimmune systemic disease was diagnosed in four (4.9%) patients. All of them were females, affected by type I HAE with disease causing mutations in SERPING1 gene.
Patient 1 is 58-year old with a history of recurrent swelling since the age of 2. At the age of 12 she presented with a photosensitive skin rash, arthralgia and autoimmune hemolytic anemia. She was diagnosed with systemic lupus erythematosus (SLE) and treated with prednisolone and azatioprine. A year later, SLE was in remission, but she continued to experience frequent HAE attacks. Immunosuppressive therapy was discontinued. Despite high concentration of anti-Ro/SSA antibodies, symptoms attributable to SLE are absent for almost 40 years. A mutation (c. 1223A>G, exon 7) was identified. Patient 2 is a 38-year old. She experienced HAE attacks since puberty. At the age of 19 the diagnosis of SLE was established and therapy with antimalarials and prednisone was initiated. An insertion/duplication in exon 4 was found. Patient 3, age 35 was diagnosed with seropositive rheumatoid arthritis at the age of 20 and initially treated with prednisolone and metotrexate. The first presentation of HAE was laryngeal angioedema at the age of 24. A mutation (c.1195C>T) in exon 7 was found. She is treated with tocilizumab. Patient 4, age 57 had a first HAE attack at the age of 19. At the age of 32 she was diagnosed with discoid lupus erythematosus and scarring alopecia. She is treated with antimalarials and low dose prednisone. She has a mutation in exon 8 (c.1397G>T).

Conclusions: Based on our findings, the prevalence of autoimmune diseases in patients with C1-INH-HAE is higher than previously reported.

POSTER 141 - MATCHED UNRELATED DONOR HEMATOPOIETIC STEM CELL TRANSPLANTATION, EFFECTIVELY RESOLVED THE CLINICAL AND IMMUNOLOGICAL DEFECTS IN A PATIENT WITH INTERLEUKIN-2-RECEPTOR ALPHA DEFICIENCY

AUTHORS

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Background: IL-2R Alpha (CD25) deficiency is a rare, genetic, primary immunodeficiency, that can cause a characteristic disorder resembling IPEX with pronounced immunodeficiency and autoimmunity. Very few successful hematopoietic stem cell transplantations (HSCTs) from FMD resulting in complete resolution of IL-2 receptor alpha deficient patients' symptoms have been reported.

Objective: To describe clinical. Immunological and molecular defects of two Saudi siblings with interleukin-2 receptor alpha deficiency and to report the outcome of a hematopoietic stem cell transplantation (HSCT) from a matched, unrelated donor (MUD) for one of them.

Design and Method: A retrospective chart review of two siblings diagnosed with IL-2R receptor alpha deficiency, with a descriptive analysis of the clinical and immunological features, pre and post HSCT.

Results: Two siblings of Saudi descent presented with chronic, profound autoimmune enteropathy, extensive dermatitis, severe failure to thrive, autoimmune thyroiditis and recurrent sino-pulmonary infections complicated by bronchiectasis and chronic sinusitis.
Immunological workups revealed abnormal IgG and IgA levels, mild lymphopenia with an inverted CD4+:CD8+ T-cell ratio, and high NK cell levels with severely depressed lymphocyte proliferation. Molecular analysis detected a homozygous loss-of-function mutation of IL2RA receptor. MUD HSCT was performed for one of the patients at the age of 12 years. Conditioning consisted of Busulfan, Fludarabine and anti-thymocyte globulin. In addition to cyclosporine and methotrexate as GVHD prophylaxis.
The patient currently is 9 months after the HSCT, He rapidly engrafted the MUD-derived myeloid cells within 3 weeks. A successful MUD-derived lymphoid cells engraftment was ensued after 5 months. He is off immunosuppressive medications. HSCT resulted in resolution of his chronic diarrhea. Rapid clinical and immunological improvement of the patient was marked by improved general status, gaining further weight and satisfactory immune reconstitution. Proper growth hormone supplementation and treatment for the patient's pre-existing respiratory complications remain in effect.

Conclusion: Our report expands the clinical knowledge and understanding of the wide array of the clinical and immunological presentations of IL2R Alpha-deficient patients. Hematopoietic stem cell transplantation using myeloablative conditioning can cure IL2R Alpha deficiency and should be considered as early as possible.

POSTER 142 - THE INHIBITORY ROLE OF M2000 (B-D-MANNURONIC ACID) ON EXPRESSION OF TOLL-LIKE RECEPTOR 2 AND 4 IN HT29 CELL LINE

AUTHORS

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Background/Objectives: Anti-inflammatory agents play a crucial role in controlling inflammatory diseases such as Inflammatory Bowel Disease (IBD) but their use is restricted due to their vast side effects. M2000 (β-D-Mannuronic acid) is a new immunomodulatory drug. According to the capacity of M2000 in suppressing some molecules involved in TLRs signaling and reducing oxidative stress we hypothesize that, this molecule may have a potential role in decreasing inflammatory responses in IBD. The aim of this study was to evaluate the cytotoxicity of M2000 and its effect on the gene expression of TLR2 and TLR4.

Methods: HEK293 cell line was grown and divided into 96-well cell plate and MTT assay was performed. HT29 cells were cultured and treated with low and high doses of M2000. Total RNA was extracted and cDNA synthesized and quantitative real-time PCR was done to quantify the TLR2 and TLR4 mRNA expression.

Results: We found that M2000 at the concentration of <1000 µg/ml had no obvious cytotoxicity effect on the HEK293 cells. Also, low and high doses of M2000 could significantly down-regulate both TLR2 and TLR4 mRNA expression. Moreover, a significant reduction in gene expression of TLR2 and TLR4 in an inflammatory condition resulted in high doses of M2000 in the presence of LPS.

Conclusion: our study which was conducted in colonic epithelial cell model, shows that M2000 can be considered as a new anti-inflammatory agent in IBD. However, more comprehensive experimental and clinical studies are required to recognize the molecular mechanism of M2000 and also its probable side effects.

POSTER 143 - PID4KIDS: A THERAPEUTIC EDUCATION PROGRAM DEVOTED TO CHILDREN WITH PIDS CONDUCTED COOPERATIVELY BY IMMUNOLOGY STUDENTS AND CARE UNIT

AUTHORS

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Therapeutic Patient Education (TPE) is of increasing importance in patients' management program by providing them the knowledge relevant to their disease. Primary immune deficiency (PID) is a particularly challenging field for TPE application. Indeed, not only immunology is a discipline endowed with many levels of complexity but, in addition, PID usually manifest early in life, in a very severe way and with several clinical faces. The PID4KIDS program (PID for Kids) is a TPE program conducted by both the Immunology care unit at the Children Hospital, Toulouse, France (where a specific TPE program initiated in 2018 based on ARS accreditation) and the BSc students enrolled in immunology program at the University of Toulouse. The PID4KIDS program addresses the challenging objective to teach young PID patients immunological notions relevant for their pathology. The program involves several steps. First, the immunology professor i) invited his students to form team-projects with the objective to assemble immunology resources dedicated to children and, ii) taught immunological notions with references to PID anytime possible. Second, the students proposed a project, which they developed over a 3-months period. The project development was assisted scientifically by PhD students and technically by a civic service volunteer. Third, upon completion, the resources were transferred to the care unit in order to be proposed to patients in TPE sessions. Two videos, one book, fact sheets and 5 board games were produced by 28 students split in 9 team-projects. A dialog between the staff of the care unit, the professor and students will be engaged to step-by step improve and adapt the content of the provided resources at the benefits of the patients. We believe our TPE approach is endowed with a series of benefits: i) the creativity of students leads to multiple, innovative and adapted strategies to trigger the interest of children, ii) the scientific quality of the resources is ensured by the project supervisors, iii) it involved a tight interaction between several entities favoring multidisciplinarity, iv) the students directly experience the social impact of learning science and develop skills owing to the pedagogical approach chosen and v) the PID patients will directly benefit from these TPE resources in an on-going program lead by a medical coordinator and a multidisciplinary team in the Hospital.
We believe these benefits will extend in the next few years to the PID patients which could be enrolled in the coming TPE sessions.

POSTER 144 - SEVER VIRAL MENINGOENCEPHALITIS IN A PATIENT WITH PURINE NUCLEOSIDE PHOSPHORYLASE DEFICIENCY

AUTHORS

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Background: Purine nucleoside phosphorylase (PNP) deficiency is a rare form of primary immunodeficiency disease, accounting for approximately 4% of patients with severe combined immunodeficiency. It presents with a triad of features, including recurrent infections, autoimmune manifestations, and various neurological abnormalities. PNP patients often first come to clinical attention because of varicella infections that are widely disseminated due to the lack of functioning T cells. Severe Varicella infection is reported approximately in 8 of patients and estimated mortality of 37%.

Objective: We report the outcomes of severe varicella meningoencephalitis in 2 of patients diagnosed with PNP in our Centre.

Case presentation: The first patient is a PNP-deficient Saudi patient who was diagnosed at age 3 year presented early in life with clinical and laboratory characteristics of severe combined immunodeficiency, including severe bacterial infections, marked T-and B-cell depression with normal immunoglobulin level. While being worked up for stem cell transplant, he developed varicella zoster related meningoencephalitis which confirmed by CSF analysis and PCR. The patient has received varicella vaccine but never had documented varicella cutaneous infection. He is suffering from severe brain injury despite adequate treatment. His planned SCT is challenged by the recent post infectious brain damage.
The second patient is a 8-year-old girl diagnosed at age 8 with PNP and lupus nephritis. While having recurrent cutaneous varicella infections cleared with IV Acyclovir. She developed sudden seizures and encephalitis and was found to have Varicella positive PCR from CSF. Despite adequate antiviral therapy patient developed severe brain injury and died 2 weeks later.

Design: Clinical

Method: Case report

Result: Sever morbidity and mortality 2nd to Varicella infection might compromise PNP survival and feasibility of SCT in patients diagnosed with PNP immunodeficiency.

Conclusion: In PNP deficient patients; early initiation of antiviral prophylaxis, to protect from severe varicella infection in addition to IVIG may be of a high benefit as soon as diagnosed to avoid significant morbidity and mortality until transplanted.

POSTER 145 - A CHILD WITH SEVERE COMBINED IMMUNODEFICIENCY AND A NOVEL COMPOUND HETEROZYGOUS VARIANTS IN JAK3

AUTHORS

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Objective: Severe Combined Immunodeficiency (SCID) is a medical emergency often characterized by life-threatening infections in early infancy. Early diagnosis and management are essential for successful outcomes.

Design and Method: An 8-month-old female child, born of a non-consanguineous marriage presented with recurrent episodes of fever, cough, and respiratory distress from first month of age. She also had persistent loose stools from 4 months of age. Chest radiograph revealed bilateral consolidation. She was referred to our Institute at 8th month of life for severe pneumonia. She had pallor, absent BCG scar, severe tachypnea with chest wall retractions, crepitations in bilateral lung fields, and hepatosplenomegaly. Fundus examination revealed features of CMV retinitis. Blood culture revealed growth of Acinetobacter baumanii. She required mechanical ventilation, and higher end antibiotics for the management of pneumonia, however, the child had severe respiratory failure and succumbed to the illness. Serology for human immunodeficiency virus was negative. Blood counts showed lymphopenia 1.32x109/L. Flow cytometry analysis was done. We performed a Next generation sequencing using an exome panel (40 genes) for primary immunodeficiency diseases.

Results and Conclusion: Flow cytometry analysis revealed low percentage of CD3+ T lymphocytes (11.3%) and CD56+ natural killer cells (1.75%) with normal numbers of CD19+ B lymphocytes (69.8%) suggestive of T-B+NK- form of severe combined immunodeficiency. Next generation sequencing revealed a heterozygous missense variation in exon 8 of the JAK3 with amino acid substitution of arginine to tryptophan was detected and second heterozygous missense variant was detected in exon 6 of JAK3 resulting in amino acid change from methionine to threonine. Both the variants were not reported in the 1000 genomes, ExAC and HGMD database. The in-silico predictions of the variants are probably damaging by PolyPhen-2, SIFT, LRT and MutationTaster2. The JAK3 variant was the first to be reported in our cohort and is a novel compound heterozygous variants.

POSTER 146 - FIRST-TIME REPORTED NECROTIZING PNEUMONIA BY TYROMICES FISSILIS IN CHRONIC GRANULOMATOUS DISEASE

AUTHORS

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Objective: To describe a patient with pulmonary abscesses, diagnosed of chronic granulomatous disease (CGD), whose microbiological diagnosis was challenging, with a final identification of Tyromices fissilis.

Case description: Caucasian male, 3 years old. No family history. Suffered from microcytic anaemia since the age of 7 months old under oral iron treatment, and had developed pneumonia at 2 years-old (bilateral peri-hilar infiltrates, managed in the outpatient clinic).
He was admitted for clinical suspicion of appendicitis, with normal appendix but enlarged peri-appendicular lymph nodes. Histology was compatible with reactive lymphadenopathies. The study of abdominal lymphadenopathies by thoracic-abdominal scan showed mesenteric lymph nodes enlargement as well as a pulmonary infiltrate, with no acute phase reactants(a). QuantiFERON tuberculosis test was negative. No empirical treatment was prescribed.
Two months later, still asymptomatic and without analytical disturbances (except anaemia), a control scan showed 2 pulmonary abscesses and mesenteric lymphadenopathies (some with calcification and necrosis)(b).
Under the suspicion of an active infection, a bronco-alveolar lavage was performed, with negative microbiology, followed by a pulmonary segmentectomy (abscesses excision). He was started on empirical antibacterial and antifungal treatment (Voriconazole).
Extended cultures and polymerase chain reaction to virus, bacteria and fungi and galactomannan for the lung sample were negative, except for the abscess samples, in which grew, 2 weeks after culture, a filamentous basidiomycete identified as Tyromices fissilis, using conventional culture methods and DNA sequences, a fungus sensitive to Voriconazole in our experimental antibiogram.
In parallel, since a fungal invasive infection was suspected, functional and genetic studies confirmed the diagnosis of Chronic Granulomatous Disease (CGD) caused by CYBB deletion, associated with McLeod syndrome (XK deletion).
The patient has had good clinical and radiological evolution under Voriconazole(d).

Conclusions: This case exemplifies the challenge of microbiological diagnosis in CGD, particularly for fungal infections, and the need to ensure appropriate material for its diagnosis, even by using aggressive methods such as lung surgery.
Tyromices fissilis is a filamentous fungus that, to our knowledge, has never been reported as pathogenic in CGD, and only in one case human after lung transplantation.
Thoracic scan evolution. Images a to care before the treatment (surgery and anti-infectious treatment). Image d is 1month after finishing 12weeks of Voriconazole. a)Right-inferior lobe (RIL) infiltrate. b) Abscess in the RIL. c) Cavitary abscess in the RIL. d) Calcified nodule in RIL, calcified hilar lymphadenopathy.

POSTER 147 - PATIENT WITH HOMOZYGOUS LOSS-OF-FUNCTION STAT-1 MUTATION UNDERWENT HAPLOIDENTICL STEM CELL TRANSPLANT: CASE REPORT

AUTHORS

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Background: The autosomal recessive form of Signal Transducers and Activators of Transcription 1 (STAT1) related immunodeficiency is rare. It is one of four known types related to STAT1gene mutation, mainly characterized by the association of infectious diseases caused by intracellular bacteria (typically mycobacteria) and viruses (typically herpes viruses). Only seven patients from five unrelated families have been identified to date. Nevertheless, four patients died with severe infection in infancy. Three underwent stem cell transplant: first one died after three months with sever EBV infection, two successfully treated and alive.

Objective: We report a patient who present with CMV pneumonitis and disseminated mycobacterial infection and managed by haploidentical stem cell transplant.

Design: Case report

Method: Description of the clinical details of the patient and analyze the investigations

Case presentation: A 4-year-old patient who presents in infancy with CMV pneumonitis followed by CMV viremia requiring long term treatment with antivirals. At age of 3 month he developed multifocal osteomyelitis that grew Mycobacterium Scrofulaceu on bone culture. in addition to EBV viremia. He underwent Hematopoietic stem cell transplant from a haploidentical donor, his sister, after conditioning regimen consisting of Thiotepa, Busulfan, Fludarabine and Anti thymocyte globulin with GVHD Prophylaxis. Hematological reconstitution was detected at day 14, with full donor engraftment demonstrated by molecular analysis of leukocytes at day 19. Skin, and gut GVHD developed which was managed by steroid and Ruxolitinib. Although he still on CMV treatment, He has been off mycobacterium therapy, and continues showing evidence of successful engraftment on 4-month post-transplant. We would still require long-term follow-up to decide about his sustainable immune reconstitution.

Conclusions: This case highlights the importance of considering complete STAT1 deficiency in the differential diagnosis of children who present with disseminated mycobacteria and severe viral illness. In addition, mentioning our experience of haploidentical stem cell transplant in this disease.

POSTER 148 - IMMUNOLOGICAL ANOMALIES IN PATIENTS WITH NOONAN SYNDROME AND RELATED DISORDERS

AUTHORS

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Objective: Noonan Syndrome (NS) and related disorders belong to a heterogeneous group of conditions defined as RASopathies characterized by short stature, dysmorphic facial features, congenital heart defects, ectodermal and skeletal anomalies, coagulopathy and cancer predisposition, in particular myeloid malignancy. Mild mental retardation and cryptorchidism in males may be associated. Although it is transmitted as an autosomal dominant trait, a recessive form associated with biallelic variants of the LZTR1 gene has been described. The genes responsible for SN and closely related clinical disorders are involved in the RAS-MAPK signal transduction pathway: PTPN11, RAF1, SOS1, RIT1, CBL, NRAS, LZTR1, SOS2, SHOC2. In these heterogeneous group of conditions, the involvement of the immune system has not been described.
We aim to describe the immunological alterations of a patients' series with NS and related disorders.

Design and Method: We report clinical, immunological and genetic features of 5 patients with RASopathy and an involvement of the immune system. In all these patients the clinical diagnosis was confirmed by molecular examination.

Results: In three patients was found the mutation of PTPN11, in one patient of SHOC2, in another one of SOS1. As shown in the Table they exhibit a heterogenous clinical presentation. All patients experienced recurrent and/or severe infections. The immunological evaluation showed lymphopenia with inversion of the CD4/CD8 and naive/memory ratio, reduction of B memory cells, IgA deficiency and hypogammaglobulinemia. In the patients with a heterozygous mutation of SOS1 and phenotype compatible with Combined Immunodeficiency (lymphopenia, reduced thymic output, increase of CD4+ central memory and effector memory) were found 2 mutations in RAG1 and RAG2 in heterozygosity using Whole Exome Sequencing. The same mutations, including SOS1, were also found in the mother that shows a milder phenotype. This patient and another one need replacement therapy with immunoglobulins.

