



IPIC2017

INTERNATIONAL PRIMARY IMMUNODEFICIENCIES CONGRESS

FOCUS ON DIAGNOSIS
AND CLINICAL CARE

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8-10 NOVEMBER
2017 // DUBAI

an IPOPI event

CONGRESS REPORT





an IPOPI event

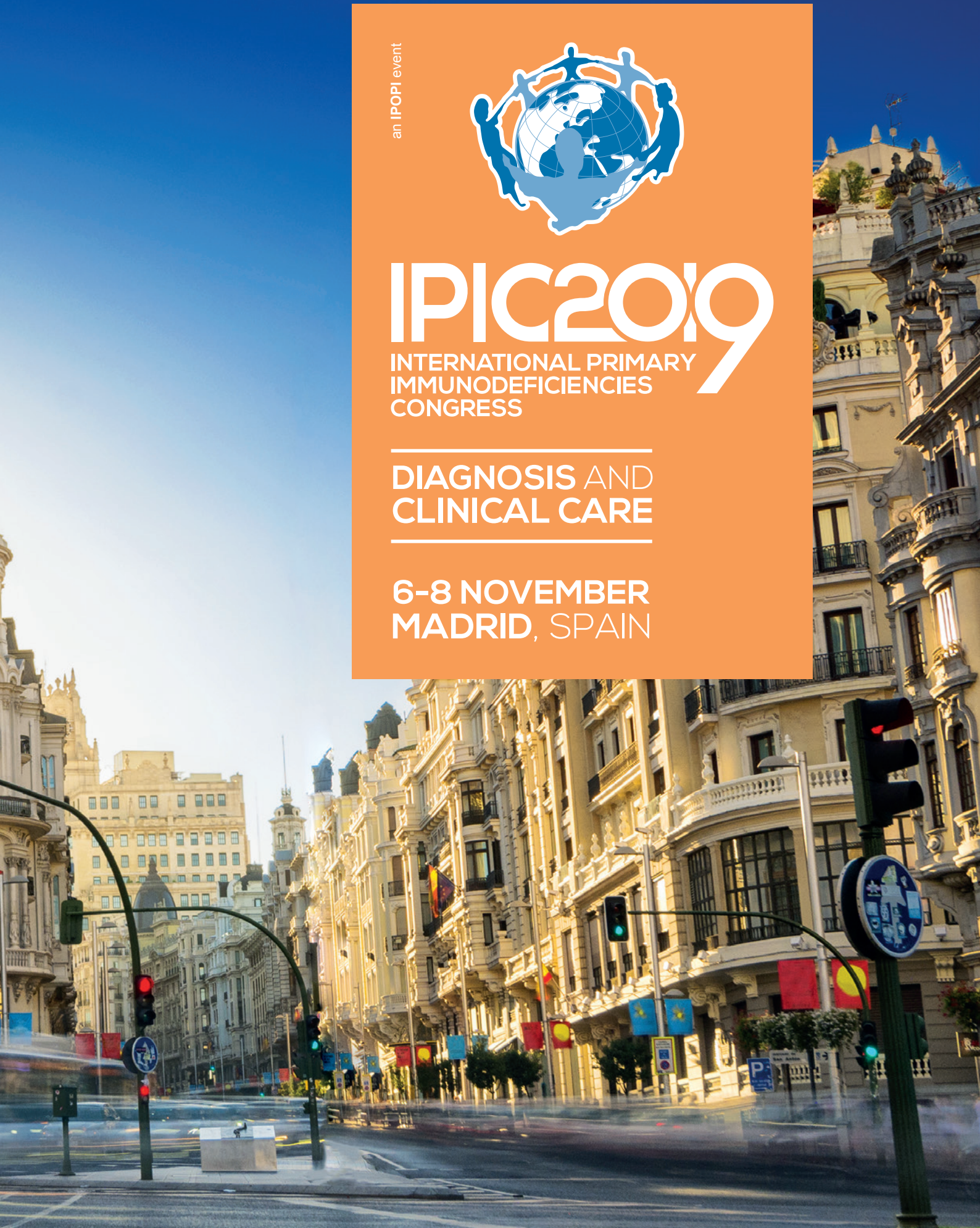


IPI C2019

INTERNATIONAL PRIMARY
IMMUNODEFICIENCIES
CONGRESS

DIAGNOSIS AND
CLINICAL CARE

6-8 NOVEMBER
MADRID, SPAIN





IPOPI - INTERNATIONAL PATIENT ORGANISATION FOR PRIMARY IMMUNODEFICIENCIES

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 63 National Member Organisations spread across all continents.

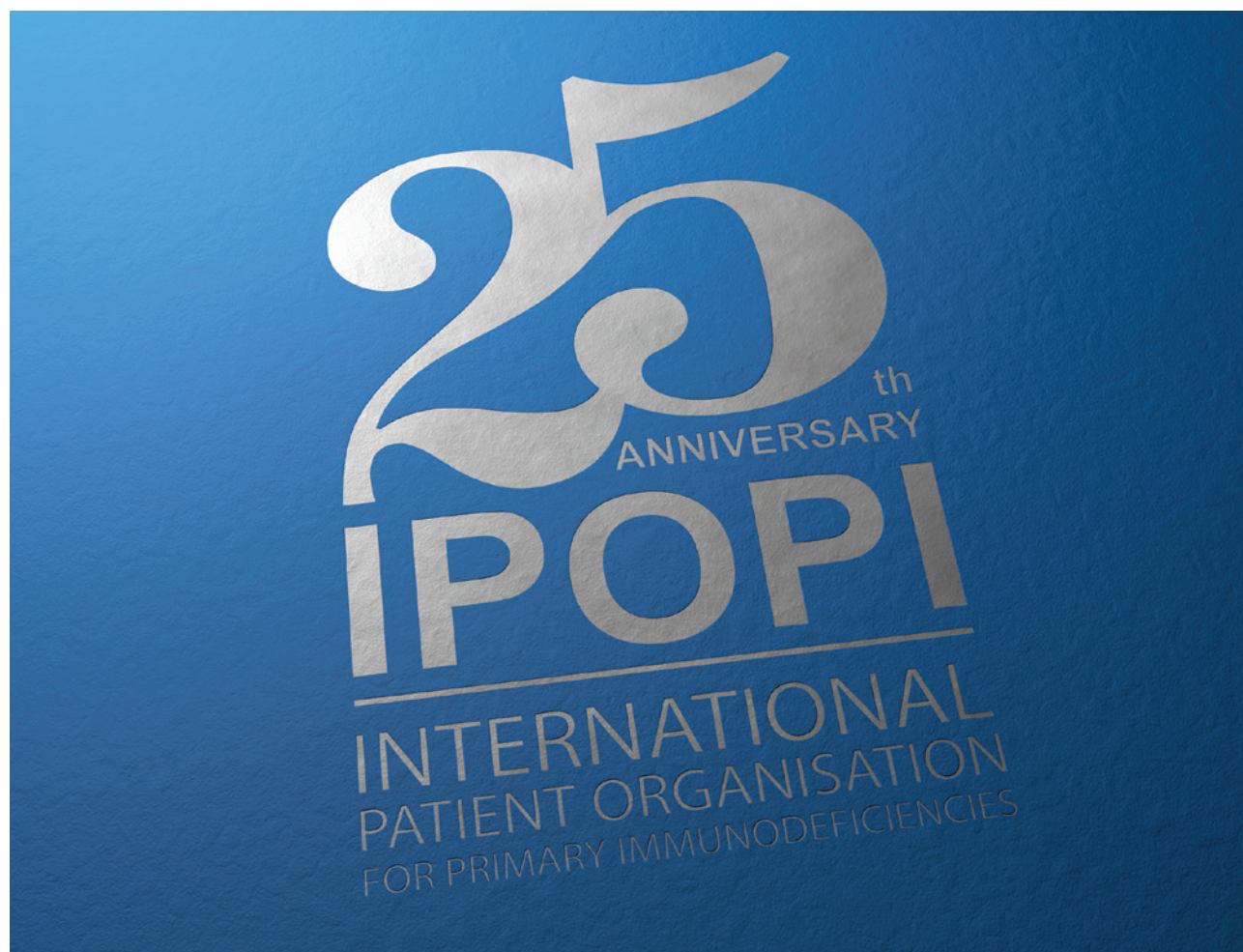
IPOPI is an international charity registered in the United Kingdom and under UK Charity Law.

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

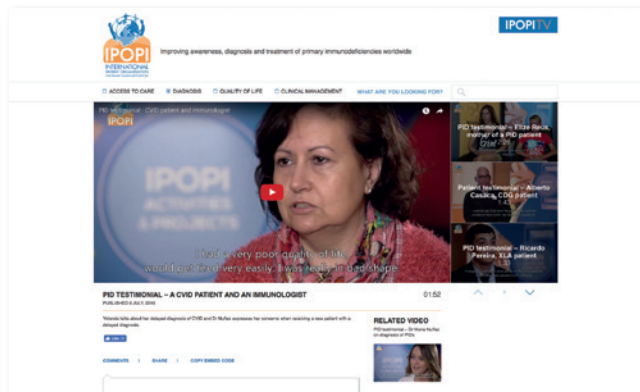
IPOPI came into being in 1992 and celebrated its 25th anniversary in 2017!



PUBLICATIONS

IPOPI led a Working Party of specialists to develop the *Primary Immunodeficiencies Principles of Care* which outlines the key elements that should be in place in each country and region to provide a “gold standard” framework of diagnosis and care for primary immunodeficiencies (PIDs). The paper was published in 2014 in *Frontiers of Immunology* and identifies 6 Principles of Care: the role for specialised centres, the importance of registries, the need for international collaborations for scientific research, the role of patients’ groups, management and treatment options for PIDs, and, management of PID diagnosis and care throughout the world. IPOPI and the PID Principles of Care Working Party invite the PID community and stakeholders to use it for their awareness and policy actions.

IPOPI has since 2011 been annually publishing series of PID information leaflets. The leaflets cover many different topics, such as: PIDs in Adults, Guide for Schools, Vaccines and Autoimmunity, Transition care, Guide for Subcutaneous Treatment, Immunoglobulin replacement therapy - One size does not fit all, among many others. All leaflets are available for download and on ebook version on the IPOPI website.



FIND US ONLINE

The best way to learn more about IPOPI 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.

Watch IPOPI TV to find all IPOPI’s video content 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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IPIC2017 CONGRESS REPORT by Dr Lizzie Rivers

IPIC2017, the 3rd International Primary Immunodeficiencies Congress organised by IPOPI, the International Patient Organisation for Primary Immunodeficiencies, was held in Dubai, UAE, on November 8-10, 2017. Over 600 delegates including patient group leaders, doctors, nurses and pharmaceutical industry representatives from over 70 countries were brought together at the event aimed at improving patient centred care for primary immunodeficiencies (PIDs) internationally. The uniqueness of IPIC comes from the fact that its programme is clinically orientated and prepared with the input from the key PID stakeholders: doctors, patients and nurses. The congress provides a multidisciplinary platform to discuss a wide range of issues relating to the diagnosis, management of the conditions and the most recent advances in the PID field.

Here, a summary is presented of the conference scientific sessions where updates in knowledge of disease as well as advances in supportive and definitive therapies for PIDs were discussed. Highlights of the conference also included patient testimonials reminding professionals in attendance why they do what they do and encouraging them to keep it going.

KEY MESSAGES:

- Molecular diagnosis plays a crucial role in improving identification of novel therapies and improving understanding of disease pathophysiology
- Some promising results are being seen with use of biologics and small molecule inhibitors in immune dysregulation, but long-term follow-up is needed
- Advances continue in haematopoietic stem cell transplant (HSCT) and gene therapy (GT) with the first clinical trials for gene editing in X-linked severe combined immunodeficiency (X-SCID) in the planning stages
- Sharing of experiences is key to improving primary immunodeficiency (PID) treatments globally

DAY 1: NOVEMBER 8, 2017

Welcome session: PIDs – not only a paediatric issue	8
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DAY 2: NOVEMBER 9, 2017

Opening session: Why treat PID at all?	10
Session 1: Screening for PIDs – early detection for optimal care	10
Session 2: PID and ethical issues	11
Session 3: Regional clinical priorities in PID treatments	12
Session 4: PIDs and dermatological issues	14

DAY 3: NOVEMBER 10, 2017

Session 5: Focus on immune dysregulation	16
Session 6: Disease-specific session	18
Session 7: PIDs and transplant advances – where are we going?	18
Session 8: Novel treatments for primary immunodeficiencies	20
Abbreviations	22
Poster Presentation	25
Congress Sponsors	152

WELCOME SESSION: PIDs – NOT ONLY A PAEDIATRIC ISSUE

KEY MESSAGES:

- PID in adults is underdiagnosed and increased awareness is needed
- Molecular diagnosis is important in identifying appropriate treatments e.g. HSCT that may not otherwise be indicated
- PIDs are chronic conditions and children require careful transition to adult services

Prof Helen Chapel opened the first session with a fascinating talk about the history of PID as a relatively recent discovery following the successes of antibiotics and vaccination programmes. Much has developed in the field since the first responsible genes were identified 20-30 years ago and we are now increasingly aware of the lifelong nature of PID. The prevalence of PID in children is increasing but adults with PID, mostly antibody failures, are still being missed (under diagnosis reported in 50-98% adult populations). This is important to recognise as treatment with immunoglobulin can be life changing in these patients. Thanks to IPOPI and IUIS PID committees, immunoglobulin replacement was reinstated in the WHO essential medicines list in 2007, allowing treatment programmes to be increasingly possible on a global scale. However, increased awareness of adult PID is still needed to optimise outcomes.

Dr Siobhan Burns echoed this sentiment very well and highlighted that molecular diagnosis in adult PID patients is crucial in identifying appropriate treatments, such as haematopoietic stem cell transplant (HSCT), which may not otherwise be indicated. Molecular diagnosis is also important in driving investigation of novel therapies and plays a significant role in family screening, with important implications in improving outcomes for those with early diagnosis. Even for patients in whom no superior treatment options result from molecular diagnosis at present, benefit can still be gained from subgroup analysis, allowing more accurate prediction of clinical course.

Prof Charlotte Cunningham-Rundles presented some interesting work towards improving recognition of PID in adults by using a computer scoring system to risk stratify the likelihood of missed PID in patients presenting with atypical organisms, unusual sites of infection or PID-associated complications such as bronchiectasis, lymphoproliferative disease and autoinflammation. Although the percentage of patients identified to be at risk of PID using this method was small (0.3% of 533 patients), most did prove to have a missed diagnosis when investigated. Retrospective review could aid identification of any common areas where diagnosis is delayed and identify areas where improved PID awareness could then be directed.

With huge advances in treatments, **Dr Nizar Mahlaoui** reminded us that PIDs are increasingly recognised as lifelong conditions with more and more children transitioning to adult services. Managing this can be complex and a poor transition is associated with poor treatment compliance and increase in disease complications. Introducing the concept of transition early, with careful consideration of individual needs going beyond the medical issues have been suggested to improve the chances of successful transition. The transition process has also been identified as a useful opportunity to re-think the diagnosis and to consider repeating any previously negative genetic tests, in view of the advances in testing that may have developed.

A patient perspective on a positive transition experience was eloquently described by **Rachel Hammond**, a patient with specific antibody deficiency. Rachel mentioned that her experience in meeting her new team together with the old team really improved her confidence in her ongoing care.





OPENING SESSION: WHY TREAT PID AT ALL?

"We treat patients because they are sick but we become specialists to make them well"

Prof Steven Holland's excellent keynote lecture on why we should treat PID at all concluded that "we treat patients because they are sick but we become specialists to make them well". Through the example of mycobacterial infections, it was highlighted that treatment allows interrogation of host-microbe interactions, which advances our knowledge of disease and subsequent treatment development. Increasing evidence demonstrates that PIDs are not the simple, monogenic diseases they may have previously been considered and that important acknowledgement should be given for an environmental role in multigenic disease. Advances in genetic testing are likely to change how we classify disease by identifying those with genetic mutations that do not manifest disease or do so in an unexpected way.

SESSION 1: SCREENING FOR PIDs - EARLY DETECTION FOR OPTIMAL CARE

KEY MESSAGES:

- T cell receptor excision circles (TRECs) screening is beneficial but more data is needed on kappa-deleting recombination excision circles (KRECs)
- In the absence of PID, low TRECs at newborn screening are linked with maternal immunosuppression in addition to prematurity and multiple births
- Pre-implantation diagnosis provides the option of having unaffected children without termination of pregnancy (TOP)
- Sharing of experiences in practicalities of screening implementation are needed to optimise practice
- Exploring how to centralise initiation of screening programmes to larger areas rather than individual countries could be beneficial in increasing uptake globally

Successes of newborn screening (NBS) for PIDs was introduced by **Prof Mirjam van der Burg** with T cell receptor excision circle (TREC) screening in all but two US states and increasingly in Europe demonstrating significant benefits in patient outcomes with early diagnosis and transplantation. Results from the prospective study of 60,000 patients in Sweden revealed low recall rate (64 patients), three of whom were confirmed to have PID, 29 of whom showed spontaneous recovery and others with confirmed low TRECs in the absence of PID associated with prematurity, multiple birth and interestingly maternal immunosuppression.

Benefit from kappa-deleting recombination excision circles (KREC) screening has also been suggested but further evidence is needed. A large multicentre retrospective study of X-linked agammaglobulinaemia (XLA) is currently planned for 2018, with hope for international collaboration, to aid evaluation of evidence on whether KRECs should be added to screening programmes.

An update from the French newborn screening pilot for severe combined immunodeficiency (SCID) was presented by **Dr Marie Audrain**. Comparison was made in outcomes between 200,000 screened versus non-screened SCID patients. Four patients with SCID were identified through the screening programme and were transplanted at 2-5 months, with only one death. One of these four had a delayed 2nd TREC sample, which delayed diagnosis and was an important lesson in the difficulties with practical aspects of screening implementation. This compared with five deaths out of 11 children diagnosed with SCID (unscreened) over the same period.

Ms Alison Lashwood presented the very positive experiences of pre-implantation diagnosis at Guy's Hospital in London. Their experience of screening embryos through biopsy at the blastocyst stage (pre-implantation) confers enormous benefit in providing ability to have unaffected children without going through termination of pregnancy (TOP). From 600 cases last year for selected diseases including PIDs, treatment cycles resulting in embryo transfer occurred in 69%, with 52% of embryos transferred resulting in live births. The process can be lengthy, so affected children need to be well enough to await creation of 'saviour siblings' and exclusion criteria of maternal age (>39 years) and extremes of body mass index (BMI) apply. With advances in treatment and increasing number of eligible conditions, it is important that couples have access to the relevant information when planning their family.

SESSION 2: PID CARE AND ETHICAL ISSUES

KEY MESSAGES:

- Rights of the child must be safeguarded above all
- Communication breakdowns between parents and staff happen occasionally despite best efforts at mediation
- Whilst it is a human response to use emotion to guide decision making, which is useful in empathy, it is not helpful in making difficult ethical decisions

A highlight of the conference was a panel session chaired by **Prof Bobby Gaspar**, where real cases were used to illustrate challenging ethical situations experienced by many medical teams. The cases were discussed by a panel of lay and medical professionals, with the addition of ethicist **Dr James Taylor** to facilitate discussions that were then opened up to the delegates. A common theme to the responses by the ethicist was that the rights of the child need to be safeguarded above all.

The first case used the example of Charlie Gard to highlight the importance of safeguarding the best interests of the child in pursuit of experimental treatment that is likely to be futile and has risks of causing harm. This case also illustrated the powerful influence of the media. Caution was raised in that only a small minority of these cases (around 18/year) are brought to the public's attention and that whilst it is a human response to use emotion to guide decision making, which is useful in empathy, it is not helpful in these difficult ethical situations.

The second case was one of obstructive parents' behaviour to the extent that it was felt Hematopoietic Stem Cell Transplantation treatment would be unsafe. Use of medical foster care was put forward as a potential necessary step to be able to provide treatment safely (where parents' consent to the treatment) but would need to balance the risks of harm to the child from parental separation. Use of patient organisations to aid communication and seeking to explore the cause of obstructive behaviour where possible were also discussed.

The third case highlighted the difficulties presented by use of genetic tests for research purposes, particularly in incidental findings of variants of unknown significance and diagnostic uncertainty. This case involved finding a variant that was felt unlikely to be the cause of symptoms, but could potentially have reflected coincidental carrier status for a significant PID, which could impact on family planning. Most felt reporting of variants of unknown significance should be encouraged (rather than reporting that no cause for the symptoms was identified), but to ensure that appropriate genetic counselling is needed where patients are allowed the opportunity to decline being told results that are not directly related to the reason for testing.



SESSION 3: REGIONAL CLINICAL PRIORITIES IN PID TREATMENTS

KEY MESSAGES:

- Sharing of experiences remains key to improving PID treatments globally
- Priorities of resource-rich regions include improving availability and funding of genetic testing (whole exome sequencing, WES, and next generation sequencing, NGS) and use of biologics
- Priorities of resource-poor settings include improving access to diagnostic tools and patient registries as well as funding availability for supportive and definitive treatments
- Reducing burden of infectious diseases in Africa must be tackled to allow PID treatment to become more of a priority
- Further work is needed in implementation of newborn screening globally, but must be in conjunction with improved supportive and definitive treatment availability in resource-poor settings
- Industry support and private/public partnerships could be beneficial in improving diagnostic tools and subsequent treatment in resource-poor settings
- Universally, priorities include raising PID awareness, particularly for adults

Representatives from **Europe (Prof Isabelle Meyts), USA (Prof Charlotte Cunningham-Rundles), Asia Pacific (Dr Adli Ali), Middle East (Dr Daifulah Al Zahrani), Latin America (LATAM) (Dr Antônio Condino Neto) and Africa (Dr James Chipeta)** were asked the same questions about their regions' clinical priorities for PID treatments. There were some clear differences between comparatively resource-rich and resource-poor settings but there were also many similar themes in inequalities seen within regions and lack of PID awareness.

Diagnostic tools are widely available in Europe and the USA. Limited availability in resource-poor settings, however, has a resultant impact on ability to make firm diagnoses with subsequent difficulty in setting up patient registries commented on from Asia Pacific, LATAM and Africa.

Reducing infectious diseases is a particular priority for Africa, which could allow PID to become more of a government priority. Whole exome and next generation sequencing (WES and NGS) are being used increasingly in resource-rich regions (namely Europe and USA), though challenges are seen in availability and funding for use in the clinical, rather than research, setting. This is a clear priority for improving PID treatment in these regions.

It was pointed out that availability of immunoglobulin globally has significantly improved, with particular thanks to IPOPI for its reinstatement in the WHO List of Essential Medicine. However, availability in some regions is limited e.g. LATAM and Africa, with access further restricted in other regions by lack of reimbursement for use e.g. Asia Pacific. Inequalities in immunoglobulin replacement were also reported with reports of immunoglobulin products being withdrawn in Romania and only available in intramuscular (IM) form in Moldova.

Definitive treatment in the form of Haematopoietic Stem Cell Transplant (HSCT) and Gene Therapy (GT) is fairly accessible in Europe and USA. Limited availability in resource-poor settings is compounded by funding issues, for example in Asia Pacific, where HSCT treatment is only reimbursed for matched sibling donors.

Newborn screening has been very successful in the USA and results from pilots in Europe are encouraging. However, more work is needed in implementing newborn screening globally. This is of course needed in conjunction with improving funding and availability of treatments including immunoglobulin replacement and HSCT in resource-poor settings. Additionally, screening could have an important impact on the particular challenge of BCGosis in the Middle East, where BCG is compulsory at birth, with huge impact on PID outcomes.

Education and raising awareness of PIDs (and registries) was a common priority for all regions, IPOPI's work was praised by all regions, with particular emphasis on its very successful role in aiding collaboration between regions to aid improvement in resources and education. However, further work is still needed in continuing to develop international research collaborations and combined registries, which could help provide the evidence base needed for government support.



SESSION 4: PIDs AND DERMATOLOGICAL ISSUES

KEY MESSAGES:

- Skin manifestations are common in PIDs – though non-specific, some patterns should make us suspicious about PIDs
- Genetic diagnosis is important in tailoring specific therapies such as Ruxolitinib for signal transducer and activator of transcription 1 gene (STAT1) gain of function (GOF) mutations and HSCT for caspase-associated recruitment domain 9 gene (CARD9) mutations
- Long term therapy is needed for fungal skin infection, but associated with high incidence of resistance
- Invasive fungal infection seen in 10% those with skin infection
- Close collaboration with dermatology is a useful way to increase PID awareness

Dr Waleed Al-Herz reminded us that there are no specific signs/symptoms in the skin disease that point particularly to PID and so patients are commonly seen by other specialties, which sometimes contributes to delayed diagnosis. Features suggestive of PID include skin infections that are recurrent and difficult to treat. Collaborations with dermatology would be a good area to target education/ awareness of PID. Some specific skin manifestations seen in PIDs include:

SKIN MANIFESTATION	PID
Granulomas	CGD, CVID, AT, SCID
Telangiectasia	AT
Albinism	Chediak-Higashi, Griscelli, Hermansky-Pudlak
Congenital hypotrichosis	Cartilage Hair Hypoplasia, Ectodermal Dysplasia, Netherton syndrome
Livedo reticularis	CGD
Eczema	HIES, IPEX, maternal engraftment, Omenn syndrome, WAS

AT – ataxia telangiectasia; CGD – chronic granulomatous disease; CVID – common variable immunodeficiency; HIES – hyper IgE syndrome; IPEX – Immune dysregulation, polyendocrinopathy, X-linked; SCID – severe combined immunodeficiency; WAS – Wiskott Aldrich syndrome

Autoimmune skin manifestations are also often seen in PID, including: lichen planus, psoriasis, vitiligo and vasculitis (seen in 6% PID, more often associated with C1, C2 and C4 mutations).