Conclusions: The finding of these immune alterations/immuno-dysregulation emphasizes the need to perform an immunological investigation in the patients affected by NS, in particular in cases with recurrent/severe respiratory infections. Expanding the series will allow to improve the characterization and clinical-therapeutic management of these patients and to increase the spectrum of associated genetic anomalies known.

POSTER 149 - THE POSSIBILITIES OF INCREASING THE EFFECTIVENESS OF REPLACEMENT THERAPY IN THE PRIMARY DEFECT OF ANTIBODY PRODUCTION

AUTHORS

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Substitutive immunoglobulin therapy is a standard in the treatment of the patients with primary a(hypo)gammaglobulinemia. However, some patients with an infectious syndrome continue to hurt and need additional therapy. The goal is to study the effectiveness of a combined administration of substitutive therapy and immunocorrector of cellular segment.
12 patients with XLA, and 16 people with CVID were under the observation who had regularly been received intravenous 10% IgG at the rate of 0.4 g/kg monthly. As an immunomodulator the azocsemer bromide was used with the course of 10 days in 12 mg/day every six months. NBT-test was used to detect the production of active forms of oxygen by neutrophils. As a control, 10 healthy blood donors were examined.
It was determined: despite the achievement of pretransfusion level of serum IgG 9.1±1.7 g/l, 30% of patients continued to register episodes of exacerbations of chronic infections foci (5.7±1.9 per year). Analysis of the cellular factor properties of innate immunity showed that in those patients the metabolism of neutrophils (Kst. NBT 1.39±0.13) were lower than the reference values (2.1±0.1). In addition to substitutive immunoglobulin therapy azocsimer bromide was administered to the given group of patients. During a year of observation the frequency of episodes of exacerbations of chronic foci of infection in the conditions of combined therapy of IVIG and additional immunocorrection was decreased to one or two episodes per year either it was absent at all. The decrease in morbidity is associated with the stabilization of the functional parameters of innate immunity cellular factors (Kst. 1.94±0.14).
The supplement of standard therapy with immunotropic drugs acting on cellular elements of innate immunity, enhance the effectiveness of substitutive therapy of immunoglobulins

POSTER 150 - POPULATION PHARMACOKINETIC ANALYSIS OF 3-WEEKLY AND 4-WEEKLY PRIVIGEN® IN JAPANESE PATIENTS WITH PRIMARY IMMUNODEFICIENCY

AUTHORS

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Objective: Immunoglobulin G (IgG) replacement therapy, administered intravenously (IVIG) or subcutaneously (SCIG), is the standard treatment for patients with primary immunodeficiencies (PID). We characterized the pharmacokinetics (PK) of serum IgG following 3-weekly or 4-weekly administration of Privigen® (IgPro10, CSL Behring, King of Prussia, PA, USA) in Japanese patients with PID, and compared it with PK in non-Japanese patients. A previously developed population PK (PPK) model (Landersdorfer CB et al., Postgrad Med 2013;125:53-61) was validated, and predicted parameters compared with clinical study results.

Design and method: The existing PPK model, containing IgG concentration data from 5 non-Japanese studies, was supplemented with data from 3 Japanese studies (Privigen® or Hizentra®, [IgPro20, CSL Behring, King of Prussia, PA, USA]) to compare the IgG PK parameters between Japanese and non-Japanese patients. The model was externally validated by simulating (300 times) IgG concentration-time profiles in Japanese patients to predict serum IgG PK characteristics and compare with observed Japanese PK data in Study IgPro10_3004 (EudraCT: 2016-001631-12).

Results: The analysis included 4502 serum IgG concentration values (34 Japanese and 168 non-Japanese patients). The PPK estimates obtained from the current analysis demonstrated a clearance (CL, % inter-individual variability [IIV]) of 0.139 L/day (24%), central volume [V2, % IIV]) of 4.01 L (92.1%), distribution clearance (Q) of 0.30 L/day, and peripheral volume of 3.51 L. These results were consistent with the previously-published PPK model (CL [IIV] of 0.142 L/day, and V2 of 3.94 L), with bootstrap mean and 95% confidence intervals (CI) in similar range. Goodness-of-fit criteria indicated that the final PPK model was consistent with observed data, with no systemic bias in model prediction. The prediction-corrected visual predictive checks confirmed that the final PPK model provided a good description of data for both SCIG and IVIG. PK parameters were equivalent between Japanese and non-Japanese patients. Body weight was determined to be a significant covariate on both CL and V2. The simulated and observed area under the concentration-time curve, and maximum and minimum serum IgG concentrations were similar (Figure), with 90% CI overlapping between simulated and observed values in Japanese patients.

Conclusions: The PK parameter estimates of serum IgG were similar between Japanese and non-Japanese patients. The PPK model, updated with Japanese patient data, was consistent with the previously published PPK model and could accurately predict both individual and population serum IgG concentration-time profiles following 3-weekly and 4-weekly Privigen®.

POSTER 151 - REFRACTORY CMV INFECTION IN SEVERE COMBINED AND COMBINED IMMUNODEFICIENCIES: RAG1, ZAP70 AND ORAI1 GENE DEFECTS

AUTHORS

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Objective: Celllular and combined immunodeficiency disorders predispose to recurrent and refractory cytomegalovirus infections. CMV infections are known risk factors causing graft rejection, and graft-versus-host disease following hematopoietic stem cell transplantation (HSCT).
The aim of this study was to investigate the frequency and the effect of refractory CMV infection on the prognosis in severe combined (SCID) and T+ combined immunodeficiency (CID) patients in the pre-HSCT period.

Design and method: Eighty-seven (SCID n=24, CID n=63) cases followed by Ege University Faculty of Medicine Pediatric Immunology Department, Izmir, Turkey were included in the study. Diagnosis and classification were performed according to the 2017 IUIS Phenotypic Classification for Primary Immunodeficiencies. Medical records of these patients were retrospectively reviewed and clinical characteristics collected using a standardized questionnaire.

Results: No statistically significant difference was found between the groups in terms of consanguineous marriage, sibling death and primary immunodeficiency in the family. The age of onset and age at diagnosis were younger in the SCID group. The presence of CMV infection in the SCID group was 12.5%(n=3) and 57%(n=36) in the CID group ($p < 0.05$). The presence of refractory CMV infection in the SCID group was 4%(n=1) and 6.3%(n=4) in the CID group (n=4)($p > 0.05$). There was a positive correlation between IgG level and CD3+CD8+TCRgammadelta cell ratio with the presence of refractory CMV ($p=0.05, R=0.216$ and $p=0.004, R=0.659$, respectively). While chronic diarrhea was more common in patients with refractory CMV infection, no significant relationship was found between growth retardation, recurrent lung infections, sepsis and mortality rates. Molecular causes detected in refractory CMV patients were RAG1 (n=3), ZAP70 (n = 1) and ORAI1 (n = 1) mutations. Important clinical and laboratory features of refractory CMV cases are given in Table 1.

Conclusion: Patients with combined and severe combined immunodeficiency should be closely monitored for CMV serology. CMV infection is an important cause of morbidity especially in T+ combined immunodeficiency patients who present at later ages and have longer survival time after 1 year of age.

POSTER 152 - SYRINGEABILITY AND INJECTABILITY COMPARISON OF COMMERCIALLY AVAILABLE HUMAN SUBCUTANEOUS IGG DRUG PRODUCTS

AUTHORS

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Objective: In human IgG replacement therapy subcutaneous administration enables self-administration by patients in a well-known home environment. As patients have to take care for multiple steps in the application, the ease of infusion is of importance. Syringeability (i.e. ease of drawing solution from vial to syringe) and injectability (i.e. force required for injection) are two major performance parameters of viscous parenteral products, which both affect ease of administration by patients or health care professionals. Aim of the work was syringeability/injectability comparison of marketed subcutaneous human IgG drug products.

Methods: Both syringeability and injectability forces were tested using respective test fixtures with Materials Testing Machine zwickiLine 1kN (Zwick, Germany) and commonly used syringe/needle combinations. 4 marketed SCIg products (2 x 20%, 2 x 16.5%) were tested. A group of test persons manually tested the force perception using the same settings. Ease of expelling was ranked from 1 (very easy to inject) to 5 (very difficult to inject) in a blinded test.

Results: Injectability and syringeability results showed less forces needed and easier handling for administration of 16.5 % SCIg relative to products with 20% protein concentration, directly related to viscosity of the product. Proper needle/injection speed selection can influence the forces needed, nevertheless, in all investigated settings the use of the 16.5 % SCIg was associated with less force than the 20% products.

Conclusions: To ease the administration of SCIg products viscosity might be an inevitable parameter for product selection, especially for adolescents or elderly patients, frequently suffering from hand dexterity symptoms.

POSTER 153 - STUDY DESIGN OF AN OPEN-LABEL MULTICENTER STUDY TO EVALUATE TOLERABILITY OF ACCELERATED SUBCUTANEOUS INFUSION OF IGPRO20: HIZENTRA LABEL OPTIMIZATION (HILO) STUDY

AUTHORS

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Objective: For patients with primary immunodeficiency (PID) subcutaneous immunoglobulin G (SCIG) replacement therapy is an established treatment method. SCIG can be administered using an infusion pump or by manual push; both methods have shown comparable serum IgG trough levels as well as safety and tolerability profiles. The currently approved infusion parameters for the SCIG IgPro20 (Hizentra®, CSL Behring, King of Prussia, PA, USA) are injection site volume of <=25 mL and injection site flow rate of <=25 mL/h in the United States and injection site volume of <=50 mL and injection site flow rate of <=20 mL/h (if well-tolerated, up to 35 mL/hour) in Europe. We evaluated individual patient tolerability response levels of higher infusion parameters for pump assisted and manual push infusions of IgPro20 in PID using forced upward titration design (NCT03033745).

Design and method: This was a multicenter, open-label, parallel-arm, non-randomized study. A total of 45 patients (including at least 14 [30%] pediatric patients aged <=17 years and at least 9 [20%] obese patients with body mass index >=30 kg/m2) were planned for inclusion. Primary endpoints were responder rates in the following study cohorts (n=15 each cohort): Pump-Assisted Volume Cohort (weekly infusions; injection volume from 25 mL to 50 mL per injection site); Pump-Assisted Flow-Rate Cohort (weekly infusions; flow rate from 25 mL/h to 100 mL/h per injection site); Manual Push Flow-Rate Cohort (2–7 infusions/week; flow rate from 30 mL/h to 120 mL/h per injection site; Figure). Each parameter level was tested for 4 weeks, after which responders (patients who tolerated that level) were switched to the next level (e.g. from 25 to 50 mL/h/site). Weekly IgPro20 dose remained stable, usually within 100–200 mg/kg as prescribed by the treating physician. Serum IgG trough levels were assessed on Day 1 and at study end.

Results: Enrolment has been completed. Results will be available early 2020.

Conclusions: This study applied a rigorous evaluation of individual tolerability levels of pump-assisted and manual push SCIG infusion parameters. Results of this study may be used to seek regulatory approval for higher infusion SCIG parameters and new administration methods.

POSTER 155 - ALLERGIC DISEASES IN PATIENTS WITH PRIMARY IMMUNODEFICIENCY

AUTHORS

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Background: Primary immunodeficiency diseases (PIDs) are characterized by an increased risk of infections, autoimmunity, and allergic disorders. Allergic disorders are also common clinical features in PIDs and may be among the presenting manifestations, possibly leading to delayed immunological diagnosis and treatment. Recognition of specific PID-associated allergic conditions could raise suspicion of an underlying PID. We aimed to provide a prevalence of allergic disorders, including atopic dermatitis, asthma, allergic rhinitis, in children with PIDs.

Methods: We studied 57 patients, aged 5 - 18 years (38 boys) with diagnosis of immunodeficiency who were ordered gamma globulin replacement therapy at our clinic. The patients' medical history have been analyzed for clinical symptoms of atopic dermatitis, asthma and allergic rhinitis as well as IgE total level and specific IgE levels against the most common allergens were measured. Diagnosis of allergic diseases was made by allergologist, based on guidelines.

Results: Within the study group, 20 patients (35%) suffered from hypogammaglobulinemia, 31 patients (54%) had IgG subclass deficiency, 3 patients (5%) had common variable immunodeficiency and 3 (5%) patients were diagnosed with agammaglobulinemia. More than half of allergic patients (54%) were diagnosed with IgG subclass deficiency. Allergic evaluation revealed that 40 patients (70%) had a clinical history of atopic dermatitis or/and asthma or /and allergic rhinitis. Thirty eight patients (66,68) were diagnosed with asthma, 13 patients (22,81%) with atopic dermatitis, 7 patients (12.3%) with allergic rhinitis. Fifteen patients (26,9%) suffered from two and 14 patients (26,3 %) from three allergic diseases. Atopy (based on IgE level) was diagnosed in 12 patients (21%).

Conclusion: Allergic disorders are prominent features in PIDs. Our study suggests that in patients presenting allergy symptoms, especially who poorly response to treatment, additional tests to identify PIDs might be conducted, even if the IgE specific antibodies tests are negative. We provide a support tool to use in clinical practice that should raise awareness of PIDs based on presenting allergic manifestations.

POSTER 156 - DEVELOPMENT OF HODGKIN LYMPHOMA IN A PATIENT WITH COMMON VARIABLE IMMUNODEFICIENCY

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Introduction: Common variable immunodeficiency (CVID) is a type of primary immunodeficiency disease (PID) which may exist with diverse manifestations including autoimmunity, granulomatous diseases, lymphoid and other malignancy types beyond recurrent infections. Usually, the incidence of malignancy in CVID patients is up to 20% and usually occurs during the 4th- 6th decade of life. In CVID, non-Hodgkin lymphoma is the most frequently observed malignancy, followed by epithelial tumors of different organs such as stomach, breast, bladder and cervix. Here, we present a rare patient who developed Hodgkin lymphoma 3 months after diagnosed with CVID.

Case: 9-year-old boy had developed mental retardation and optic atrophy after 20 minutes convulsion at 35th day of life and he used an anti-epileptic carbamazepin for 3 years. His immunological evaluation due to having frequent bronchitis (x5/year) and otitis (x13/year) showed panhypogammaglobulinemia with low IgG (365 mg/dl), IgA (<26 mg/dl) and IgM (<18 mg/dl). Lymphocyte subsets were normal. Anti-Rubella IgG (19U/mL), anti-HAV IgG (11.3 U/mL), anti-CMV IgG (1U/mL) titers were all low and isohemagglutinins were negative. Therefore, he was diagnosed as CVID. During the third IVIG infusion and left cervical 3x4 cm lymphadenopathy (LAP) was detected. Fine needle aspiration biopsy material demonstrated Reed-Stenberg cells. Abdominal ultrasonography was normal. Neck ultrasonography showed pathologic LAP developments including left jugulo-digastric (32 mm) and supraclavicular regions. Hypermetabolic LAP at left supraclavicular region and diffuse hypermetabolic appearance of bone marrow in PET-CT suggested lymphoproliferative malignancy. Material from excisional biopsy positively stained by anti-CD30/-CD15 monoclonal antibodies and gascin indicated Hodgkin lymphoma (nodular sclerosing, stage 3A). However, PCR testing for EBV was negative. He is now receiving reduced dose ABVD (Adriamycin, Bleomycin, Vinblastine, Dacarbazine) regimen for Hodgkin lymphoma.

Conclusion: Malignancy risk is high in CVID and the patients should be examined meticulously when they are admitted for routine IVIG treatments. This help to diagnose and treat their malignancy development early.

POSTER 157 - IDENTIFYING CHILDREN WITH PRIMARY IMMUNODEFICIENCY DISORDERS FOR DEVELOPING EFFECTIVE PREVENTION STRATEGIES: EVIDENCE FROM SOUTH INDIA

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Background: Persons with primary immunodeficiency disorders (PIDD) who receive oral poliovirus vaccine (OPV) or are household contacts of OPV recipients are at risk of excreting immunodeficiency-associated vaccine-derived polioviruses (iVDPVs). iVDPVs can be transmitted and cause paralytic polio. The objective of this study was to determine the feasibility of identifying infants and young children with PIDD in south india, and among those identified, to estimate the proportion excreting iVDPVs.

Methods: Patients admitted at 5 referral and teaching hospitals from the hospital catchment area were screened for PIDD using a standardized clinical case definition. PIDD was confirmed using results of testing for age-specific quantitative immunoglobulins (QIGs) levels. Stool specimens were collected according to WHO guidelines from children with confirmed PIDD.

Results: During January–May 2017, 10 patients were identified who met the clinical case definition for PIDD; their median age was 1.4 years (range: 2 months to 10 years). Six (46%) of the patients had age-specific QIG results that confirmed PIDD. Stool specimens from four patients tested negative for polio vaccine viruses. All four had received OPV between 50 and 264 days prior to study recruitment.

Conclusion: Identifying children with PIDD at referral and teaching hospitals in INDIA is feasible, but a larger number of patients is needed to estimate the risk for iVDPV excretion. The national polio eradication program should expand surveillance for PIDD case-patients and regularly test persons with PIDD for poliovirus excretion. These efforts will be essential for developing effective prevention and control strategies In India following OPV cessation, where even a minimal iVDPV risk could have significant public health consequences.

POSTER 158 - SEVERE COMBINED IMMUNE DEFICIENCY WITH DISSEMINATED MYCOBACTERIUM TUBERCULOSIS INFECTION AFTER BCG VACCINATION

AUTHORS

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Introduction: SCID is an uncommon, serious Primary Immune Deficiency (PID) that combines absence of T and B-lymphocyte function, caused by different genetic defects that lead to extreme susceptibility to infections. The only effective treatment is Hematopoietic Stem Cell Transplantation.

Case presentation: A 5 month old, female patient is admitted at Hospital del Niño “Manuel Ascencio Villarroel” in Cochabamba-Bolivia. No consanguinity background, a 2 month old brother died because of sepsis complications. She receives BCG at birth and routine vaccination at 2 months. She presented a lump at underarm region (a), no scar at BCG site of injection. Background: atopic dermatitis and amoxicillin allergy. She presents no response to antibiotics, bad evolution with purulent secretion, local volume gain and fever. Blood tests show lymphopenia and chest X-ray shows absence of thymus. During the next days she presents diarrhea and intestinal obstruction. Adequate imunoglobulin levels except for high IgE. Immunophenotypic test shows CD4+ T-cell (548 cells/ml) and CD19+ B-cell- lymphopenia (175 cells/ml). GeneXpert test for gastric fluid reports Mycobacterium tuberculosis, specific treatment is initiated together with IVIG. The underarm abscess evolves badly with necrotic areas (b) and we get to the diagnosis of lymphatic and disseminated Mycobacterium tuberculosis infection. During the following days the patient presents respiratory and septic complications, the patient is discharged by family request, and patient dies at home a few hours later.

Discussion: SCID is a severe PID with very poor prognosis due to infectious complications. In countries where BCG vaccination is still practiced disseminated tuberculosis is sometimes the presentation of the disease, usually with fatal course.

POSTER 159 - J PROJECT TO DISCOVER SIMILARITY AND DIFFERENCES BETWEEN THE PATIENTS WITH THE PRIMARY IMMUNODEFICIENCY IN EASTER – CENTRAL EUROPE AND IN OTHER COUNTRIES

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The J Project physician education and clinical research collaboration program was set up in 2007 to identify the Primary Immunodeficiency (PID) patients in Eastern and Central Europe (ECE). Professor Laszlo Marodi, Hungary is a founder and leader of this project. The J Project has spread and reached milestone successes in terms of the number of diagnosed and treated patients and at the later stage, establishing genetic centres for mutational analysis in ECE countries. The first cohort study on genetic and demographic features of X-linked agammaglobulinemia was published in 2009. The next multicentre clinical study summarised clinical the biggest group children with Nijmegen Breakage Syndrome (NBS), with the founder mutation c.657 661 del15 in exon 6 of the NBS gene, called the Slavic mutation in 2015. Presently the most important collaboration study showed that the majority (77%) of patients with homozygous RAG1 p.K86fsTer33 originated from Vistula watershed area in Central and Eastern Poland, with high frequency in other Easter Europe countries. Different BCG vaccine substrains used in ECE have been obtained as a result of genetic changes which occurred during repeated subculture. All ready now, the comparable study to demonstrate the less reactogenic substrain in the region is under investigation.

POSTER 160 - APPROACH TO THE DIAGNOSIS OF AUTOIMMUNITY IN PRIMARY IMMUNODEFICIENCY

AUTHORS

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Following infections, autoimmune manifestations are the second most common clinical consequence of primary immunodeficiency diseases (PIDs). The coexistence of immunodeficiency and autoimmunity may appear to be paradoxical since one generally represents a hypoimmune state and the other a hyperimmune one. These lead to difficulties in the diagnosis of autoimmune complications in PID patients. The diagnosis of autoimmune disorders in PID patients is not straightforward and requires a history, physical exam, laboratory testing, imaging, and sometimes pathological investigations. Due to the hypogammaglobulinemic condition in PADs and even some types of CIDs, diagnostic tests which are based on antibodies may be not useful in these patients. On the other hand, normal levels of immunoglobulins may be present in some patients, while they do not produce sufficient specific antibodies, therefore most autoantibodies are not found in these patients. Specific antibody deficiency (SAD) and CVID are obvious examples of PAD in which production of autoantibodies is low/negative. In addition, in CVID, IgA is frequently deficient, which means there is a lack of antibodies in this immunoglobulin class. Despite a close relationship between diagnosis of autoimmunity and autoantibodies, some PID patients are persistently negative for disease-specific autoantibodies. Moreover, the use of monthly IVIg may interfere with some of the special immunologic tests, therefore it may be helpful to use frozen serum for future testing if IVIg therapy is being initiated. Taking a biopsy from the involved organ is another diagnostic strategy if it is clinically indicated. In patients without PIDs the affected tissue has a typical and well known histology, whereas in PID patients, as an effect of immunoglobulins and immune cells deficiency, affected tissue can have a different histological appearance. Medical imaging and radiography are also used for diagnosis of autoimmune disorders. In some types of PIDs, radiosensitivity is another problem that limits the use of medical radiation for diagnosis of autoimmunity. Therefore, management of autoimmunity in patients with PID requires special considerations because dysregulations and dysfunctions of the immune system along with persistent inflammation, impair the process of diagnosis and treatment.

POSTER 161 - A RARE PRIMARY IMMNUNODEFICIENCY: SELECTIVE IGM DEFICIENCY, CASE REPORT IN PEDIATRIC

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Introduction: Selective IgM deficiency (SIgMID) is a rare primary inmunodeficiency with the prevalence around of 0.03% some literature describes a slightly greater penetration of SIgMID in men (1.97%) against females (1.42%). Many theories try to explain this condition such as an intrinsic defect in B – cell maduration into IgM – secreting cells also a lack of helper function of CD4+ cells or excesive activity of CD8 + suppressor cells. We present the first case of selective IgM deficiency in children diagnosed in El Salvador.

Case Report: A 13 years old boy was referred to our outpatient clinic with 4 years of presented right chronic suppurative otitis media and destruction of the mastoid bone was observed by means of a computarized axial tomography. On his past medical history he was a premature newborn and he had around 12 episodes of pneumonia in the firsts 2 years of life. His mother has Antiphospholipid Syndrome (primary) and she had 2 miscarriages prior to the birth of our patient.
His physical examination was a normal height and weight and the rest of his evaluation was unremarkable. At that moment, laboratory tests revealed no abnormalities in WBCs and platelets but the unusual and chronic course of his condition led to immunological tests and the results showed low levels of IgM and CD 19 cells (Table 1 and 2) and with these findings Selective IgM deficiency was suspected. Because prophylaxis with azitromycin was not enough we began intravenous human immunogloulin (IVIG) treatment.

Discussion: Selective IgM deficiency according to the diagnostic criteria of the European Society for Immunodeficiencies is defined as a serum IgM level repeatedly below 2 standard deviations of normal with normal levels of serum IgA, IgG and IgG subclasses, normal vaccination responses, absence of T cell defects and absence of causative external factors. In our country we have limitations in the field of PID because we do not have many specialists and resources to investigate these conditions and with our patient we do not have available polysaccharide tests to complete the diagnosis. We suspect selective IgM deficiency and his evolution with IVIG has been excellent. Worldwide IgM deficiency is poorly described and has been associated with severe and/or recurrent infections, atopy and autoimmunity this is the reason that brings to think about a multifactorial origin and genetic trials are needed to understand this uncommun primary immunodefiency.

POSTER 162 - EXPERIENCE OF THE CLINICAL IMMUNOLOGY SERVICE OF A PUBLIC UNIVERSITY HOSPITAL IN CALI, COLOMBIA

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Introduction: The Clinical Immunology outpatient service was stablished in the Hospital Universitario del Valle (HUV) in Cali, southwest of Colombia in July 2015. The clinic evaluate an average of 10 to 12 patients weekly (new and follow up patients). Most of the cases are referred in the context of Recurrent Infection syndrome, hypogammaglobulinemia, disseminated mycobacterial disease and severe autoimmune or allergic disease.

Methods: Here is presented the characteristics of patients consulting to the Clinical Immunology outpatient service in the Hospital Universitario del Valle (HUV) in Cali.

Results: The Clinical Immunology outpatient service has evaluated 317 patients classified as: confirmed Primary Immunodeficiencies (PID)=78 patients, Secondary Immunodeficiencies= 21 patients, Autoimmunity/Rheumatic disease= 52 patients, Severe/Refractory Allergy= 68 patients and Infectious diseases with high suspicious of PID in follow up= 44 patients.
According to the IUIS-2017 classification, 78 patients with confirm Inborn Errors of Immunity (PID) were diagnosed: I. Immunodeficiencies affecting cellular and humoral immunity 3; II. CID with associated or syndromic features 15; III. Predominantly Antibody deficiencies 33: V. Congenital defects of phagocyte number, function or both 7; VI. Defects in intrinsic and innate immunity 6; VII. Autoinflammatory disorders 8, VIII. Complement deficiencies 4; IX. Phenocopies of PID 2. The mean age is 16 years with a Male:Female ratio 40:38.

Conclusion: The Clinical Immunology service constitutes an opportunity for low income people with public health care insurance in the southwest of Colombia. The combine effort of Universidad del Valle and Hospital Universitario del Valle has contributed to improve the suspicious, diagnosis and treatment of patients living with Inborn Errors of Immunity.

POSTER 163 - PRIMARY IMMUNODEFICIENCY IN INFECTION-PRONE CHILDREN: CLINICAL CHARACTERISTICS AND IMMUNOLOGICAL FINDINGS

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Background: Primary immunodeficiency diseases (PIDs) comprise a heterogeneous group of disorders mainly characterized by increased susceptibility to infections. The aims of this study were to estimate the occurrence rate of PID in the paediatric and to describe their demographic, clinical and immunological characteristics. During a period of 2 years, in two paediatric speciality clinics in southern India, children being seen for infections and fulfilling specific criteria were evaluated according to a predefined examination schedule. The initial analysis consisted of complete blood counts with analysis of lymphocyte subpopulations (T, B, NK cells), measurement of immunoglobulins (IgG, IgA, IgM, IgE and IgG subclasses), and assessment of the complement system (classical, alternative and lectin pathways). In addition, results of these immunological analyses in other children from the same area and time period were evaluated.

Results: In total, 59 children (53.6% males) met the criteria and were included. The most common infection was recurrent otitis media. Immunological analyses results for about two thirds of the patients were outside age-related reference intervals. Further examination in this latter group identified 15 children with PID (9 males); 7 (2.7%) had genetically defined PID, representing 4 different diagnoses, and another 8 (3.1%) had a clinically defined PID - common variable immunodeficiency. No additional PID patient was identified from the evaluation of laboratory results in children not included in the study. The median age at diagnosis was 3.5 years (range 1-12 years).

Conclusions: The occurrence rate of PID was about 4 new cases per year in this population. Several different PID diagnoses were found, and the application of specified criteria to identify PID patients was useful. In children who are prone to infection, the use of a predefined set of immunological laboratory analyses at their first examination was beneficial for early identification of patients with PID.

POSTER 164 - RECURRENT SALMONELLA ENTERITIDIS MENINGITIS AS ATYPICAL PRESENTATION OF MHC CLASS II DEFICIENCY

AUTHORS

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Objective: Major histocompatibility complex (MHC) class II deficiency is combined immunodeficiency characterized by recurrent and severe gastro-intestinal and pulmonary infections, but infections in other locations can occur. Herein, we report the case of patient presenting with recurrent Salmonella Enteritidis meningitis.

Design and methods:

The patient is a male aged of 5 months.

Biological investigation included:

- Measurement of serum IgG, IgA and IgM levels by nephelometry
- Immunophenotyping of T, B, NK cells and evaluation of HLA DR expression by flow cytometry.
- Bacteriological analysis of stool and cerebrospinal fluid (CSF) by conventional methods.
- Evaluation of antibody response against Campylobacter and Yersinia enterocolitica by ELISA.
- Screening for the 752 del G25 mutation by sequencing of RFXANK gene.

Results: The patient is offspring of consanguineous marriages. The first manifestation was meningitis, followed by a second episode as soon as the antibiotic treatment was stopped. The patient had also very few episodes of diarrheae. Bacteriological analysis of CSF, revealed the presence of Salmonella Enteritidis and the susceptibility of the strain showed resistance to Penicillins and Ciprofloxacine. The several stool cultures performed were negative.
Antibody response against Campylobacter and Yersinia enterocolitica was negative.
The patient showed lack of MHC class II expression, CD4 lymphopenia and decrease in IgA and IgM levels.
DNA sequencing identified the homozygous mutation 752 delG25 in RFXANK gene, this deletion is recurrent in Algerian patients.

Conclusion: Despite, having typical immunological and genetic profile of the deficiency, the patient had clinical presentation dominated by recurrent Salmonella Enteritidis meningitis, the source of contamination could not be identified.

POSTER 165 - AGAMMAGLOBULINEMIA LINKED TO THE CHROMOSOME X: MULTIDISCIPLINARY APPROACH

AUTHORS

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Introduction: Agammaglobulinemia linked to chromosome X is a genetic disorder where B percursors lymphocytes are unable to mature to become in B lymphocytes and eventually in plasma cells, being prone to serious or recurrent infections in first months of life. Diagnosis is established with clinic and laboratory (immunoglobulin and genetic quantification). It is essential to make a detailed medical history with laboratory relevant for a correct diagnosis.

Material and methods: Child without a family history of Immunodeficiencies; at 2 months of age he had meningoencephalitis post-vaccination with SABIN. At 4 months of life, he developed septic shock, by Pseudomona sp, that reverses with antibiotics. At 6 months of age, he repeats a septic picture that requires higher spectrum antibiotic therapy. At 9 months of age, he had adenovirus infection. It continued until the month 18, with a repetition of infectious pictures, so it was derived by suspicion of immunodeficiency to the Immunology service of Garrahan Hospital (BsAs), because the province of Salta does not have such service.
Immunoglobulin dosing: IgG 108 mg/dL; IgA 7 mg/dl; IgM 20 mg/dL. Molecular Study: BTK gene sequencing: Mutation p.R520X in homozygous state in the exon 15 of the BTK gene in the child and in heterozygous state in the mother (disease carrier). Agammaglobulinemia linked to chromosome X was diagnosed, and treatment with Gammaglobulin EV was initiated and then he continued prophylactic treatment with Subcutaneous Gammaglobulin.

Results: The family attends the hemophilia and rare diseases foundation for counseling. The foundation carried out a comprehensive approach by the multidisciplinary team (medical, biochemical, nursing, psychology, social work). Containment and guidance allowed the empowerment of the disease and adherence to treatment, with fulfillment of the protocol. As a result, parents were able to infuse the child at home, thus avoiding infections and impacting on improving the quality of life of the child and his family.

Conclusion: Accurate diagnosis together with specific treatment and constant control are the best tools for the proper management of these patients, achieving a decrease in infectious and inflammatory processes and their aftermath, as well as improving quality of life and survival. The patient must be addressed in an integral and multidisciplinary manner in a reference center of Primary Immunodeficiencies.

POSTER 166 - 2ND POLISH NBS MEETING – A STEP TOWARD TRANSLATIONAL MEDICINE.

AUTHORS

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Background & Objective: Nijmegen Breakage Syndrome (NBS) is a rare DNA-repair disorder, characterized by microcephaly with typical bird-like facial dysmorphy, premature aging, combined immunodeficiency, chromosomal instability, and high predisposition to malignancy. Due to founder effect almost all affected persons carry identical homozygous deletion (c.657_661del5) of NBN gene and the majority of patients come from Central-Eastern European countries.

Methods: A meeting NBSki w koszyczku was organized by the NBS Families Support Group under the auspices of CMHI and Polish Society of Pediatric Oncology and Hematology. It was exclusively dedicated to patients with this rare syndrome and their parents/families. Twenty-two families and twelve experts attended this one-day-event in Warsaw. The current knowledge retrieved from results of a 3-year-grant (ERA-NET-E-Rare-3/I/EuroCID/04/2016 grant), comprising clinical and laboratory analysis of 52 Polish living patients, was presented and discussed with families. The main topic was dedicated to indications and results of hematopoietic stem cell transplantation.

Conclusions: In order to meet the expectations of patients and their parents the 1st edition of “NBS guidelines for patients and families” is under construction as an outcome of the above meeting. Being the largest NBS support group worldwide we feel obliged to share our experience with NBS patients from other countries.

POSTER 167 - A CASE OF UNUSUAL SEVERE TUBERCULOSIS IN A CHILD WITH A VARIANT OF UNKNOWN SIGNIFICANCE OF THE IFN-GAMMA RECEPTOR 1: WIDENING THE SPECTRUM OF MENDELIAN SUSCEPTIBILITY TO TUBERCULOSIS?

AUTHORS

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Objective: To describe unusual severe tuberculosis (TB) in a child with an IFNγ-receptor 1 (IFNgR1) variant of unknown significance.

Design/methods: Selected children presenting to Tygerberg Hospital, Cape Town, with unusual, severe or recurrent TB, and their immediate families, were investigated with whole exome sequencing (WES) and IFNgR1 functional assays if indicated. IFNgR1 expression on peripheral blood mononuclear cells (PBMCs) was measured by standard surface flow cytometry. IFNgR1 function was determined by phosphorylated Signal Transducer and Activator of Transcription 1 (STAT1) concentration after IFNg stimulation (Phospho-specific flow cytometry). IFNg-induced IL-12 production and IL-12-induced IFNg production by patient PBMCs was determined by ELISA after 48 hours' co-stimulation with phytohemagglutinin. We present a case of unusual TB in a child, and the genetic and phenotypic spectrum in the family.

Results: KK presented at 9 years of age with pulmonary TB (PTB) and TB meningitis (TBM). She was BCG-immunized, HIV exposed but uninfected. Computerised tomography of the brain, chest radiograph and cerebrospinal fluid (CSF) analysis were compatible with TB (not bacteriologically confirmed). Immunological screen was normal (total lymphocyte count, lymphocyte CD subsets, serum immunoglobulins and neutrophil burst).
KK's sister AK, HIV negative, was diagnosed with PTB and TBM 6 days after the index, at 23 months. She had received 6 months of isoniazid preventive therapy at birth (maternal exposure). She was not given BCG. She had 2 immune reconstitution-type episodes, while adherent to appropriate treatment.
The mother, HIV infected, was concurrently diagnosed with a second episode of PTB. The father, otherwise healthy, had latent TB infection (quantiferon test).
IFNGR1 variants were found in KK and the father, while a NOD2 variant was detected in the mother, AK and KK (all variants heterozygous). IFNgR1 functional assays were done in the index and father (Table).

Discussion: Mutations in the genes regulating the IFNg and IL-12 signalling pathway result in susceptibility to typically non-pathogenic mycobacteria. In high TB burden settings, such mutations may present with increased susceptibility to severe, persistent, recurrent, or unusual forms of disease caused by Mycobacterium tuberculosis.
TBM is unusual in children >5 years old. We detected a putatively disease-associated variant in IFNgR1 in the index, but its role in the unusually severe clinical phenotype is uncertain (the father with the same variant was unaffected), as is the impact of the co-existent NOD2 variant. This case suggests variable expression and penetrance of the IFNgR1 variant, and a possible role for epigenetic and immunological co-factors.

POSTER 168 - PROLONGED EVENT FREE SURVIVAL IN 3 CHILDREN WITH AUTOIMMUNE LYMPHOPROLIFERATIVE SYNDROME: A CLINICAL EXPERIENCE FROM A TERTIARY CARE CENTRE AT CHANDIGARH, NORTH INDIA.

AUTHORS

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Objective: To describe the spectrum of manifestations in 3 children with autoimmune lymphoproliferative syndrome (ALPS).

Design and method: Analysis of records of 3 children diagnosed with ALPS.