Dr Bodo Grimbacher presented an audit of skin manifestations in 36 patients with chronic granulomatous disease (CGD). Common findings included: abscesses, folliculitis, facial erythema (which seems to improve with antifungal treatment, suggesting a fungal component), hidradenitis, angular stomatitis and eczema. Interestingly, there did not seem to be any difference between autosomal recessive and X-linked forms. Although skin manifestations are often non-specific, targeted gene sequencing may be helpful in identifying underlying PID. Screening of 207 patients with chronic mucocutaneous candidiasis found a mutation in 27% (*AIRE*, *CARD9*, *DOCK8*, *IL17Ra*, *SPINK5*, *STAT1* and *STAT3*). Genetic testing for other PIDs can be targeted also in eczema, which is particularly prominent in Wiskott Aldrich syndrome (WAS), hyper-IgE (HIES), Omenn syndrome and maternal engraftment and recurrent skin infections, seen in CGD and signal transducer and activator of transcription 3 (STAT3) loss of function (LOF). Vitiligo in the context of immune deficiency may be suggestive of common variable immunodeficiency (CVID), for which Dr Grimbacher's lab have developed a panel of 120 genes.

Management of chronic fungal skin infections in PID can be difficult, as highlighted by **Prof Olivier Lortholary**. We were also reminded that invasive fungal infection seen in 10% those with fungal skin infection, which may require screening for. The identification of causative agent in fungal nail infections can be aided by the knowledge that dermatophytes tend to affect the nail itself, whereas candidiasis tends to affect paronychia regions. Two specific PIDs where fungal skin infections are common are caspase-associated recruitment domain protein CARD9 deficiency and STAT1 gain of function

(GOF) mutations. CARD9 deficiency presents with deep dermatophytosis and candida. Commonly, this manifests with severe/ recurrent tinea capitis and oral candidiasis, along with lymph node, central nervous system (CNS), lung and bone infection and treatment with posaconazole or itraconazole is suggested. STAT1 gain of function mutations present with chronic mucocutaneous candidiasis (CMCD), resulting from impaired IL-17. Bacterial and viral infections are also commonly seen (74% and 38% respectively) due to janus kinase (JAK) dependency, requiring the addition of antibiotic prophylaxis to long term antifungal treatment. Antifungal resistance is high, seen in around 39%. Advice on antifungal treatments included:

FUNGAL AGENT	TREATMENT
Dermatophytes	Terbinafine (followed by posaconazole, then itraconazole)
Yeasts	Posaconazole
Oral candidiasis	Miconazole (posaconazole is also effective, but the oral suspension should be used)
Oropharyngeal/ oesophageal candidiasis	Fluconazole
Severe/ recurrent relapses	Fluconazole
Resistance	Echinocandins (e.g. Micafungin), but only available as intravenous (IV) form

Voriconazole is also a very effective antifungal agent, but needs therapeutic drug monitoring and long-term toxicity with photosensitivity can lead to increased susceptibility to skin cancer so dermatology follow-up is recommended.

In addition to the use of genetics in diagnosing PID in the face of skin manifestations, molecular diagnosis is also useful in identifying potential therapies that might not otherwise be indicated, for example Ruxolitinib for STAT1 GOF and HSCT for CARD9 deficiency.

The session ended with an enlightening patient testimony from Mr Andrea Gressani, who is living with CGD (untransplanted). A very honest description of his experience included the challenge of taking medication every day, even when feeling very well. A thoughtful analogy used was that this experience was like “fighting a war (but with a very good army!)”.



SESSION 5: FOCUS ON IMMUNE DYSREGULATION

KEY MESSAGES:

- Overlap of immune dysregulation with atopy makes diagnosis difficult
- IgE is raised in 80% of atopic eczema
- An association between dust inhalation and granuloma development in sarcoidosis may apply to those with common variable immunodeficiency (CVID)
- Granulomatous disease in CVID is often underestimated
- A potential role for Rituximab in CVID has been suggested by the observation of lack of granulomas in X-linked agammaglobulinaemia (XLA) (where B cells are absent)
- Therapeutic benefit of anti-IL-6 has been suggested in STAT3 GOF mutations
- Gene identification has driven development of novel therapies e.g. janus kinase (JAK) inhibitors for STAT1 GOF mutations and cytotoxic T lymphocyte-associated protein 4 (CTLA4)-immunoglobulin for lipopolysaccharide-responsive and beige-like anchor protein (LRBA) deficiency
- Use of Campath has shown promise in haemophagocytic lymphohistiocytosis (HLH) with reduced toxicity compared with chemotherapy
- Use of specialist centres is needed for effective monitoring of short and long term effects and toxicities associated with novel therapies

Immune dysregulation in PID is often quite difficult to differentiate from allergy, highlighted in a useful overview by **Prof Antônio Condino Neto**. Skin inflammation is a common feature of immune dysregulation, seen particularly in IPEX (X-linked immune dysregulation and polyendocrinopathy), WAS, HIES and Omenn syndrome. It is also, however, more commonly seen in atopic eczema, where raised IgE occurs in as much as 80% of patients. Clues pointing towards PID can be identified with careful infection history and looking for specific features, for example coarse facial features or retained primary teeth.

An interesting overview of granulomatous disease in PID was given by **Prof Martin Van Hagen**, applying lessons learned from sarcoidosis. Lung granulomas are commonly seen in both sarcoidosis and CVID but detailed analysis has allowed for some important differences to be identified, for example more hilar lymphadenopathy is seen in sarcoidosis and sarcoid granulomas have predominance in the apices. Additionally, vaccine responses are typically normal in sarcoidosis. An association between dust inhalation and granulomas in sarcoidosis can be applied to CVID, where appropriate screening and advice (particularly occupational) may help reduce the incidence. Granulomatous disease in CVID is probably underestimated as suggested by recent study using scintigraphy. A potential role for Rituximab has been suggested by the observation of lack of granulomas in X-linked XLA (where B cells are absent).

Autoimmunity is common in PID (58%) and **Prof Alain Fischer** reminded us that most commonly this takes the form of cytopaenias, which are known to be a negative prognostic indicator in PID. Gene identification has allowed development of targeted therapies, including JAK 1/2 inhibitors for STAT1 GOF mutations, cytotoxic T cell-associated protein 4 immunoglobulin (CTLA4-Ig) as targeted replacement therapy for lipopolysaccharide-responsive and beige-like anchor protein (LRBA) deficiency and anti-IL-1/6 for STAT3 GOF mutations, phosphatidylinositol-3 kinase (PI3K) for activated PI3K delta syndrome (APDS) and mammalian target of rapamycin (mTOR) inhibitors for autoimmune lymphoproliferative syndrome (ALPS). Prof Fischer presented experience of these treatments with 11 stimulators of interferon gene (STING) patients treated with the JAK2 inhibitor Ruxolitinib, which looks safe but with relatively short follow-up so far. Interestingly, a suspicion about extra-haematopoietic expression of STAT1 has been raised following the observation of a STING-associated vasculopathy with onset in infancy (SAVI) patient with full chimerism post HSCT who had good correction of lung lesions, but no improvement in brain or skin complications. Median follow-up of 14 months for 14 LRBA deficiency patients who have been treated with Abatacept (CTLA-4-Ig) (7.5-20mg/kg every 2 weeks) has shown positive effects on the lungs, cytopaenias and liver. PI3K inhibitors have been used so far for six of their patients with APDS, with improvement in lymphoproliferation as well as normalisation of transitional and naïve B cells. Caution has, however, been raised about the other potential effects of PI3K inhibition given its tumour suppressor role, raising a potential risk of lymphoma (though this has not been seen so far). Experience of HSCT in PIDs with large autoimmune component (from ESID registry) has shown encouraging outcomes from 100 patients with PIDs including IPEX, ALPS, LRBA deficiency and STAT3 GOF mutations with survival of 22/26 and 24/29 in matched related and unrelated HSCTs (but 10/14 and 18/28 in mismatched). Use of specialist centres will undoubtedly improve ease of monitoring short and long-term benefits and toxicities of these novel therapies.

Experience of treating haemophagocytic lymphohistiocytosis (HLH) in France was presented by **Dr Despina Moshous**, where Alemtuzumab has been used in 23 patients with HLH to control hyperactive T cells, with the advantage of reduced toxicity compared with the chemotherapeutic agent Etoposide used in the 2004 protocol. Their cohort comprised 26% neonates, with the youngest patient 30/40 (1.7kg) and oldest 17 years, with 95% surviving to HSCT. A potential role for JAK inhibitors to block macrophage activation in HLH has also been suggested following mouse work and anti-interferon gamma (IFN γ) has also been used with some success.



SESSION 6: DISEASE-SPECIFIC SESSION

KEY MESSAGES:

- Link between carbamazepine use and hypogammaglobulinaemia has been established
- Appropriate pattern recognition receptor (PRR) recognition, amplification and response are key in innate and adaptive immunity, in addition to control of inflammation
- Importance of molecular diagnosis in tailoring treatments reiterated, with the concept of exome scrubbing advocated – if no mutation is found, keep looking!

Dr Waleed Al-Herz presented a useful update on antibody deficiencies. An association between hypogammaglobulinaemia and carbamazepine has recently been identified, but correlation with infectious history and functional analysis has been suggested to be of particular importance prior to considering commencement of immunoglobulin replacement. Long term follow-up was discussed as being particularly important in IgA deficiency, and might also be considered in hypogammaglobulinaemia of infancy, in view of the association with developing CVID later on. As with earlier talks, the role of genetic testing in antibody deficiencies was emphasised as being important in tailoring treatment.

An overview of innate immunodeficiencies was led by **Dr Jordan Orange**, where the role of appropriate pattern recognition receptor (PRR) recognition, amplification and response were described as important in inflammation as well as in innate and initiation of adaptive immunity. Increasing evidence suggests that it is an imbalance of these processes that can lead to autoinflammatory conditions. The importance of molecular diagnosis in these innate immunodeficiencies was highlighted by data from 1000+ patients who underwent whole exome sequencing (Houston project), which provided diagnosis in 40% cases, with changes in management in a significant number. Cases with a blend of mutations were also identified in this project, giving rise to new phenotypes and the need for 'exome scrubbing' was raised, whereby the lack of finding a responsible mutation should prompt further looking.

SESSION 7: PIDs AND TRANSPLANT ADVANCES – WHERE ARE WE GOING?

KEY MESSAGES:

- Improved outcomes for HSCT are being seen following the introduction of T cell depletion for haploidentical infusions and development of unrelated cord banks
- Safety of GT has increased following development of lentiviral vectors and relocation of promoters
- GT for adenosine deaminase-deficient (ADA)-SCID is now first line therapy where matched donor is not available
- Gene editing for PIDs is under development, with the first clinical trials for X-SCID in the planning stages

The experience of HSCT in Riyadh was presented by **Dr Saleh Al Muhsen**, where the population is unique due to high rates of consanguinity, resulting in overrepresentation of autosomal recessive (AR) conditions compared with other areas. The advantage of a consanguineous population, however, is that there is a higher chance of finding matched family donor for HSCT. Advances in HSCT in this area have included the establishment of a local unrelated cord bank in 2008 and introduction of T cell depletion for haploidentical infusion in 2017. A summary of their experience of HSCT for SCID (mostly T-B-NK+) shows median age of transplant is 6 months with conditioning in 50% and overall survival in 72%, where most of those who died had not engrafted.

An update on gene therapy (GT) using viral vectors for gene addition in X-SCID, adenosine deaminase-deficient (ADA)-SCID, WAS and CGD was presented by **Prof Alessandro Aiuti**. Treatment regimens vary with condition, with some chemotherapy still needed to aid engraftment. His group's experience of GT for ADA deficiency includes treatment of 18 patients, with 100% overall survival and 82% event-free survival after median follow-up of seven years. Immune reconstitution seems good, with patients having stopped immunoglobulin replacement and growing well. **Prof Bobby Gaspar** added that 48 children with ADA-SCID have now been treated with GT overall, with 100% survival and only one child still receiving enzyme replacement therapy. The success has meant that it is now first line treatment for patients where

a matched donor is not available for HSCT. GT is also looking very promising for WAS, where Professor Aiuti presented outcomes for 8 patients treated with GT using lentiviral vectors, with survival of 100% after 2-7 years follow-up. Corrected cells have been seen in all lineages, with a selective advantage seen in lymphocytes. Improvement in infections has been seen, with patients off immunoglobulin replacement and normal vaccine responses. Improved platelet counts have also been seen, with reduced frequency and severity of bleeding episodes. Disappearance of eczema has been seen in all except one patient and no autoimmunity has developed. Early GT for X-SCID using gamma retroviral vectors was associated with development of leukaemia, which has not been seen following relocation of the gene promoter. Outcomes for GT in X-CGD have some far shown low engraftment and work is ongoing to improve this. Clinical trials are in progress for JAK-3, IL-7 receptor alpha (IL-7Ra), recombinaise activating gene (RAG) and Artemis-deficient SCIDs.

The idea of gene editing was first posed in 1978, but it has taken 30 years to develop in vitro. **Dr Matthew Porteus** presented an update on progress in the gene editing field, where a DNA break in stem cells is created and donor DNA is introduced at break sites using a cells' DNA repair machinery (non-homologous/homologous end joining, NHEJ/HEJ). Problems with development have been encountered by the need for high concentration of donor DNA and innate immunity host response in recognising this donor DNA and activating IFN. The use of adeno-associated virus AAV6 vectors and nucleoporation are being used to help get by this. X-SCID is a priority in Dr Porteus's lab, where they are using a hybrid gene therapy/editing approach to target exon 1 and insert codon optimised cDNA. They have found that using a short donor without truncated nerve growth factor (tNGFR) had much better genome targeting, which has provided the hypothesis that the simpler the vector, the better the chance of integration. Encouraging results have been suggested by normal STAT5 phosphorylation in T cells. Genome targeting in mice following stem cell (CD34) correction was better intra-hepatically (20%) compared with femoral (9.5%), which was similar in patients (n=4), with 89% donor cells in the spleen. Encouragingly, selective advantage was seen in modified cells. Off target effects from zinc finger nucleases (ZFNs) at four sites > 1% are not thought to be functionally important and clinical trials now have FDA approval. Dr Porteus's group's study showed two off target sites with indels in 0.1%. Lentiviral insertions led to 500 mutations, which compared with 200,000,000 from conditioning and 120,000 from CT scans.

A remarkable patient testimonial by **Dr Eva Varga** described her and her daughter's experiences of treatments for HIES that have really advanced since the 70s, with use of immunoglobulin replacement, aggressive skin therapy and possibility of HSCT. Dr Varga has been determined to minimise how her condition impacts on her quality of life and works very successfully as a GP, where she is able to use her experiences to help her patients. Her personal benefit from Ganoderma lucidum (reishi mushrooms), sauna and physiotherapy also provided useful ideas for improving symptom support that may be helpful for others with the same condition.



SESSION 8: NOVEL TREATMENTS FOR PRIMARY IMMUNODEFICIENCIES

KEY MESSAGES:

- Immunity is needed for control of inflammation
- Anti-IL-23 (Ustekinumab) may be useful in the control of inflammation in leucocyte adhesion defect (LAD)
- JAK inhibitors (Ruxolitinib) may be useful in controlling autoimmunity and inflammation in STAT1 GOF mutations, but caution should be taken in the context of severe infection
- Advances are being made in immunoglobulin replacement with enhanced individualised therapy, but challenges still exist in improving affordable access worldwide

Prof Eric Oksenhendler highlighted some difficulties with older therapies such as the risk of severe hypogammaglobulinaemia with Rituximab that can last for up to two years and concern about increased risk of significant bacterial infection (including disseminated mycobacterial and opportunistic infections) with anti-tumour necrosis factor (TNF) therapy. CTLA-4-Ig (Abatacept), as mentioned in earlier talks, seems to be showing good results in CTLA-4/ LRBA deficiency, though longer follow-up is needed.

Prof Steven Holland talked about the role of monoclonal antibodies in targeted PID treatment, with a reminder about the importance of immunity in regulating inflammation. Encouraging results have been seen with the use of anti-IL-23 (Ustekinumab) for leucocyte adhesion defect (LAD), where lack of the down-regulation of IL-23 secretion needed by tissue neutrophils leads to inflammation. The use of JAK inhibitors (e.g. Ruxolitinib), which down-regulate cytokine receptors, to control disease resulting from excessive IFN secretion in SAVI and STAT1 GOF mutations have also shown promising results in treating autoimmunity, inflammation and candidiasis. Outcomes in the context of severe infection were not so good, however, with progression of invasive fungal infection seen despite reduction in STAT1 phosphorylation. An additional cautionary tale can be gained from the experience of Ruxolitinib use in rheumatoid arthritis (RA) patients, where reactivation of varicella zoster virus (VZV) is often seen.

Clinical use of specific inhibitors in the treatment of PIDs was added by **Prof Olivier Hermine**, with encouraging results seen in use of mTOR inhibition with rapamycin for ALPS (1-3 mg/m², serum level 5-10ng/ml) with very few side effects. Additional benefits have been seen from JAK-inhibitors and anti-TNF, anti-IL-1/ 6 in STAT3 GOF mutations. Plerixafor is a small molecule inhibitor of C-X-C chemokine receptor 4 (CXCR4), where gain of function mutations lead to lymphopaenia, hypogammaglobulinaemia, bronchiectasis and warts. Interestingly, a use for thalidomide in CGD has been described to be beneficial through increased reactive oxygen species (ROS) production. Caution was raised in the use of small molecule inhibitors, however, with potential for malignancy and allergy associated with PI3K, mTOR and JAK inhibition. However, they remain an exciting group of potential therapies that may at least serve a useful function in the bridge to HSCT.

With significant advances in immunoglobulin development, lessons have been learned in optimising components and drug delivery, which were highlighted by **Prof Klaus Warnatz**. Reduced IgA composition appears to be important in increasing tolerance and a better safety profile is seen with a decrease in pro-coagulant factors and haemagglutinins. The biological safety has significantly improved, with no viral transfer seen in recent years. Although use of a trough IgG level was highlighted as being of potential use in tailoring treatment doses, we were reminded of the greater importance being on infection history to modify therapy. Advances in delivery methods has allowed for better development of individualised therapy, for example, with the use of hyaluronidase to increase the subcutaneous space allowing for increased subcutaneous volumes to be infused per site, with reduction in infusion times. Further development in inhaled and gastrointestinal (GI) administration is underway, but the greatest challenge in immunoglobulin development remains the need for increased affordable access worldwide.

Prof Bobby Gaspar closed the conference with an inspiring talk on how PIDs are driving the future of science, using the example of SCID; a condition previously associated with 100% mortality, now remarkably moving towards 100% survival. Much of the work presented at this conference serves as a powerful reminder of the importance of sharing experiences in progressing PID treatments and drives us to continue to tackle remaining challenges.



AAV6	Adeno-associated virus 6
ADA-SCID	Adenosine deaminase-deficient SCID
AIRE	Autoimmune regulator protein
ALPS	Autoimmune lymphoproliferative syndrome
APDS	Activated PI3K delta syndrome
AR	Autosomal recessive
AT	Ataxia telangiectasia
BCG	Bacillus Calmette-Guérin vaccine
BMI	Body mass index
CARD9	Caspase-associated recruitment domain 9
CGD	Chronic granulomatous disease
CMCD	Chronic mucocutaneous candidiasis
CMV	Cytomegalovirus
CNS	Central nervous system
CT	Computed tomography
CTLA-4	Cytotoxic T cell-associated protein 4
CVID	Common variable immunodeficiency
CXCR4	C-X-C chemokine receptor 4
DNA	Deoxyribonucleic acid
DOCK8	Dedicator of cytokinesis 8
ESID	European Society for Immunodeficiencies
FDA	Food and Drug Administration
GI	Gastrointestinal
GOF	Gain of function
GP	General practitioner
HEJ	Homologous end joining
HIES	Hyper IgE syndrome
HLH	Haemophagocytic lymphohistiocytosis
HSCT	Haematopoietic stem cell transplant
IBD	Inflammatory bowel disease
IFN	Interferon
Ig	Immunoglobulin
IL	Interleukin
IL17Ra	Interleukin 7 receptor alpha
IM	Intramuscular

IPEX	Immune dysregulation, polyendocrinopathy, X-linked
IPIC	International Primary Immunodeficiencies Conference
IPOPI	International Patient Organisation for Primary Immunodeficiencies
IUIS	International Union of Immunological Societies
JAK	Janus kinase
kg	Kilogram
KRECs	Kappa-deleting excision circles
LAD	Leucocyte adhesion defect
LATAM	Latin America
LOF	Loss of function
LRBA	Lipopolysaccharide-responsive beige-like anchor protein
mTOR	Mammalian target of rapamycin
NGS	Next generation sequencing
NHEJ	Non-homologous end joining
PI3K	Phosphatidylinositol-3 kinase
PID	Primary immunodeficiency
PRR	Pattern recognition receptor
RA	Rheumatoid arthritis
RAG	Recombinase activating gene
ROS	Reactive oxygen species
SAVI	STING-associated vasculopathy with onset in infancy
SCID	Severe combined immunodeficiency
SPINK5	Serine Peptidase Inhibitor Kazal Type 5
STAT1/ 3/ 5	Signal transducer and activator of transcription 1/ 3/ 5
STING	Stimulator of interferon
TNF	Tumour necrosis factor
tNGFR	Truncated nerve growth factor
TRECs	T cell receptor excision circles
VZV	Varicella zoster virus
WAS	Wiskott Aldrich syndrome
WES	Whole exome sequencing
WHO	World Health Organisation
XLA	X-linked agammaglobulinaemia
X-SCID	X-linked SCID
ZFNs	Zinc finger nucleases



POSTER	PRESENTER	TITLE
1	BEN-ALI M.	HOMOZYGOUS TCF3 MUTATION IS ASSOCIATED WITH SEVERE HYPOGAMMAGLOBULINEMIA AND ACUTE LYMPHOBLASTIC LEUKEMIA
2	PHAN N.	CASE SERIES REPORT OF HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS IN PRIMARY IMMUNODEFICIENCIES: A SINGLE-INSTITUTION STUDY AT THE CHILDREN'S HOSPITAL 1, HO CHI MINH, VIETNAM
4	HEROPOLITANSKA-PLISZKA E.	CUTANEOUS AND SOLID ORGANS GRANULOMAS IN PATIENTS WITH NIJMEGEN BREAKAGE SYNDROME (NBS) – DIAGNOSTIC AND TREATMENT CHALLENGE
5	RICHTER A.	MANUAL PUSH SUBCUTANEOUS IMMUNOGLOBULIN ADMINISTRATION IN PATIENTS WITH PRIMARY AND SECONDARY IMMUNODEFICIENCIES AND AUTOMIMMUNE DISORDERS: A CASE SERIES OF 18 PATIENTS
6	RAMAKERS J.	CINCA-SYNDROME PRESENTING AS HYPEREOSINOPHILIC SYNDROME
7	BRODSZKI N.	ALONE OR ADD-ON? INHALING NEBULISED IMMUNOGLOBULINS: 18 MONTHS OF REAL LIFE EXPERIENCE
8	NG.PAULINE	ADA-SCID: THE BURDEN AND IMPACT ON THE PATIENT, CAREGIVER AND FAMILY. A QUALITATIVE RESEARCH IN USA, ITALY, FRANCE AND UK
9	KATPATTIL S.	DISEASE BURDEN FOR PATIENTS WITH PRIMARY IMMUNODEFICIENCY DISEASES - A COMPARATIVE STUDY
10	SHARMA M.	PRENATAL DIAGNOSIS AND CARRIER SCREENING FOR PRIMARY IMMUNODEFICIENCY DISEASES
12	PRANDZIOCH B.	HOW TO EDUCATE CHILDREN ABOUT PID? STUDY CASE FROM POLAND: EDUCATIONAL BOARD GAME
13	ALRUMAYYAN N.	THE IMPACT OF BCGITIS CAUSED BY BCG VACCINE ON THE OUTCOME OF SEVERE COMBINED IMMUNODEFICIENCY PATIENTS: A SINGLE-CENTER EXPERIENCE
14	MOHAMMED ALI R.	PRIMARY IMMUNODEFICIENCY IN THE ADULT POPULATION; A GROWING PERCEPTION THAT NEEDS ATTENTION IN THE MIDDLE EAST.
15	ADELI M.	TRIMETHOPRIM-SULFAMETHOXAZOLE PROPHYLAXIS INCREASE RISK OF MYELOSUPPRESSION IN PRIMARY IMMUNE DEFICIENCY DISEASE PATIENTS: RETROSPECTIVE THREE GROUPS COMPARISON STUDY
16	MOHAMMAD M.	GOOD SYNDROME, A DISEASE WITH VARIED PRESENTATIONS
17	COOPMANS E.	ANTERIOR PITUITARY DYSFUNCTION IN PATIENTS WITH PRIMARY ANTIBODY DEFICIENCIES
18	CESONI MARCELLI A.	ADIPONECTIN EXPRESSION AND EFFECT OF IMMUNOGLOBULIN THERAPY IN PATIENTS WITH COMMON VARIABLE IMMUNODEFICIENCY
19	MEESILPAVIKKAI K.	JAK1/2 INHIBITOR BARICITINIB AS A POTENTIAL THERAPY IN A PATIENT WITH GAIN-OF-FUNCTION MUTATION IN SIGNAL TRANSDUCER AND ACTIVATOR OF TRANSCRIPTION 1 (STAT1)
20	NG Y.	MOLECULAR DIAGNOSIS OF SCID PATIENTS BY A CUSTOM DESIGNED TARGETED NEXT GENERATION SEQUENCING PANEL
22	THUC H.	IMMUNOGLOBULIN REPLACEMENT THERAPY FOR CHILDREN WITH PRIMARY IMMUNODEFICIENCY DISEASES IN VIETNAM
24	YEL L.	OVERALL AND PEDIATRIC PATIENT PREFERENCES FOR RECOMBINANT HUMAN HYALURONIDASE (RHUPH20)-FACILITATED SUBCUTANEOUS INFUSION OF IMMUNOGLOBULIN G (FSCIG) IN PATIENTS WITH PRIMARY IMMUNODEFICIENCIES
25	YEL L.	ANALYSES OF EFFICACY AND TOLERABILITY IN PATIENTS WITH PRIMARY IMMUNODEFICIENCY DISEASES TREATED BY DIFFERENT MODES OF ADMINISTRATION OF IMMUNOGLOBULIN THERAPY DURING THREE CONSECUTIVE STUDIES
26	YAZDANI R.	EVALUATION OF PI3K/AKT/FOXO PATHWAY IN PATIENTS WITH COMMON VARIABLE IMMUNODEFICIENCY