Results:

CASE 1: A 6 year old boy, presented with fever, lymphadenopathy, pallor and jaundice of 8 months duration. On examination, he had pallor, lymphadenopathy, splenohepatomegaly. Investigations revealed pancytopenia; Direct Coombs test (DCT) was 4+ against IgG; elevated Vitamin B12 (Table). Bone marrow biopsy revealed normocellularity with erythroblastopenia. IgM parvovirus was reactive. Double negative T cells (DNTs), soluble FAS ligand (FasL) levels were elevated, suggesting ALPS. He was started on intravenous methylprednisolone pulse (30 mg/kg), intravenous immunoglobulin therapy (2 gram/kg). Injection rituximab (375 mg/m2), mycophenolate mofetil (MMF), followed by oral sirolimus was added in view of partial response in cytopenias over 3 months follow up. He showed gradual recovery in cytopenias and has not required blood transfusions over the last 5 months. Lymphadenopathy has subsided and splenomegaly is regressing. Targeted next generation sequencing (NGS) using a 44 gene primary immunodeficiency panel revealed a heterozygous, pathogenic variant in Exon 3 of FAS gene (c.197 G>A, p.Gly 66 Asp).

CASE 2: A 6.5 year old girl, born to a 3rd degree consanguineously married couple, had recurrent episodes of pallor with splenomegaly (required multiple PRBC transfusions since infancy). On examination, had splenohepatomegaly. Investigations revealed pancytopenia; reticulocyte count 11.5%; DCT positive for C3d; hypergammaglobulinemia; elevated lactate dehydrogenase (LDH) and DNTs (table). Bone marrow examination was normal. She was started on oral prednisolone (2 mg/kg/day followed by tapering) with MMF. She showed good response, spleen size has reduced and no more PRBC requirement. Mutation analysis, revealed homozygous nonsense nucleotide substitution mutation in Exon 1 of FASL (343 C>T).

CASE 3: A 55 year old boy, presented with recurrent episodes of fever and pallor requiring multiple PRBC transfusions since 1.5 years of age. He had severe pallor, jaundice, massive splenomegaly. Investigations revealed pancytopenia; reticulocyte count 10%; LDH 980 U/L; DCT was negative; DNTs were 19.75%; Soluble FasL and Soluble IL-10 were elevated (table). He responded well to oral prednisolone and MMF. NGS did not reveal any pathogenic variant in FAS and FASL gene. This could probably be due to a somatic mutation in FAS gene, which can be detected only by variant analysis in sorted DNTs.

Conclusion: We describe our experience of managing 3 children with ALPS over a follow-up period of 90 patient months.

POSTER 169 - COMMON VARIABLE IMMUNODEFICIENCY (CVID) LIKE PRESENTATION IN A YOUNG INDIAN PATIENT WITH NOVEL MUTATION IN DOCK2 GENE

AUTHORS

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Objective: Common variable immunodeficiency (CVID) is the most common symptomatic primary immune deficiency (PID) and is characterized by recurrent sinopulmonary infections, hypogammaglobulinemia and impaired specific antibody responses. Next generation sequencing (NGS) has revolutionized the field of PIDs and several patients initially classified as having CVID have now been found to have causative genetic mutations.

Design and method: To report the case of a young Indian male who had CVID like presentation and whole exome sequencing revealed a novel mutation in the DOCK2 gene.

Results: A 5-year-old boy presented to us in 2001. He had had recurrent episodes of pneumonia in the past. On examination, he was failing to thrive and had cervical lymphadenopathy. Laboratory investigations revealed low IgG (226 mg/dl, N=540-1600), low IgA (44mg/dl, N=50-240), normal IgM (83 mg/dl, N=50-180), normal CD3+ T cells (91.2%) and low CD19+ B cells (1.5%). A clinical diagnosis of CVID was considered and he was initiated on replacement intravenous immunoglobulin (IVIg) therapy. He remained clinically well, started gaining weight and had no infections. At 22 years of age he presented with loss of weight, abdominal pain and decreased appetite. On examination, he was found to have hepato-splenomegaly. Laboratory investigations showed thrombocytopenia (platelet count 40x109/L, N=150-140x109/L), low CD4+ T cells (13.73% of all CD3+ T cells) and low CD4:CD8 ratio (0.19). T cell functional analysis was carried out using phytohaemagglutinin (PHA) stimulation and Carboxyfluorescein Diacetate Succinimidyl Ester (CFSE) staining.
It showed that proliferative index of the patient's lymphocytes (6.9) was significantly less as compared to an age matched healthy control, thereby suggesting an impaired T cell function. Bone marrow aspirate and biopsy revealed no abnormality. Whole exome sequencing was carried out at this time that revealed a homozygous mutation in the DOCK2 gene at c.640C>T resulting in change of Arginine to Tryptophan at position 214. He is being continued on IVIg replacement and has been counseled for hematopoietic stem cell transplantation.

Conclusions: We report a novel mutation in DOCK2 gene in a patient with CVID like presentation. NGS is a valuable tool for elucidating the genetic etiology in CVID.

POSTER 170 - IN DIFFERENTIAL DIAGNOSIS OF IDIOPATHIC THROMBOCYTOPENIC PURPURA: WISKOTT-ALDRICH SYNDROME

AUTHORS

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Introduction: Thrombocytopenia is often observed laboratory sign during childhood, which makes you think a lot of different diseases in the differential diagnosis. An algorithm for evaluating etiology of thrombocytopenia is based on thrombocyte size, decreased production or increased consumption of thrombocytes as well as being congenital or acquired causes. Immune-mediated thrombocytopenia, related to acquired and increased consumption, is the most frequent factor in children. Here, an interesting idiopathic thrombocytopenic purpura (ITP) patient who developed eczema during follow-up and later diagnosed as Wiskott-Aldrich syndrome (WAS) by genetic analysis is being presented.

Case Presentation: 1-year-old male patient was brought to us with symptoms of chronic cough, itchy rash, bleeding on oral mucosa and anemia. Thrombocyte number was 20.000/µL. After intravenous immunoglobulin (IVIG) at a dose of 0,8 gr/kg was given to him due to diagnosis of ITP, thrombocyte number increased up to 50.000/µL and discharged home. One month later, he was hospitalized due to fever, cough, bloody stool and urine for 4 days. At this time, CBC showed Hb: 2.6 gr/dL, reticulocyte: 8% and thrombocyte: 10.200/µL. MPV value in CBC mostly could not be read by the machine. Erythrocyte and thrombocyte suspensions were given and bone marrow aspiration demonstrated increased number of megakaryocytes. Bone marrow biopsy was normal. Direct Coombs test was negative. No sign of hemolysis was seen on blood smear. IgG, A, M levels were normal except for mildly elevated serum IgE. Pediatric immunology evaluated this patient by reason of frequent infections and bloody stool, but did not think humoral immunodeficiency or cow's milk allergy by normal skin prick test. Pediatric gastroenterology also did not indicate any gastro-intestinal problems. Scintigraphy for Meckel's diverticulum was normal. Skin appears from time to time itchy erythematous rash appearing eczema and Molluscum contagiosum-like lesions. With this clinical story, being male and having eczema indicated WAS and genetic diagnosis was made. Hemizygous variant mutation [p.Arg34* (c.100C>T)] was detected on the exon 1 of WAS gene.

Conclusion: Physicians should keep WAS in mind in a patient presenting with chronic cough, itchy rash, and gastrointestinal bleeding suggesting an allergic disorder. Infections and immunologic abnormalities in this syndrome vary from mild to severe depend on the patient. Nowadays, confirmation of diagnosis can be made by mutation analysis.

POSTER 171 - NK CELLS AND THEIR ROLE IN COMMON VARIABLE IMMUNODEFICIENCY

AUTHORS

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Introduction: Common variable Immunodeficiency (CVID) is the most Common symptomatic humoral immunodeficiency and could presented as many forms like: malignancy, autoimmunity, granulomatous disease and recurrent pulmonary infections.
The objetive of the study it's to evaluate the levels of NK cells in a group of patients with CVID.

Methods: we conducted a cross sectional study that included all the patients with the diagnosis of CVID at the Primary Immunodeficiencies Clinic in the Hospital Especialidades of XXI Medical Center in Mexico. All patients with confirmed diagnosis according to ESID criteria for CVID. We performed a lymphocyte flow cytometry that includes CD 16/56 cells, CD3, CD4 and CD8, also the patients filled a poll with demographic and clinical data. The se study was aprove at The Etica and Research local Committee, R-2018-3601-148. The statistical analysis was performed with Spss software version 22.

Results: we included 37 patients, average age of 40.33 years (+/-14.46). 62.2% Female and 37.8% male. 48.6% of the patients with autoimmune diseases; 10.8% with malignancy and the most common was thyroid papillary carcinoma (2), oneHodgkin Lymphoma and one patient with chronic myeloid leukemia.
67.7 % with bronchiectasis as a complication of recurrent pulmonary infections. Of the total of patients 5 died. The average of NK cells was 173 (50-596). We compared the patients with malignancy with the group without and found that the first had lower NK cells (125 vs 226) p 0.036.

Conclusions: we found lower levels of NK cells in the patients with malignancy, and also in the patients that died; this could provided data about the role of NK cells in the Development of malignancy and even of dead, but we need more Studios about these subject.

POSTER 172 - KNOWLEDGE AND PRACTICE OF PRESCRIBING POLYCLONAL HUMAN IMMUNOGLOBULIN THERAPY BY THE DOCTORS IN REFERRAL TEACHING HOSPITALS IN KHARTOUM IN 2018

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Introduction: Intravenous immunoglobulin (IVIG) are biological products used in the treatment of a large number of inflammatory and immunological conditions. They are essential in the treatment of patients with immunodeficiency. These products are made by fractionating plasma from thousands of blood donors, hence the potential hazards of viral transmission, adverse reactions, the growing difficulties in obtaining safe plasma and the cost implications of using the products. There is a general perception of poor knowledge and practice of using IVIG in Sudan, and poor demand management. However, nothing is known about the magnitude of these problems.

Objectives:

1. To investigate the level of knowledge, and the practice of IVIG prescription with regards to indications, availability, doses and side effects among doctors in referral hospitals within Sudan.
2. To identify the limitations of prescribing IVIG among doctors.

Methodology: A descriptive cross-sectional study conducted at 7 referral hospitals within Khartoum, capital of Sudan. The population included physicians who prescribe IVIG in medical and pediatric departments within these hospitals. Data was collected using non-supervised self-completed questionnaires containing multiple choice and “self-rating” questions. Responses to the questions were translated into a scoring system that corresponded to the number of correct answers. Then an overall score of the level of knowledge and different practices of using IVIG was classified into unsatisfactory, satisfactory and high scores. Data was analyzed using Statistical Package for the Social Sciences (SPSS).

Results: An overall scoring on the knowledge on IVIG was classified as satisfactory (score 5-8) among 50.8% of the study population. In contrast, 25.5% of physicians, mainly junior doctors, had an unsatisfactory level of knowledge (score 0-4), while 23.7% scored high rates (score 9-13). In contrast to knowledge scores, 32.3% of the population showed an unsatisfactory rate on the practice scores (0-4), whereas only 7.3% of the respondents reflected good practice by higher scores of 9-13. Satisfactory practice (score 5-8) was shown by 60.4% of the population. Cost and availability were the main limiting factors affecting prescriptions of IVIG.

Conclusions: While the majority of the respondents showed satisfactory knowledge and practice scores, there was a discrepancy between high and low scores in knowledge when compared to those of practice among the respondents. These results call for training programs for doctors and the establishment of local guidelines that will govern and standardize the use of IVIG. This will hopefully lead to rationalizing the use of the products and lead to better demand management.

POSTER 173 - GRANULOMATOUS HEPATITIS AND HYPOGAMMAGLOBULINEMIA IN A YOUNG GIRL CAUSED BY NOVEL MUTATION IN ZBTB24 GENE

AUTHORS

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Objective: Immunodeficiency, centromeric instability and facial anomalies syndrome 2 (ICF2) is a rare primary immunodeficiency disorder cause by mutation in ZBTB24 gene. This syndrome has varied clinical presentation and not more than 30 cases have been reported so far. Patients may have recurrent infections with common variable immunodeficiency (CVID) or combined immunodeficiency (CID) like presentation. Hypogammaglobulinemia is a hallmark feature of ICF2, however, granulomatous hepatitis has not been reported.

Design and methods: To report a case with granulomatous hepatitis and hypogammaglobulinemia caused by novel mutation in ZBTB24 gene

Results: A 7 year old girl, resident of Bangladesh and born to consanguineous parents, was symptomatic since the age of 6 months with complaints of recurrent fever episodes. She was evaluated elsewhere before presenting to us and received a course of anti-tubercular treatment. In view of persistent symptoms, she was referred to another hospital where she was found to have elevated liver transaminases and liver biopsy showed epitheliod cell granuloma in the portal tract. A clinical diagnosis of sarcoidosis was considered and she was referred to our institute. On examination, she was found to have broad nasal bridge and hepatomegaly. Rest of the examination was unremarkable. Laboratory investigations revealed elevated liver transaminases (alanine transaminase 139 U/L [N upto 44], aspartate aminotransferase 154 U/L [N upto 44], alkaline phosphate 1748 U/L [N= 50-136]), low IgG (478 mg/dL [N 540-1610]), low IgM <25 mg/dL, normal IgA (229 mg/dL [N 50-240]), normal B cell percentage (8%), low CD4+ T cells percentage 29.4% with reversal of CD4+T cells to CD8+ T cells ratio (0.54) and low switched memory B cells {CD27+IgM-IgD-} (1.69% [N=6.5-29.1%]). A clinical possibility of common variable immunodeficiency or combined immunodeficiency with granulomatous hepatitis was considered. She was initiated on intravenous immunoglobulin replacement therapy (400 mg/kg), cotrimoxaole prophylaxis, oral prednisolone (initial dose 1 mg/kg/day that was gradually tapered) and azathioprine (2 mg/kg/day). She showed clinical improvement: fever subsided, appetite improved and she gained weight. Liver transaminases improved gradually. Whole exome sequencing revealed a homozygous mutation in the exon 2 of ZBTB24 gene (c.433_434del p.Ala145ProfsTer7). She is on follow-up for last 30 months and is getting regular replacement IVI therapy. She is clinically well, is gaining weight, had no significant infections and liver transaminases have recovered.

Conclusion: This is the first report of ICF2 syndrome presenting with granulomatous hepatitis.

POSTER 174 - PATIENT'S ATTITUDES FOR ROUTE OF IMMUNOGLOBULIN REPLACEMENT THERAPY; MARMARA EXPERIENCE

AUTHORS

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Objective: Immunoglobulin replacement therapy (IgRT) for patients with primary immunodeficiencies (PID) have various options such as hospital vs home based and intravenous (IVIG) vs subcutaneous (SCIG) routes. The aim of this study is to evalaute the attitudes and surveys for quality of life and treatment satisfaction among our PID patients.

Design and Method: 74 PID patients (33F, 41M) receiving IGRT were enrolled into the study. Demographic, clinical and laboratory data were recorded. Treatment satisfaction questionnaire (TSQM-9) and KINDLE for quality of life were administered.

Results: According to IUIS classification; 36 patients were syndromic CID, 22 primary antibody deficiencies (PAD), 14 CID, 7 immunedisregulation (ID), 2 SCID and 1 SCN. Current age was median 13 (1-61 years). Median age at disease onset was 4 years (0-55) and median age at IGRT onset was 5 years (0-55). IgRT administered IV for 53 patients while 21 SC. Immunoglobulin concentrations were %10 for 43 patients (58%) and %5 for 31 patients (42%) Among them, 48/74 patients (64.8%) had no side effects and 62/74 (84%) patients did not require routine premedication. Mean dose (gr/kg) was 0.41 (±0.2) with a dose interval median of 21 days (7-28). Infusion duration mean was 3.3 hours (±1.7). IgG trough/steady mean was 1298 mg/dl (±543). Days of hospitalisation per year was 11±26 days. VAS median for therapy satisfaction was 9 out of 10 (3-10). Mean school/work day loss per month was 1 (±3). Infections/year median was 3 (0-12).

Conclusions: Degree of satisfaction was high among patients receiving both IVIG and ScIG. In choosing IgRT modalities, consideration of patients' preference, personal conditions, age and sharing the decision improves the patients' satisfaction regarding IgRT.

POSTER 175 - HEREDITARY ANGIOEDEMA IN CHILDREN: A CLINICAL EXPERIENCE OVER 20 YEARS FROM NORTH WEST INDIA.

AUTHORS

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Hereditary angioedema (HAE) is an uncommon primary immunodeficiency disorder characterized by Deficiency of C1-esterase inhibitor (C1-INH) leading to diffuse, painless, and non-pitting edematous swelling of soft tissues. HAE is an uncommon autosomal dominant disorder which is potentially life threatening medical condition. The study was carried out to analyze the clinical and laboratory features of patients diagnosed with C1-esterase inhibitor deficiency. Index case had frequent episodes of angioedema and required prophylactic treatment with stanozolol. Sanger sequencing of the SERPING1 gene was performed in 3 patients to detect specific variants in the coding regions and flanking splice junctions was performed. A novel disease causing heterozygous variant c.1429T>G; p.Phe 477Val was detected in the exon 8 of SERPING1 gene. Similar variant was observed in mother of index patient. The pathogenic nature was inferred using 3 free, online bioinformatics tools for prediction of functional effects of amino acid substitution in proteins i.e. Provean, PolyPhen-2 and FATTHM. This was also confirmed by the markedly decreased functional activity of the protein encoded by this variant.

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).

POSTER 176 - PARTIAL DIGEORGE SYNDROME IN A CHILD WITH RECURRENT INFECTIONS

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DiGeorge syndrome (DGS) is a developmental disorder that results from an abnormal cephalic neural crest migration, differentiation or signaling in the third and fourth pharyngeal arches during embryonic development. Deletion of chromosomal region 22q11.2 is the commonest cytogenetic abnormality in patients with partial and complete DiGeorge syndrome. Clinical hallmarks include cardiac defects, dysmorphic features, thymic hypoplasia, cleft palate, and hypocalcemia. We report a case of 15-month-old immunized boy with predominant motor delay presenting with recurrent episodes of upper respiratory tract infections and one episode of aspiration pneumonia.

Case report: The index child was born to nonconsanguineous parents. No history of similar illness was observed in family. The child has been symptomatic since 4 months of age in the form of fever, cough, runny nose and was treated with anti-pyretics and oral antibiotics. Child was diagnosed with ASD and VSD at day 1 of life and in first month he developed aspiration pneumonia. He was discovered to have cleft palate, which was operated at 12 months of age. He has T cell lymphopenia with decreased CD3+ Total lymphocytes (1.37 x109/L); decreased CD4+ Helper T lymphocytes (0.80 x109/L) and Cytotoxic T lymphocyte (0.45 x109/L). Calcium, PTH, Vitamin D levels were normal. USG and CT scan revealed absent thymus. Fluorescence in situ hybridization (FISH) and Multiplex Ligation Dependent Probe Amplification (MLPA) was positive for 22q11.2

Conclusion: Patient with DiGeorge syndrome have impaired cell-mediated immunity with decreased number and function of T lymphocytes. However, an exclusive defect in the humoral immune response has also observed in these patients. DGS is traditionally diagnosed with fluorescence in situ hybridization (FISH). However, Multiplex Ligation Dependent Probe amplification (MLPA) is a rapid, economical, and reliable alternative method for establishing the diagnosis of 22q11.2 deletion syndrome.