POSTER	PRESENTER	TITLE
27	SABUR H.	HEMATOPOIETIC STEM CELL TRANSPLANTATION FOR SEVER COMBINED IMMUNODEFICIENCY OR OMENN SYNDROM DUE TO ARTEMIS DEFECT: A SINGLE CENTER EXPERIENCE
28	KARIM A.	STAT3 RELATED HYPER-IGE SYNDROME IN A BOY WITH HIGH EOSINOPHILIA AND A NONSENSE MUTATION IN THE LINKER DOMAIN
29	V S V.	TREOSULFAN BASED CONDITIONING REGIMENS – REDUCED TOXICITY WITH EXCELLENT OUTCOMES IN CHILDREN WITH PRIMARY IMMUNE DEFICIENCY
30	KANDASAMY K.	HAEMATOPOIETIC STEM CELL TRANSPLANTATION FOR IL 10 RECEPTOR DEFICIENCY IN TWO CHILDREN WITH EARLY INFLAMMATORY BOWEL DISEASE: THE JOURNEY TO CURE IN AN UNRECOGNIZED AND YET LIFE-THREATENING CONDITION
31	PETERSHEIM D.	MECHANISMS OF GENOTYPE-PHENOTYPE CORRELATION IN AUTOSOMAL DOMINANT ANHIDROTIC ECTODERMAL DYSPLASIA WITH IMMUNE DEFICIENCY
32	LITZMAN J.	INTRAVENOUS IMMUNOGLOBULIN TREATMENT INCREASES ACTIVATION OF GRANULOCYTES IN PATIENTS WITH COMMON VARIABLE IMMUNODEFICIENCY DISORDERS (CVID)
33	FUST R	DECREASING BURDEN OF TREATMENT” – PATIENT-REPORTED EXPERIENCES OF SUBCUTANEOUS FACILITATED IMMUNOGLOBULIN TREATMENT (FSCIG) IN ADULTS WITH PRIMARY AND SECONDARY IMMUNODEFICIENCY
34	GONZALEZ-GRANADO L.	CONSTITUTIONAL MISMATCH REPAIR DEFICIENCY (CMMRD) & HYPOGAMMAGLOBULINEMIA: A TWO WAY ROAD FOR PID DIAGNOSIS
35	YAZDANI R.	DIFFERENT CLASSIFICATION OF CVID PATIENTS USING B-CELL SUBSETS
36	CUPONE	A PROSPECTIVE, OBSERVATIONAL STUDY ON BI-WEEKLY 20% SUBCUTANEOUS IMMUNOGLOBULIN THERAPY IN PATIENTS WITH PRIMARY IMMUNODEFICIENCY: THE IBIS STUDY
39	KECHOUT N.	LEUKOCYTE ADHESION DEFICIENCY TYPE I IN ALGERIAN PATIENTS
41	CARRABBA M.	MYVIP: A WEB-BASED TOOL FOR THE THERAPEUTIC ALLIANCE BETWEEN ITALIAN PIDS PATIENTS AND DOCTORS
42	PARIS K.	ADVERSE EVENTS AND TOLERABILITY OF THE NEW HUMAN SUBCUTANEOUS IMMUNOGLOBULIN 20% IN PEDIATRIC PATIENTS (<18 YEARS OLD) WITH PRIMARY IMMUNODEFICIENCY DISEASES
43	JEDDANE L.	PRIMARY IMMUNODEFICIENCIES ON SMARTPHONE: A NEW APP FOR PID CLASSIFICATION
44	LEIBL H.	LONG-TERM SAFETY OF HYALURONIDASE-FACILITATED SUBCUTANEOUS IMMUNE GLOBULIN 10% IN PATIENTS WITH PRIMARY IMMUNODEFICIENCIES IN THE UNITED STATES: INTERIM RESULTS OF A POST-AUTHORIZATION SAFETY STUDY
45	CAMCIOGLU Y.	OUTCOME OF ASPERGILLUS INFECTIONS IN PATIENTS WITH CHRONIC GRANULOMATOUS DISEASE
48	SHABANI M.	A CASE OF DOCK8 DEFICIENCY WITH PURE CUTANEOUS MANIFESTATIONS
49	PILANIA R.	INFECTIONS, AUTOIMMUNITY AND MALIGNANCIES IN WISKOTT ALDRICH SYNDROME: A SINGLE CENTRE EXPERIENCE FROM NORTH-WEST INDIA
53	NG Y.	DIAGNOSTICS OF PRIMARY ANTIBODY DEFICIENCIES THROUGH TARGETED NEXT GENERATION SEQUENCING PANEL
54	SAHU S.	A CASE REPORT ON GAIN-OF-FUNCTION MUTATION IN STAT1 GENE WITH CHRONIC MUCOCUTANEOUS CANDIDIASIS FROM INDIA
55	GULERIA S.	CHRONIC GRANULOMATOUS DISEASE PROFILE IN CHILDREN FROM A TERTIARY CARE INSTITUTION IN NORTH INDIA
57	SAGHAFI S.	ABDOMINAL AORTIC COARCTATION IN A DEDICATOR OF CYTOKINESIS 8 PATIENT
60	SHANDILYA J.K.	BONE INFECTION IN CHRONIC GRANULOMATOUS DISEASE: EXPERIENCE AT OUR CENTER, PGIMER, INDIA.

POSTER	PRESENTER	TITLE
62	STRAY-PEDERSEN A.	SECOND-TIER NEXT GENERATION SEQUENCING IN NEWBORN SCREENING PROVIDES RAPID MOLECULAR DIAGNOSTICS OF SEVERE COMBINED IMMUNODEFICIENCY
63	GRYWALSKA E.	RECOMBINANT HUMAN HYALURONIDASE FACILITATED SUBCUTANEOUS IMMUNOGLOBULIN TREATMENT IN ADULT PATIENTS WITH PRIMARY IMMUNODEFICIENCIES: A POLISH SINGLE-CENTER EXPERIENCE
64	ABDALLAH S.	IN SILICO ANALYSIS OF SINGLE NUCLEOTIDE POLYMORPHISM (SNPS) IN HUMAN RAG 1&RAG2 GENES OF SEVERE COMBINED IMMUNODEFICIENCY FROM FUNCTIONAL ANALYSIS TO POLYMORPHISMS IN MICRORNA
66	GABBOUJ F.Z.	THE HYPER IG-E SYNDROME (HIES)
68	BORTE M.	FEW ADRS WHEN SWITCHING PRIMARY IMMUNE DEFICIENCY PATIENTS TO THE NEW IVIG PANZYGA®
69	KILIC GULTEKIN S.	ASSESSMENT OF BONE MINERALIZATION IN SCN PATIENTS WITH HAX1 OR ELANE MUTATIONS
70	STANCIU	A NEW CASE OF POLYGLANDULAR AUTOIMMUNE SYNDROME TYPE IIIC WITH PRIMARY ANTIBODY FAILURE
71	BERNER T.	TREATMENT PREFERENCE ON THE NEW SUBCUTANEOUS IMMUNOGLOBULIN 20% TREATMENT IN PATIENTS WITH PRIMARY IMMUNODEFICIENCY DISEASES IN EUROPE
72	MECKLEY LM.	TREATMENT SATISFACTION DURING PIVOTAL CLINICAL TRIALS WITH THE NEW SUBCUTANEOUS IMMUNOGLOBULIN 20% IN PATIENTS WITH PRIMARY IMMUNODEFICIENCY DISEASES PREVIOUSLY TREATED WITH INTRAVEOUS IMMUNOGLOBULIN
75	BIENVENU B.	RAPID PUSH INFUSION IS A WELL-TOLERATED, COST-EFFECTIVE ADDITIONAL METHOD FOR SUBCUTANEOUS SELF-INJECTIONS OF GAMMANORM®: A RANDOMIZED CROSS-OVER TRIAL IN ADULT PID PATIENTS
76	ASGARDOON M.	PRIMARY IMMUNODEFICIENCY DISORDERS: AWARENESS SURVEY OF PHYSICIANS IN IRAN
77	GULERIA S.	CHRONIC GRANULOMATOUS DISEASE PROFILE IN CHILDREN FROM A TERTIARY CARE INSTITUTION IN NORTH INDIA
78	CRONE J.	ETHICS OF COMPENSATED PLASMA DONATION
79	LUONG T.	SIX CASES WITH WISKOTT ALDRICH SYNDROME IN VIETNAMESE CHILDREN: CLINICAL MANIFESTATIONS AND TREATMENT OUTCOME
80	MCCOY B.	THE ONBOARDING EXPERIENCE AND TOLERABILITY OF THE NEW 20% HUMAN IMMUNE GLOBULIN FOR SUBCUTANEOUS ADMINISTRATION IN NORTH AMERICA
81	SOMER A.	PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY IN A CHILD WITH DOCK 8 DEFICIENCY
83	PILANIA R.	LIVER ABSCESS IN CHRONIC GRANULOMATOUS DISEASE: A SINGLE CENTRE EXPERIENCE FROM A TERTIARY CARE CENTRE IN NORTH INDIA
85	SHARMA M.	MYRIAD FACES OF CHRONIC GRANULOMATOUS DISEASE: ALL IN THE FAMILY
86	R. R.	MONOCLONAL GAMMOPATHY IN A CHILD WITH WISKOTT - ALDRICH SYNDROME: A RARE OCCURRENCE
88	BENHSAIEN I.	MAJOR HISTOCOMPATIBILITY COMPLEX CLASS II DEFICIENCY: DIAGNOSIS CIRCUMSTANCE
89	HATIRNAZ NG O.	TREC/KREC ANALYSIS AND THEIR CLINICAL CORRELATION IN SEVERE COMBINED IMMUNE DEFICIENCY
91	CARRABBA M.	CHRONIC GASTROINTESTINAL INVOLVEMENT IN COMMON VARIABLE IMMUNODEFICIENCY DISEASES (CVID)
92	KUMRAH R.	LATE PRESENTATION OF CHRONIC GRANULOMATOUS DISEASE
93	ISLAM M.	PRIMARY IMMUNODEFICIENCY DISORDERS IN BANGLADESH: AN EXPERIENCE AT A TERTIARY HOSPITAL IN BANGLADESH.

POSTER	PRESENTER	TITLE
94	RAYZAN E.	A CASE OF AUTOSOMAL RECESSIVE CHRONIC GRANULOMATOUS DISEASE CAUSED BY CYBA MUTATION WITH A HOMOZYGOUS SYMPTOM-FREE MOTHER
95	CAMCIOGLU Y.	AN OBSERVATIONAL STUDY ABOUT SWITCHING FROM IVIG TO SCIG?
96	EBZEEVA I.	HEREDITARY ANGIOEDEMA TYPE I MONITORING EXPERIENCE AMONG ADULTS.
97	SHERKAT R.	THE KILLER CELL IMMUNOGLOBULIN-LIKE RECEPTOR 2DS2 COULD BE A PROTECTIVE FACTOR AGAINST HEPATITIS B VIRUS INFECTION
100	PATEL S.	CURE FOR CHILDREN WITH SEVERE COMBINED IMMUNODEFICIENCY - NOW A REALITY IN INDIA!
101	PARKER A.	INDIVIDUALS WITH MODERATE IGG DEFICIENCY ARE SEROLOGICALLY DIFFERENT FROM THOSE WITH SEVERE IGG DEFICIENCY AND THOSE WITH NORMAL IGG.
104	DRABWELL J	BURDEN OF IMMUNOGLOBULIN TREATMENT IN PRIMARY IMMUNODEFICIENCY DISORDERS: FINDINGS FROM AN INTERNATIONAL PATIENT SURVEY
106	FUST R	SUCCESSFUL PATIENT-DRIVEN SELF-ADMINISTRATIONS OF FACILITATED SUBCUTANEOUS IMMUNE GLOBULIN (FSCIG) TREATMENTS WITH MECHANICAL SYRINGE INFUSION SYSTEM AND A NOVEL ADJUSTABLE FLOW RATE CONTROLLER (AFRC)
107	SELMANOVIC V.	ASYMPTOMATIC GIARDIASIS IN X-LINKED AGAMAGLOBULINEMIA PATIENT WITH SEVERE LUNG DISEASE, CHRONIC GINGIVITIS AND SHORT STATURE
108	OZDEMIR O.	A GIRL WITH AUTOIMMUNE LYMPHOPROLIFERATIVE SYNDROME
109	OZDEMIR O.	A PATIENT WITH RECURRENT HERPES INFECTION: CASE REPORT
110	MUNTEANU A.	EXTENDED LYMPHOCYTE IMMUNOPHENOTYPING FOR IMMUNODIAGNOSIS OF RECURRENT INFECTIONS OCCURRING IN THE ABSENCE OF PRIMARY IMMUNODEFICIENCY
111	FUST R.	HOW TO SELECT OPTIMAL NEEDLE LENGTH FOR SUBCUTANEOUS IMMUNE GLOBULIN INFUSIONS (SCIG)
112	FUST R.	INCIDENCE OF DRUG LEAKAGE WHEN GIVING SUBCUTANEOUS IMMUNE GLOBULIN (SCIG) AND FACILITATED SUBCUTANEOUS IMMUNE GLOBULIN (FSCIG) TREATMENTS – IS IT MORE FREQUENT THAN EXPECTED?
113	SHARMA A.	CRYPTOCOCCAL INFECTIONS IN CHILDREN ASSOCIATED WITH PRIMARY IMMUNODEFICIENCY DISEASES: EXPERIENCE FROM CHANDIGARH
114	ZAINAL ABIDIN M.A.	CHARTING THE BEST COURSE FOR A PATIENT WITH CHRONIC GRANULOMATOUS DISEASE WITH COMPLEX PERIANAL FISTULA
115	ISMAIL I.H.	HYPER IGE SYNDROME: OFTEN A MISSED DIAGNOSIS IN COUNTRIES WITH LIMITED FACILITY FOR MOLECULAR ANALYSIS
116	KIM J.H.	IGG3 SUBCLASS DEFICIENCY AS A PREDICTIVE MARKER OF MORTALITY IN PATIENTS ADMITTED TO ICU
117	ISMAIL I.H.	SEVERE COMBINED IMMUNODEFICIENCY: MALAYSIA'S FIRST SUCCESSFUL HLA-IDENTICAL HAEMATOPOIETIC STEM CELL TRANSPLANTATION IN A 1½-MONTH-OLD CHILD
118	MUKTIARTI D.	IMMUNE DYSREGULATION, POLYENDOCRINOPATHY, ENTEROPATHY, X-LINKED (IPEX) SYNDROME: THE FIRST CASE REPORT FROM INDONESIA
120	KARAKOC-AYDINER E	ADVERSE REACTIONS TO IVIG IN PRIMARY IMMUNE DEFICIENCY PATIENTS; MARMARA EXPERIENCE
121	KARAKOC-AYDINER E	RAPID SCIG INFUSION IN PRIMARY IMMUNE DEFICIENCY PATIENTS; MARMARA EXPERIENCE
122	DUFF C.	INITIATION OF 20% SUBCUTANEOUS IMMUNOGLOBULIN THERAPY IN PATIENTS WITH PRIMARY IMMUNODEFICIENCY NAÏVE TO IG THERAPY
124	LUONG L.	SHOULD PENICILLIOSIS BE CONSIDERED AS A SIGN OF PRIMARY IMMUNODEFICIENCY DISEASE: A CLINICAL CASE REPORT

POSTER	PRESENTER	TITLE
125	ERIC Z.	AUTOIMMUNE LYMPHOPROLIFERATIVE SYNDROME TYPE III: A CASE REPORT
128	WIDHANI A.	MYCOPHENOLATE MOFETIL FOR TREATMENT OF SEVERE THROMBOCYTOPENIA IN PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS AND AUTOSOMAL RECESSIVE HYPER-IGE SYNDROME, A CASE REPORT
130	LEWANDOWICZ-USZYN-SKA A.	DO CHILDREN WITH RECURRENT INFECTIONS GROW WELL?
132	SIDDIQUE A.	MEASURING TREATMENT SATISFACTION IN PATIENTS WITH PRIMARY IMMUNODEFICIENCY DISEASES RECEIVING IMMUNOGLOBULIN INFUSIONS
133	EBZEEVA I.	PENTAGLOBIN USE EXPERIENCE AMONG PATIENTS WITH GENERAL VARIABLE IMMUNODEFICIENCY.
134	MIDTTUN K.	HEALTH-RELATED QUALITY OF LIFE OF NORWEGIAN ADULTS WITH PRIMARY IMMUNODEFICIENCY
137	SURATANNON N.	NEUROBLASTOMA AMPLIFIED SEQUENCE (NBAS) MUTATIONS; THE SPECTRUM OF DISEASE
138	VAN DER ENT M.	HEALTH RELATED QUALITY OF LIFE IN PATIENTS WITH COMMON VARIABLE IMMUNODEFICIENCY RECEIVING IMMUNOGLOBULIN REPLACEMENT THERAPY
141	ERRAMI A.	MUTATION OF IL12RB1 REVEALED BY BCGITIS: ABOUT 4 CASES
142	BENHSAIEN	AUTOIMMUNE LYMPHOPROLIFERATIVE SYNDROME (ALPS) : A PRIMARY IMMUNODEFICIENCY
146	KHAZAEI H.	CORRELATION BETWEEN SERUM AMOUNTS OF TOTAL IGE, C3 AND C4 LEVELS IN PATIENTS SUFFERED FROM IGA DEFICIENCY WITH AND WITHOUT ALLERGIC RHINITIS SYMPTOMS
147	KANARIOU M.	A GAIN OF FUNCTION STAT3 MUTATION LEADING TO TUBERCULOSIS, AUTOIMMUNE AND LYMPHOPROLIFERATIVE MANIFESTATIONS.
149	SOMER A.	FUNGAL PNEUMONIA IN A CHILD WITH CHRONIC GRANULOMATOUS DISEASE COMPLICATED WITH HEMOPHAGOCYTOSIS
151	PIRES C.	THE DIFFICULTY IN DIAGNOSING CHRONIC GRANULOMATOUS DISEASE IN BRAZIL
152	YUNIHAUSTI E.	LATE ONSET COMMON VARIABLE IMMUNODEFICIENCY PRESENTING AS CYTOMEGALOVIRUS ASSOCIATED DEMYELINATION: A CASE REPORT
154	KANARIOU M.	DIAGNOSIS OF PRIMARY IMMUNODEFICIENCY DISEASES AT THE MAJOR GREEK CENTER DURING THE LAST SIX YEARS
155	MOKHANTAR K.	COMMON VARIABLE IMMUNODEFICIENCY : ABOUT 25 CASES
156	HADDAJI A.	FREQUENT AUTOINFLAMMATORY DISEASES IN MOROCCO : FAMILIAL MEDITERRANEAN FEVER AND MEVALONATE KINASE DEFICIENCY :ABOUT 8 CASES
159	HAMADA A.	EFFECT OF CHRONIC PHYSICAL STRESS ON IMMUNE SYSTEM
165	HERMANN C.	SENEQA: STUDY ON THE UTILISATION OF HYQVIA (10% NORMAL IMMUNOGLOBULIN AND RECOMBINANT HUMAN HYALURONIDASE) IN ELDERLY PATIENTS
166	PRAMANIK L.	CASE REPORT: SUCCESSFUL TREATMENT OF LEUKOCYTE ADHESION DEFICIENCY TYPE 1 SYNDROME AND RECURRENT PYODERMA GANGRENOSUM WITH ALLOGENEIC STEM CELL TRANSPLANTATION
170	LEWANDOWICZ-USZYN-SKA A.	22Q11.2 DELETION SYNDROME THE CAUSE OF PHYSICAL DEVELOPMENT DISORDERS – CASE REPORT
171	JEDDANE L.	LABORATORY DIAGNOSIS OF PRIMARY IMMUNODEFICIENCIES: WHICH TEST, WHICH METHOD?



POSTER 1 - HOMOZYGOUS TCF3 MUTATION IS ASSOCIATED WITH SEVERE HYPOGAMMAGLOBULINEMIA AND ACUTE LYMPHOBLASTIC LEUKEMIA**AUTHORS**

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TCF3 (E2A) gene encodes E12 and E47 transcription factors which are essential in differentiation process of common lymphoid progenitors into B-lineage cells and are key regulators of B-cell development. Herein, we report the first homozygous TCF3 patients. They presented reduced peripheral B cells, hypoagammaglobulinemia and acute lymphoblastic leukemia.

The two patients were born to Tunisian first cousin parents. Patient P1 had recurrent pneumonia and meningitis since early childhood and mild facial dysmorphism. At age 7 years he presented pancytopenia and splenomegaly, the diagnosis of B-ALL was confirmed. At the age of 10 years, he died despite chemotherapy was resumed. Patient P2 suffered from recurrent pneumonia and failure to thrive. She also had facial dysmorphism. At age 14 years, she developed acute lymphoblastic leukemia. Immunological investigations revealed a very low number of peripheral CD19+B cells in patient P1 and ~3% CD19+B cells in patient P2. All immunoglobulin classes were absent in patient P1, while borderline low IgG and significantly decreased IgA and IgM serum immunoglobulin levels were observed in patient P2.

Whole exome sequencing revealed a novel homozygous mutation within exon 9 of TCF3 (c.C807T) and resulted in a premature stop codon (p.Q270X). Both parents were heterozygous. The truncated protein, with no helix-loop-helix (HLH) functional domain, was absent as shown by a western Blot.

In contrast to previous E47 deficient patients, patient P2 had normal expression of IgM but decreased levels of CD27+ memory B cells as well as of switched memory CD27+IgD- B cells. Detailed analysis of the T cell immunophenotype, revealed a significant increase in effectors memory CD8+ T cells and absent terminally differentiated effector T cells (TEMRA).

Considering the crucial role of TCF3 in the regulation of normal B cell development, it is not surprising that disruption of this transcription factor causes a profound B cell defect. Since TCF3 is also known to be affected (translocations and deletions) in B-ALL, this could explain the clinical phenotype herein observed. Indeed, a decrease in the level of PAX5 transcripts was observed in patient P1. This is consistent with data in mice showing that the loss of PAX5 in mature B cells leads to the development of aggressive progenitor B-cell lymphomas.

POSTER 2 - CASE SERIES REPORT OF HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS IN PRIMARY IMMUNODEFICIENCIES: A SINGLE-INSTITUTION STUDY AT THE CHILDREN'S HOSPITAL 1, HO CHI MINH, VIETNAM

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Objective: Hemophagocytic lymphohistiocytosis (HLH) is a fatal hematological disorder with diverse etiology and occurs infrequently among patients with primary immunodeficiency (PID), in whom the pathogenesis of the inflammatory syndrome may be distinctive.

Design and methods: From 2010 to 2017 we have 250 new HLH patients who presence at least five out of six diagnostic criterias according to the HLH-2004 protocol except the soluble CD25 level and NK cell cytotoxicity test. All of them were performed quantitative serum immunoglobulin tests and flow cytometry measurements of B, T, NK cell subsets in peripheral blood. Only a few patients had undergone genetic testing to confirm primary HLH or PID diagnosis.

Results: We have six HLH cases associated with PID. In which, the HLH syndrome developed at or before the diagnosis of PID in two agammaglobulinemia and two severe combined immune deficiency (SCID) patients. In contrast, the HLH syndrome developed after the diagnosis of congenital neutropenia in two cases, which included one female with type 2 Griscelli syndrome (GS2) and one male with Chediak Higashi syndrome (CHS). GS2 was confirmed by mutations in RA-B27A p.T75K[c.224 C>A] and p.P126fsX3[c.377delC]. CHS diagnosis was made by recognition of the clinical and laboratory characteristics. Three cases associated with Epstein-Barr virus (EBV), two cases associated with cytomegalovirus (CMV), especially, GS2 patient had both of virus. All patients had severe bacterial infection: sepsis, enteritis, osteomyelitis, otitis media. CHS patient had chickenpox. One patient with agammaglobulinemia had fungal bloodstream infection. Of the two patients with agammaglobulinemia, one case developed HLH and juvenile rheumatoid arthritis that required oral steroids and IVIg prophylaxis; the other patient received immunochemotherapy with HLH-2004 protocol but died after 9 months of treatment. Of the two cases with SCID, one (T-B-NK-) had secondary HLH with Still's disease, followed by early death without HLH treatment; the other (T-B-NK+) with EBV associated HLH was treated by HLH-2004, rituximab, IVIg prophylaxis and is alive after ten months of follow-up. Patient with GS2 was treated with dexamethasone, etoposide and G-CSF, but she died after 19 months of treatment. Patient with CHS is still alive after 108 months of treatment with dexamethasone and etoposide with many steroid side effects.

Conclusions: The prognosis of patients with PID and HLH is poor, emphasizing the importance of early diagnosis and appropriate management, including allogeneic hematopoietic stem cell transplantations.

PATIENT NUMBER	PID	AGE AT HLH (MONTHS)	HLH AT/ BEFORE PID	ASSOCIATED VIRUS	ASSOCIATED AUTOIMMUNE DISEASE	TREATMENT	IVIg PROPHYLAXIS	FOLLOW-UP TIME (MONTHS)	OUTCOME
1	GRISCELLI (RAB27A)	50	NO	EBV, CMV		IVIg, ETOPOSIDE, GCSF, STEROIDS	NO	19	DEAD
2	CHEDIAK HIGASHI (CLINICAL)	60	NO	EBV, VZV		IVIg, ETOPOSIDE, STEROIDS	NO	108	ALIVE
3	SCID (T-B-NK-)	81	YES		STILL DISEASE	IVIg, STEROIDS	NO	1	DEAD
4	SCID (T-B-NK+)	18	YES	EBV		IVIg, HLH 2004, RITUXIMAB	YES	10	ALIVE
5	AGAMMAGLOBULINEMIA	26	YES		JRA	IVIg, STEROIDS	YES	4	ALIVE
6	AGAMMAGLOBULINEMIA	9	YES	CMV		IVIg, HLH 2004	NO	9	DEAD

POSTER 4 - CUTANEOUS AND SOLID ORGANS GRANULOMAS IN PATIENTS WITH NIJMEGEN BREAKAGE SYNDROME (NBS) – DIAGNOSTIC AND TREATMENT CHALLENGE

AUTHORS

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Objective: Cutaneous granulomas without an identifiable infectious etiology are a rare manifestation of primary immunodeficiency (PID). It is known from the literature, that majority of them are reported in: ataxia-telangiectasia (A-T), severe combined immunodeficiency, and combined variable immunodeficiency. There are single case reports of successful treatment strategies such as TNF inhibitors or HSCT.