POSTER 177 - EARLY ONSET INFLAMMATORY BOWEL DISEASE IN A CHILD WITH X-LINKED INHIBITOR OF APOPTOSIS PROTEIN DEFICIENCY WITH A NOVEL MUTATION

AUTHORS

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Objectives: To report a child with early onset inflammatory bowel disease (IBD) who was found to have X-linked inhibitor of apoptosis protein (XIAP) deficiency with a novel mutation.

Design and methods: A 2-year-old male toddler presented with chronic watery diarrhea and failure to thrive since the age of 6 months. He had 2 episodes of multiple skin abscesses in last 3 months. Family history was non-contributory. On examination he was emaciated, had pallor, sparse hypopigmented hairs and angular stomatitis. Rest of the examination was unremarkable. Laboratory investigations revealed hemoglobin 68 gm/L, white blood cell count 16.2x109 cells/L (P37/L42/M15.2), absolute lymphocyte counts 6.8x109 cells/L, platelet counts 688x109/L, C-reactive protein 148.39 mg/l (N<6) and erythrocyte sedimentation rate 64 mm in 1st hour. Renal function and liver function tests were normal. His anti-tissue transglutaminase antibody (tTG) (0.2 U/ml), anti-deamidated gliadin peptides (DGP) (3.23 U) and sweat chloride were normal. Stool analysis for pathogens and routine microscopy was unremarkable. His Human Immunodeficiency Virus (HIV) serology was non-reactive. He underwent esophageal, antral and duodenal biopsy which showed chronic superficial gastritis and lymphoid nodular hyperplasia in duodenal biopsy.

Results: Based on initial work up, as celiac disease and cystic fibrosis was unlikely in this child, possibility of Primary Immunodeficiency with autoimmunity and early onset inflammatory bowel disease (IBD) was thought off and he was investigated further. His immunological work up showed serum IgG 9.9 g/L (3.7-15.8), IgA 1.53 g/L (0.3-1.3), IgM 2.07 g/L (0.45-2). Nitroblue tetrazolium test (NBT) and dihydrorhodamine test (DHR) were normal. Lymhocyte immunophenotyping showed normal CD3+ T cells (72.63%; 9.1 x 109/L) and CD19+ B cells (7.37%; 0.6 x 109/L). B cell immunophenotyping revealed mild decrease in unswitched memory B cells (5.63%). Next Generation Sequencing for PIDs revealed homozygous mutation in XIAP gene (c.926_929delATTG;p.Asp309fs), which is a novel, likely pathogenic mutation. So diagnosis of XIAP with IBD was made and he was initiated on oral prednisolone (1 mg/kg/day) and azathioprine (2 mg/kg/day). He responded to the treatment and loose stools subsided.

Conclusion: XIAP deficiency is a rare, inherited immunodeficiency characterized by recurrent infections, predisposition for hemophagocytic lymphohistiocytosis (HLH) and early onset IBD. It should be one of the differentials in children with early onset IBD. We also report a novel mutation in our child.

POSTER 178 - NONSENSE MUTATION OF IL12RB1 GENE IN THREE MOROCCAN CHILDREN WITH SEVERE MYCOBACTERIAL INFECTIONS

AUTHORS

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Introduction: Mendelian susceptibility to mycobacterial diseases (MSMD) is a rare primary immunodeficiency caused by inborn errors of IFN-γ immunity and characterized by a selective susceptibility to weakly virulent mycobacteria and severe diseases [1]. Since 1996, disease-causing mutations have been found in 13 genes (IFNGR1, IFNGR2, IL12RB1, IL12RB2, IL23R, IL12B, ISG15, STAT1, TYK2, IRF8, CYBB, NEMO and SPPL2A), underlying 23 different genetic disorders [2-4]. Although IL-12Rβ1 deficiency is the most common form of MSMD, the number of reported cases remains low. We report here the clinical and immunological features of MSMD syndrome in three children from 3 unrelated Moroccan families carrying the same IL12Rβ1 nonsense mutation.

Methods: To measure the response to IL-12 and IFN-γ, blood samples from patients and healthy controls were activated in vitro with BCG, BCG+IL-12, and BCG+IFN-γ. Immunological assessments and genetic analysis were also done for the 3 patients.

Results: All patients had been vaccinated with BCG vaccine. Two patients (P1, P2) were born to consanguineous parents and developed locoregional BCGitis at early age (5 and 2.5 months respectively) with further complications. P2 had also suffered from several infections by salmonella enteritidis, reported in 1/3 of IL12RB1 patients [1], causing dysentery and pericarditis and led to his death at the age of 3 years. P3 had no adverse reaction to BCG vaccination. He developed severe pulmonary tuberculosis at the age of 12.5 years leading to his death after 3 months despite treatment with rifampin, isoniazid, pyrazinamide and streptomycin. All patients had negative HIV serology, positive results for NBT and DHR tests and normal serum immunoglobulin levels and numbers of subpopulations. Analysis of IL12/IFN-γ axis had shown abolished response to stimulation by IL12p40 and normal or low response to stimulation by IFN-γ.
Genetic analyses have shown a homozygous nonsense mutation (c.913A>T) in the exon 9 of IL12RB1 gene creating a premature stop codon (p.K305X) with an autosomal recessive inheritance. This mutation is likely to be the cause of the abolished IFN-γ production following stimulation with BCG+IL-12. This mutation was reported to be a loss of expression of the receptor on the cell surface [5], affecting both IL-12 and IL-23 signalling pathways.

Conclusion: MSMD is a group of genetic diseases that can lead to complex clinical manifestations, or even death, in affected patients. Therefore, early prenatal or postnatal diagnosis is crucial in suspected patients to prevent complications related to live vaccine and to provide the appropriate treatment.

POSTER 179 – CVID: ARE GENETICS AND PHENOTYPES RELATED?

AUTHORS

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Patients with Common Variable Immunodeficiency Disorders (CVID) present with heterogeneity of clinical conditions as infections, autoimmunity, granulomatous infiltrations and lymphoid hyperplasia, that have been included in the current ESID definition. The explanation of this heterogeneity has not yet been clarified, even though many gene defects have been identified in CVID patients. This study describes the phenotype and the genotype of a cohort of CVID adult patients.

Methods: A cohort of 47 adults (21M, 26F) diagnosed for CVID according to the current ESID criteria has been considered and their clinical characteristics, laboratory findings recorded.
A total of 53 genes involved in Primary Antibody Deficiency, Agammaglobulinemia and CVID were screened by using the Ion Torrent next generation sequencing (NGS) target panel platform.

Results: We found that CVID patients with phenotype characterized by “only infections” were 36.2%, while all the remaining 63.8% of patients presented several overlapping conditions characterised by
polyclonal lymphoproliferation (46.8%), autoimmune cytopenias (23.4%), granulomatous infiltrations of lungs (14.9%), and/or the liver (6.4), lymphoid hyperplasia (27.7%). We found that 29.5% of patients had chronic enteropathy, and 42.8% of those had celiac disease (histological diagnosis).
All the 47 CVID patients (91.5% sporadic) underwent NGS analysis. Twenty patients were found carrier for at least one variant in disease-related genes: BTK, TNFRSF13b (TACI), CTLA4, NFKB1, CD40, CD19, TNFSF12, TTC37, CXCR4.
Two sisters carried the same causal mutation on TACI gene (c.[204dupA];[C542A]), but they have different phenotype, one developed Burkitt lymphoma after that EBV relapsed.
A couple of brother and sister were found heterozygous for CTLA4 (c.[519delG]). They presented very different phenotype: one severely affected and one healthy. Another patient with a causing-disease mutation on CTLA4 developed EBV-related Hodgkin’s Lymphoma. Two patients were found heterozygous for a novel variant with unknown causal role on the gene TNFSF12 (c.G305A) and on the gene TTC37 (c.A4597G), respectively.
Considering patients with chronic enteropathy, 50% were found carriers of mutation in four different genes: TACI, CTLA4, CXCR4, CD40. Considering autoimmune cytopenias, 36.4% of patients were found carriers of variations on two genes: TACI and CTLA4.

Conclusions: Targeted NGS genetic testing can be used a first-line molecular testing to identify a causal genetic mutation in CVID patients. It is not yet possible to correlate genotype and phenotype in CVID patients. Molecular diagnosis is not required for the diagnosis of CVID, but can be critically important for treatment optimization and accurate genetic counselling.

POSTER 180 - INVESTIGATING THE LONG-TERM OUTCOMES OF ADULT PATIENTS WHO UNDERWENT HAEMATOPOIETIC STEM CELL TRANSPLANT FOR PRIMARY IMMUNODEFICIENCY DURING CHILDHOOD

AUTHORS

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Objective: Many primary immunodeficiencies (PIDs) start in childhood and are life-threatening. Treatment includes haematopoietic stem cell transplant (HSCT). Due to improved techniques, more transplants are undertaken and patients are living longer. However long-term complications can significantly affect future health and quality of life.
Previous research has focused on short-term medical outcome and little is known about health outcomes in adulthood, or the social and psychological circumstances of this population. Therefore, this project aimed to understand the long-term physical, social and psychological outcomes for a growing population of adults who underwent HSCT for PID during childhood.

Design and Method: Eighty-three patients, aged 16 and over, who underwent HSCT for PID at Great Ormond Street Hospital, five or more years previously were recruited to participate in the study. They were asked to complete questionnaires and undertake practical tasks to assess their current functioning and circumstances. Information was also gathered from medical notes. Data was compared with population norms and a control group of participant-nominated siblings or friends.

Results and Conclusions: The psychological, social, physical and cost-effectiveness outcomes from this study will be presented. The implications of these findings and suggestions for future research and service development will be discussed.

This abstract presents independent research funded by the National Institute for Health Research (NIHR) under its Research for Patient Benefit (RfPB) Programme (Grant Reference Number PB-PG-0215-36145). The views expressed are those of the authors and not necessarily those of the NIHR or the Department of Health and Social Care.

POSTER 181 - IMMUNODEFICIENCY IN A CHILD PRESENTING WITH ECTHYMA GANGRENOSUM AND NORMAL IMMUNOGLOBULIN LEVELS

AUTHORS

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Objective: To present a case of X-linked agammaglobulinemia manifesting as ecthyma gangrenosum

Design and Method: Case report

Case Presentation: A 10-month old Filipino male was transferred to Philippine General Hospital due to difficulty of breathing and decrease in sensorium. He had a five-day history of a reddish maculopapular lesion at the left shoulder which progressed to erythematous macules all over the extremities. The lesions then morphed into vesicles then became hemorrhagic bullae with noted involvement of the perianal area. He had fever with Tmax of 39°C with occasional non-productive cough and postprandial vomiting (~3x/day) nine days prior to admission in our institution.
The patient's uncle in the maternal side died at a young age due to pneumonia. His older brother had cough and abscesses in the scalp, shoulders and arms at 7 months old and died at the age of 1 year and 4 months due to pneumonia and sepsis. He also had a step brother who died at 1 year old, also due to pneumonia.
On physical examination at the ER, he had bilateral crackles, right greater than the left lung fields, with multiple lesions described as circular with sharply demarcated borders and central necrosis, located on bilateral lower extremities.
He was given intravenous immunoglobulin (IVIG) at 400mg/kg during the 16th and 22nd hospital day. He was discharged improved after 2 months. Currently the patient is healthy with good weight gain. There have been no new skin lesions and no repeated admissions despite being given irregular IVIG infusions, due to financial constraints and the distance from this institution where the IVIG infusions were given.

Results: Serum protein electrophoresis revealed a marked decrease in the gamma globulin fraction at 0.2% (11.1-18.8) and lymphocyte subset enumeration showed a CD 19 of 20 mm3 (NV: 600-3,100). The serum immunoglobulins were as follows: IgG 688 IU/mL (NV: 6050-1,600), IgA 114.2 IU/mL (NV: 40-350), IgM 48.6 IU/mL (NV: 50-300). Genetic testing revealed X-linked substitution (nonsense) mutation in exon 8 of the BTK gene.

Conclusion: Ecthyma gangrenosum can be a presentation of XLA especially if there is a strong family history. Therefore, XLA should be included in the differential diagnosis of a child with an increased susceptibility to infection and neutropenia.

POSTER 182 - RARE PARENTS: AN EXPERIENTIAL AND INFORMATIVE GROUP ABOUT WELL-BEING IN PRIMITIVE IMMUNODEFICIENCIES

AUTHORS

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Introduction: The management of chronicity in PID is important to maintain a good quality of life. Chronicity and rarity can be associated to a psycho-physiological stress, which may be dangerous if protracted over time.
There is a different response to stress associated to chronicity in equal stress conditions, some families are more resilient than others. More resilient families crossed Basic Experiences of the Self many times with a positive outcome being able to live any situation (even disease) to the full. The intervention on wellness with rare parents starts from the knowledge of their illness experience that sometimes becomes unsustainable even in the absence of acute events to manage. In fact, when chronic stress is added to chronic illness, psychophysiological symptoms increase and family quality of life get worse. Working on wellness allows to restore calm, through deep diaphragmatic breathing, vagotonia, relaxation of muscular tensions and the reduction of negative thoughts.

Method: The intervention with PID's parents was an experiential and informative group (to understand but also to feel and to live). We have worked both in terms of awareness and information, and through functional techniques aimed at experiential work. We have considered both alterations to which chronicity and rarity can predispose, and previous alterations of personal and family functioning that, if presents, make the impact of the disease even more troublesome and prevent good management. The intervention included a session of two hours, one time a week, for a total of 8 sessions, at the office of the Primitive Immunodeficiency Sicilian Association - SPIA onlus.

Results: The most common alterations in parents functioning, coping with a rare chronic disease are:
Control. Continuous sense of health alert (thoracic breath, sympatheticotonia, muscular hypertension).
Letting Go. Difficulty in letting go, abandoning yourself to the other who holds.
Calm. If the Control is high, the person cannot Let go and it also becomes difficult to Rest and feel the Calm and Tranquility; difficulty even in Patience.
Vitality. Chronicity can make gray life. Energy, Playing, getting Joy even from small things may become an accessory to Well-being.
Projectuality. The positive expectation on life can be altered, with negative repercussions on the ability to plan the present and the future.

Conclusions: Parents can rebalance many deprivations and alterations that disease entails. Educate and guide parents to crossing Fundamental Experiences related to Well-being, helps the whole family to be resilient and able to fully enjoy life.

POSTER 183 - CLINICAL AND IMMUNOLOGICAL EVOLUTION IN WHIM SYNDROME

AUTHORS

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Introduction: WHIM syndrome (Warts-Hypogammaglobulinaemia-Immunodeficiency-Myelokathexis) is an inborn error of immunity with autosomal dominant inheritance, characterized by warts, hypogammaglobulinaemia, immunodeficiency and myelokatexis. Biologically, neutropenia, sometimes very severe, is relevant for the diagnosis. But in contrast to severe congenital neutropenia, in WHIM syndrome leucopenia with lymphopenia are also present.
Aim. To highlight clinical and immunological particularities and its evolution in WHIM syndrome.

Material and method: Three patients aged 2-30 years, coming from two families and diagnosed with WHIM syndrome.

Results: All patients had medium severity infections with onset in the pre-school age: recurrent oral aphte, pneumonia (2 cases), ulcero-necrotic tonsilitis, suppurative otitis media and mastoiditis (1case), urinary tract infections (3 cases), persistent bronchitis (1 case). No patient presented warts at the time of diagnosis. In all cases chronic neutropenia was the suggestive laboratory sign. The diagnosis was confirmed at 2 years, 10 years and 22 years of age. Clinical exam was normal at the diagnosis in all 3 cases. The adult patient developed warts at the age of 30 years. Laboratory investigations have revealed in all cases severe leucopenia with very severe neutropenia, B-cell lymphopenia with a variable T-lymphocyte count and NK cells. All patients had normal serum immunoglobulin level at the diagnosis, 2 patients subsequently developing IgA and IgG deficiencies needing immunoglobulin substitution. Abdominal ultrasound revealed anatomical renal anomaly in all cases: one case with left renal ptosis and the other two with right ectopic kydney. The bone marrow aspiration showed in all cases the hypercellularity with marked hyperplasia of the granulocyte series in all evolutive stages (myelokathexis). This finding together with neutropenia and the type of infections suggested WHIM syndrome, which was genetically confirmed.

Conclusions: In WHIM syndrome the most suggestive element for diagnosis is neutropenia accompanied by lymphopenia and obligatory myelokathexis. Repeated infections are suggestive for chronic neutropenia, and hypogammaglobulinaemia may develops later. The association with renal anomalies can be explained by the fact that the CXCR4 gene plays a role in renal embryogenesis.

POSTER 184 - SEVERE ATOPIC DERMATITIS AS THE PRESENTING MANIFESTATION OF A CHILD WITH SEVERE COMBINED IMMUNODEFICIENCY.

AUTHORS

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Objective: Mutations in severe combined immunodeficiency (SCID) causing genes are rare genetic causes of atopic dermatitis. Hypomorphic mutations in RAG1 gene are known to present with a myriad of clinical manifestations. Here we describe a patient with severe atopic dermatitis and compound heterozygous mutation in RAG1 gene.

Methods: Retrospective case review.

Result: A 3.5-year-old boy, born out of a third-degree consanguineous marriage, presented with a history of erythematous, scaly rash with severe pruritus since the age of 4 months. This rash was very difficult to treat and required multiple courses of oral steroids, oral cyclosporine in addition to a variety of topical antibiotics and immunosuppressive medications. There was also history of recurrent episodes of pneumonia and diarrhea since the age of 6 months, requiring multiple courses of intravenous antimicrobials.
At one year of age, the child developed multiple skin abscesses and bilateral ear discharge requiring hospitalization.
At 3.5 years of age, he developed multiple skin and soft tissue abscesses over the dorsum of right-hand, left groin, chest wall and scalp. Pus culture showed methicillin resistant Staphylococcus aureus. In addition, there was candidial infection over the skin of the abdomen.
Investigations revealed leucocytosis (10.2 x10^9/L), with absolute neutrophil count of 4.69 x10^9/L, absolute lymphocyte count of 1.22 x10^9/L and absolute eosinophil counts of 2.86 x10^9/L.
Immunological work up revealed elevated levels of IgG, IgG1 and IgE (Figure). Flow cytometry revealed decreased number of T and B cells; NK cell count was normal. Naïve T cells were reduced in number, reversal of the CD4:CD8 ratio and elevated HLA DR expression was noted (Figure). Possibility of hypomorphic severe combined immunodeficiency was considered. Genetic analysis done by next generation sequencing revealed a compound heterozygous mutation in RAG1.
Hypomorphic forms of severe combined immunodeficiency, especially RAG deficiency, may have novel clinical manifestations and a delayed presentation

POSTER 185 - EXOME SEQUENCING FOR DIAGNOSIS OF AN UNUSUAL CAUSE OF NEUTROPENIA.