Nijmegen Breakage Syndrome (NBS), an autosomal recessive genetic instability syndrome, is caused by hypomorphic mutation of the NBN gene, which codes for nibrin protein. Cardinal features of NBS comprise microcephaly, immunodeficiency, hypersensitivity to ionizing (X-ray) irradiation and increased cancer susceptibility.

Material: There are 122 NBS patients in PID Registry of Department of Immunology CMHI. 64 (52%) of NBS patients are alive at average age of 2.4-34.1 years. In 12 (9,8%) patients granulomas were histologically confirmed at average age of 4.6 years. 3 of these patients died at average age of 21.2 years. In 11 patients the lesions were located on the skin of face (10) and/or upper/lower limbs (10). In 3 patients skin granulomas were infiltrating into adjacent bones and were spread in the spleen, in 1 of these patients we also found disseminated granulomatous changes in lungs and multiple bones. In 1 patient the changes were limited only to the lungs imitating disseminated tuberculosis. In 3 patients *Mycobacterium* spp was detected in skin biopsy by PCR, but this finding was not repeated in several other biopsies/patients. Among patients with granulomas 6 of 12 patients require IVIG/SCIG substitution due to IgG hypogammaglobulinemia and/or low IgG2 and IgG4. NBS patients have been cured for progressive granulomas with broad-spectrum antibiotics, including rifampicin, antifungal agents, topical and systemic steroids, and IVIG without satisfactory clinical response.

Conclusions: We think that in differential diagnostics of impaired DNA-repair patients with granulomas, not only A-T, but primarily NBS should be taken into consideration. We hypothesize that the pathogenesis of granulomas in these patients is related to immune dysfunction due to low absolute numbers of CD3+T and CD4+T lymphocytes, reduced CD4+/CD8+ ratio, prevalence of memory CD4+CD45RO cells, almost complete lack of naive CD4+CD45RA cells, and increased proportion of gamma/deltaTCR+T cells, which predispose to infection with intracellular pathogens. We also believe that searching for underlying pathogen might help to tailor the efficacious treatment for individual patients.

POSTER 5 - MANUAL PUSH SUBCUTANEOUS IMMUNOGLOBULIN ADMINISTRATION IN PATIENTS WITH PRIMARY AND SECONDARY IMMUNODEFICIENCIES AND AUTOMIMUNE DISORDERS: A CASE SERIES OF 18 PATIENTS

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Objective: For patients with primary and secondary immunodeficiencies, and a number of autoimmune disorders, manual push subcutaneous immunoglobulin G (SCIG) administration potentially represents an effective treatment alternative to intravenous (IVIG) or SCIG therapy using the conventional pump method. This case series study evaluated the comparative efficacy, safety, and cost-effectiveness of manual push SCIG administration.

Design and method: This was a case series analysis of 18 patients opting for manual push SCIG administration with Hizentra® (CSL Behring, Bern, Switzerland; n=14) or Gammanorm® (Octapharma, Lachen, Switzerland; n=4), in a dosing regimen appropriate for their specific history and characteristics. Mandatory serum IgG levels measurements were taken before and after SCIG treatment initiation; other measurements were made as deemed necessary. Costs associated with SCIG home therapy were evaluated using a home care company quotation. Adverse events (AEs) were reported by patients.

Results: Manual push SCIG was used as antibody replacement therapy in 15 patients (primary immunodeficiency: n=8; secondary immunodeficiency: n=7), and as immunomodulatory therapy in 3 patients. In patients new to SCIG antibody replacement therapy (n=8), serum IgG levels rapidly increased to therapeutic range, despite the absence of a loading phase. In patients switching from IVIG to SCIG (n=7), manual push SCIG administration had no detrimental effect on IgG trough levels, except for two patients who received a reduction in dosing. Furthermore, the incidence of infection did not change. Patient-reported AEs were mild local reactions (e.g. injection site redness and swelling) comparable with those reported previously with SCIG therapy; all resolved within 12 hours. Cost analysis indicated that manual push SCIG administration would result in substantial cost savings compared with both IVIG (£4884 per patient-year) and pump-administered SCIG (£1160 per patient-year). Manual push SCIG would also result in time savings of 34.7 hours per patient-year versus pump-administered SCIG.

Conclusions: Manual push administration increased treatment flexibility and provided cost and time efficiencies compared with both IVIG and pump-administered SCIG.

POSTER 6 - CINCA-SYNDROME PRESENTING AS HYPEREOSINOPHILIC SYNDROME

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Hereby we expand the clinical spectrum of CINCA syndrome by severe eosinophilia.

A male newborn of 4 weeks of life was admitted to our hospital with fever, high inflammatory markers and migratory urticarial rash since his first day of life, unresponsive to broad spectrum antibiotic and antimycotic therapy. Extensive infectious work-up was negative.

The WBC showed leucocytosis with severe eosinophilia of 30% and absolute eosinophil count of $8.0 \times 10^9/L$. An extensive diagnostic work-up for hypereosinophilic syndrome, screening for hereditary inflammatory diseases (CINCA in Exon 3, TRAPS in exons 2,3,4 and 6) and repeated BM aspirations and immunologic analysis were normal apart from eosinophilia.

The symptoms and eosinophilia showed partial response to systemic steroid treatment at high doses of 2 mg/kgBW/day methylprednisone but reappeared each time when tapering the dose.

As the overall clinical presentation was compatible with a diagnosis of CINCA syndrome, we initiated treatment with anakinra at dose of 1mg/kgBW/day at 7 month of age. The patient showed excellent response with complete remission of hypereosinophilia.

We repeated a full range analysis of the CIAS1 gene on chromosome 1q44 and found a heterozygous Glycin 755 to Arginin Substitution on exon 4 of the CIAS1 gene, which was described previously in another patient with clinically diagnosed CINCA-syndrome.

Eosinophilia has already been described as part of the clinical spectrum of CINCA. To our knowledge, we describe the first case of CINCA syndrome with severe hypereosinophilia. CINCA syndrome should be considered as a differential diagnosis for hypereosinophilic syndrome. In patients with clinical diagnosis of CINCA syndrome and negative screening for CIAS1 mutations in exon 3 a full range analysis of CIAS1 gene should be performed.

POSTER 7 - ALONE OR ADD-ON? INHALING NEBULISED IMMUNOGLOBULINS: 18 MONTHS OF REAL LIFE EXPERIENCE

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Objective: Approximately 70% of patients with primary immunodeficiency disease (PID) suffer from antibody deficiency. Despite apparently adequate levels of replacement immunoglobulinG (IgG) acute/chronic upper respiratory tract infections (URTI) are still a problem in some patients. Viral and bacterial pathogens have been detected in secretions from the airways of PID patients with these infections but also from PID patients with no apparent infections at the time of testing. although IgG replacement therapy effectively reduces infections in PID patients (particularly severe infections such as pneumonia), the effect of IgG on URTI (especially viral infections), is less clear.

Here we present the effect of inhaled nebulized immunoglobulin (INHIG) on PID patients with antibody deficiencies. The main aim of this pilot study was to ascertain whether the topical administration of immunoglobulin could reduce the number of episodes of URTI.

Method: The patients were 3 boys, siblings, aged 3, 5 and 6 years respectively. The 5 and 6 years old have CVID and were on subcutaneous IgG (SCIG) replacement while the youngest brother had slight hypogammaglobulinemia and was on prophylactic antibiotics. Despite the treatments they were suffering of frequent URTI and all of them had recurrent otitis media.

The parents filled a meticulous symptom diary during 2 months of the above-mentioned treatment period; during the 2 months of SCIG withdrawal and then during the 15 months long INHIG treatment. For the analysis, we calculated the number of days per week with any of the following 7 symptoms: Rhinitis, Purulent Rhinitis, Sore throat, Cough, Fever, Earache and Otitis media.

INHIG consisted of 4 ml dose of 5% IVIG nebulized with the eFLOW® nebulizer twice daily.

Results: The patients tolerated the INHIG well and no adverse events of any kind were registered. The time for inhalation was around 10 min per patient. The number of URTI was noticeably decreased except for a winter period of approximately 3 months during which SCIG was temporarily reinitiated. The burden of infections in this family was reduced markedly, resulting in much less days missed from daycare and for the parents much fewer days missed from work (data not shown)

Conclusions: Our results suggest that in patients with URTI despite adequate replacement therapy inhaled nebulized immunoglobulin reduces the incidence of URTI and may serve as a valuable physiological prophylaxis in the prevention of infections. The findings also implicate that PID patients with predominantly URTI could use INHIG as the sole treatment method.

POSTER 8 - ADA-SCID: THE BURDEN AND IMPACT ON THE PATIENT, CAREGIVER AND FAMILY. A QUALITATIVE RESEARCH IN USA, ITALY, FRANCE AND UK

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Objective: Adenosine deaminase - severe combined immunodeficiency (ADA-SCID) is a serious disease that significantly impacts the development and quality of life (QOL) of children if immune function is not restored. Little is known about the burden to caregivers during the diagnostic process and treatment thereafter. The objective of this qualitative research was to gain insights into the burden of ADA-SCID, exploring the emotional, physical, social impact on patients' and caregivers' lives.

Design and Methods: Research was conducted through telephone interviews of caregivers of ADA-SCID patients recruited in the USA, France, UK, and Italy through patient associations and direct referral from HCPs. The study inclusion criteria were caregiver's child must have a diagnosis of ADA-SCID with onset within the first year of life and must not be involved in GSK gene therapy studies (including siblings). The research was compliant with the relevant country's market research regulations.

Results: 9 parents (3 UK, 1 France, 3 USA, 2 Italy) were recruited. The onset of symptoms was between birth - 3 months. Asthma, viral infections and cystic fibrosis appear to be common misdiagnoses and the correct diagnosis is often made after a long journey to numerous HCPs. Time between onset of symptoms and misdiagnosis was between 0.5 - 27 months and the time to correct diagnosis between 2 - 27 months.

Frequently reported concerns that impacted the child's QOL included a constant battle for good physical health, sleeping and eating difficulties, failure to form relationships, and the need for isolation. Aspects that most affected caregiver QOL were the toll of providing continuous care, isolation and time spent at the hospital. 7 caregivers reported that they were no longer able to work. Emotional impact was commonly reported in both caregivers and patients. Caregivers reported that their children had difficulty forming relationships due to lack of socialization from isolation, which resulted in mood swings, anger and anxiety. All caregivers reported feeling anxious, and 5 reported feeling depressed. Having a child with ADA-SCID impacted on the entire family, including marriage and siblings. Available treatments are accepted, but likelihood of success and side effects especially chemotherapy conditioning with SCT raises most caregiver concern.

Conclusion: The impact of ADA-SCID is significant physically, socially, emotionally and financially on patients, caregivers and families. The period of uncertainty before correct diagnosis adds greatly to the disease burden, but the option of treatment brings a positive outlook.

POSTER 9 - DISEASE BURDEN FOR PATIENTS WITH PRIMARY IMMUNODEFICIENCY DISEASES - A COMPARATIVE STUDY

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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 hospitalisations/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 10 - 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 form an essential component of management in families with children afflicted with PIDs.

Objectives: Prenatal diagnosis, carrier screening and genetic counseling 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 2 patients and amniocentesis was done in one patient. Maternal contamination was ruled out by a 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 twelve families with a child affected with a PID. Five cases were of Wiskott-Aldrich syndrome, 3 of Chronic granulomatous disease and one case each of X-linked agammaglobulinemia, severe combined immunodeficiency, hemophagocytic lymphohistiocytosis and congenital neutropenia. Out of these twelve, seven were affected and five were not affected. The parents were counseled and all parents with affected fetuses opted for a medical termination. Carrier screening was done for seven patients, of which four were detected to be carriers.

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

POSTER 12 - HOW TO EDUCATE CHILDREN ABOUT PID? STUDY CASE FROM POLAND: EDUCATIONAL BOARD GAME

AUTHORS

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People aged under eighteen make major group of patients suffering from PID. Many children are being diagnosed during their early childhood, with disease staying with them for their entire life. This is why it is crucial to educate the patients at the youngest possible age, develop desirable pro-health attitudes and teach key life competences making them better prepared to cope with PID.

Even the young children are able to understand basic issues related to their illness and learn behaviors helping them avoid infections as well as react quickly whenever there is any threat. Even pre-schoolers can name their emotions and talk about them, finding constructive solutions of coping with their feelings. This knowledge gives us necessary background to start teaching the youngest of PID patients.

Having that in our minds, we have created a PID-devoted board game named 'Race for the Immunity'. The game presents basic issues related to the illness in the simple way. Children can play it with their family or friends, using it to learn or teach the others.

There are two types of cards used in the game: the 'Knowledge Cards' and 'Challenge Cards'. The former are important source of information about PID, adjusted to the child's cognitive abilities. The cards contain questions about the illness, hygiene and pro-health behaviors. Answering them, children gain new and valuable knowledge about their condition.

The 'Challenge Cards' are supposed to develop proper attitudes among the children. The game awards health supporting and infection avoiding behaviors, while the risky attitudes are followed by negative effects (like missing a turn or going backwards). It means the game impacts children in many ways; not only providing them with knowledge but also showing them how to implement it in their everyday life what may significantly raise the quality of their life.

We are convinced that there is still a lot to do in the area of the youngest PID patients education. Using an example of our educational board game, we want to start discussion about the importance of pediatric patients needs, encouraging everyone to support actively this kind of initiatives.

POSTER 13 - THE IMPACT OF BCGITIS CAUSED BY BCG VACCINE ON THE OUTCOME OF SEVERE COMBINED IMMUNODEFICIENCY PATIENTS: A SINGLE-CENTER EXPERIENCE

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Objective: To study the harmful effect of early administration of BCG vaccine on the outcome of Hematopoietic stem cell transplantation for SCID patients in comparison to SCID patients who didn't receive the vaccine at birth. Aiming also at modifying the BCG vaccine administration schedule in light of its questionable efficacy and potential harm.

Patients & METHODS: A retrospective cohort study for all patients diagnosed and treated as SCID in our institution King Faisal Specialist Hospital & Research Centre (KFSH&RC) in Riyadh, Saudi Arabia,. Patients divided into two groups, the first group SCID patients who received BCG vaccine at birth and the second group SCID patients who did not receive the BCG vaccine, we looked at patients treated between January 2014 and December 2015.

Inclusion criteria: Confirmed SCID patients from January 2014 to December 2015 who received or did not receive BCG immunization whether transplanted at KFSH or not transplanted. Exclusion criteria: IL-12 and IF-gamma cascade defect, Congenital HIV, Transplanted outside KSA.

Results: We analyzed 36 patient, 16 didn't receive the BCG vaccine and 20 did. We focused on the morbidity and mortality (in form of hospital stay, PICU admissions, the use of anti-mycobacterial drugs (the duration and the number of drugs), GVHD and the engraftment after HSCT). The mortality was higher in the group who received BCG (8/20) which is 40% while in those who didn't (2/16) died which is 12.5 %. The total days of hospital stay for both groups were 3418 days, the patient who received BCG spent total of 2742 days in compare to 676 days in those who didn't with a p value of 0.0003. The analysis of the other morbidity variables are underway.

Conclusion: BCG vaccine affect dramatically the morbidity and mortality of HSCT in SCID patient. Patients who received BCG vaccine spent 4 times more days in the hospital and ICU than those who didn't. We think that delaying the vaccine after the age of 6-9 months, which is the age of presentation of SCID, will decrease the cost and improve the outcome in HSCT in SCID patient especially in our community where SCID incidence is high.

POSTER 14 - PRIMARY IMMUNODEFICIENCY IN THE ADULT POPULATION; A GROWING PERCEPTION THAT NEEDS ATTENTION IN THE MIDDLE EAST

AUTHORS

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Background: Primary immunodeficiency (PID) is a disease affecting all age group. (1) The inherited idea is that PID affects mainly children. However, increased incidence of adult onset PID is reported all over the world. (1) The commonest Adult PIDs are IgA deficiency, Common Variable Immunodeficiency (CVID), Specific Antibody Deficiency (SPAD). (1) In the Middle East (ME), most data in the literature are from pediatric age group. (2)

Material and Methods: 36 patients of PID attending adult PID service in Qatar; 15 patients are diagnosed in adult age. Diagnosis is established based on the diagnostic criteria of the European Society for Immunodeficiency. Data were collected and a statistical analysis was done.

Results: Data are presented on the table. CD4 was low in 3 patients (1 SPAD, 1 Unclassified Immunodeficiency (UN. PID) & 1 CVID).

Discussion & Conclusion: PID in adult population is not uncommon as in the old medical perception. (1) Due to improvement in health care, hygiene and education in the last decades, more cases outgrow childhood without diagnosis. The rate of consanguinity is high in Qatar and ME. Moreover, adult PID service in the ME is highly needed for social and cultural factors with the belief that the age of adulthood is lower compared to western countries. Hence, building adult service for PID in ME is mandated to track and evaluate bigger population with recurrent infections for proper diagnosis & management.

References: 1. Rosenberg E, Dent PB, Denburg JA. Primary Immune Deficiencies in the Adult: A Previously Underrecognized Common Condition. J Allergy Clin Immunol Pract 2016;4:1101-7; 2. Al-Herz W, Al-Mousa H. Combined immunodeficiency: the Middle East experience. J Allergy Clin Immunol 2013 Mar;131(3):658-60; 3. Dong J, Liang H, Wen D, Wang J. Adult Common Variable Immunodeficiency. Am J Med Sci. 2016 Mar;351(3):239-43.

PIDs	No. of patients	Mean age of Dx	M: F	Median IgG, IgA, IgM (mg/dl)	Median IVIG dose/ month (g)	Presentation	Commonest organisms
CVID	3	29.33 ± 6.01	2 : 1	IgG- 171 IgA-9.7 IgM- 4.4	70	<ul style="list-style-type: none"> • URTI, LRTI infection • Bronchiectasis • Autoimmune arthritis • Autoimmune hepatitis • Lymphoma Allergy • Severe asthma 	<p>P. Aeruginosa H. influenza S. pneumoniae Moraxella CMV</p>
UN. PID	2	20.50 ± 0.50	2 M	IgG- 123.68 IgA-6.03 IgM- 6.74	47.5		
SPAD	7	26.29 ± 6.45	3 : 4	IgG- 804.5 IgA-13.6 IgM- 90.6	20		
Selective IgA deficiency	1	31	M	IgG- 2260 IgA-6.67 IgM- 79.5			
Selective IgM deficiency	1	67	F	IgG- 2130 IgA- 236 IgM- 27.2			
Complement deficiency	1	17	M	IgG- 1160 IgA-96.4 IgM- 43		<ul style="list-style-type: none"> • Recurrent meningitis 	N. Meningitidis

POSTER 15 - TRIMETHOPRIM-SULFAMETHOXAZOLE PROPHYLAXIS INCREASE RISK OF MYELOSUPPRESSION IN PRIMARY IMMUNE DEFICIENCY DISEASE PATIENTS: RETROSPECTIVE THREE GROUPS COMPARISON STUDY

AUTHORS

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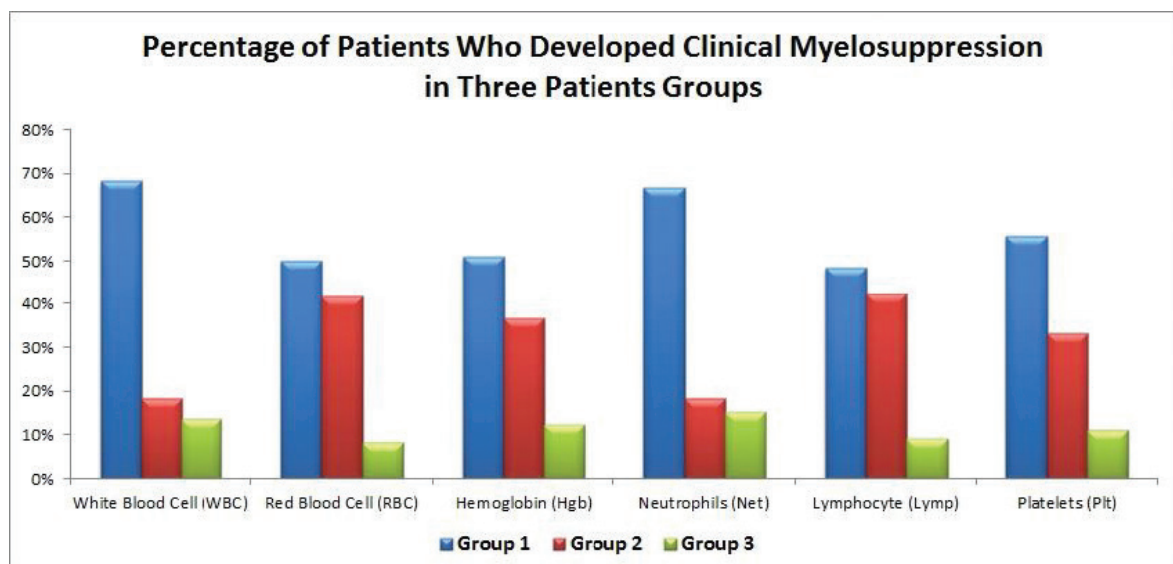
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Objective: To compare and describe the incidence of myelosuppression effect of prophylactic Trimethoprim-Sulfamethoxazole (TMP-SMX) in three patients groups: 1) immune competent patients received prophylactic TMP-SMX for urinary tract infection (UTI), 2) primary immune deficiency (PID) patients received prophylactic TMP-SMX, and 3) primary immune deficiency (PID) patients who did not received prophylactic TMP-SMX

Method: A retrospective, three groups study, of existing data for all PID patients (on and off TMP-SMX prophylaxis) and UTI patients received prophylaxis TMP-SMX in Qatar. Data about CBC results (WBC, Neutrophils, Lymphocytes, and RBC, Hemoglobin, and Platelet counts) at baseline and at maximum myelosuppression observed during the period of TMP-SMX administration, were collected

Results: A total of 112 patients were included in this study (41 PID patients on TMP-SMX prophylaxis, 45 PID patients not on TMP-SMX prophylaxis, and 26 UTI patients on prophylaxis TMP-SMX). There are significant differences noticed in the percent of patients who developed clinical myelosuppression (i.e. less than normal value for age) in Neutrophil count (66.7% vs. 18.2% vs. 15.2%, p-value <0.0001), Hemoglobin (51% vs. 36.7% vs. 12.2%, p-value 0.008), and White Blood Cells (68.2% vs. 18.2% vs. 13.6%, p-value <0.0003) in group 1, 2, and 3, respectively. Significant difference in the myelosuppression between the groups was most likely due to the combination of TMP-SMX effect on PID patients rather than disease or the drug itself.

Conclusion: Primary immune deficiency (PID) patients are at higher risk to develop myelosuppression secondary to TMP-SMX prophylaxis (especially neutrophil count) comparing to immune competent patients or other PID patients who did not received prophylactic TMP-SMX. Future larger prospective study is required to confirm this association



POSTER 16 - GOOD SYNDROME, A DISEASE WITH VARIED PRESENTATIONS

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Objective: Good syndrome(GS) or thymoma-immunodeficiency, is a very rare adult-onset immunodeficiency syndrome. It comprises the association of thymoma and combined B-cell and T-cell immunodeficiency with increased susceptibility to infections. It was first described in 1954 by Dr. Robert Good. (1, 2)

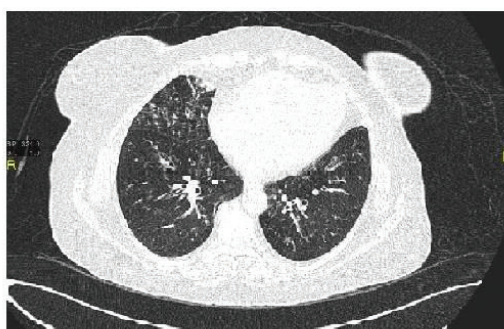
Design and Method (Case Report): A 60 years old Qatari female presented with one-year history of a dry cough and shortness of breath. She had a history of gingival lichen planus diagnosed 1995, resected lympho-epithelial thymoma in 1996, and myasthenia symptoms controlled on steroids and azathioprine and stopped on 2009. She had recurrent sinopulmonary infections, three hospital admissions for community-acquired pneumonia and recurrent oral candidiasis treated with long-term antifungal. Investigations: PFT: severe obstructive ventilatory defect with air trapping. Chest CT scan: bilateral tiny centrilobular nodules with tree – in bud nodularity suggestive of infection. (See Image) Bronchoscopy examination showed abundant fibrinopurulent exudate, suggestive of acute inflammation. BAL CMV PCR was positive of 2253 viral copies. EBV and adenovirus were also positive at lower titers. Bacterial, mycobacterial, and fungal cultures were negative. HIV test was negative. Immunological workup showed IgE < 2 ku/l, low IgG2 90.8 (N 169-786mg/dl), low IgG4 at 2.1 (N 3-201mg/dl), and normal IgG, IgA, and IgM. Patient had poor antibody response post pneumococcal vaccination. Flow cytometry showed low CD 19 cells 65 (N 107-698 cell/microL) and normal CD4, CD8, NK cell count and CD4/CD8 ratio. The patient received valganciclovir oral for 3 weeks for possible CMV pneumonitis and started on monthly IV Ig for working diagnosis of GS.

Results and Conclusion: Despite the compatible history our patient has with GS, her immunological profile shows only low B lymphocytes, impaired antibody response, and normal T cell count. Most of reported GS cases have impaired T-cell counts and function and almost all had low immunoglobulin level. (2, 3) Good Syndrome is a disease with heterogeneous presentations and yet unclear etiology. (4, see table)

References: 1. The 2015 IUIS Phenotypic Classification for Primary Immunodeficiency. - J Clin Immunol 2015; 2. P Kelleher, S A Misbah. What is Good's syndrome? Immunological abnormalities in patients with thymoma (Review). J Clin Pathol 2003;56:12–16; 3. Good's syndrome remains a mystery after 55 years: A systematic review of the scientific evidence - Clinical Immunology 2010; 4. <https://rarediseases.info.nih.gov/diseases/8622/immunodeficiency-with-thymoma>.

Laboratory findings	Approximate number of patients (when available)	Our Case
Hypogammaglobulinemia	152 / 152 (100%)	NO
Panhypogammaglobulinemia with absence of all globulins (IgG, IgA, and IgM)	82 / 110 patients (74.5%)	NO
Low levels of only IgG	10 / 110 patients (9.1%)	NO
Low levels of only IgA	2 / 110 patients (1.8%)	NO
Absent IgE levels	9 / 110 patients	Yes
Immunoglobulin subgroups	Specified in only one case with normal IgG1 but depressed levels of IgG2, IgG3 and IgG4?	Yes
Peripheral B cell	Low (<3%) or absent 88 / 75 (87%) Normal B cells in 9 / 75 patients (13%)	Yes
Low T cells	8 / 40 (15%) - 28 patients (70.0%) had normal number of T-cells	NO
Low CD4 count (<360/ μ l or <36%)	41 / 58 (70.2%) - 15 / 58 (28.8%) had normal CD4 count	NO
Low CD4/CD8 ratio	51 / 67 (76.1%)	NO

Laboratory findings in patients with Good syndrome with available data (copied from Kalesidis et al - 2010)



Right middle lobe centrilobular nodules and ground glass changes

POSTER 17 - ANTERIOR PITUITARY DYSFUNCTION IN PATIENTS WITH PRIMARY ANTIBODY DEFICIENCIES

AUTHORS

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Background and Objective: Disorders caused by deficiency in anterior pituitary function are rare, with an estimated prevalence of 45.5 cases per 100,000 individuals. Remarkably, several studies have demonstrated the occurrence of deficits in anterior pituitary function in primary antibody deficiency (PAD) patients. In this study we aim to investigate the prevalence of endocrine dysfunction in adult PAD patients, including common variable immunodeficiency (CVID) and selective antibody deficiency (IgG-subclass deficiencies and selective antibody deficiency with normal immunoglobulins).

Methods: A prospective, single-centre, cross-sectional study was conducted in CVID (n=38, mean age 48 ± 17 years) and selective antibody deficiency (n=24, mean age 53 ± 15 years) patients. Endocrine functions were assessed by measuring morning cortisol, ACTH, free T4, TSH, IGF-1, GH, AMH, FSH, LH, Estradiol, Testosterone, Prolactin, Inhibin-B, and SHBG. Subsequently, insulin tolerance test, metyrapone and/or GHRH-arginine test were performed to assess for adrenal insufficiency (AI) and growth hormone deficiency (GHD).

Results: Three out of 38 CVID patients and two out of 24 selective antibody deficiency patients demonstrated thyroid dysfunction. Evidence for reproductive dysfunction was found in four out of 8 women with CVID (aged < 41 years) where hormone levels revealed premature ovarian failure. One of 7 women with CVID (aged 41-50 years) had premature ovarian failure and one of 2 women with selective antibody deficiency had possible PCOS because of elevated AMH. Moreover, one of 13 men with CVID had primary testicular failure and three out of 9 men with selective antibody deficiency secondary hypogonadism due to hypopituitarism was diagnosed. In two out of 18 CVID patients we report partial AI and one out of 11 patients with selective antibody deficiency had secondary AI. Furthermore, one of 16 patients with CVID and one of 10 patients with selective antibody deficiency had severe GHD, while one patient in the selective antibody deficiency group had mild GHD. Interestingly, combined pituitary hormone deficiencies were detected in two women with CVID (TSH and gonadotropin) and in one man with selective antibody deficiency (ACTH and GH).

Conclusion: To our knowledge, this is the first study to describe a high prevalence of endocrine dysfunction in adult patients with PAD. Underlying disease mechanisms may include genetic defects, which requires further evaluation. Increased insight in genetic defects underlying PADs may explain concomitant endocrine dysfunction. As these dysfunctions may cause considerable health burden, assessment of endocrine axes should be considered in PAD patients.

Keywords: common variable immunodeficiency, hormones, endocrine

POSTER 18 - ADIPONECTIN EXPRESSION AND EFFECT OF IMMUNOGLOBULIN THERAPY IN PATIENTS WITH COMMON VARIABLE IMMUNODEFICIENCY

AUTHORS

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Objective: Common variable immunodeficiency (CVID) is a primary immunodeficiency characterized by chronic activation of immune system with impaired antibody production. Even if the mechanisms underlying the chronic immune activation associated with CVID remain unclear, several studies demonstrated an altered cytokines profile and abnormalities in immune cellular subpopulations consistent with a substantial chronic inflammatory condition. Recently, the dysregulation of adipokine's secretion from white adipose tissue has been recognized as a central mechanism in the development and progression of immune disorders. Among the others, adiponectin, which circulates as complexes of low, middle and high molecular weight (respectively LMW, MMW and HMW), has demonstrated an anti-inflammatory and immunosuppressive action. Our objective is to verify whether adiponectin is involved in CVID and its correlation with immunoglobulin therapy.

Design and Method: We evaluated total adiponectin levels and its oligomerization state in 52 CVID patients and 54 healthy controls. Adiponectin levels also were measured in 8 CVID naïve (never treated) patients and in 5 patients with diagnosis of chronic inflammatory demyelinating polyneuropathy (CIDP). This in order to investigate the effect of IgG on adiponectin expression. Samples of serum from CVID naïve patients and CIDP patients were collected before immunoglobulin therapy (0.4 g/kg and 2 g/Kg respectively) and after at different times (24 h, 7, 14 and 21 days). All CIDP patients had already previously received intravenous immunoglobulin as immunomodulating therapy.

Results: Total adiponectin levels were decreased in CVID patients compared to controls ($17 \pm 0.4 \mu\text{g/mL}$ vs $27 \pm 0.7 \mu\text{g/mL}$, $p < 0.0001$); the densitometric evaluation of oligomeric distribution showed a lower statistically relevant expression of the HMW oligomers in CVID patients compared with controls. Adiponectin levels were higher in CVID patients with IgA levels at the diagnosis $> 7 \text{ mg/dl}$ compared to patients with IgA levels at the diagnosis $\leq 7 \text{ mg/dl}$ ($1.8 \pm 0.3 \mu\text{g/mL}$ vs $1.6 \pm 0.3 \mu\text{g/mL}$; $p = 0.03$). Moreover, adiponectin levels quickly and dramatically increased in CVID patients after the first immunoglobulin replacement therapy but did not change in CIDP patients.

Conclusions: This is the first study that evidences a strong reduction of adiponectin expression in CVID. The increase of adiponectin levels after immunoglobulin replacement therapy in CVID naïve patients, but not in CIDP patients, suggests that IgG is able to induce the increase of adiponectin levels only in the presence of the specific cellular and/or molecular background proper of CVID. These data strongly strengthens the hypothesis that adiponectin could be involved in the pathogenesis of CVID.

POSTER 19 - JAK1/2 INHIBITOR BARICITINIB AS A POTENTIAL THERAPY IN A PATIENT WITH GAIN-OF-FUNCTION MUTATION IN SIGNAL TRANSDUCER AND ACTIVATOR OF TRANSCRIPTION 1 (STAT1)

AUTHORS

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In the past decade, patients with heterozygous signal transducer and activator of transcription 1 (STAT1) gain-of-function (GOF) mutations have been progressively reported worldwide. Chronic mucocutaneous candidiasis (CMC) is the hallmark of this disorder, but clinical features also include bacterial infections, viral infections and autoimmune manifestations. Since curative treatment for these patients is still unavailable, most of the patients with STAT1 GOF mutations receive prolonged systemic antimicrobial therapy that could lead to drug resistance. Immunotherapies or immunosuppressive therapies are also considered in some patients, although the effectiveness still needs to be evaluated in more detail. The novel Janus kinase (JAK) 1/2 inhibitor, baricitinib, selectively and reversibly inhibits JAK1 and JAK2 by oral administration. Baricitinib hampers the activated interferon (IFN)-JAK-STAT1 signalling in immune-mediated diseases and was recently approved for treatment of rheumatoid arthritis. Based on its mechanisms of action, baricitinib could be a potential candidate for the treatment of patients with STAT1 GOF mutation.

Design and methods: The enrolled patient is a 24-year-old Dutch female known with a heterozygous STAT1 GOF mutation at c.1957G>A (p.(V653I)) of the SH2 domain. The patient experienced recurrent Candida stomatitis and esophagitis with atypical viral and bacterial infections. Apart from infectious complications, she also developed autoimmune manifestations with positivity for antinuclear antibodies (ANA), anti-Sjögren's-syndrome-related antigen A (Ro), and anti-centromere protein B autoantibodies (anti-CENP-B). STAT1 phosphorylation, cytokine production and STAT1 target genes expression were evaluated in patient blood samples and long-term T lymphocyte cultures with and without stimulation by baricitinib.

Results: T lymphocytes from the patient revealed enhanced phosphorylation of STAT1 after stimulation with either IFN- α , IFN- γ or interleukin (IL)-6, which was reduced upon addition of baricitinib. Higher expression of the STAT1 regulated gene CD274 (PD-L1) was also reduced by baricitinib to a level comparable to that of age-matched healthy controls. Baricitinib was also found to restore IL-17A production by patient PBMCs, although IL-17A levels were still lower when compared to healthy controls.

Conclusions: The in vitro application of baricitinib reduced hyperphosphorylation of STAT1 and also expression of the STAT1 target gene CD274 (PD-L1). In addition, IL-17A production by PBMCs was partially restored after treatment with baricitinib. Based on these in vitro data we hypothesize that baricitinib may have potential clinical implications in patients with STAT1 GOF mutations.

POSTER 20 - MOLECULAR DIAGNOSIS OF SCID PATIENTS BY A CUSTOM DESIGNED TARGETED NEXT GENERATION SEQUENCING PANEL

AUTHORS

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Molecular characterization is important for prognosis and treatment strategies in primary immunodeficiencies (PID). The phenotypic and molecular mechanisms of SCIDs are beginning to be enlightened with increased number of studies. Targeted Next Generation Sequencing (NGS) is a powerful approach for the diagnosis of the diseases with genetic and clinic heterogeneity like PIDs. Here, we created a PCR based targeted NGS panel, which contains 18 most common disease related genes and screened 38 SCID, Leaky SCID and OMENN patients. Two SCID patients with four known variants (RAG1 and ADA compound heterozygosity) were used as a control. Allelic segregations were also checked in the families by Sanger sequencing. The observed mean of targeted regions were found with at least 20X coverage was 96,35% and the coding regions were found 97,89% in the panel. In total, 23 disease-causing variants (13 known, 8 novel) were identified in 22 of 38 SCID patients. All known variant were identified and confirmed successfully. The variants were found in RAG1 (n=5), RAG2 (n=2), ADA (n=3), DCLRE1C (n=2), NHEJ1 (n=2), CD3E (n=2), IL2RG (n=3), JAK3 (n=3) and IL7R (n=1). Familial segregations were also shown for all pathogenic variants. The accuracy of our custom-made NGS panel was found 58% for the SCID cohort. Targeted NGS screening and immunophenotyping, together, provides useful data to evaluate the clinical and molecular diagnosis and leads to successful management of SCID patients. Sinem Firtina was funded by the Scientific and Technological Research Council of Turkey (TUBITAK) 2211-C. This project was supported by Istanbul University Research Fund (No: 52575 and 20499).

POSTER 22 - IMMUNOGLOBULIN REPLACEMENT THERAPY FOR CHILDREN WITH PRIMARY IMMUNODEFICIENCY DISEASES IN VIETNAM

AUTHORS

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Background: Immunology department of National Children's Hospital (NCH) which has been established for 7 years is the only center in the North of Vietnam taking care for PID children.

The Immunoglobulin replacement therapy is covered by public health insurance but the coverage depends on the age and type of insurance. The SCIG has not been approved yet in Vietnam.

Method: Interview patients with PID on regular treatment and their caregivers.

Children above 5yo were assessed the QoL with the CHQ-PF50.

Results: 25 respondents (1 girl, 24 boys) completed the survey. Mean age: 6.8±4.2 (min: 2, max: 17yo). 100% patients received IVIG therapy in hospital with dose 400-600mg/kg. Most of them (85%) have 4-weekly infusions, 2 patients have treatment every 5 weeks and one has IVIG every 6 weeks due to family circumstances. They have been treated for 33 months on average. The oldest has 9 years experienced IVIG.

The mean distance between patient's house and NCH is 120km, the longest is 300km. Children accompanied with 1 or 2 caregivers spend an average of 3h traveling by bus. It normally takes 28±4.5h hospitalized for a period of treatment, including 6.7±2.1h taking infusion and other hours waiting for administrative procedures. So children often miss school/parents get off of work for 2-3 days per month. 47.6% and 52.4 % of them said that it affects a lot on their studies and jobs. 33.3% of patients and 38.1% of parents are affected quite a bit.

The mean cost for a period of treatment is about 1000 US dollars. In total, not counted the insurance coverage but including cost of travel, food and other expenditures, most families spend around 120\$. Some families have to pay 200- 300\$ per treatment of IVIG because their insurances only cover 80%.

66.7% of caregivers thought that the child's health in general is good. More than 50% of them thought it is better than the last year. The child's physical functioning and role/social- physical are limited a little. Around 80% of parents have impact on their time and emotion.

Conclusions: We need to reduce the expense of time and cash, then improve the QoL of patients as well as families. It is necessary to train the medical staffs in local hospitals in taking care of PID patients, and have advocacy plans to change policies of health insurance that make IVIG been available in provincial hospitals or SCIG at home.

POSTER 24 - OVERALL AND PEDIATRIC PATIENT PREFERENCES FOR RECOMBINANT HUMAN HYALURONIDASE (RHUPH20)-FACILITATED SUBCUTANEOUS INFUSION OF IMMUNOGLOBULIN G (fSCIG) IN PATIENTS WITH PRIMARY IMMUNODEFICIENCIES

AUTHORS

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Objective: Among the available routes of immunoglobulin (IG) administration for patients with primary immunodeficiencies (PID), recombinant human hyaluronidase (rHuPH20)-facilitated subcutaneous (SC) infusion of immunoglobulin G (fSCIG) offers the option to self-administer at home on a 3-4 week basis as an alternative to intravenous (IV) and conventional subcutaneous (SC) IG administration. This analysis assessed treatment preferences of patients who switched to fSCIG after previously receiving IVIG or conventional SCIG during the Phase 3 study.

Design and Method: In this prospective, non-controlled study, patients with PID were treated with IVIG for 3 months, followed by fSCIG at 3–4 week intervals for approximately 12 months. At the end of study, patients completed a preference questionnaire that assessed preference to continue fSCIG and a range of treatment attributes, such as convenience, infusion time and frequency of administration. Treatment attributes were measured using a 5-point Likert scale (from “dislike very much” to “like very much”). Patients aged greater than or equal to 14 years completed the questionnaire themselves and pediatric patients aged 2–13 years had a caregiver/parent complete the questionnaire.

Results: A total of 87 PID patients aged greater than or equal to 2 years were enrolled in the study; 69 completed the questionnaire, of which 13 were aged <14 years. Overall, 57 (83%) patients indicated they would choose to continue receiving fSCIG over IV or conventional SC administration. The parents of all 13 (100%) patients aged <14 years would choose to continue receiving fSCIG. The majority of patients liked/liked very much most aspects of fSCIG, especially the ability to fit treatment into their schedules (80% overall; 85% peds), overall convenience (77% overall; 85% peds), and administration frequency (71% overall; 85% peds) of fSCIG.

Conclusion: Most patients, including children, preferred fSCIG over IV or conventional SC IG administration. Real world patient experience with fSCIG may elucidate how these patient preferences might impact treatment adherence.

POSTER 25 - ANALYSES OF EFFICACY AND TOLERABILITY IN PATIENTS WITH PRIMARY IMMUNODEFICIENCY DISEASES TREATED BY DIFFERENT MODES OF ADMINISTRATION OF IMMUNOGLOBULIN THERAPY DURING THREE CONSECUTIVE STUDIES

AUTHORS

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Objective: The modes of immunoglobulin (Ig) administration for primary immunodeficiency diseases (PID) differ in pharmacokinetics, infusion parameters, and tolerability. We report the efficacy and tolerability data for 30 patients with PID who were treated using all 3 modes of Ig therapy administration in sequence from intravenous (IVIG) to subcutaneous (SCIG) to hyaluronidase-facilitated SCIG 10% (fSCIG) during consecutive clinical studies—creating a unique opportunity to follow this cohort of patients across these modalities of therapy.

Design and Methods: In Study 1, patients received IVIG 10% every 3-4 weeks (~3 months), followed by weekly SCIG 10% (~12 months); in Study 2, patients were switched to fSCIG 10% every 3-4 weeks; then, in Study 3 (extension of Study 2), they continued with the same fSCIG dose (for ~2.7 years in Studies 2 and 3).

Results: Longitudinally, in 3 consecutive studies, the annualized rate per patient of validated acute serious bacterial infections and all infections, respectively, was low: IVIG (0.00/4.17), SCIG (0.09/3.68), and fSCIG (0.04/2.42). The rate of causally related systemic adverse events (AEs)/patient-year was lowest in patients receiving fSCIG (0.88) versus IVIG (5.60) and SCIG (1.93). The rate of causally related local AEs/patient-year was higher for fSCIG (1.57) compared to conventional SCIG (0.92). Median IgG trough levels (g/L) at steady state were similar for IVIG (10.20; n=23) at a 4-week infusion interval, for SCIG (12.30; n=30) at weekly infusion intervals, and for fSCIG (9.93; n=24) at every 4-week infusion interval.

Conclusion: Evaluation of the same patient cohort in 3 consecutive studies over more than 3 years demonstrated that all 3 modes of administration provided similar efficacy, relative rates of local and systemic AEs, and tolerability, as expected.

POSTER 26 - EVALUATION OF PI3K/AKT/FOXO PATHWAY IN PATIENTS WITH COMMON VARIABLE IMMUNODEFICIENCY

AUTHORS

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Objective: Common variable immunodeficiency (CVID) is the most frequent symptomatic primary immunodeficiency, characterized by hypogammaglobulinemia. PI3K/AKT/FOXO pathway has important role in survival and differentiation of B-cells. Since defect in this pathway could be involved in defective survival and differentiation of B-cells, we evaluated this pathway on B-cells from CVID patients.

Design and Methods: B-cells from 10 patients and 10 healthy individuals were purified by negative selection and were stimulated by anti-IgM and anti-CD40 antibody for 24 hours. We evaluated protein and gene expression of PI3K, AKT and Foxo molecules in B-cells by flowcytometry and real-time PCR, respectively. Moreover, the level of phosphorylated AKT in B-cells has also been measured by flowcytometry. Furthermore, spontaneous and induced apoptosis of B cells have been evaluated. Four-color flow cytometric immunophenotyping determinations of B-cell subsets were also performed using FACSCalibur.

Results: We have not identified significant difference between protein and gene expression of PI3K, AKT and Foxo molecules in B-cells from patients than controls. However, we surprisingly found phosphorylated Akt (p-AKT) levels are significantly lower in B-cells from patients compared with controls. Moreover, our results demonstrate increased spontaneous and induced apoptosis of B cells in patients. Furthermore, our patients presented a significant reduction in B-cell subset numbers than normal cases.

Conclusions: Our results suggest that impairment in phosphorylation of AKT leads to induction of apoptosis in B-cells from CVID patients. Thus, defective p-AKT and increased apoptosis leads to abnormality in B-cell subset numbers, as B cells could be unable to complete their maturation and differentiation.

Key words: Common Variable Immunodeficiency, Signaling, B-cells

POSTER 27 - HEMATOPOIETIC STEM CELL TRANSPLANTATION FOR SEVERE COMBINED IMMUNODEFICIENCY OR OMENN SYNDROM DUE TO ARTEMIS DEFECT: A SINGLE CENTER EXPERIENCE

AUTHORS

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Background: Artemis (DCLRE1C) is essential for V (D) J recombination, DNA double-strand break repair and antigen receptor gene rearrangement for T and B-lymphocytes. Artemis defect will results in T-B-NK+ severe combined immunodeficiency (SCID). Hematopoietic stem cell transplantation (HSCT) is a curative treatment known.

Objective: To determine the characteristics and the outcome for Artemis defect SCID from a single center experience.

Method: A retrospective review of medical records of genetically confirmed Artemis defect SCID patients from a single center at King Faisal Specialist hospital and research center, Riyadh, Saudi Arabia.

Results: Nineteen patients with Artemis defect SCID identified. 13/19 patients who received HSCT underwent data analysis. Median age of diagnosis was 0.5 month (0-36 months); median age at HSCT was 6 months (1-84 months), median age at follow up post HSCT 96 months (10-204 months). Presenting symptoms were recurrent otitis media 3/13(23%), chest infection 4/13(30.7%), neonatal sepsis 3/13(23%), exfoliating skin rash 1/13(7.7%), skin abscess 1/13(7.7%), did not develop symptoms 4/13(30.7%), no records 2/13(15.3%). CD3 <500 mm³ in 76.9%. Lymphocyte proliferation was severely depressed in 92.3% of the patients. The donors for HSCT were; in 5/13 matched sibling donor (MSD), 4/13 matched related donor (MRD), 3/13 cord blood (CB), and one received haploidentical. 7/13(53.8%) received conditioning, 8/13(61.5%) received GVHD prophylaxis, and 8/13(61.5%) developed acute GVHD. 2/13 died before age of 2 years and one lost follow up. 10/13(77%) survived. In long-term follow up for 10 living subjects had stable engraftment. 8/10 are clinically well with no recurrent infection, CD3 >1000 mm³ and normalized lymphocyte proliferation. Two patients are chronically ill one with chronic sclerodermas GVHD and one with bronchiolitis obliterans. 4/10 patients are still on regular IVIG.

Conclusion: Artemis defect SCID patients post HSCT results in 77% survival rate. This result was comparable to previous studies

POSTER 28 - STAT3 RELATED HYPER-IGE SYNDROME IN A BOY WITH HIGH EOSINOPHILIA AND A NONSENSE MUTATION IN THE LINKER DOMAIN

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STAT3 related Hyper-IgE syndrome in a boy with high eosinophilia and a nonsense mutation in the linker domain
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Introduction: The hyper-IgE syndrome is a multisystem primary immunodeficiency disorder characterized by pyogenic skin and lung infections, pneumatocele formation, severe eczema, and extreme elevation of serum IgE. Additional manifestations include distinctive facial features, hyperextensibility of the joints, abnormal dentition, and pathological fractures. Both autosomal recessive (AR) and autosomal dominant (AD) inheritance have been described, but most HIES cases are sporadic. Mutations in the signal transducer and activator of transcription-3 gene (STAT3) on chromosome 17q21 is major causes of AD and sporadic HIES.

Case Report: YP, 2.5 years male born to non-consanguineous parents with three elder siblings, 2 girls and a boy. Fever for 4 days and skin abscesses over right lower chest (5x4 cms) and left calf (2x2 cms), boggy and lacked warmth and redness. He had a possible varicella infection at 1 year of age. At 2 years he was admitted for community acquired pneumonia with right pyo-pneumothorax requiring intercostal drainage and developed lower lobe lung collapse. Empyema fluid grew methicillin sensitive *Staphylococcus aureus*.

Materials and Methods: EDTA and Heparin blood was obtained for CBC, Flow cytometry and DNA sequencing. Genomic DNA was isolated by using standard methods. All 23 exons and exon/intron boundaries were separately amplified by PCR. Sequences were analyzed using the Codon Code Aligner software.

Results: Marked eosinophilia was noted on differential count (57%) with an absolute eosinophil count of 21,432/Cumm. Serum IgE was 9752 IU/ml. His NIH score was 23. pSTAT3 was 51.5%, MFI 341 (Control 50.5% MFI 733) Normal. TH17 cells were low 0.3% (control 0.8%). Genetic analysis showed a heterozygous, nonsense mutation in exon 17 (linker domain) of the STAT3 gene g.68737 C>T, c.1552 C>T, p.R518X.

Conclusion: Linker domain of STAT3 is highly conserved. Mutation in the linker domain is very rare and only a single case report is found in the literature. With a nonsense mutation (a novel mutation) in the linker domain, as seen in the index case, the resultant truncated STAT3 protein would lack both the SH2 and the transactivation domains, the former responsible for STAT dimerization and the latter for phosphorylation, resulting in a non-functional allele unable to exert the dominant negative effect on the normal allele in a heterozygous state resulting in a milder phenotype. Another interesting feature was the extremely high eosinophilia.

POSTER 29 - TREOSULFAN BASED CONDITIONING REGIMENS – REDUCED TOXICITY WITH EXCELLENT OUTCOMES IN CHILDREN WITH PRIMARY IMMUNE DEFICIENCY

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Introduction: Primary immune deficiency(PID) has varied presentation and mortality rate is high without hematopoietic stem cell transplantation(HSCT). Careful planning is required to tailor the conditioning regimen to minimise immediate and late toxicity.Optimal supportive care to prevent graft versus host disease or graft rejection,cytomegalovirus reactivation and other infectious complications is needed. We present our data of a treosulphan based conditioning regimen in these children.

Patients and Methods: We conducted a retrospective study in the department of Hematology, Oncology and Blood and Marrow transplantation unit in Apollo Speciality Cancer Hospitals during the year 2002-2017. All children who were diagnosed to have PID based on PID work up and by gene analysis who received Treosulphan based conditioning were included in the study. Age at diagnosis, conditioning regimen , source of stem cells, regimen related toxicity, graft versus host disease(GvHD),donor chimerism post transplantation and outcome were collected and analysed.

Results: A total of 46 children who were diagnosed to have PID(Male-28, Female-18)received treosulphan based conditioning regimen. The conditions were heterogenous and included HLH 14(32%),SCID-21(48%),LAD-2(4%),CVID-2(4%),WAS-1(2%),Hyper IgE 1(2%),Hyper IgM 1(2%) MSMD 2(4%),IL10 Ra deficiency 2(4%). The median age at presentation was one year. Allogeneic related PBSC was used in 11(24%), bone marrow in 12(27%),unrelated in 1(2%),cord blood in 10(22%) and haploidentical bone marrow in 11(25%).