AUTHORS

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Objective: Specific granule deficiency is rare primary immune deficiency with only a few cases reported worldwide. Mutations in the CEBPE gene (encoding for transcription factor CCAAT/enhancer binding protein-epsilon) cause this disease. We report an additional family with specific granule deficiency caused by a novel mutation in CEBPE gene.

Methodology: Retrospective case review.

Results: A 7 year old girl presented with history of recurrent skin infections since the age of 6 months. She developed fever and swelling of chin that was associated with redness and pain. She received intravenous (i.v.) antimicrobials and required incision and drainage of the lesion. However, only minimal pus discharge was noted and the lesion healed in a few weeks with scarring. Between the ages of 1 – 4 years she had four episodes of cervical abscesses requiring i.v. antimicrobials and surgical drainage. At 6 years she developed high grade fever and a carbuncle like lesion in nape of the neck. Cultures grew – Staphylococcus aureus, Proteus spp. and Pseudomonas spp. She was treated with a prolonged course of i.v. antimicrobials. She required skin grafting twice as the lesion was extensive. The graft, however, did not hold and the lesion gradually healed over next 2 months with scarring (Figure 1A). Similar lesions over multiple areas of the back and chest were noted in the following year. Her 6 year old younger male sibling also had similar manifestations with recurrent skin infections requiring i.v. antibiotics and surgical debridement, which on one occasion grew Staphylococcus aureus. There was also history of one sibling death in infancy due to infection (Figure 1B).
On evaluation both siblings were noted to have profound neutropenia (Figure 1C, 1D, 1E).
Next Generation Sequencing (NGS) by an exome panel revealed no pathogenic variants in ELANE, HAX-1,CSF3R, SBDS, GATA2. Subsequently, a whole clinical exome panel revealed a homozygous 11 base pair deletion in Exon 2 of the CEBPE gene (c.655_665del) that resulted in a frameshift and premature truncation of the protein 46 amino acids downstream to codon 220 (p.Lys220GlnfsTer46). To the best of our knowledge this mutation has never been reported previously.
Figure 1: A) Nasty scars resulting from poorly healing wounds in index child; B) Pedigree of the family; C) summary of basic investigations in both siblings; D) absolute neutrophil counts in index child; E) absolute neutrophil counts in younger sibling. The remarkable similarity in the absolute neutrophil count of each sibling is noteworthy.

POSTER 186 - SOCIAL RIGHTS FOR PATIENTS WITH PID AND THEIR FAMILY IN FRANCE: A SOCIAL OBSERVATORY TO MAKE THE POINT

AUTHORS

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Background: Primary immunodeficiencies (PIDs) are a group of close to 400 rare chronic inherited disorders. These conditions are life threatening if not treated adequately. In France PIDs are recognised as “long lasting affections”, which leads to free care and to different kind of supports that emanate, under some conditions, from public or private organisations.
Each year, IRIS (French patient organisation for PIDs) answers more than 250 online and call requests, in addition to these raised during weekly sessions at hospital, PID patients’ days and the social media. The impact of their condition on daily life is often at stake.

Objective: The social observatory aims at identifying the knowledge patients have on existing social welfare benefits related to their condition, the difficulties they may encounter in accessing them and their uncovered needs.

Method: The first step of the observatory consists in a survey among patients with PIDs done through a self-administered questionnaire. The outcomes of this first survey will set the scene and allow comparisons in the future.

Results: 501 respondents (Women 53%, mean age 38). 68% are adults over 18 years of age (35 % work, 18 % retired, 11 % no professional activity, 4% long-term sick leave). 74% have a humoral PID.
70% of the respondents feel that they are not familiar with the welfare benefits they could claim. Their main sources of information are their physician (53%), the internet (38%) and the patient association (21%). Social workers only arrive in fourth position (16%).
In children, 52% consider important or very important the impact of their condition on schooling. Mainly because of days off (85%). Health status of the child had led one parent to stop working temporarily (42%) or definitely (18%).
In adults, 53% declare that their condition has an impact on their career path: career change (21%), part-time work (16%) or change of employer (6%). Absences from work are managed with sick leave: when due to the health issues (57%), when due to treatment also (26%).
45% of the respondents have had problems to access loan insurance and 23% with loans themselves.

Conclusion: Social rights need to be more known by patients and healthcare providers and the social welfare system needs to know more about PIDs, to take into account the chronicity of these conditions, so that the patients in need can really access to support, they are entitled to get and have the administrative burden alleviated.

POSTER 187 - VERRUCIFORM EPIDERMODYSPLASIA: THREE CASES REPORTS

AUTHORS

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Introduction: The verruciform epidermodysplasia is a primitive immunodepression due to a genetic abnormality. It is characterized by an abnormal sensitivity of the skin to the papilloma virus. Objective: A report of three cases of patients with verruciform epidermodysplasia.

Design and method: Descriptive study of patients followed in the long term for a primitive immunodepression.

Results: There were 03 patients aged 8, 18 and 20 years old. In their medical history, recurrent severe pneumonia was noted in each; so, in the first, there we noted a neonatal respiratory distress, recurrent skin infections, recurrent diarrhea and a meningitis at age 06. The third patient had cardiac surgery for pericardial calcification. 2nd grade parental consanguinity was noted in the first patient and 3rd grade in the other two. The age of onset of symptoms was less than 10 years. The dermatological examination noted: flat papules and warty plaques located on the hands in the first patient; palmar-plantar and face in the second, and on the hands, feet, back and face in the third patient. In addition, the second patient had achromic macules as versicolor pityriasis broadcasts on the trunk. No functional signs have been reported. Extradermatological examination showed only dental dystrophies in the first patient. The diagnosis of verruciform epidermodysplasia was confirmed by cutaneous histopathology. In biology: HIV serology was negative in all three patients; alpha 1, alpha 2 globulin and IgG were elevated in the first patient; CD4 cells were low at 107 / m3 in the second; the third patient had pancytopenia with red blood cells at 1870 / m3, Neutrophiles at 1060 / m3, lymphocytes at 330 / m3, aregenerative normocytic normochromic anemia at 8.78 g / dl and platelets at 84000 / m3; this third patient presented also in the blood smear showed macroplaquettes, pseudo-pelger bodies and large active lymphocytes, with medullary hypoplasia in the medullogram. The cutaneous lesions had evolved well under retinoid treatment.

Conclusion: The diagnosis of verruciform epidermodysplasia is often late because of its lack of knowledge. In front of an evocative clinical picture, histopathology is essential to confirm the diagnosis. In our regions, the lack of a technical platform and the low socio-economic level limit the investigations at the patients. However, the prognosis depends on the precocity of the management.

POSTER 189 - PRIMARY IMMUNODEFICIENCY IN A LOW RESOURCE SETTING - A REPORT OF TWO CASES

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Objective: To report two cases of primary immunodeficiency in a low resource setting

Case Report:

CASE 1: A 5-month old male infant was admitte with persistent oral thrush from 2 weeks of age, associated with poor feeding and fever. He had been seen several times in the outpatient setting with the oral thrush. Laboratory evaluation revealed a pancytopaenia. Blood culture did not reveal growth of any organism. Serum immunoglobulin levels were mostly within the normal range. A diagnosis of septicaemia was made and broad spectrum intravenous antibiotics and antifungals were initiated. He developed abdominal distension with ascites and hepatomegaly 3 days later. Gene expert test performed on the ascitic fluid revealed Mycobacterium tuberculosis. Antituberculous treatment was initiated. However, the infant succumbed to illness a few days later. Post-mortem evaluation revealed disseminated infection with Mycobacteria morphologically consistent with BCG, invloving the lungs, thymus (Figure 1), spleen, brain and liver. A post-mortem diagnosis of possible Severe Combined Immunodeficiency was made.

CASE 2: A 10-month old male infant presented with a 2 day history of cough and fever. He had three prior admissions within the past 2 months, with a diagnosis of severe pneumonia in all instances. Laboratory evaluation revealed hypogammaglobulinaemia. Treatment was initiated with antibiotics and immunoglobulin replacement therapy. He has progressed well and is currently on out patient follow-up with monthly immunoglobulin replacement therapy.

Conclusion: Primary Immunodeficiencies (PIDs) remain underdiagnosed in Africa mainly due to lack of awareness and limitations due to poor access to immunological and genetic testing. This impacts directly on patient outcome, due to inadequate and/or late diagnosis. There is need to spread awareness on PIDS in low resource settings, and to increase capacity for early diagnosis.

POSTER 190 - NK CELLS AS A NEW BIOMARKER OF POTENTIAL RISK OF DEVELOPING CLINICAL COMPLICATIONS IN PATIENTS WITH COMMON VARIABLE IMMUNODEFICIENCY.

AUTHORS

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Introduction: The common variable immunodeficiency (CVID) is a pimary immunodeficiency that has a marked decrease of immunoglobulines asociated with recurrent infeccions. Biomarkers of risk for these complications are currently unavailable. In this study we will evaluate the association between the NK cells levels and the complications developed along the follow-up of a cohort of patients with IDVC.

Methods: A retrospective study was performed on 50 patients with IDVC. After reviewing the medical records the complications presented during that time by the patients were recorded in a database. Quantifications of NK cells were made by flow cytometry of 4 colours with the phenotypic CD3-CD56+/CD16+. T de Student, Chi-cuadrado and logistic regression statistical tests were used to assess the possible role of the biomarker as a risk factor.

Demographic variables: 23 were men and 27 women. The average age was 46 years.

Results: We observed levels significantly lower of NK cells in patients hospitalyzed with infections (75±83 vs 170±129cells/uL,p=0.03), in patients with lymphoproliferation (76±70 vs 163±130cells/uL,p=0.019) and there was a trend towards significantly lower NK cells in patients who had pneumonia (104±90 vs 163±133cells/uL,p=0.19) and in patients with autoimmune events (93±91 vs 162±130cells/uL,p=0.16). Based on the cut-off point of NK cells described as a risk factor in a previous study in IDVC (count of NK<50cells/uL), we observed that 50% of patients admitted for severe infections had levels of NK cells<50cells/uL, compared to only 15% among those who did not have this event(p=0.017). As for the risk of developing autoimmune processes we observed that 50% of patients with NK cells<50cells/uL developed autoimmune events compared to only 17% of patients without this complication(p=0.037).
The presence of NK cells<50 was also a risk factor for death 75% of the deceased patients had low NK cell counts compared to the other 25% who did not have the risk factor(p=0.008).
When we analyzed the levels of IgG<600 together with NK<50, we observed that NK values remain a risk factor for hospital admissions independently of IgG levels (1.87-57.4cells/uL,P=0,008). The logistic regression analysis confirmed that patients with levels of NK cells<50cells/uL were most exposed at risk of hospitalization by severe infection and death.

Conclusion: Based on the results we can conclude that levels of NK cells<50cells/uL can be considered as a risk factor for negative evolution in patients with IDVC regardless of IgG levels. This could be useful in the process of selection of patients who need more frequent controls.

POSTER 191 - NEW THERAPEUTIC OPTION WITH MUCOSAL AUTOVACCINE IN PATIENTS WITH SUPPURATIVE HIDRADENITIS.

AUTHORS

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Introduction: Suppurative Hidradenitis (HS) is an inflammatory, chronic, recurrent disease originating in the apocrine glands. Conventional therapies consist of surgical interventions, antiandrogens, antibiotics, inhibitors the tumor necrosis factor alpha, photodynamic therapies and others.
Hurley classification Stage 1: Presence of one or more abscesses without fistulosos pathways or defective scarring.
Stage 2: abscesses separated from each other in a recurrent way, few tracts and scars.
Stage 3: Multiple abscesses tracts and scars.

Materials and methods: This is a prospective observational study of patients diagnosed with HS in the immunology service Hospital Gregorio Marañon, included patients with stages 1 and 2 who have previously received therapy conventional without good response, treatment with mucosal autovaccine is placed based on the cultures obtained from the lesions of the patients during 6 months and later it was evaluated according to protocol the number of lesions, use of antibiotic, surgeries and incomes before and after treatment with a 1-year follow-up.
Statistical analysis was performed by student T

Results: The analysis of a cohort of 20 patients with hidradenitis of which 5 were male (25%) was performed. and 15 women (75%) With an average age of 42 years.
Treatment with mucosal Autovaccine was indicated in 7 of the 20 patients
It was observed in terms of the number of lesions prior to the use of Bactek an average of 5.89 that compared with the number of lesions after the use of Bactek with an average of 3.56, this difference is significant with an IC of 95% and a p of 0.001.
As for the number of surgeries prior to the use of Bactek was observed an average of 1.5 that compared with the number of surgeries after the use Bactek with an average of 0.33 was observed a statistically significant difference with an IC of 95% and a P of 0.002

Conclusions: Patients with HS Stage 1 or 2 who have not responded to conventional therapy would benefit from treatment with mucosal vaccine as it reduces the number of annual injuries, the need for antibiotic use and the need for surgical drainage. It might be useful to conduct a clinical trial to evaluate in a larger group of patients with HS this treatment

POSTER 192 - HEMIPARESIS, SEIZURES AND ALTERED BEHAVIOUR IN A BOY WITH HYPOGAMMAGLOBULINEMIA: A DIAGNOSTIC AND THERAPEUTIC CHALLENGE

AUTHORS

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Objective: To discuss challenging case of hypogammaglobulinemia

Design and method: A 4 year old boy presented with fever for one month and loose watery stools for initial 7 days. He had oral ulcers and conjunctival congestion at day 22 of illness. No history of any significant illness in past and family history was non-contributory. On examination he had molluscum contagiosum lesions over face, neck and legs.

Results: In view of prolonged fever and extensive molluscum contagiosum a provisional diagnosis of combined or T-cell immunodeficiency disorder was considered. His Human Immunodeficiency Virus rapid test was non-reactive; Serum IgG (3.5 g/L) and IgA (3.9 g/L) were decreased; IgM (3.9 g/L) levels were normal. He also had low B lymphocyte counts (CD3+ 82%; CD19+ 2.62%; CD56-12.3%). The diagnostic possibilities of X-linked agammaglobulinemia, common variable immunodeficiency and Hyper IgM syndrome were considered.
Child again presented after 45 days with left simple partial seizures and left hemiparesis. There was no history of fever, rash or trauma. On neurological examination he had left hemiparesis with upper motor neuron signs with no signs of meningeal irritation or cranial nerve palsy. On investigation, cerebrospinal fluid (CSF) analysis revealed elevated protein (1.55 g/L), hypoglycorrhacia [0.59 g/L (plasma: 1.4 g/L)]; there were no cells. CSF Gram stain and culture did not reveal any organism. CSF Polymerase Chain Reaction for Herpes simplex 1 and 2, Cytomegalovirus, Dengue, Chikungunya, Japanese encephalitis, Rabies, Nipah, Polio, Coxsackie virus, Echovirus, Enterovirus 70 and 72, Measles, Mumps, Rubella, Mycobacterium tuberculosis, Pneumococcus, Toxoplasma and Cryptococcus were unremarkable. Magnetic Resonance Imaging (Fig) showed altered signal intensities in right para-central lobule, suggestive of viral encephalitis. Immunoglobulins assayed at this time revealed IgG-3.96 g/L; IgA<0.17 g/L; IgM<0.25 g/L. Immunophenotyping revealed normal B cells, reduced switched and un-switched memory B cells (Table). Diagnosis of common variable immunodeficiency with enteroviral encephalitis was proffered and he was initiated on intravenous acyclovir, phenytoin and weekly intravenous immunoglobulin (IGIV) (1 gm/kg). Seizures did not recur after addition of oral levetiracetam. He continues to be on weekly IGIV and was showing gradual improvement. 16 months after the diagnosis, he started having progressive diminution of vision along with new onset seizures. On evaluation, he was detected to have retinal degeneration and EEG was suggestive of Subacute Sclerosing Pan Encephalitis (SSPE).

Conclusions: underlying immunodeficiency remains uncertain in this case! Hypogammaglobulinemia, may, at times pose significant diagnostic and therapeutic challenge.

POSTER 193 - A NOVEL VPS13B FRAMESHIFT MUTATION IN A NEUTROPENIC PATIENT WITH COHEN SYNDROME

AUTHORS

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Background: Cohen syndrome (CS) is a rare syndrome with diverse clinical manifestations including failure to thrive, hypotonia, hypermobile joints, microcephaly, intellectual disabilities, craniofacial and limb anomalies, neutropenia and a friendly character. Its inheritance pattern is autosomal recessive. It is associated with mutations of the vacuolar protein sorting 13 homolog B (VPS13B) gene, which is involved in the development of the ocular, hematological and central nervous systems. This gene encodes a transmembrane protein which is a crucial element in preserving the integrity of the Golgi complex. To date, more than 150 mutations of VPS13B have been reported in over than 200 CS patients. Missense or nonsense mutations are the most common mutations.

Methods: Whole Exome Sequencing (WES) was performed to identify the genomic abnormality.

Case presentation: A 4-year-old girl, born to consanguineous parents, was referred to the pediatric clinical immunology outpatient clinic for investigation of recurrent neutropenia with a history of recurrent infections in the past year. On physical examination, she had the characteristic facial features of CS, developmental delay and speech disorder. She had a cheerful disposition, and her mother gave a history of feeding difficulties in her first months of life. Her lab results revealed moderate neutropenia. Serum IgG, IgM, IgA and IgE levels were normal. She fulfilled the clinical diagnostic criteria for CS. WES revealed a novel homozygous frameshift variant in VPS13B (LRG_351t1: c.7095del; p.Ser236Alafs Ter49).

Conclusion: We reported a novel homozygous frameshift variant in VPS13B (LRG_351t1: c.7095del; p.Ser236Alafs Ter49) in a 4-year-old girl with CS.