Regimen related toxicity seen predominantly were rash in 12 children(27%), conjunctivitis in 1(2%), mild mucositis in 8(18%), severe grade 4 mucositis in 2(4%). There was no major respiratory, neurological toxicity or sinusoidal obstruction syndrome. After initial complete chimerism, all children demonstrated mixed chimerism after 60 days and early withdrawal of immunosuppression was feasible. Acute GvHD was seen in 8(17%) and chronic GVHD 3(6%),Graft rejection in 1(2.2%). The mortality rate was 37% with the cause being sepsis in 5(29%), cytokine release syndrome as DAH/ARDS in 4(24%), disseminated CMV 2(12%),disseminated Aspergillosis1(6%),encephalopathy in 2(12%), refractory immune cytopenia in 1(6%), progressive HLH in 1(6%) and chronic liver GVHD in 1(6%).

Conclusion: Treosulphan based conditioning regimen is ideally suited for these children as they present with significant co-morbidity. The graft kinetics are followed carefully with withdrawal of immunosuppression early when chimerism drops to less than 95% to prevent graft rejection. This is particularly relevant in India where busulphan pharmacokinetics is not universally available for these children in whom individualised therapy is the key to a successful outcome.

POSTER 30 - HAEMATOPOIETIC STEM CELL TRANSPLANTATION FOR IL 10 RECEPTOR DEFICIENCY IN TWO CHILDREN WITH EARLY INFLAMMATORY BOWEL DISEASE: THE JOURNEY TO CURE IN AN UNRECOGNIZED AND YET LIFE-THREATENING CONDITION

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Background: Inflammatory bowel disease in the very young children could be a manifestation of a primary immune deficiency. World literature has reports of about 10 such children and the case reports of two children with this rare condition is presented.

Patients: Two boys aged ten months and two years were diagnosed to have IL 10R deficiency confirmed by whole exome sequencing. They had presented with recurrent loose stools with blood, persistent perianal ulcers, failure to thrive and vasculitic skin lesions. They were born of third degree consanguineous marriage and had a history of a previous male sibling death due to similar symptoms. Hematopoietic stem cell transplantation (HSCT) was offered after improving their nutrition. However, there were no compatible family donors or unrelated donors. We performed TCR alpha/beta depleted haploidentical HSCT from his father in the ten month old boy after myeloablative conditioning using a treosulphan based regimen. Donor specific antibodies were strongly positive in the two year old boy due to the underlying autoimmunity. We performed an unrelated donor transplantation using a 9/10 matched donor after receiving two doses of anti CD20 antibody as immunosuppressant prior to HSCT.

Results: The children were closely monitored for electrolyte imbalance and gastrointestinal bleeding and low dose steroid was used all through the peritransplant period. Semi-elemental trophic feeds through a nasogastric tube and partial parenteral nutrition was used to support nutrition. Neutrophil and platelet engraftment occurred by D+15 and D+23 respectively and complete donor chimerism was documented on day 30 and 60. The median duration of follow up is 2 months. Cytomegaloviral reactivation and mild graft versus host disease of the gut have been the main complications. The children are tolerating full oral feeds with elemental formula feeds and are steadily gaining weight with no major infections and gradual healing of the perianal ulcers.

Conclusion: IL10 / IL10R deficiency can be cured with HSCT with a definite improvement in quality of life including complete resolution of inflammatory bowel disease. Data presented in the abstract is however preliminary as both the children are in early post HSCT. The children will be on close follow up for late rejection and autoimmunity. With increasing awareness about the condition and the availability of whole exome sequencing, more children with this life-threatening condition will have a chance for a normal life in the future.

POSTER 31 - MECHANISMS OF GENOTYPE-PHENOTYPE CORRELATION IN AUTOSOMAL DOMINANT ANHIDROTIC ECTODERMAL DYSPLASIA WITH IMMUNE DEFICIENCY

AUTHORS

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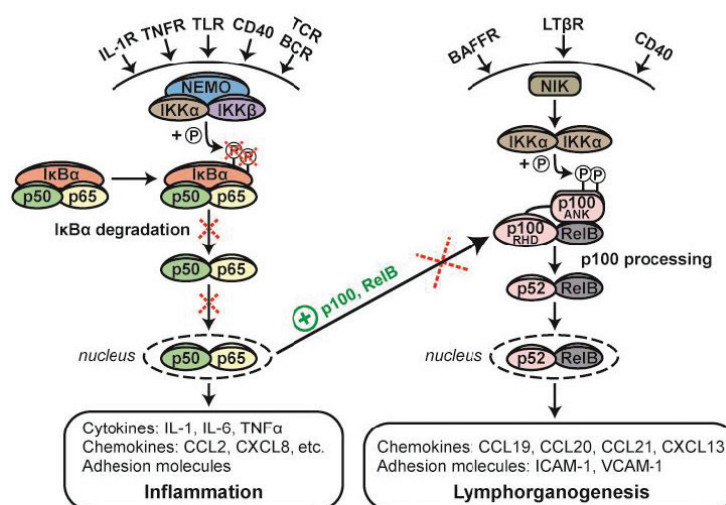
Background: Autosomal dominant anhidrotic ectodermal dysplasia with immune deficiency (AD EDA-ID) is caused by heterozygous point mutations at or close to S32 and S36 or N-terminal truncations in IκBα that impair its phosphorylation and degradation, and thus activation of the canonical NF-κB pathway. The outcome of hematopoietic stem cell transplantation is poor in AD EDA-ID despite achievement of chimerism. Mice heterozygous for the S32I mutation in IκBα have impaired non-canonical NF-κB activity and defective lymphorganogenesis.

Objective: To establish genotype-phenotype correlation in AD EDA-ID.

Methods: A disease severity scoring system was devised. Stability of IκBα mutants was examined in transfected cells. Immunological, biochemical, and gene expression analyses were performed to evaluate canonical and non-canonical NF-κB signaling in skin-derived fibroblasts.

Results: Disease severity was greater in patients with IκBα point mutations than in patients with truncation mutations. IκBα point mutants were expressed at significantly higher levels in transfectants compared to truncation mutants. Following stimulation with lipopolysaccharide (LPS) for 48 hours, IκBα accumulated significantly in fibroblasts from AD EDA-ID patients, and more so in patients with point mutations. Canonical NF-κB-dependent IL-6 secretion and upregulation of the NF-κB2/p100 and RelB components of the non-canonical NF-κB pathway were diminished significantly more in patients with point mutations compared to those with truncations. Non-canonical NF-κB-driven generation of the transcriptionally active p100 cleavage product p52, and upregulation of CCL20, ICAM1 and VCAM1, important for lymphorganogenesis, were diminished significantly more in LPS+α-LTβR-stimulated fibroblasts from patients with point mutations compared to those with truncations.

Conclusions: IκBα point mutants accumulate at higher levels compared to truncation mutants and are associated with more severe disease and greater impairment of canonical and non-canonical NF-κB activity in AD EDA-ID.



ANK, Ankyrin repeat domain; BAFFR, B cell-activating factor receptor; BCR, B cell receptor
IL-1R, Interleukin-1 receptor; LTβR, Lymphotoxin beta receptor; RHD, Rel homology domain
TCR, T cell receptor; TLR, Toll-like receptor; TNFR, Tumor necrosis factor receptor

POSTER 32 - INTRAVENOUS IMMUNOGLOBULIN TREATMENT INCREASES ACTIVATION OF GRANULOCYTES IN PATIENTS WITH COMMON VARIABLE IMMUNODEFICIENCY DISORDERS (CVID)

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Background: Intravenous immunoglobulin (IVIG) administration is associated with post-infusion increase of serum pro-inflammatory cytokine levels. The goal of our study was to determine, whether patients with common variable immunodeficiency disorders (CVID) have increased levels of serum markers of granulocyte activation and whether this activation is influenced by IVIG administration.

Methods: Plasma levels of granulocyte activation markers - elastase, myeloperoxidase and neutrophil gelatinase-associated lipocalin (NGAL) were determined by ELISA in 46 CVID patients (25 females, 21 males aged 22-82 years). All CVID patients were in a stable state without apparent acute infection. Twenty-eight healthy persons (19 females, 9 males, aged 22-78 years) were used as a control group.

In 23 patients (12 females, 11 males, aged 22-82 years) on IVIG treatment plasma levels of elastase, myeloperoxidase and NGAL were determined before and one hour after the IVIG infusion. No infusion was accompanied by an adverse reaction.

The results were compared by mean of Mann-Whitney rank-sum test and by Wilcoxon signed-rank test.

Results: Plasma levels of elastase, myeloperoxidase and NGAL were markedly increased in CVID patients compared to healthy controls ($p < 0.001$ in all cases, Mann-Whitney test). This difference remained significant also after CVID patients with CRP > 10 mg/l ($n = 7$) were excluded.

Evaluating the effect of IVIG administration on leukocyte activation markers, the increases of plasma level of myeloperoxidase, elastase and NGAL were observed, however only the increase of elastase reached statistical significance ($p = 0.001$, Wilcoxon test).

Conclusions: All these data point to activation of granulocytes in CVID patients, even in patients without apparent acute exacerbation of infection. IVIG administration leads to additional activation of granulocytes, however it probably does not lead to acute adverse reactions, at least in majority of patients.

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POSTER 33 - DECREASING BURDEN OF TREATMENT – PATIENT-REPORTED EXPERIENCES OF SUBCUTANEOUS FACILITATED IMMUNOGLOBULIN TREATMENT (fSCIG) IN ADULTS WITH PRIMARY AND SECONDARY IMMUNODEFICIENCY

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Because patients with immunodeficiency's require therapy indefinitely, the form of administration as well as setting where the therapy takes place are important factors which can affect these patients' health-related quality of life (HRQOL). The goal is to individualize treatment regime to provide optimal medical outcomes and HRQOL for all patients in need of treatment. One problem is that replacement treatment demand frequently hospital visits due to infusion frequency of 3-4 times /month. Recently, hyaluronidase -facilitated subcutaneous immunoglobulin (fSCIG) with recombinant human hyaluronidase have turned up as an option. This treatment with hyaluronidase can be pre-administrated subcutaneously and followed by the human immunoglobulin infused in the same needle. This therapy provides opportunity to administer an increased dose at once with the same infusion rate as with intravenous treatment. The aim of this study was to evaluate patient-reported experience of fSCIG in adults with immunodeficiency.

A descriptive convergent mixed-method approach was used. Two different departments from one regional county hospital and one university hospital in the southeast region of Sweden participated. In total 32 participants were eligible. A telephone interview based on a study protocol was performed with nine questions about treatment experience, satisfaction, intervals and about ancillary supplies. The response-options were described on a score-scale, ranged from 1-10. Open-ended questions were analyzed with content analysis and descriptive statistics were calculated using percent.

The integration of the results led to two main factors. First, there are prohibiting factors, exemplified by problems due to technical issues and ancillary supply issues. It was also described by the difficulties in the stepwise procedure and patients experiencing affecting symptoms due to the treatment. The second was promoting factors, illustrated in the score-scale from patients experiencing advantage with longer treatment intervals and in combination with the timesaving aspect. Another illustrative promoting factor was the increased well-being described by patients. This was also confirmed in the item about "change in quality of life" in the score scale. A feeling of less illness could be detected and is interpreted as a promoting factor for decreasing burden of treatment.

A key to successful treatment is that the patient is providing proper support and managing the expectations to ensure that they achieve the maximum effect from treatment. Understanding which factors that promote and prohibit the treatment is important to be able to target the treatment of fSCIG, which may lead to a decreased burden of treatment for patients with immunodeficiency.

POSTER 34 - CONSTITUTIONAL MISMATCH REPAIR DEFICIENCY (CMMRD) & HYPOGAMMAGLOBULINEMIA: A TWO WAY ROAD FOR PID DIAGNOSIS

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Introduction: It is well known that patients with Constitutional MisMatch Repair Deficiency (Constitutional MisMatch Repair Deficiency, CMMRD), OMIM #276300) suffer from an autosomal dominant disease which confers elevated risk to develop recurrent infections, hypogammaglobulinemia, tumors in infancy -mostly hematological and CNS. This group of diseases are caused by biallelic inactivating mutations in mismatch repair system. The aim is to characterize their clinical, immunological and molecular findings.

Methods: We identified 4 cases in three families (three consanguineous unrelated families). Clinical and lab data were collected from probands and parents. Immunoglobulins, T and B-cell subsets were studied in deep.

Targeted NGS sequencing of CMMRD genes was performed (MLH1, MSH2, MSH6 & PMS2) confirmed disease causing mutations. The pathogenic variants were tested in relatives. In all tissue samples, both healthy and tumoral ones, microsatellites instability, immunohistochemistry from repairing MMR proteins.

Results: The first case was diagnosed of a non-Hodgkin B-cell Lymphoma (at the age of 2 years) and two pre-T lymphoblastic lymphomas (age 3 & 8 y).

We found in homozygous status a pathogenic mutation (class 5) in MSH6 c.2653A>T, p.(Lys885*). The second patient was diagnosed of T-cell lymphoblastic lymphoma (7 mo), carrying a homozygous mutation (probably deleterious (class 4) MLH1 c.332C>T, p.(Ala111Val). Familial screening revealed a new heterozygous carrier by the time she was diagnosed of neuroblastoma (6 yo). MMR immunohistochemistry showed absent MSH6 expression in healthy tissue from the first patient, while microsatellite instability was only reported in B-cell non-Hodgkin Lymphoma. A third patient was diagnosed of PMS2 deficiency by the time he had glioblastoma while he was receiving chemotherapy during induction phase of acute lymphoblastic leukemia. All patients had café-au lait spots, disturbed B-cell population (increased transitional B-cells) and two of them (the patients with PMS2 and MLH1 deficiency) had hypogammaglobulinemia requiring IVIG

Conclusion: Café-au lait spots with or without hypogammaglobulinemia in the presence of a disturbed B-cell subsets might lead to the diagnosis of Constitutional MisMatch Repair Deficiency .

Age (y) at onset	Café au lait spots	Tumor	IgG,A,M (mg/dL)	B-cell subsets	DNA repair defect & radiosensitivity	Gene	Outcome
0.8	Yes	Lymphoblastic Lymphoma	IgG 99 IgA 9 IgM 18	Low CD19+ cells/uL (CD19+ CD38+++ IgM+++): 91% (HD 2.7%)	Yes	MLH1	Death (unresponsive to chemotherapy)
6	Yes	Neuroblastoma	WNR	Increased Transitional B-cells	N.D.	MSH6	Complete remission after chemotherapy
4	Yes	Lymphoblastic Lymphoma (relapsed)	Not tested	N.D.	N.D.	MSH6	Alive (after HSCT)
3	Yes	Acute lymphoblastic Leukemia Glioblastoma	IgG 106 IgA 17 IgM 24	N.D.	Yes	PMS2	Alive (active disease)

POSTER 35 - DIFFERENT CLASSIFICATION OF CVID PATIENTS USING B-CELL SUBSETS

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Background: Common variable immunodeficiency (CVID) is a primary immunodeficiency with heterogeneous complications. The aim of this study was to classify CVID patients based on four known classifications (Paris, Freiburg, EURO-class and B-cell patterns) by measurement of B-cell subsets and to assess the relation of each classification with clinical manifestations.

Methods: All B-cell subsets were measured (absolute count and percentage) using four-color flow cytometry in 30 CVID patients and 30 healthy individuals. Moreover, we evaluated antibody responses to pneumococcal vaccine in patients.

Results: A significant reduction in percentage of terminal B-cell subsets (total, marginal zone-like, switched memory, IgM-only memory, total memory B-cells and plasmablast) and absolute count of all B-cell subsets along with a strong increase in CD21low B-cells has been observed in patients. Patients with splenomegaly and hepatomegaly clustered in group Ia, smB+21low and group 1 based on known classifications and significantly tended to have a decreased transitional and marginal zone-like B-cells count, as well as an increase in CD21low B-cell counts. Patients with lymphadenopathy, bronchiectasis and allergy had a significant decrease in absolute count of total memory, switched memory and total B-cells, respectively.

Conclusion: Classification of patients could provide useful information to guide clinician in long-term follow-up of CVID patients. Our data demonstrate that it may be more accurate to use absolute counts of B-cell subpopulations in CVID patients because absolute counts of B-cell subsets are more associated with clinical manifestations compared with their percentage and also four known classifications.

Keywords: B cell subsets; common variable immunodeficiency; classifications.

POSTER 36 - A PROSPECTIVE, OBSERVATIONAL STUDY ON BI-WEEKLY 20% SUBCUTANEOUS IMMUNOGLOBULIN THERAPY IN PATIENTS WITH PRIMARY IMMUNODEFICIENCY: THE IBIS STUDY

AUTHORS

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Objective: Replacement therapy with immunoglobulins (Ig) represents the standard treatment for patients with primary immunodeficiency (PID). In order to minimize side effects, reduce infusion time, achieve a more constant level of serum IgG (s-IgG) and improve quality of life, many patients treated with monthly intravenous Ig (IVIg) or weekly subcutaneous Ig (SCIG) switched to a double weekly dose of 20%-SCIG (Hizentra®) administered bi-weekly (every 2 weeks). However, field-practice evidence on s-IgG levels and incidence of infection after switching remains scant, and only data from retrospective studies are available.

The multicenter IBIS study aimed at prospectively investigating the effects of bi-weekly Hizentra® administration compared with previous IVIg/SCIG treatment regimens in PID patients.

Design and Method: This was a multicenter, observational cohort study consisting of a retrospective data collection phase – during IVIg/SCIG treatment – and a prospective phase starting at the initiation of bi-weekly Hizentra®. Each phase lasted 12 months. Trough s-IgG levels, number of serious bacterial infections (SBI), number of other infections and number of hospitalizations were evaluated.

Results: In total, 35 patients (24 males; mean age 26 years, range 2-56) were enrolled. Data on serum IgG were available for 23 (64%) patients while 32 (89%) had available information about infections and number of hospitalizations.

Mean trough s-IgG levels collected during the retrospective (784±210 mg/dL; 95% CI 6.94-8.74) and the prospective (855±190 mg/dL; 95% CI 7.79-9.31) phase were comparable. Two episodes of SBI (pneumonia) were reported during the retrospective phase in two different patients; on the other hand, only one patient reported a single SBI during bi-weekly treatment with Hizentra® (visceral abscess), with a rate of 0.063 and 0.031 per patient-year, respectively. During both the retrospective and the prospective period, 24 patients (75%) reported other infections, with bronchitis being the most frequent (n=9) during treatment with IVIg/SCIG and pharyngitis (n=11) during bi-weekly treatment with Hizentra®. One patient required hospitalization during previous IG regimen, while no hospitalizations were reported during the prospective phase.

Mean duration of antibiotic therapy (per patient) was 11±13 days (interquartile range: 0-20) during the retrospective phase and 12±17 days (0-16) during the prospective phase.

Conclusions: In a field-practice setting, bi-weekly administration of Hizentra® as replacement therapy in PID patients showed a non-inferior safety and efficacy profile compared with the previous regimen.

POSTER 39 - LEUKOCYTE ADHESION DEFICIENCY TYPE I IN ALGERIAN PATIENTS

AUTHORS

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Objectives: Leukocyte adhesion deficiency type 1 is caused by the lack or low expression of CD18. We report in this work the clinical, immunological and genetic findings for 5 Algerian patients.

Methods: We investigated 5 patients (4 boys and 1 girl). The expression of CD18 was evaluated on granulocytes by flow cytometry using labeled monoclonal antibodies directed against CD18. Genomic DNA was purified using salting-out method. All coding exonic regions of CD18 gene were amplified and direct sequencing of the PCR products was performed using the Big-Dye3.1 kit (Applied Biosystems).

Results: All the patients developed omphalitis in the neonatal period. Three patients were diagnosed at age of 1 month, and the two others at 13 months and 6 years respectively. All patients suffer from severe respiratory and digestive infections as well as skin abscesses without pus. Major leukocytosis was found (21000 to 83000/mm³). The CD18 expression on granulocytes was <1% of the normal value. For the first patient, the sequencing identified two homozygous missense mutations: c.533 C>T in exon 6 and c.1358 G>A in exon 11. Homozygous non-sens mutation: c.562 C >T in exon 6 has been identified for the 4 other patients. Thus, the three mutations affect CD18 differently in its capacities to support CD11/CD18 expression and adhesion. We have also characterized a common polymorphism (c.1062 A>T) in exon 9 for all patients and two other polymorphisms at exons 10 (c.1101C>A) and 11 (c.1323 T>C) for two families that have the same exonic mutation. All patients received multiple courses of IV antibiotic, anti-fungal and none received hematopoietic stem cell transplantation. Despite the severity of the defect, three patients are still alive at age of 8, 7 and 3 years respectively. One died at 7 months and one is lost of follow up.

Conclusion: Leukocyte adhesion deficiency is a rare defect. Our patients suffer from severe form without the typical delayed cord separation. We identified point mutations affecting coding sequences that have been reported. These mutations are responsible for the severe form of the disease, with an unpredictable clinical evolution but usually fatal.

POSTER 41 - MYVIP: A WEB-BASED TOOL FOR THE THERAPEUTIC ALLIANCE BETWEEN ITALIAN PIDS PATIENTS AND DOCTORS

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Background: Due to advances in multimodal therapies, Primary Immunodeficiency diseases (PIDs) are becoming chronic diseases. Patients Therapeutic Education (ETP) is an education and support model for people living with chronic diseases and it promotes the quality of care. Health care delivery systems are quickly changing about quality of care. Treatment needs to provide coordinated care that is person rather than disease centred while preserving the quality of life. A personalised and coordinated follow-up that focuses on the individual's quality of daily living and early intervention is necessary. Patients with chronic conditions need to feel secure in the knowledge that their illnesses is closely monitored, to participate in their own health management more effectively, and need to feel that they had not been forgotten by their doctors and were taken good care of even outside the hospital/clinic.

Aim: This project aims to provide a freely accessible and dynamic web-based tool specific for PIDs patients ("MyVIP"). The goal of this "electronic-ETP" is to support the commitment of the patient to his/her care, using a personalised approach and direct consultation of his/her own PIDs doctor, in order to decrease the risk of complications and improve quality of life.

Results: A web-based app has been designed for patient and doctor real time consultation in order to have a promptly answer to the medical needs, through an instantaneous internet message system. This app has several modules: personal information, treatment tracking, knowledge centre, self-assessment questionnaires, interactive platform, and reminders. MyVIP contains schedules for therapies, upload and repository for medical documents. It provides longitudinal electronic medical records, updated therapies and follow up calendar.

The patient fills a web-page menu with multiple fields for new signs and symptoms that he/she is complaining for, uploading documents and images if necessary. The referring physician receive the message and answers directly to the patient. This specialised and safe tool would like to avoid the use of social networks for medical communications between patients and doctors. The usability and effectiveness of "MyVIP" will be evaluated in future studies.

The project was supported by the Italian PIDs Patients Association (AIP) that retains the copyrights of the tool.

POSTER 42 - ADVERSE EVENTS AND TOLERABILITY OF THE NEW HUMAN SUBCUTANEOUS IMMUNOGLOBULIN 20% IN PEDIATRIC PATIENTS (<18 YEARS OLD) WITH PRIMARY IMMUNODEFICIENCY DISEASES

AUTHORS

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Rationale: Combined safety and tolerability data from two phase 2/3 studies of CUVITRU (Ig20Gly), the new ready-to-use subcutaneous 20% solution, in patients <18 years with primary immunodeficiency diseases (PID) in Europe and North America are presented.

Methods: Children already receiving Ig replacement therapy (300-1000 mg/kg Q3-4W) for 3 or more months with serum IgG trough level >500 mg/dL were included. Patients received weekly Ig20Gly infusions at volumes and rates up to 60 mL/site and 60 mL/hr/site, respectively.

Results: Fifty pediatric patients aged <6 (n=6), 6-<12 (n=22), and 12-<18 (n=22) years with PID received 2624 Ig20Gly infusions for a mean treatment duration of 358.7, 371.6, and 375.6 days, respectively. No serious adverse events (AEs) that were deemed related to Ig20Gly occurred. All causally-related AEs were mild or moderate. Excluding one 13-year-old patient incurring 12/17 causally-related systemic AEs and 79/119 causally-related local AEs in this age group, causally-related systemic AE rates/infusion (excluding infections) were 0.010, 0.003, and 0.005, and causally-related local AE rates/infusion (excluding infections) were 0.000, 0.039, and 0.036, respectively, for age groups <6, 6-<12, and 12-<18 years. Median infusion volumes were 14.0 (6.5-26.0), 15.0 (6.4-43.0), and 30.0 (10.0-67.5) mL/site; median maximum infusion rates were 18.0 (2.5-40.0), 20.0 (4.4-80.0), and 30.0 (5.0-120.0) mL/hr/site; and median infusion durations were 0.75 (0.4-3.0), 0.78 (0.3-3.5), and 1.05 (0.3-3.5) hours, respectively for age groups <6, 6-<12, and 12-<18 years.

Conclusions: These data confirm that pediatric patients with PID in Europe and North America tolerated Ig20Gly well, at infusion rates up to 60 mL/hr/site and infusion volumes up to 60 mL/site with low rates of local and systemic AEs.

POSTER 43 - PRIMARY IMMUNODEFICIENCIES ON SMARTPHONE: A NEW APP FOR PID CLASSIFICATION

AUTHORS

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Primary immunodeficiencies comprise at least 300 genetically-defined single-gene inborn errors of immunity. The International Union of Immunological Societies (IUIS) Expert Committee on Primary Immunodeficiency meets every other year to update the classification of human primary immunodeficiencies (PIDs). In recent years, two forms of classification have been published by the IUIS PID expert committee: a complete catalog of known PIDs subdivided in 9 tables sharing a given pathogenesis, and a more user-friendly classification based on phenotype and laboratory results.

This last classification has been welcomed by the PID community and is now updated at the same rate as the original classification. Here, we present you a new application available on smartphone (Android or ios) displaying the 2015 phenotypic classification published by Bousfiha et al (J Clin Imm, 2015).

This application presents the 9 figures on your smartphone, so that you can get your PID diagnosis literally at the bedside. You can also access to the table including your suspected diagnosis by using the function "Search by disease name", or by clinical or laboratory features using the function "Search by manifestation". You can also find our guidelines to investigate a suspected case in 10 recommendations.

In addition, the application contains the age-related reference values for the analyses used in the tree-based decision-making process included in the figures (CBC, Ig levels and lymphocyte numeration). Moreover, three case studies are proposed to you to train yourself (part of the workshops proposed by ASID).

This application makes the IUIS classification available for anyone, anywhere and at anytime.

POSTER 44 - LONG-TERM SAFETY OF HYALURONIDASE-FACILITATED SUBCUTANEOUS IMMUNE GLOBULIN 10% IN PATIENTS WITH PRIMARY IMMUNODEFICIENCIES IN THE UNITED STATES: INTERIM RESULTS OF A POST-AUTHORIZATION SAFETY STUDY

AUTHORS

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Objective: HYQVIA, an immune globulin infusion 10% (human) with recombinant human hyaluronidase (rHuPH20) to facilitate subcutaneous immunoglobulin infusion (fSCIG), was approved as a replacement therapy in adults with primary immunodeficiencies (PID) in the United States. To acquire additional safety data on the long-term use of fSCIG and assess the prescribed treatment regimens and administration in routine clinical practice, a global post-authorization safety study was initiated in the United States in November 2015.

Design and Method: An ongoing prospective, non-interventional, open-label, uncontrolled, multicenter study to assess local and systemic effects of fSCIG in adult patients within a routine clinical setting, including evaluation for the presence of anti-rHuPH20 antibody titers on a voluntary basis. Patients aged ≥ 16 years with PID, who have been prescribed and/or have started fSCIG are eligible for enrollment. Patients are followed according to standard clinical practice and their treatment regimen is at the discretion of the treating physician.

Results: As of October 31, 2016, 50 patients had been enrolled at 13 US study sites and 28 patients who had ≥ 1 documented fSCIG treatment were included in this safety analysis; none of the 19 patients with immunogenicity data exhibited positive binding (titer of $\geq 1:160$) or neutralizing antibody titers. Seven patients reported 8 serious adverse events (AEs); none were considered treatment related. Two patients (7.1%) experienced non-serious causally-related local AEs, one each. Four patients (14.3%) experienced 9 non-serious systemic-related AEs.

Conclusion: This interim analysis of the prospectively-collected data of fSCIG use in routine clinical practice indicates that fSCIG treatment is well tolerated and has not been associated with positive binding or neutralizing anti-rHuPH20 antibody titers in patients with immunodeficiencies.

POSTER 45 - OUTCOME OF ASPERGILLUS INFECTIONS IN PATIENTS WITH CHRONIC GRANULOMATOUS DISEASE

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Chronic granulomatous disease (CGD) is a rare primary immunodeficiency due to mutations of the genes encoding protein subunits of the nicotinamide adenine dinucleotide phosphate (NADPH) complex. Affected patients are susceptible to severe life-threatening infections with *Staphylococcus aureus* and *Aspergillus* species. Although rigorous use of antibacterial and antifungal prophylaxis and interferon gamma have reduced bacterial infections, there is still a danger of life-threatening invasive fungal infections.

Herein, we report our successful experience in treatment of invasive *Aspergillus* infections in 5 CGD patients.

CGD was diagnosed by nitroblue tetrazolium or DHR activity assays and mutations determined by genotyping.

Aspergillus infections developed in five (1 female, 4 male) of 30 patients (16.6%) with CGD. The mean age of patients was 81.6 months (3-168 months). The mean age of CGD diagnosis was 10 months (1-30 months). Three patients were with X-linked form and had mutations in CYBB gene (gp91phox), where as 2 of them had autosomal form of the disease and had mutations at CYBA gene (p22phox). The mean duration between *Aspergillus* infections and the diagnosis of CGD was 27.8 months (1-63 months). Two patients who had been admitted to hospital with *Aspergillus* infection, diagnosed with CGD and they were not receiving prophylaxis but three of them were on trimethoprim-sulfamethoxazole, itraconazole and interferon-gamma prophylaxis.

The most frequent clinical presentation of infections were pulmonary. Bilateral diffuse nodules, suggestive of invasive aspergillosis were present in computed tomography. Septated hyaline hyphae were observed and the respiratory specimen culture of 3 patients yielded *Aspergillus fumigatus*. Two patients had suppurative lymphadenitis, which required percutaneous drainage. *Aspergillus flavus* and *Aspergillus fumigatus* were isolated in the cultures. All of the patients were unresponsive to previous broad spectrum intravenous antibiotics. Galactomannan antigens were all negative. Surgical drainage was performed in 2 of lymph node and 1 of the pulmonary aspergillosis. All of the patients made a remarkable clinical and radiologic recovery after mean 62 days of intravenous voriconazole treatment (21-120 days).

Invasive *Aspergillus* infections always should be considered whenever investigating a patient with CGD unresponsive to intravenous antibiotics. Regular follow-up visits are recommended for early diagnosis and aggressive treatment with an optimal outcome of fungal infections. Patients has to avoid from decayed organic and fungal spores.

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POSTER 48 - A CASE OF DOCK8 DEFICIENCY WITH PURE CUTANEOUS MANIFESTATIONS

AUTHORS

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Introduction: DOCK8 deficiency is an autosomal recessive form of hyper-IgE syndrome, a combined immunodeficiency disease. The majority of patients with DOCK8 deficiency harbor deletions in DOCK8 gene and due to the recessive pattern of inheritance most patients are born in consanguineous families. Clinical manifestations of patients with DOCK8 deficiency include eczema, skin abscesses, recurrent fungal and severe viral infections, recurrent respiratory infections, neurologic manifestations and susceptibility to autoimmune disorders, allergies and malignancies. Diagnosis is made by elevated IgE level and high eosinophil count and is confirmed by genetic analysis.

Presentation of the case: Herein, we report a 6-year-old Iranian girl from a non-consanguineous family who was referred to our center with pure cutaneous manifestations. The patient had a 2-year history of diffuse skin lesions described as eczema and furuncles infected with *Staphylococcus aureus*. The patient had not experienced any respiratory infections or neurological manifestations. She had eosinophil count of 1700, elevated serum IgE level to 5330 IU/ml and decreased CD16, CD56 and CD45 levels. Genetic analysis confirmed the diagnosis of DOCK8 deficiency.

Discussion: This patient's presentation is individual due to the mild clinical manifestations, not filling the clinical diagnostic criteria of hyper-IgE syndrome. Furthermore, the deletion mutation in DOCK8 gene of the patient is not inherited. Thus, we present a sporadic case of DOCK8 deficiency with pure cutaneous manifestations.

Conclusion: Although scoring systems have been designed for the diagnosis of hyper IgE syndrome, this case suggests that we may need to have a better understanding of the clinical and genetic features of this disease in order to make early diagnoses and develop therapeutic strategies for improving the prognosis of similar patients.



	Patient's data	Normal range	Unit
Cell count			
WBC	12970	4000-12000	/mm ³
Eosinophil	1700 (13.1)	(1-4%)	/mm ³ (%)
Lymphocyte	4930	(29-65%)	/mm ³ (%)
Neutrophil	5620	(30-60%)	/mm ³ (%)
Platelet	331000	200000-490000	/mm ³
Ig concentration			
IgG	926	462-1680	mg/dL
IgA	86	33-202	mg/dL
IgM	173	38-251	mg/dL
IgE	5330	<144	IU/ml
Immunophenotyping			
CD3	77	60-77.5	%
CD4	42	31-47.5	%
CD8	20	16-27	%
CD4/CD8 ratio	2.1	1.3-3	
CD19	16	13-29	%
CD20	18	13-29	%
CD16	3.5	4.5-16	%
CD56	3.5	5-20	%

POSTER 49 - INFECTIONS, AUTOIMMUNITY AND MALIGNANCIES IN WISKOTT ALDRICH SYNDROME: A SINGLE CENTRE EXPERIENCE FROM NORTH-WEST INDIA

AUTHORS

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Introduction: Wiskott Aldrich syndrome (WAS) is a primary immunodeficiency with X-linked recessive inheritance characterized by triad of thrombocytopenia with microplatelets, eczema and recurrent infections. Apart from infections, patients with WAS can have myriad of manifestations. We herein describe various infections, autoimmune and malignant complications in our cohort of patients with WAS.

Aim & objectives: To describe the profile of various infections, autoimmunity and malignancies in a cohort of WAS from Pediatric Immunodeficiency Clinic, Advanced Pediatrics Centre, Postgraduate Institute of Medical Education and Research (PGIMER), Chandigarh, a tertiary care referral institute in North-West India

Result: Total 46 cases of WAS were diagnosed between 1995- 2017. The median age at diagnosis was 20 months (IQR, 6.75- 55.5). Pneumonia was the most common (22/46, 43%) infection followed by otitis media (15/46, 33%). Other less common infections were skin and soft tissue infections (4/46, 9%), meningitis (3/46, 6.5%) osteomyelitis and septic arthritis (3/46, 6.5%), lymphadenitis (4/46, 8.7%), molluscum (2/46, 4.4%), and varicella zoster (1/46, 2%). Staphylococcus aureus was the most common organism isolated (6/46, 13%) followed by Cytomegalovirus (4/46, 8.5%). Other less common organisms were Pseudomonas aeruginosa, Pseudomonas oryzihabitans, Candida sp and streptococcus species. Autoimmune manifestation were present in 9/46 patients (19.5 %). Most common autoimmune manifestation was skin vasculitis (6/46, 13% patients) followed by autoimmune hemolytic anaemia (AIHA) (5/46, 11%) and anti thyroid antibodies (2/46, 4%). Primary Sclerosing cholangitis, anti-nuclear antibodies and Guillain–Barré syndrome (GBS) was seen in one patient each. All 9 patients with autoimmune manifestations had history of eczema and recurrent infections. Patients with AIHA, primary sclerosing cholangitis, SLE like presentation and skin vasculitis were given oral prednisolone; patients with hypothyroidism were given thyroxin replacement and patient with GBS was managed with intravenous immunoglobulin (at 2 gm/kg). One patient developed CNS lymphoma at 3 years of age.

Discussion: Pneumonia was common infection in our cohort. S. aureus and CMV were most common organisms isolated. Skin vasculitis was the most common autoimmune manifestation in our cohort of patients. This is in contrast to previously reported series where autoimmune hemolytic anaemia and neutropenia were found to be most common manifestations.

POSTER 53 - DIAGNOSTICS OF PRIMARY ANTIBODY DEFICIENCIES THROUGH TARGETED NEXT GENERATION SEQUENCING PANEL

AUTHORS

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Primary Antibody Deficiencies (PAD), are the most common form of primary immunodeficiencies. PADs are characterized by a significant reduction of immunoglobulins and recurrent infections due to the abnormal development or function of B-cells. The diversity of genetics causes and clinical features is mostly responsible for the delayed diagnosis of PAD patients. More than 20 genes have been associated with PAD and the diagnostic approach appears to laborious, inefficient and time consuming, however the advantage of next generation sequencing (NGS) technologies has given the possibility to investigate multiple genes simultaneously, to provide opportunities for diagnosing patients with complex disorders of the immune system such as PAD. Here we designed a custom-made panel covering 22 known genes related with PAD and studied 64 cases (19 Agammaglobulemia, 49 CVID, 3 HlgM) by Illumina MiSeq platform. All the variations were validated by Sanger Sequencing and family segregations were confirmed if possible. In the preliminary analysis, we have identified PAD related variation in 18% of the patients (12/64) in BTK (n=4), CD19 (n=1), CD40LG (n=1), IGHM (n=1), ICOS (n=1), TNFRSF13B (n=1), TCF3 (n=2), PIK3R1 (n=1) genes. Five out of these 12 variations were novel. Further sequence analysis and the validations of other detected genes are ongoing both in proband and parents. Here we demonstrated that NGS technologies represent a cost-effective and rapid genetic methods for the evaluation of complex PAD.

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POSTER 54 - A CASE REPORT ON GAIN-OF-FUNCTION MUTATION IN STAT1 GENE WITH CHRONIC MUCOCUTANEOUS CANDIDIASIS FROM INDIA

AUTHORS

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Chronic mucocutaneous candidiasis (CMC) is a primary immunodeficiency disease with susceptibility to infection of the skin, nails, and mucous membranes with *Candida* species. Association of Autosomal Dominant - Chronic mucocutaneous candidiasis (AD-CMC) and sporadic CMC with STAT1 gene mutation is well known, resulting in impaired IL-12 and IL-23 mediated Th1 and Th17 responses. Gain-of-function mutation in the coiled-coil domain and DNA binding domain of STAT1 results in hyperphosphorylation of STAT1 (Y701). We report a case of a 3 year old male child with recurrent scalp and oral candidiasis since early infancy with verrucous lesions in the penis. Patient showed a reduced (0.3%) Th17 cells (CD4+ IL17A+ IFN gamma-) in PMA-ionomycin stimulated peripheral blood mononuclear cells (normal control 1.1%). STAT1 was found to be hyperphosphorylated in the patient 87% (MFI index- 19.8) as compared to normal control 44% (MFI index- 2.7), whereas, STAT3 phosphorylation was found to be normal 52% (MFI index-9.06) control 45% , (MFI index- 9.1) upon stimulation with 100ng IL-6 for 15 minutes. Considering these clinical and laboratory findings STAT1 gene sequencing was performed which revealed a transition mutation at position 24120 of genomic DNA (g.24120 c.874 G>A p.D292N). Polyphen score was 0.784 (possibly damaging) and SIFT score was 0.08 (tolerated). This mutation was found to be already reported in literature.

POSTER 55 - CHRONIC GRANULOMATOUS DISEASE PROFILE IN CHILDREN FROM A TERTIARY CARE INSTITUTION IN NORTH INDIA

AUTHORS

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Introduction: Chronic Granulomatous Disease (CGD) is a rare phagocytic disorder due to defect in NADPH oxidase complex. It is characterized by recurrent infections with catalase positive organisms. Data on causative microorganisms helps in early initiation of antimicrobials for this life threatening disease.

Objective: To analyze the profile of CGD in children.

Design and Methods: It is a retrospective study. Forty eight children diagnosed with CGD during the period from August 1993 to April 2017 in Primary Immunodeficiency Clinic, Advanced Pediatrics Centre, PGIMER, Chandigarh, were included in the study. Diagnosis of CGD was based on an abnormal granulocyte oxidative burst evaluated by either nitroblue tetrazolium test (NBT) or flow cytometry based dihydrorhodamine (DHR) 123 assay or both. Twenty eight of the forty eight cases had genetic confirmation of diagnosis. Case records were analyzed for patient demographic characteristics, infection pattern and microbiological profile.

Results: 38 (79.16%) patients were male. Earliest age of disease manifestation noted was 14 days and one patient had first manifestation of this disease at the age of 20 years. In 7 (14.58%) patients CGD was diagnosed at first infection. X-linked CGD was found in 18 (37.5%) and autosomal recessive CGD in 30 (62.5 %) patients. Lung was the most common site of first infection (39.13%), followed by lymph nodes (30.43%), skin & subcutaneous tissue (19.56%). At least one organism was isolated in 31 (64.58%) patients. The commonest organism isolated was *Aspergillus* (45.16%) followed by *Staphylococcus aureus* (16.12%), *klebsiella* (9.67%), *Burkholderia cepacia* (6.45%) and *candida* (6.45%). Pattern of infections was similar in X-linked recessive and autosomal recessive groups; however, X-linked CGD had an earlier age of onset and more frequent episodes of infections.

Conclusions: Autosomal recessive form of CGD was found to be more common. Fungal pneumonia was the most common infection at diagnosis of CGD. Patients with X-linked CGD had more frequent infections.

POSTER 57 - ABDOMINAL AORTIC COARCTATION IN A DEDICATOR OF CYTOKINESIS 8 PATIENT

AUTHORS

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Objective: Dedicator of cytokinesis 8 (DOCK8) deficiency is a rare primary immunodeficiency, multisystem disorder with recurrent skin and lung infections along with high serum IgE and eosinophilia. Vasculitis is seen rarely in some of these patients. We report a case with a large DOCK8 gene deletion along with an abdominal aortic coarctation (CoA); a narrowing of the aorta. Association of CoA in DOCK8 deficiency was not reported previously whilst vasculitis could be as a possible sign in these patients.

Design and method: A 9-year-old girl born to consanguineous parents was referred to Immunology, Asthma and Allergy Research Institute (IAARI) five years ago due to recurrent hospitalization upon prolonged pneumonia, recurrent otitis media, herpetic gingivo-osteomatitis, several molluscum contagiosum and lung tuberculosis history.

Results: The screening and advanced immunologic tests were done which resulted in leukocytosis with eosinophilia and high IgE level, decreased IgM and low specific antibody response. In addition, genetic tests revealed a large deletion in DOCK8 gene, exons 1 to 27. The patient is candidate for hematopoietic stem cell transplantation (HSCT) as a definite therapeutic option and we are looking for a matched donor. The Immunoglobulin replacement was administrated since two years ago. In the patient's follow-up, hypertension was detected since three months ago. By evaluating, abdominal coarctation was diagnosed as the cause of hypertension which was corrected by stent replacement. Consequently, due to mentioned treatment, blood pressure was normalized.

Conclusions: CoA pathogenesis may be due to vasculitis or a post inflammatory process and investigation approach must be done for diagnosis. Up to our knowledge, this case is the first DOCK8 large deletion reported patient which was in association with abdominal CoA. Further workup on such DOCK8 patients is needed to give more clues on vasculitis suspected DOCK8 patients.

POSTER 60 - BONE INFECTION IN CHRONIC GRANULOMATOUS DISEASE: EXPERIENCE AT OUR CENTER, PGIMER, INDIA

AUTHORS

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Background: CGD is phagocyte disorder due to defective oxidative burst, which predisposes to infections by catalase positive microorganisms. Though suppurative adenitis, persistent pneumonia and deep abscesses are common manifestations, bone infections can also manifest in CGD that require prolonged antimicrobials and antifungals. The indolent spread of fungus from lung to ribs and vertebra often results in chest-wall and vertebral deformities. Bone infections constitute approximately 25% cases of CGD.

Objective: To study the clinical profile of bone infections in CGD.

Design and method: Case records of 52 CGD children followed-up at our centre (1993 to 2017), were retrieved and analyzed retrospectively. Diagnosis of CGD was based on abnormal granulocyte oxidative burst, evaluated by either NBT or DHR-123 assay. Genetic confirmation of diagnosis was available for 32 cases. CBC, immunoglobulin profile, blood-cultures, chest X-ray and abdomen ultrasonogram were performed in almost all cases. CT, MRI, FNA from tissues and body fluid cultures were done in selected cases.

Results: Six (6/52) patients with bone infections were identified (11.5%). Male female ratio was 5:1. Three patients had XL-CGD and 3 had AR-CGD (2-NCF1 defect). Three XL-CGD boys had contiguous spread of fungal infection from lung parenchyma to ribs. One XL-CGD boy had spread of *Aspergillus* spp. from lungs to rib and thoracic vertebra at 4-years of age, resulting in rib deformities and kyphosis, cleared with 6 months of oral voriconazole. Another 2-year-old boy had spread of *Mucor* spp. to ribs from vertebra and succumbed to severe pneumonia. The third XL-CGD boy had spread of *Aspergillus flavus* from lungs to ribs requiring surgical resection of 2 ribs for clearance of infection. One patient with NCF1 defect had osteitis of right-tarsal bones at age of 15-years, improved with 3-months of oral cloxacillin and cefixime. Another patient with NCF1 defect (10-years-old) had a left-elbow osteomyelitis and pus-culture from the intra-osseous-abscess revealed *Aspergillus terreus*. He improved with 4-weeks of IV amphotericin. A 11-year-old girl with AR-CGD had rib and vertebral osteitis, resulted from the spread of infection from lungs, improved with a prolonged IV amphotericin.

Conclusion: Majority of the bone infections (5/6) were due to fungus (3-*Aspergillus*, 1-*Mucor*, 1-probable *Aspergillus*) and four of them had contiguous spread from lungs to ribs. CT helped in the identification of rib and vertebral osteitis in all the cases, even when there is no clinical or X-ray evidence of rib involvement. The bone involvement needed prolonged antifungal therapy to clear the infection.

POSTER 62 - SECOND-TIER NEXT GENERATION SEQUENCING IN NEWBORN SCREENING PROVIDES RAPID MOLECULAR DIAGNOSTICS OF SEVERE COMBINED IMMUNODEFICIENCY

AUTHORS

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Severe combined immunodeficiency (SCID) and other T cell lymphopenias are identified by newborn screening (NBS) measuring T cell excision circles (TRECs) in dry blood spot DNA. Second tier next generation sequencing (NGS) on the same dry blood spot DNA was introduced as part of our prospective pilot research project.

Among our 15,000 TREC-screened newborns, 3 individuals with SCID having disease-causing variants in IL2RG, RAG2, and RMRP, were identified within 2-3 days after TRECs measured low <10/μL, utilizing NGS with Ion-PGM-TM PID-panel on same DNA extract. TRECs <20/μL were observed in 3 with congenital heart defects, 4 intestinal malformations, 3 premature with BW <1000g, and 2 others. Four were PID-panel tested without relevant findings, and 7 showed normalization of TRECs.

For three additional patients, born outside the pilot screening area, TREC-testing was requested at 3-6 months of age due to infections and poor growth. Low TRECs detected, and one patient surprisingly had a IKZF1-variant p.Asn159Ser, recently reported in a Japanese child with immunodeficiency and lymphoblastic leukemia. Directed by this gene finding, our patient underwent transplantation, and is doing well.

NGS integrated in the NBS algorithm and hospital service, rapidly delineate the specific molecular diagnosis, provide information useful for therapy and follow-up, and may reduce the number of recalls and repeated sampling.

POSTER 63 - RECOMBINANT HUMAN HYALURONIDASE FACILITATED SUBCUTANEOUS IMMUNOGLOBULIN TREATMENT IN ADULT PATIENTS WITH PRIMARY IMMUNODEFICIENCIES: A POLISH SINGLE-CENTER EXPERIENCE

AUTHORS

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Objective: Human subcutaneous immunoglobulin (SCIG) is an established replacement therapy for patients with primary immunodeficiency disorders (PIDs). Recombinant human hyaluronidase (Hy) is a spreading factor that temporarily digests hyaluronan in the skin interstitium enabling large volumes of drug solutions to be infused and absorbed subcutaneously. IGHy is a new combination product whereby Hy is injected subcutaneously, followed by human immunoglobulin 10%. IGHy can be administered at a reduced frequency compared with non-facilitated subcutaneous injection of human immunoglobulin, and with a lower frequency of infusion reactions than with intravenous administration. The aim of our study was to assess the efficacy, safety and tolerability IGHy in adults with PIDs in a single Polish Immunology Department.

Design and method: Eleven patients with PIDs were included in the study. IGHy was administered between January 2017 and June 2017. Nine patients were previously treated with 1.6% SCIG and 2 were newly diagnosed, treatment-naïve.

Results: During observational period one serious bacterial infection, requiring 7-day antibiotic therapy was noted, and three patients were suffering from mild viral rhinitis. In patients in whom the IGHy dose was maintained or reduced compared to weekly SCIG, the median trough serum IgG level was not significantly different (972 vs. 954 mg/dl, $p=0.923$). Among 61 infusions with IGHy, there were reported only 3 local treatment-related adverse events (AE, i.e. infusion-site reaction – 0.04/infusion). No serious AE was reported. Of 61 IGHy infusions, 96% required no change of administration due to AE. 100% of patients or their caregivers expressed preference for IGHy compared with Ig administered intravenously or Ig administered subcutaneously every week.

Conclusions: This observational study, with maximum duration of 6 months, is the only available report of IGHy replacement therapy in adults with primary immunodeficiency diseases. We revealed low infection rate and mild local reactions along with well-tolerated infusions given in a single site.

POSTER 64 - IN SILICO ANALYSIS OF SINGLE NUCLEOTIDE POLYMORPHISM (SNPS) IN HUMAN RAG 1&RAG2 GENES OF SEVERE COMBINED IMMUNODEFICIENCY FROM FUNCTIONAL ANALYSIS TO POLYMORPHISMS IN MICRORNA

AUTHORS

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Severe combined immunodeficiency (SCID) is an inherited Primary immunodeficiency PID, which is characterized by the absence or dysfunction of T lymphocytes. Defects in RAG1 and RAG2 are known to cause a T-B-NK+ form of SCID. Recombinase activating genes RAG1 and RAG2 (OMIM 179615,179616 respectively) are expressed exclusively in lymphocytes and mediate the creation of double-strand. DNA breaks at the sites of recombination and in signal sequences during T- and B- cell receptor gene rearrangement. This study was focused on the effect of nonsynonymous single nucleotide polymorphisms in the function and structure of RAG1& RAG2 genes using in silico analysis. Only nsSNPs and 3'UTR SNPs were selected for computational analysis. Predictions of deleterious nsSNPs were performed by bioinformatics software. Five damaging nsSNPs (rs112047157, rs61758790, rs4151032, rs61752933, rs75591129) were predicted in RAG1 and two damaging nsSNPs (rs112927992, rs17852002) in RAG2, all of this nsSNPs found on domain that important in binding and mutation effect in its protein function. We hope to provide more information that needed to help researchers to do further study in SCID especially in our country where consanguineous marriage is common.

Keywords: severe combined immunodeficiency (SCID), primary immunodeficiency (PID), T lymphocytes, RAG1&2, non-synonymous Single Nucleotide Polymorphisms (nsSNP)

POSTER 66 - THE HYPER IG-E SYNDROME (HIES)

AUTHORS

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Introduction: The hyper Ig-E syndrome (HIES) is left to rare primary immunodeficiencies, characterized by diverse clinical manifestations, particularly sensitivity to staph infections and fungal as well as a heterogeneous genetic origin; the classic form of HIES is transmitted as an autosomal dominant manner [1] and is characterized by the following clinical picture: Rash, recurrent pneumonia, facial features (facial asymmetry, Nose Broad, Sunken eyes, prominent Front, rough appearance with the size exaggerated pores of the facial skin), dental anomalies, cranial abnormalities. HIES exhibits against sensitivity to certain bacteria infections mainly Staphylococcus.

AIMS: This study is about the genetic profile of hyper IgE syndrome in Morocco and the highlight of the STAT3 gene mutations.