POSTER 194 - RATIONALE AND DESIGN OF A NONINTERVENTIONAL STUDY ON THE USAGE AND OUTCOMES OF CUVITRU IN PATIENTS OF ANY AGE WITH PRIMARY IMMUNODEFICIENCY DISEASES: CORE STUDY

AUTHORS

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Objective: The highly concentrated immunoglobulin (IG) formulation—immune globulin subcutaneous (human) 20% solution (Ig20Gly/Cuvitru)—was designed to allow for subcutaneous (SC) infusion of IG in small-infusion volumes and to reduce infusion times compared with less-concentrated products. The CORE study will collect representative real-world information about the utilization, safety, tolerability, and patient experience of Ig20Gly.

Design and Methods: CORE is a noninterventional, prospective, longitudinal study being conducted in Germany and Switzerland (DRKS00014562). Patients of all ages are eligible for participation if they provide written informed consent, have primary humoral immunodeficiency diseases requiring gamma globulin replacement, received any SCIG therapy (for at least 3 months at a stable dose) prior to Ig20Gly, received Ig20Gly according to drug-label specifications, and are expected to continue treatment with Ig20Gly. Planned enrollment size is 150 patients at 30 sites who will be followed for 1 year (3 visits). Patient and usage data, including maximum infusion rate and volume, number of infusion sites, infusion duration, dose and dosing schedule, number and reason for discontinued, slowed, or interrupted infusions, patient experience including satisfaction, and healthcare utilization, will be collected during respective visits. Adverse drug reactions will be recorded according to regulatory requirements.

Results: Thirteen patients have started the study to date, and enrollment is ongoing. The first patient was enrolled on 26 November 2018 and study completion is expected in March 2021.

Conclusions: The CORE study is expected to provide a detailed and complete description of Ig20Gly usage under real-life conditions and to describe the patient experience after switching from other SCIG therapies.

POSTER 195 - NATIONAL COMPREHENSIVE CARE PROGRAM FOR CUBAN PRIMARY IMMUNODEFICIENCY PATIENTS 2013-2019.

AUTHORS

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Introduction: Primary immunodeficiencies (PID) are diseases characterized by defects of the immune system as a result of intrinsic or genetic defects that have been considered rare or unusual. Approximately 1/10000 individuals suffer PID and 70 to 90% remain undiagnosed worldwide.

Objective: To develop a National Comprehensive Care Program for patients diagnosed with PID in Cuba.

Methods: This program includes all Cuban PID patients registered and training for primary health care clinical status physicians, outreach and interaction with other medical specialties mainly Pediatrics, Infectious Diseases, Otorinolaryngology, Hematology, Pneumology and diagnostic verification such as flow cytometry, fluorescence in situ hybridization and molecular studies carried out at the Institute of Hematology and Immunology. Cuba has 114 immunologists (1 x 99 500 hab.) in 14 provincial immunology groups, providing outpatient services for children and adults, and 27 second and third level care centers in Havana including 11 scientific research institutions.

Results: The program has allowed: the Cuban Immunodeficiency Group, technological advances for new diagnosis, Cuban Registry and its incorporation to LASID; training in the diagnosis and treatment through national and international workshops and experience centers, improvement of the national diagnosis, better treatment of PID and secondary immunodeficiencies, early diagnosis in the provincial hospitals and better quality of life, immunization criteria for immunocompromised patient, better interrelation with other specialties as pediatrics, infectology, hematology and others, national registry of angioedema hereditary, better availability of specific medications, research for therapeutic alternatives, use of stimulating factors of colonies (Leuco CIM and Hebervital of national production),the introduction of subcutaneous gamma treatment (GAMMANORM OCTAPHARMA),use of gamma interferon in phagocytosis defects,clinical treatment research like Biomodulin T (national production) and national multicentric research projects.

Conclusions: Cuban national comprehensive care program is an example of a collaborative network for medical attention, immunodiagnostic and research in this field.

POSTER 196 - COMMON VARIABLE IMMUNODEFICIENCY: CLINICAL AND IMMUNOLOGICAL PROFILE OF ALGERIAN PATIENTS

AUTHORS

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Background and aims: Common variable immunodeficiency (CVID) is a primary antibody deficiency characterized by hypogammaglobulinemia, impaired production of specific antibodies and increased susceptibility to infection. CVID shows a considerable phenotypical and genetic heterogeneity.
The aim of this work is to study the clinical and immunological characteristics of 12 Algerian patients suspected of CVID.

Materials and methods: This study analyses 12 patients, 9 females and 3 males. The mean age was 15 years, the mean age at first symptoms was 6 years, the mean age at diagnosis was 15 years, and the mean delay for diagnosis was 5 years.

The exploration included:

- Measurement of IgG, IgA,IgM levels by nephelometry.
- Lymphocyte immunophenotyping: LT (CD4+CD8+), LB: (CD19+, CD20+), memory B cells (CD27+ IgD-), naïfs B cells (CD27- IgD+) NK, by flow cytometry.
- Measurement of specific IgG antibodies against Tetanus Toxoid and Diphtheria Toxoid to determine protective status for 9 patients by Elisa.

Results: The most common symptoms were bronchiectasis (41%), pneumonia (41%), acute otitis media (16%), splenomegaly (33%), chronic diarrhea (33%), abscess (22%) and sinusitis (16 %). Auto-immune diseases were reported for 2 patients (rheumatoid arthritis and auto-immune hemolytic anemia).
The immunological investigations showed for 7 patients (58%) a normal level of B lymphocyte, 5 patients (42%) with a low level of B lymphocyte, and 1 patient (8%) have a B (CD19+) lymphopenia (0%). All patients have absence of memory B cells (CD27+IgD-). The CD4/CD8 ratio is < 1 for 5 patients. 7 patients had very low levels of IgG, IgA and IgM. 1 patient had a low level of IgG and IgM, and another patient had decreased level of IgM.
Measurement of specific IgG antibodies against Tetanus Toxoid (TT) and Diphtheria Toxoid (DT) to determine protective status for 9 patients, showed for 4 patients (33%) no protective antibody against (TT) and against (DT).

Conclusion: The delay of diagnosis of common variable immunodeficiency remains unacceptable. Recurrence of upper respiratory tract infection or pneumonia should lead to systematic evaluation of serum immunoglobulin, lymphocyte subset analysis and vaccine response.
There was widespread variation in the levels of serum immunoglobulin isotypes as well as in the percentages and absolute numbers of B cells, confirming the heterogeneity of the disease.

POSTER 197 - INBORN ERRORS OF IMMUNITY: TWO AND HALF DECADE OF EXPERIENCE FROM A SINGLE CENTRE IN NORTH INDIA

AUTHORS

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Genetic diagnosis wasestablished in 281 patients (54.35%) - X-linked agammaglobulinemia (XLA) (n=58/65; 20.64%),Chronic Granulomatous Disease (CGD) (n=57/67; 20.29%), Severe Combined Immunodeficiency (SCID) (n=46/67; 16.37%),Wiskott-Aldrich syndrome (WAS) (n=32/50; 11.38%), Leukocyte adhesion type 1 deficiency (LAD1) (n=15/21; 6.05%),Blau syndrome (n=12; 4.27%), X-linked HyperIgM syndrome (n=9/12; 3.20%), Hereditary angioedema (HAE) (n=7/16; 2.49%), Ataxia-Telangiectasia (AT) (n=6/15; 2.14%), Autosomal dominant Hyper-IgE Syndrome (HIES) (n=6; 2.14%), Mendelian Susceptibility to Mycobacterial Diseases (MSMD) (n=6/13; 2.14%),(Complement C1q A Chain) early complement deficiency (n=5; 1.78%), Congenital Neutropenia (n=3/10; 1.07%), Chronic Mucocutaneous candidiasis (CMC) (n=3/7; 1.07%), Dedicator of cytokinesis 8 (DOCK8) deficiency (n=3; 1.07%), Neonatal-onset multisystem inflammatory syndrome (NOMID) (n=3; 1.07%),Autoimmune Lymphoproliferative Syndrome (ALPS) (n=2/4), Deficiency of IL-1 Receptor Antagonist (IL-1RA) (n=1), Familial HemophagocyticLymphohistiocytosis (HLH) (n=1/4), GATA-binding factor 2 (GATA-2) deficiency (n=1/2), Pyogenic Arthritis, Pyodermagangrenosum and Acne (PAPA syndrome) (n=1), X-linked Lymphoproliferative Syndrome (XLP) (n=1/2), and Tumor Necrosis Factor Receptor Associated Periodic Syndrome (TRAPS) (n=1). Secondary malignancy was reported in eight of 517 patients (1.55%) comprising fourpatients with non-Hodgkin's lymphoma, two with lymphoma (unspecified) and one case each of Hodgkin's lymphoma and Thymoma.

POSTER 198 - TARGETED NEXT GENERATION SEQUENCING FOR PRIMARY IMMUNODEFICIENCY DISEASES AT A TERTIARY CARE CENTRE FROM NORTH INDIA

AUTHORS

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Introduction: Primary immunodeficiency diseases are a heterogeneous group of inborn errors of immunity. More than 360 genes have been reported to cause different PIDs encompassing components of both the innate and adaptive arms of immunity. Diagnostic workup for PIDs is a multistage, tiered approach involving complex immunological and genetic tests. Genetic testing for the molecular basis of different PIDs is an important element of diagnostics. Traditionally, automated Sanger sequencing has been employed for diagnosis of primary immunodeficiency diseases. However, Sanger sequencing is a labor intensive, time-consuming and relatively expensive method. Targeted next generation sequencing is a rapid diagnostic method and is being increasingly used for the diagnosis of primary immunodeficiency diseases. However,

Objectives: To characterize pathogenic genetic variants in patients with well-characterized as well as not clearly defined PIDs at our centre

Patients and methods: A total of 44 genes were tested in 57 patients with different forms of PIDs diagnosed and managed for the period of 8 months from August 2018 to March 2019, using a custom designed panel based on the GRCh38 human genome assembly. The panel was designed using the Ion Ampliseq designer and samples were analyzed on the IonS5 platform. Data analysis was performed using the Ion Reporter software.

Results: Pathogenic disease causing variants could be detected in 39 of the 57 patients (68.4%). The distribution of the cases is depicted in Figure 1. The 39 patients in which pathogenic variants were identified included 11 cases of LAD type I, 7 cases of SCD, 6 cases each of XLA and CGD, 2 cases each of DOCK8 deficiency, STAT3 GOF defect and MSMD and one case each of WAS, GATA2 and ALPS.

Conclusion: Targeted next generation sequencing is a rapid, cost effective and unbiased approach for characterizing pathogenic disease causing variants in PIDs. However, the limitations and pitfalls of this powerful tool must be considered during variant analysis.

POSTER 199 - COMMON VARIABLE IMMUNE DEFICIENCY: TWO CASES WITH EARLY AND LATE DIAGNOSIS

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Background: Common variable immun deficiency (CVID) is the most frequent symptomatic primary deficiency in adults. But sometimes the diagnosis can be time consuming. Here we report two case of CVID one with late and the other with early diagnosis.

CASE 1: 28 years old female patient. She was diadnosed as having bronchiectasis for last 10 years. She had serious pneumonia episodes almost ever year. The patient had undergone lobectomy for bronchiectasis 7 years ago. She has been referred to our outpatient clinic following the last pneumonia to explore if there is any immune related etiology in january 2019. Laboratory findings were as follows; lymphocyte count 1200 mm3, Ig A <0,1 g/L, Ig G <0,07 g/L, Ig M<0,2 g/L, CD19+ lymhocyte %8,7. The patient was started on intravenous immunoglobulin (IVIG) treatment. Ig G increased to 9.6 g/L. No infection was observed during follow-up.

CASE 2: 31 years old female patient. She has been referred to our outpatient clinic in october 2016 followingdiagnosis of pneumonia for first time. She was diagnosed with pneumonia 1 week ago. There was no history of serious infection before. Laboratory findings; lymphocyte count 1100 mm3, Ig A <0,1 g/L, Ig G: 0,104 g/L, Ig M<0,2 g/L, CD19+ lymhocyte %13,1. The patient was started on intravenous immunoglobulin (IVIG) treatment. Ig G increased to 8.3 g/L. During follow the patient had only three episodes of upper airway infection.

Conclusion: The diagnosis of first case was delayed due to lack of awareness of immune deficiency as an etiological factor for frequent and severe pneumonia and bronchiectasis. However, the second case was diagnosed on time, just after the first serious pneumonia because of physician enthusiam and awareness. Both cases were referred to us by the clinic for chest diseases. Increasing awareness of immune deficiencies will ease of early recognition and timely of cases, hence saving of resources.

POSTER 200 - PHYSICIANS' KNOWLEDGE AND ATTITUDES FOR IGG REPLACEMENT THERAPY FOR PRIMARY IMMUNODEFICIENCY IN TURKEY

AUTHORS

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Introduction: Immunoglobulin replacement therapy (IGRT) is commonly used prophylaxis in primary immunodeficiency treatment. The aim of this study is to evaluate the knowledge and attitudes of physicians about IGRT.

Materials and Methods: 33 physicians (10M,23F) were participated in the study, while 75% of the participants were pediatric, 25% adult allergy-immunology specialists. The mean work duration of the physicians in the field was 7.8 ± 4.6years.

Results: All physicians replied as IVIG treatment should be used for antibody deficiencies, whereas surprisingly 3.3% not for combined immunodeficiencies and immune dysregulations. Among participants, 93.8% replied as IGRT efficacy should be monitored with serum-IgG levels and 78.1% replied as IgG should absolutely be kept >700mg/dl. Additionally, 96.9% of them replied as treatment efficacy should be monitored by number of infections and 93.7% by hospitalization admissions. Only, 59.4% answered the query as end-organ-damage could completely be prevented by IGRT. All physicians reported that they prescribed IV IGRT more frequently. Moreover, 68.8% of the physicians reported that side effects of IV IGRT were common, but all felt confident to manage them. While minority (31.3%) of them thought that side effects were common in SC, majority (77.4%) felt confident to manage them. Furthermore, 61.29% of all participants stated that they were experienced in both IV and SC IGRT whereas, 35.5% was experienced only IV and 3.2% for SC only.

Conclusion: Majority of allergy-immunology physicians was reported to be administering IV IGRT and feeling more confident to manage side effects. On the other hand, 2/3 of the them were experienced in both IV and SC IGRT.

POSTER 201 - STAT3 ACCUMULATES IN RESPONSE TO IL-6 DRIVEN EXPRESSION OF RANTES (CCL5) AND OTHER KB DEPENDENT GENES IN A PATIENT WITH AUTOSMOAL DOMINANT HYPER IGE SYNDROME.

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Introduction: STAT3 accumulates in response to IL-6 driven expression of RANTES (CCL5) and other kB dependent genes in a patient with Autosmoal Dominant hyper IgE syndrome
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Objective: To assess the downstream signaling molecules in the unphosphorylated STAT3: unphosphorylated NFkB (U-STAT3: U-NFkB) pathway, viz. RANTES, IL-8, IFN-b and the STAT3 in a patient of autosomal dominant hyper IgE syndrome with mutation in STAT3 gene (c.2141 C>T, pT714I).

Material & Methods: NIH score, TH17/memory B cell numbers, and pSTAT3 were assessed. PBMCs were isolated from whole blood of the patient and healthy controls (n=6) using Ficoll gradient centrifugation and incubated with or without interleukin-6 (IL-6) (80ng/ml) for 36 hrs at 37°C in humidified C02 incubator maintained at 5%. Total RNA was isolated and cDNA was synthesized. PCR array was performed using an 11 genes set (RANTES, IL6, ICAM1, SOCS3, ZFP36L2, CSF1, STAT3, MRAS, IL8, IFN-, RORC, b-actin and GAPDH). The threshold cycle (Ct) values were derived for all genes. Fold-changes in gene expression were calculated using 2 delta delta Ct formula. Any fold change higher than 2.0 was taken as significant. Differential gene expressions between unstimulated and IL-6 stimulated samples were then compared.

Result: PCR array results showed significant up regulation of these genes in patient compared to controls; RANTES (14.93 vs. 4.09 folds), IL-8 (7.46 vs. 3.14 folds), IL-6 (4.59 vs. 2.63 folds) ICAM (4.59 vs. 2.38 folds) & STAT3 (48.5 vs. 4.30 folds) in patient as well as healthy controls after 36hrs of IL-6 stimulation. Out of all genes IFN-b (-2.83 vs. 0.48 folds) showed significant down regulation.

Conclusion: Transactivator domain (TA) domain of STAT3 is highly conserved and mutations are rare. Unphosphorylated STAT3 induced to a high level, due activation of STAT3 gene in response to long term treatment to IL-6 allows activation of the U-STAT3: U-NFkB complex, inducing the expression of RANTES and other kB dependent gene such IL-6, IL-8, ICAM-1. Patient with mutation in TA domain (T714I) also activates RANTES expression albeit at a much more exaggerated manner which acts as a novel transcription factor and brings about a pro-inflammatory state that could significantly contribute to the clinical features of HIES.

POSTER 202 - CHILDREN'S IMMUNOLOGY: TEAMWORK

AUTHORS

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Body

The manifestations of primary immunodeficiencies (PIs) of the children are diverse changes in many systems and organs. Consequently such patients can be treated by other specialists without receiving qualified support from the immunologist. Thus, skin lesions under primary immunodeficiencies can be manifested by the skin infection (chronic granulomatous disease, severe combined immunodeficiencies); eczema (hyper-Ig E syndrome, Viscott Aldrich syndrome, Omen syndrome). Such children should get a consultation of a dermatologist and an allergist. In addition, selective IgA is associated with bronchial asthma, allergic rhinitis, atopic dermatitis, and food allergy. Due to these manifestations, such children should also see the allergists.

Children may come to the rheumatologist for advice, since autoimmune diseases (with a major manifestation of arthritis) may be the first sign of the manifestation of congenital immunodeficiency. As a rule, they are deficiencies in the production of antibodies and auto-inflammatory diseases. Also, one of the most serious manifestations of PID can be oncological pathology, examining which the oncologists and the oncohematologists diagnose the following conditions: non-Hodgkin's lymphoma, Hodgkin's lymphoma, acute lymphoblastic leukemia, myelodysplastic syndrome, rhabdomyosarcoma, ganglionyroblastoma, etc.

While having initial signs of the illness patients with a general variable immunodeficiency (acute purulent periosteum, a pair of dental cysts), Crohn's disease (enamel defects, erosion), Marshall syndrome (stomatitis), APECED-syndrome (adentia) should be recommended the dentist’s consultaton.

In addition, it should be noted that the children with primary immunodeficiencies usually apply for the ENT specialist’s prescriptions because of the problems of frequent purulent otitises, sinusitis during the year, persistent candidiasis infection of the mucous membranes. Pulmonologists face the problem of repeated pneumonia in patients during the year, the presence of bronchiectasis, the ineffectiveness of antibiotic therapy.

Taking into account the latest achievements and positive global experience, we insist on the fact that the success of diagnosis and treatment depends on the co-ordinated work of pediatricians who are first faced with newborn babies and are well aware of the growth of their patients in the future and specialists who need to pay attention to unusual manifestations of different pathologies.

POSTER 203 - RASH IN NEONATES IS NOT ALL BENIGN

AUTHORS

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Objective: To report a child with neonatal onset rash, initially deemed to be benign and later found to have omenn syndrome.

Design and methods: A 2.5- month-old female child presented with erythematous, exfoliative rash since day 5 of life, bilateral purulent ear discharge and recurrent episodes of loose stools since day 20 of life. The child also had fever and cough for 5 days associated with respiratory distress and lethargy. She was born to third degree consanguineously married parents, and one elder female sibling had died at the age of 6 months, due to pneumonia. Parents sought treatment in multiple hospitals elsewhere but symptoms persisted. At presentation, she was found in a state of respiratory failure and shock. She was endotracheally intubated and initiated on intermittent positive pressure respiration (IPPR). She had generalized exfoliative rash (Fig. 1), pallor, generalized lymphadenopathy, oral thrush, hepatosplenomegaly, decreased breath sounds in right basal areas and bilateral crepitations on chest auscultation.

Results: Laboratory investigations showed hemoglobin 125 gm/L, total leucocyte count 11 x 109/L (P33 L15 E48), absolute lymphocyte count 1.6 x 109/L, absolute eosinophil count of 5.2 x 109/L and platelets 553 x 109/L. X-ray chest revealed bilateral inhomogeneous opacities with right pleural effusion. He had panhypogammaglobulinemia (IgG 1.23 g/L, IgA <0.17 g/L, IgM <0.25 g/L). Lymphocyte immunophenotyping by using 4 colour flow cytometry showed low CD3+ T cells – 7.67% (48-75%), low CD19+ B cells- 0.69% (14-39%), increased proportion of natural killer cells (82.67%; normal-2-14%), decreased naïve T lymphocytes (6.42%; control-63.64%). Nitroblue tetrazolium (NBT) dye reduction test was normal. These investigations were suggestive of SCID (T – B+ NK+) with clinical profile of omenn syndrome. Molecular analysis revealed mutation in recombination activating gene 1 (RAG 1). She was initiated on intravenous ceftriaxone (100 mg/kg/day), vancomycin (60 mg/kg/day) and cotrimoxazole (20 mg/kg/day). She was also continued on IPPR and inotropic support. Despite the therapy she continued to have deterioration and died at 5 hours of hospital admission due to refractory shock.

Conclusion: All rash in neonates and infants are not benign. Rash may be a feature of underlying life threatening systemic disorder and through history and clinical examination may give a clue to the diagnosis. Flow cytometry and NGS can help in quick and early diagnosis of PIDs and molecular analysis can help in antenatal diagnosis through PNDT in next pregnancy.

POSTER 204 - CHRONIC STAPHYLOCOCCUS AUREUS CARRIERS A POSSIBLE PRIMARY IMMUNODEFICIENCY DISEASE: A CASE REPORT.

AUTHORS

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Introduction: Chronic staphylococcus Aureus carriers usually present with complications following surgical interventions, and patients with Diabetes Mellitus, catheter site infections in dialysis patients, patients admitted to intensive care units or immunocomprised patients. Patients with this presentation can be the first clue to a rather serious condition like Primary Immunodeficiency Diseases.

Case Report: A.A. is a 26 years old man who presented with history of recurrent skin blisters, rashes and abscesses since the age of 6 years. Two years prior to his clinic presentation, he had two episodes of gluteal abscesses, which were surgically removed. He is atopic, but he denied a history of allergic rhinitis. The patient had a positive family history of skin abscesses in his father.
In March 2018, the patient developed an intense severe headache, associated with numbness and tingling on his right side. Neurologist requested MRI brain which revealed Brain Abscess. Later, the patient travelled abroad where surgical evacuation was done. Culture and sensitivity revealed Pseudomonas spp. and Staphylococcus Aureus spp., testing for Mycobacterium Tuberculosis was negative. On examination he had no lymphadenopathy, but there was bilateral crepitations more on right side from middle to lower lobes. Complete blood count as well as Immunoglobulin levels were normal. Serum complement c3 and c4 levels were normal. CT chest: right side middle and lower lobe cystic and bronchiectatic changes, with ground glass appearance, and intralobar sequestration, consistent with chronic infection.
Dihydrorhodamine by flowcytometry was Suboptimal but leaning towards a normal oxidative burst. Lymphocytes' subsets revealed normal CD3 T cells counts, normal CD19 B cells, CD 16 NK cells counts. Myeloperioxidase and Glucose-6-Phosphate Dehydrogenase were within normal. The patient was put on prophylactic antibiotic, mainly Azithromycin 500 mg tabs OD on alternate days.

Conclusion: This case report discusses a patient with a serious presentation of brain abscess. Investigations revealed him to be a chronic staph carrier with history of skin abscesses and symptoms suggestive of allergic rhinitis which he didn't seek medical advice for. He had bronchiectaisis on high resolution CT chest. Repeated lymphocyte subsets and DHR results were also within normal range. In such cases, extended lymphocytes subsets and possibly Next Generation Sequencing or Whole Exome Sequencing can truly unravel the ambiguous nature of them especially if they were associated with hypomorphic mutations. Given the unavailability of genetic or molecular diagnosis in Sudan, the patient remained prophylactic antibiotics and regular follow up.

POSTER 205 - GENERALIZED VERRUCOSIS AND HPV SUSCEPTIBILITY ASSOCIATED WITH COMBINED IMMUNE DEFICIENCY

AUTHORS

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Background and Objective: HPV infections are an underappreciated manifestation of primary immunodeficiency. Whereas mutations in EVER1, EVER2, GATA2 and CXCR4 are typically associated with extensive HPV infections, other primary immune defects can be also associated or even revealed by an HPV infection. We report a case of generalized verrucosis revealing a combined immune deficiency in a Moroccan 8 years old girl.

Observation: An 8 years old Moroccan girl with consanguineous parents, presented in pediatric consultation for profuse warts in the upper and lower limbs, in the trunk and at the face. These lesions have been evolving since the age of 3 years old, without any other recurrent infections, secondary immunodeficiency, or a family history of primary immunodeficiency or similar lesions. Laboratory studies showed a neutropenia: 0.58 103/ mm3; (VN : 1.5 103/mm3-7 103/mm 3), a NK lymphopenia : CD 16+, CD56+ = 64/mm3 ; (VN : 100/mm3 -480 /mm3), B-cell lymphopenia : CD 19+ = 130/mm3 ; (VN : 270/mm3 - 860/mm3) and CD4+ lymphopenia: 254/mm3 (650/mm3-1500/mm3). HPV genotyping and genetic mutations identifying are still ongoing.

Discussion and conclusion: These findings were consistent with a combined immune deficiency caused probably by MST1 deficiency. MST1 deficiency leads to naive T-cell lymphopenia and an impaired egress of mature T lymphocytes from the thymus to secondary lymphoid organs, associated with an impaired chemotactic response to several chemokines. MST1 deficiency was also associated with a susceptibility to Verruciform Epidermodysplasia and other viral infections. However, the infectious phenotype differs between patients and more studies are needed to clarify the common cellular pathogenesis in patients with mutations associated with an HPV susceptibility.

POSTER 206 - INTERLUKIN 12 RECEPTOR BETA 1 (IL12RB1) DEFICIENCY

AUTHORS

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Two siblings born to consanguineous parents, one male 12 years old presented with history of recurrent pneumoniae, dysentery, recurrent abscesses, lymphadenopathy, complicated later with anemia, thrombocytopenia. His immune profile showed reduced CD3, CD4, CD8 counts, elevated immunoglobulins levels, Normal DHR test. His younger sister suffered at the age of 2 months from supraclavicular & axillary lymph node abscesses complicating BCG vaccine proved to be TB lymphadenitis. Molecular testing of this family showed Interlukin 12 receptor beta 1 deficiency.

POSTER 209 - ASSOCIATION BETWEEN VITAMIN D METABOLISM GENE POLYMORPHYSMS AND RISK OF ADULT'S ASTHMA

AUTHORS

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Introduction: Several studies have shown a strong correlation between the serum vitamin D level and asthma severity and deficits in lung function.

Objective: Study the relationship between vitamin D and the severity of asthma by targeting five SNPs of vitamin D metabolism genes pathway in a Tunisian adult asthmatics population.

Methods: Our case-control study includes 154 adult asthmatic patients and 154 healthy Tunisian subjects. We genotyped many variants in three human genes encoding key components of the vitamin D metabolism, CYP2R1, CYP27B1, GC. The GC gene rs4588 and rs7041 polymorphisms were analysed by using the PCR-RFLP method, while rs10741657 and rs12794714 for CYP2R1 gene and rs10877012 of CYP27B1 gene were investigated by using TaqMan PCR genotyping techniques.

Results: We found that the presence of at least one copy of the rs12794714 A, allele was associated with lower risk of developing asthma (OR = 0.61). Further, the rs12794714 is a protector factor against asthma severity (OR =0.5). However, the presence of rs10877012 TG genotype is a risk factor related to asthma severity (OR =1.89). When we classified the population according to sex, our results showed that rs10877012 TT genotype was a risk factor for women subjects (OR= 6.7). Moreover, the expression of TT genotype was associated with a higher risk of asthma in non-smoker patients (OR = 7.13).

Conclusions: we found that rs12794714 and rs10877012 SNPs were associated with asthma risk.

POSTER 210 - COMMON VARIABLE IMMUNODEFICIENCY DIAGNOSED IN A 12 YEAR -OLD GIRL WITH GROWTH DELAY

AUTHORS

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Introduction: Common variable Immunodeficiency (CVID) is the most common symptomatic primary immunodeficiency. The disease is characterized by recurrent infections, mainly of the upper and lower respiratory tract, autoimmune manifestations, lymphoproliferation and hypogammaglobulinemia. The majority of the patients are diagnosed in adult life even though about 20% are diagnosed before the age of 20 years.

Case report: We describe a 12 year-old girl with growth delay and hypogammaglobulinemia which was referred to our department for further investigation. The patient was the second child of a non-consanguineous family. Family history was negative for immune disorders. Her past medical history was uneventful and severe infections or hospitalizations were not reported. Weight and height delay was noticed since the age of 10 years old and hypogammaglobulinemia was found during the laboratory control after 2 years. Quantitative immunoglobulin measurement revealed an IgG level of 441 mg/dL (reference range, 977-1862), an IgA level of 7 mg/dL (reference range, 69-331), and an IgM level of 19 mg/dL (reference range, 76-302). Specific antibody response after immunization with 23-valent pneumonococcal polysaccharide vaccine was at low levels. Immunophenotyping of peripheral blood by flow cytometry shown normal values and percentage of T, B and NK cells and reduced memory switched B-cells (IgD-IgM-CD27+: 1.2%). Organomegaly was not found in abdominal U/S. After one year, the phenotype and laboratory findings remained unchanged. The patient commenced on immunoglobulin replacement therapy, initially intravenously and afterwards subcutaneously. She has gain weight and height. Genetic analysis is pending.

Conclusion: Our case represents an example of the heterogeneity of Primary Immunodefiencies. Although clinical presentation does not match to the diagnostic criteria, the immunological parameters were compatible with the diagnosis of Common Variable Immuunodeficiency.

POSTER 211 - SKEWING OF SODIUM ANTIMONY GLUCONATE MEDIATED THERAPY FOR A PREDOMINANT PROTECTIVE T CELL RESPONSE DURING SCID-VISCERAL LEISHMANIASIS COINFECTION

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Background: Visceral Leishmaniasis is a macrophage associated disorder for the treatment of which antimony based drugs like SAG and SSG were the first choice in the recent past. It progresses into cerebral leishmaniasis if not treated early. The clinical value of antimony therapy is now declined against SCID-VL coinfection because increasing cases of Sodium Antimony Gluconate (SAG) resistance have reached outstanding proportion in Bihar, India.

Methods: We have evaluated the effect of combining CD2 with conventional antimonial (sb) therapy in protection in BALB/c mice infected with either drug sensitive or resistant strain of Leishmania donovani with 3x107 parasites via-intra-cardiac route. Mice were treated with anti CD2 adjunct SAG sub-cutaneously twice a week for 4 weeks. Assessment for measurement of weight, spleen size, anti-Leishmania antibody titer, T cell and anti-leishmanial macrophage function was carried out day 0, 10, 22 and 34 post treatments.

Results: The combination therapy was shown boosting significant proportion of T cells to express CD25 compared to SAG monotherapy. Although, the level of IFN- was not statistically different between combination vs monotherapy ($p = 0.298$) but CD2 treatment even alone significantly influenced IFN- production than either SAG treatment ($p = 0.045$) or with CD2 adjunct SAG treatment ($p = 0.005$) in Ld-S strain as well as in Ld-R strain. The super-oxide generation began enhancing very early on day 10 after SAG treatment with CD2 during which SAG action was at minimum. Unlike SAG treatment, treatment of SAG with CD2 also led to production of nitric oxide and TNF-, resulting in resulting in most effective clearance of L. donovani from infected macrophages.

Conclusions: Our results indicate that CD2, which can boost up a protective Th1 response, might also be beneficial to enable SAG to induce Macrophages to produce Leishmanicidal molecules and hence control the infection in clinical situation like SCID-VL Coinfection along with overcomming drug resistance

POSTER 212 - MICROSPORIDIAL MYOSITIS IN ADULT ONSET IMMUNODEFICIENCY: CASE-BASED REVIEW

AUTHORS

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Introduction: Polymyositis is a diagnosis of exclusion. In patients with odd features, it can be of infective etiology. A high index of suspicion is required for diagnosis.

Methods and results: A 55-year old gentleman presented with gradual onset proximal muscle weakness. Examination revealed mild distal weakness but no rash. Muscle enzymes were raised and tests for autoantibodies were negative. Biopsy revealed microsporidiosis. In view of this unusual infection, immunodeficiency was considered and he was found to have lymphopenia which antedated his illness. Later, he developed cranial nerve palsies due to multiple lesions in the pons. In addition, he had Cytomegalovirus viremia.
Literature was reviewed to identify 20 cases of microsporidial myositis, its presentation, underlying immunodeficient state, and clinical course.

Conclusion: Infective polymyositis should be considered in a patient with paucity of autoimmune features clinically and serologically. Lymphopenia can be a pointer to underlying immunodeficiency. CMV infection could be the contributor to or bystander-effect of Idiopathic Lymphopenia.

POSTER 213 – CLINICAL AND LABORATORY MARKERS DIFFERENTIATE HYPER IGE SYNDROME FROM SEVERE ATOPIC DERMATITIS

AUTHORS

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Introduction: Hyper IgE syndrome (HIES) is characterized by severe eczema, recurrent skin and lung infections, and increased serum IgE. The major diagnostic challenging for clinicians is that HIES patients can share many features with severe atopic dermatitis (SAD), making a diagnostic dilemma during assessment. Therefore, determination of clinical and laboratory markers that distinguish both conditions could be helpful for early diagnosis and treatment.

Methods: HIES (STAT3 and DOCK8) and SAD patients who were followed-up in our clinic and underwent DNA sequencing analyzes for genetic diagnosis were included. Clinical and laboratory features were evaluated.

Results: There was 33 patients (DOCK8: 13, STAT3: 10, SAD: 10). The age of diagnosis between the groups was similar as 5.4 (1.2-14) years in the DOCK8, 5.1 (1.7-41) years in the STAT3 and 4.1 (2.3-22) years in the SAD. The presence of sinopulmonary infections were significantly frequent in DOCK8 than STAT3 and SAD (p:0.008, p:0.001, respectively). In contrast, characteristic facial appearance (p:0.015, p:<0.001) and skin abscess (p:0.029, p:<0.001) were significantly higher in STAT3 compared to DOCK8 and SAD. Neonatal rash was significantly higher in STAT3 than in SAD patients (p:0.015). Pneumotocele was other signifiant stimuli for STAT3 (p=0.026). Viral cutaneous infections were observed in 69% of DOCK8, 30% of STAT3, 10% of SAD. Autoimmune manifestations were seen in 15% of DOCK8, 10% of STAT3 and SAD. Fractures with minor trauma were observed in 30% of STAT3 and 8% of DOCK8 patients. Malignancy was detected only in DOCK8 (acute myeloid leukemia, vulvar squamous carcinoma). IgE levels were significantly higher in STAT3 and SAD than DOCK8 (p:0.024, p:0.017, respectively). The IgM was low in 38.5% of DOCK8, 10% of STAT3 and 20% of SAD. DOCK8 patients had significantly lower CD3+T cells (p=0.001, p=<0.001) and CD4+T cells (p:0.032, p:0.001) compared to STAT3 and SAD. CD8+T cells percentages were significantly lower in DOCK8 than STAT3 (p:0.043). There was significant decrease in non-switched (p=0.024) and class-switched memory B cells (p:0.024) in patients with DOCK8 compared to patients with SAD. Moreover, in STAT3 patients; non-switched memory B cells were significantly lower than the SAD group (p=0.020).

Conclusion: Distinctive clinical and laboratory markers are helpful to differentiate HIES patients from SAD.


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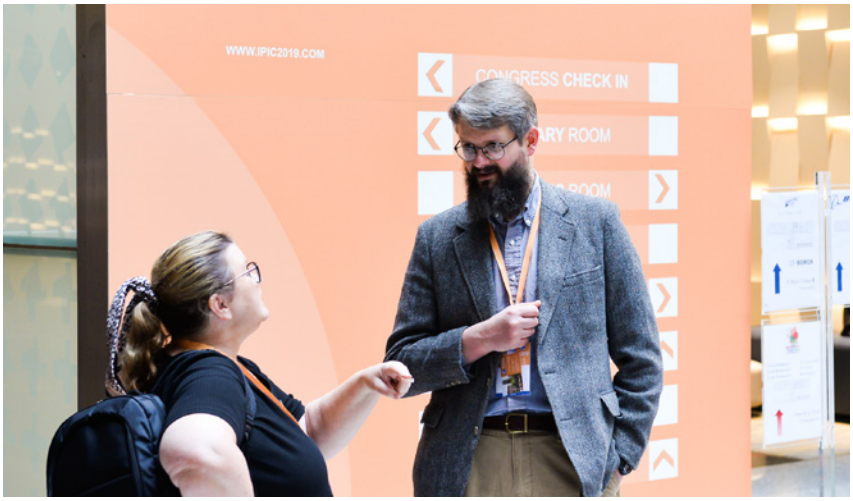
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