Material and Methods: This is 20 cases (patients) who present themselves at the children's hospital -CHU Rabat each Thursday during medical consultations at the P1 pediatrics or already hospitalized. During consultations, patients are questioned by the gate of the score and physically examined to validate the presence of characteristic clinical presentation and other laboratory tests and x-rays required to confirm the diagnosis (some patients already have a clinical record of others not). DNA extraction, PCR and sequencing techniques are used in genetic analysis.

Results: Patients with a score <20, does not show the hyper IgE syndrome, those whose score is between 20-40 Revenue Is this are patients with this syndrome, a score > 40 indicates severe form of this syndrome. Among the prospective results is the discovery of the mutation of STAT3 in a sporadic way or family transmission and the HOT SPOT region with the Moroccan population by comparing it with other DNA profiles.

Discussion Hyper IgE syndromes were first described in 1966, and until recently remained one of the few primary immunodeficiencies without a genetic etiology. However, now two genetic defects have been described: STAT3 mutations act in a dominant negative manner to cause of autosomal dominant HIES, and Tyk2 deficiency acts in a recessive manner to cause one of the cases of AR-HIES. We now need to focus on understanding the pathogenesis of these complicated diseases. Understanding how STAT3 deficiency leads to the many facets of this disease will hopefully help us understand diseases that are more common, such as idiopathic scoliosis, atopic dermatitis, staphylococcal skin abscesses, and the coronary artery aneurysms of Kawasaki disease. Understanding the pathogenesis of STAT3 deficiency will allow us to create better therapies to prevent the morbidity and mortality.

POSTER 68 - FEW ADRS WHEN SWITCHING PRIMARY IMMUNE DEFICIENCY PATIENTS TO THE NEW IVIG PANZYGA®

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Background: IVIG and SCIG represent the standard therapy for many types of primary immune deficiencies (PID), secondary immune deficiencies (SID) and some autoimmune diseases. Although IVIG solutions are in general well tolerated, several studies show that differences in IgG products lead to differences in tolerability and that switching IgG preparations triggers an increase in adverse drug reactions.

Methods: A post hoc-analysis of the data obtained during study GAM-01 and subsequent extension study GAM-03 on the efficacy, pharmacokinetics and safety of a new intravenous Immunoglobulin (panzyga®) in PID patients was performed. 51 patients were switched from their previous IVIG solution to treatment with panzyga®. Initial infusion rate was 0.01 mL/kg/min (60 mg/kg/h). Infusion rate could be increased to max 0.08 mL/kg/min (480 mg/kg/h) in a predefined pattern.

Results: Only 2 out of 51 (4%) patients experienced a treatment related adverse event during the first infusion after product switch from their previous IVIG to panzyga®. After 3 panzyga® infusions a total of 5 patients (10%) had experienced mild ADRs. 4 of these 5 patients experienced further ADRs during the study suggesting that they might be generally prone to reactions.

Conclusion: Several authors reported an increased ADR rate in their patients after being switched from one mostly well tolerated product to a different one. Ameratunga observed ADRs in 14% of PID patients after switch, Dashti-Khavidaki noted ADRs related to 34 IVIG infusions after switch. In the present study a switch from any IVIG solution to panzyga® triggered a low number of treatment related AEs.

Ameratunga R, Sinclair J, Kolbe J. Increased risk of adverse events when changing intravenous immunoglobulin preparations. Clin Exp Immunol 2004;136:111–3.

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POSTER 69 - ASSESSMENT OF BONE MINERALIZATION IN SCN PATIENTS WITH HAX1 OR ELANE MUTATIONS

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Introduction: Severe congenital neutropenia (SCN) is a heterogeneous group of disorders characterized by a severe decrease in the number of blood neutrophils ($<0.5 \times 10^9/l$), and a maturation arrest of bone marrow progenitor cells mainly at the promyelocyte/myeloid stage. A high incidence of decreased bone mineral density (BMD) has been described in patients with SCN. There is no study to evaluate the difference in terms of bone mineral density in SCN patients with HAX-1 or ELANE mutations.

Objectives: We aimed to evaluate BMD and biochemical serum markers of bone metabolism in SCN patients with HAX1 and ELANE mutations. Genetic mutations of the patients were obtained from the file records.

Methods: Serum calcium (Ca), phosphate (P), alkaline phosphatase (ALP), magnesium (Mg), parathyroid hormone (PTH), 25-hydroxyvitamin D and BMD of the patients with SCN were evaluated.

Results: Eleven patients with SCN were included in the study. The female / male ratio of the patients was 1.7 (7/4). HAX1 mutation was detected in 8 patients, while 3 patients had ELA2 mutation. Median age was 15 years (min: 4, max: 26 years). Serum Ca, Mg, P and ALP levels were normal in all patients. Mean serum 25 OH vitamine D levels was 19.4 ± 9 microgram /L. The 25-OH vitamin D levels were found to be low in 3 of 8 patients with HAX1 mutation and in 2 of 3 patients with ELA2 mutation. The mean PTH level was 39.7 ± 20.2 pg/mL in all groups. Only one patient in HAX1 mutation group had high level of PTH associated with osteopenia while patients with ELA2 mutations had normal limits of PTH. Reduced bone mineral density was detected in 7/8 of patients with HAX1 mutation. Osteoporosis (z score <-2) was found in 4/8 and osteopenia (z score <-1) in 3/8 of them. Osteoporosis was detected only in 1/3 of patients with ELA2 mutation,

Discussion: Osteoporosis is an important comorbidity in SCN patients probably due to increased bone resorption. After being defined the genetic mutations of SCN, there is no discriminative data regarding the difference of bone mineralization in patients with ELA2 or Hax1 mutations. Our study implied us that reduced bone mineral density in patients with HAX1 deficiency were more likely compared with patients with EA2 deficiency. Further studies involving more patients are needed to clarify the status of bone mineralization in Hax1 or ELA2 deficiency.

POSTER 70 - A NEW CASE OF POLYGLANDULAR AUTOIMMUNE SYNDROME TYPE IIIC WITH PRIMARY ANTIBODY FAILURE

AUTHORS

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Primary antibody deficiency syndromes are a rare group of disorders present at any age, with complex polygenic disorders. We report the forth case of polyglandular autoimmune syndrome (PAS) type IIIC worldwide with complex clinical features and no family history of endocrine disorders or primary immunodeficiencies.

Our patient was diagnosed with PAS type IIIC due to the presence of autoimmune thyroiditis, autoimmune alopecia and primary ovarian insufficiency, associated with lymphoproliferative disease and primary antibody failure. Treatment included lifelong intravenous immunoglobulins, supplements and antibiotics. The clinical complexity and rare occurrence made it challenging to determine a diagnosis and provide better treatment for the patient.

Therefore, the current case provides an insight of the challenges involved in order to determine primary antibody failure signs in the presence of PAS.

POSTER 71 - TREATMENT PREFERENCE ON THE NEW SUBCUTANEOUS IMMUNOGLOBULIN 20% TREATMENT IN PATIENTS WITH PRIMARY IMMUNODEFICIENCY DISEASES IN EUROPE

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Rationale: Subcutaneous immunoglobulin (SCIG) offers an opportunity for patients with primary immunodeficiency diseases (PID) to self-infuse at home, potentially reducing treatment burden and improving satisfaction. This analysis assessed treatment preference with CUVITRU (Ig20Gly), the new SCIG 20%.

Methods: Forty-eight European patients with PID treated with intravenous immunoglobulin (IVIG) 10% for 3 months followed by Ig20Gly for 12 or more months within a phase 2/3 study were assessed for treatment preference with a questionnaire. Questionnaires were administered at the end of the study to evaluate preferences about treatment aspects using a 5-point Likert scale and included questions regarding patients' preferred location of therapy and preference to continue Ig20Gly. Questionnaires were completed by the caregiver/parent (13 years or younger) or patient (14 years or older).

Results: Overall, 88% of all patients stated that they would prefer to receive Ig20Gly rather than other Ig treatments with 84% of younger (13 years or younger) and 91% of older (14 years or older) patients preferring Ig20Gly. Home infusion was preferred by 88% of all patients. The aspects of treatment with the highest proportion of 'like'/'like very much' responses were "ability to fit treatment into my own schedule" (96%) and "ability to self-administer without medical supervision" (94%).

Conclusions: At the end of the study, both children and adults preferred to continue to receive Ig treatment using Ig-20Gly—overall, the vast majority (88%) of patients indicated they preferred the investigational therapy.

POSTER 72 - TREATMENT SATISFACTION DURING PIVOTAL CLINICAL TRIALS WITH THE NEW SUBCUTANEOUS IMMUNOGLOBULIN 20% IN PATIENTS WITH PRIMARY IMMUNODEFICIENCY DISEASES PREVIOUSLY TREATED WITH INTRAVEOUS IMMUNOGLOBULIN

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Rationale: Treatment satisfaction (TS) is an important consideration for immunoglobulin (Ig) treatment. This analysis compared TS during the intravenous immunoglobulin (IVIG) and CUVITRU (Ig20Gly; the new ready-to-use 20% subcutaneous immunoglobulin 20%), treatment periods of two pivotal phase 2/3 studies (North America [NA] and European [EU]) conducted in patients with primary immunodeficiency diseases (PID) treated with IVIG therapy prior to study entry.

Methods: During the pivotal studies, patients were treated with Ig20Gly for ~12 months following 3 months of treatment with IVIG. TS was assessed using the Life Quality Index (LQI; higher scores indicate greater satisfaction) instrument at the end of the IVIG period and after the completion of the Ig20Gly period among patients entering the studies from IVIG therapy. Wilcoxon Signed Rank test evaluated statistical significance.

Results: Patients reported significant improvement in the Therapy Setting LQI domain relative to the IVIG therapy period after treatment with Ig20Gly, improving from 17.5 to 20.0 ($P < 0.001$; $n = 46$) and 18.0 to 21.0 ($P = 0.002$; $n = 30$) in the NA and EU study, respectively. Patients also reported improvements during the Ig20Gly period compared to the prior IVIG period in the Treatment Interference LQI domain in the NA study (36.5 vs 33.5; $P = 0.049$; $n = 46$) and the EU study (39.0 vs 34.5; $P = 0.016$; $n = 30$).

Conclusions: After 12 months on Ig20Gly, patients reported improvements in treatment satisfaction in the Treatment Interference and Therapy Setting domains compared with IVIG. Clinicians may consider improved satisfaction in offering Ig20Gly to patients with PID currently treated with IVIG.

POSTER 75 - RAPID PUSH INFUSION IS A WELL-TOLERATED, COST-EFFECTIVE ADDITIONAL METHOD FOR SUBCUTANEOUS SELF-INJECTIONS OF GAMMANORM®: A RANDOMIZED CROSS-OVER TRIAL IN ADULT PID PATIENTS

AUTHORS

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Objective: Primary immunodeficiency (PID) requires lifelong immunoglobulin replacement therapy (IgRT) to prevent infections. IgRT may be administered subcutaneously once a week by a pump. Rapid push is used for subcutaneous infusions of small volumes of Ig every other day. By pushing the plunger of a syringe the patient adapts the flow rate to his own comfort.

Study "Gamexpress" aimed to compare the impact of pump vs. rapid push infusions on patient's life quality index, satisfaction, quality of life and cost-effectiveness.

Design and Methods: "Gamexpress" was a randomized, cross-over, non-inferiority study conducted in adult PID patients accustomed to weekly subcutaneous immunoglobulin (SCIg, gammanorm® 16.5%) infusions by pump at home. Patients either started with pump or syringe (rapid push) for 3 months followed by cross-over to the alternate infusion modality for another 3 months. Primary endpoint was the PID-LQI factor I (PID-Life Quality Index: treatment interference).

Results: Thirty adult patients entered the study of which 28 completed the two crossover periods. While the non-inferiority ratio was set high at 90%, this study showed a PID-LQI factor 1 ratio of 89.4% (95% CI [80.9%; 99.9%]). However, no statistically significant differences were found for other LQI components, satisfaction (TSQM), or quality of life (SF-36v2). Even 8 patients (28.8%) declared to prefer rapid push, while 19 (67.9%) preferred pump; for 1 patient (3.6%) data was missing. Infusions were well tolerated employing both devices. Of the rapid push infusions, 67.2% led to local reactions versus 71.8% of pump infusions ($p=0.11$). Rapid push and pump both achieved similar IgG trough levels, and no difference was found in the rate of infections. Rapid push was cost-effective with 79% of administration cost saved compared to pump.

Discussion: Some patients expressed a preference for the rapid push as already demonstrated In another study enrolling 104 patients (Shapiro J Clin immunol 2010). In Shapiro's study, the majority (71%) selected rapid push rather than pump as preferred method. Of note: two thirds of these patients were below 18 years.

Conclusion: Since IgRT is a lifelong treatment in PID patients, individualization of treatment to optimally please the patients' different needs is of paramount importance. Rapid push is a new administration method that complements the physician's armamentarium and may be the preferred administration mode for many PID patients. Rapid push infusion is significantly more cost efficient than pump infusions

POSTER 76 - PRIMARY IMMUNODEFICIENCY DISORDERS: AWARENESS SURVEY OF PHYSICIANS IN IRAN

AUTHORS

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Background: Primary immunodeficiency disorders (PID) are a group of hereditary disorders characterized by an increased susceptibility to severe and recurrent infections, autoimmunity, lymphoproliferative disorders, and malignancies if not diagnosed and treated appropriately.

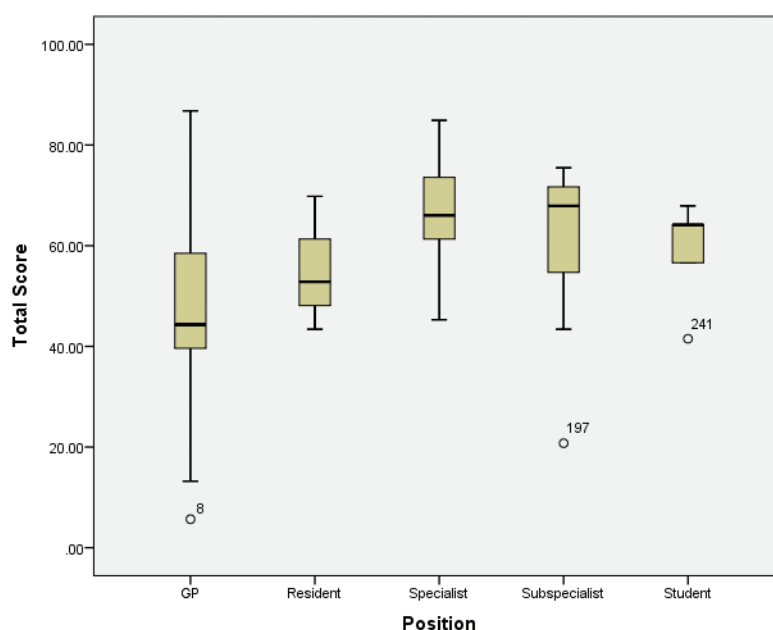
Many patients with PID are undiagnosed, underdiagnosed, or misdiagnosed due to lack of physicians' awareness, which leads to increase in morbidity and mortality.

Method: In this study, 9 states of Iran were chosen for evaluating physicians' awareness of PID. The Population study was pediatricians (specialties and subspecialties), pediatric residents and general practitioners. A valid and reliable questionnaire was prepared for awareness scoring assessment.

Results: among 794 physicians, 466 general practitioners (GP), 90 pediatric residents, 124 pediatric specialists, and 20 pediatric subspecialists were included in this study. Mean of the age of participants was 40.96 ± 10.63 years (range from 24 to 91). The mean period of practicing medicine was 12 ± 9.53 years. Mean total knowledge score of participants was 51.30 with a standard deviation of 18.76. 161 participants (20.4%) answered more than 2/3 of all questions correctly. Mean scores in the management of PIDs was 66.25 ± 54.55 , followed by laboratory findings as 49.57 ± 25.07 , clinical symptoms as 54.42 ± 17.85 and associated syndromes as 42.32 ± 28.57 .

Conclusion: This survey demonstrates that there is a lack of both the knowledge and practice of pediatricians in the field of PID in Iran. Implementation of strategies to raise pediatricians' awareness and assure the earliest diagnosis, appropriate treatment, and proper care management is critical.

Keywords: Primary immunodeficiency, Physician, Survey, Awareness



POSTER 77 - CHRONIC GRANULOMATOUS DISEASE PROFILE IN CHILDREN FROM A TERTIARY CARE INSTITUTION IN NORTH INDIA

AUTHORS

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Introduction: Chronic Granulomatous Disease (CGD) is a rare phagocytic disorder due to defect in NADPH oxidase complex. It is characterized by recurrent infections with catalase positive organisms. Data on causative microorganisms helps in early initiation of antimicrobials for this life threatening disease.

Objective: To analyze the profile of CGD in children.

Design and Methods: It is a retrospective study. Forty eight children, diagnosed with CGD during the period from August 1993 to April 2017 in Primary Immunodeficiency Clinic, Advanced Pediatrics Centre, PGIMER, Chandigarh, were included in the study. Diagnosis of CGD was based on an abnormal granulocyte oxidative burst evaluated by either nitroblue tetrazolium test (NBT) or flow cytometry based dihydrorhodamine (DHR) 123 assay or both. Twenty eight of the forty eight cases had genetic confirmation of diagnosis. Case records were analyzed for patient demographic characteristics, infection pattern and microbiological profile.

Results: 38 (79.16%) patients were male. Earliest age of disease manifestation noted was 14 days and one patient had first manifestation of this disease at the age of 20 years. In 7 (14.58%) patients CGD was diagnosed at first infection. X-linked CGD was found in 18 (37.5%) and autosomal recessive CGD in 30 (62.5 %) patients. Lung was the most common site of first infection (39.13%), followed by lymph nodes (30.43%), skin and subcutaneous tissue (19.56%). At least one organism was isolated in 31 (64.58%) patients. The commonest organism isolated was *Aspergillus* (45.16%) followed by *Staphylococcus aureus* (16.12%), *klebsiella* (9.67%), *Burkholderia cepacia* (6.45%) and *candida* (6.45%). Pattern of infections was similar in X-linked recessive and autosomal recessive groups; however, X-linked CGD had an earlier age of onset and more frequent episodes of infections.

Conclusions: Autosomal recessive form of CGD was found to be more common. Fungal pneumonia was the most common infection at diagnosis of CGD. Patients with X-linked CGD had more frequent infections.

POSTER 78 - ETHICS OF COMPENSATED PLASMA DONATION

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Objective: Nearly 70% of the plasma-derived medicinal products (PDMPs) are derived from donors who are provided monetary compensation. In 2010, an International Consensus Conference on Risk-Based Decision Making for Blood Safety noted, "As blood systems are focusing more on responsible use of health care resources, questions arise as to the most effective way to manage risk at a level that is tolerable and sustainable." Subsequently, the Alliance of Blood Operators developed a risk-based decision-making framework for blood safety (Framework). Considering these two parallel dimensions, we reanalyzed whether an absolutist position against donor compensation taken by some countries is any longer relevant or would be appropriate if evaluated utilizing a risk-based decision-making approach.

Design and Method: We used the Framework to integrate stakeholder concerns into an overall risk profile focusing on two elements most relevant to our analysis: the assessment component of the ethical discussion and the participation strategy for engaging relevant stakeholder (e.g. patients) that has been missing from past analyses. We also applied the analytical structure of the Nuffield Council on Bioethics.

Results: We found notable distinctions between donor plasma destined for further manufacture into PDMPs and labile whole blood and its components (e.g., red blood cells [RBCs], platelets, and plasma) for direct transfusion. The latter does not routinely undergo significant processing designed to mitigate the risk from transfusion-transmitted infections. Our assessment differentiated the two and focused on ethical issues as they related to the unique features of compensating donors of plasma destined for manufacture into PDMPs when donated in countries with well-established regulatory structures. We found in no case has the prevalence of an emerging infectious disease been linked to donor compensation for PDMPs. Most donations are motivated neither by pure altruism or self-interest and that the most direct incentives, including compensation, are not alone reasons to prohibit an activity. The policy of some countries is to meet identified patient need for PDMPs by importing PDMPs produced from compensated donations while at the same time advocating a seemingly contradictory policy of prohibiting donor compensation within their own borders.

Conclusions: Given advances in PDMPs and donor safety, one of the remaining threats to safety is a policy that undermines an adequate and sustainable supply of PDMPs. Actions that limit patient access to treatment without considering supply issues raise the possibility that global patient needs will be eclipsed in pursuit of ethical ideals that are both impractical and unnecessary.

POSTER 79 - SIX CASES WITH WISKOTT ALDRICH SYNDROME IN VIETNAMESE CHILDREN: CLINICAL MANIFESTATIONS AND TREATMENT OUTCOME

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Objective: Wiskott Aldrich Syndrome (WAS) - an X-linked recessive immunodeficiency disorder - is characterized by thrombocytopenia with reduced mean platelet volume, eczema, recurrent infection and an increased risk of autoimmunity and malignancy, caused by mutations in the WAS protein gene. We reported children with WAS gene defects at Children's Hospital 1 in recent five years when molecular genetic testing was developed rapidly in Ho Chi Minh City, Vietnam.

Design and Method: Based on clinical features, six cases with suspected WAS were confirmed by WAS gene sequencing. Information of their past history, clinical examination, routine laboratory tests, immunological tests, treatment and course of disease were collected and investigated.

Results: Six patients with WAS were enrolled from 2013 to 2017. The WAS diagnosis was confirmed at the age from 4 months to 9 years old after a 3-month follow-up of immune thrombocytopenia. Three patients had sibling brothers who died of brain hemorrhage caused by thrombocytopenia and one patient had the mother as a WAS gene carrier. Bloody stool was found in 4/6 cases and eczema was recognized in 3/6 cases. All 6 cases had recurrent infections including colitis, pneumonia, otitis media and sepsis with different pathogens such as *Burkholderia cepacia*, coagulase-negative *Staphylococcus*. Only one patient suffered from both Epstein-Barr virus and cytomegalovirus infections. Three cases had hepatosplenomegaly and their bone marrow aspiration showed normal results. The platelet counts less than 30,000/ μ L with reduced mean platelet volume (6.5 ± 0.7 fL) were found in all cases while the erythrocyte and leukocyte counts were within normal ranges. Most of cases (5/6) were associated with high IgE levels ($1,306.2 \pm 121$ UI/ml) whereas IgA, IgM, IgG levels were normal. One case also had autoimmune hemolytic anemia with positive direct anti-globulin test. Results of WAS gene sequencing showed two types of genetic defects including 2 nonsense mutations and 4 mis-sense mutations. All of them were treated with intravenous immunoglobulin and antibiotics during the hospitalization but none could afford regular immunoglobulin prophylaxis. After a median follow-up of 36 months, two patients with WAS died of severe sepsis and pneumonia.

Conclusions: In addition to classic signs and symptoms, children with WAS had some uncommon manifestations which could result in delayed diagnosis or improper treatment. Consequently, WAS should be suspected in male children with thrombocytopenia especially who have poorly-responded to initial treatment accompanied with atypical symptoms or a family history of primary immunodeficiency disease.

POSTER 80 - THE ONBOARDING EXPERIENCE AND TOLERABILITY OF THE NEW 20% HUMAN IMMUNE GLOBULIN FOR SUBCUTANEOUS ADMINISTRATION IN NORTH AMERICA

AUTHORS

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Introduction: Data from a phase 2/3 North American clinical trial provided an opportunity to understand the onboarding experience of the new SCIG 20% (Ig20Gly) in patients with primary immunodeficiency diseases (PID). This new highly-concentrated SCIG 20% allows for fast infusion rates and large infusion volumes/site that minimizes infusion time and the number of infusion sites.

Methods: Associations between the rate of causally-related local adverse events (AEs) and the infusion parameters were evaluated in patients (3-83 years) receiving weekly Ig20Gly for ~1.3 years at infusion rates up to 60 mL/hr/site and infusion volumes up to 60 mL/site as tolerated.

Results: Of the 77 enrolled patients, 53 (69%) had no previous SCIG-experience. Overall, 91% (67/74) of patients treated with Ig20Gly completed the study; none of the discontinuations (n=7) were due to causally-related systemic or local AEs. Overall, 72% of patients reached an infusion rate of 60 mL/h/site. There was no association between the number of infusions with causally-related local AEs (0.4%, 1.4%, 1.1%, 0.3%, respectively) and the infusion volume/site (30-39, 40-49, 50-59, 60 mL/site or more, respectively). Median total infusion time was 0.95 hours. Most (99.8%) infusions were completed without a rate reduction, interruption, or discontinuation due to associated tolerability concerns or AEs.

Conclusions: Irrespective of infusion rates up to 60 mL/hr/site and infusion volumes up to 60 mL/site, infusions of Ig-20Gly were well-tolerated during onboarding through the end of the study. The rate of local AEs was not associated with increasing infusion rates or volumes per site. The percent of patients who experienced causally-related local AEs during onboarding was low and decreased further over time.

POSTER 81 - PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY IN A CHILD WITH DOCK 8 DEFICIENCY

AUTHORS

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Progressive multifocal leukoencephalopathy (PML) is a severe demyelinating disease of the central nervous system that is caused by reactivation of the polyomavirus JC in the patients with underlying immunosuppressive conditions. Combined immunodeficiency due to dedicator of cytokinesis 8 protein (DOCK8) deficiency is a very rare form of T and B cell immunodeficiency characterized by recurrent cutaneous viral infections, susceptibility to cancer and elevated serum levels of immunoglobulin E (IgE). Herein we report a child with DOCK 8 deficiency who experienced PML during his follow-up.

A 15-year old child was first referred to our immunology clinic with the preliminary diagnosis of Hyper-IgE syndrome. On attendance, he had papillomatous lesions on both hands in addition to a protruded lesion on his nose which grew in time and occluded both nostrils. Biopsy revealed HSV-1 positivity. He was given valacyclovir treatment but since no obvious regression was observed, he was started on interferon alfa 2b treatment, and the lesion showed prominent regression. His flow analysis confirmed the absence of DOCK8 expression. There is a first cousin marriage between his parents. And he has a younger brother with DOCK8 deficiency as well. On clinical follow-up, he attended to our clinic with newly onset generalized tonic clonic seizure. Cerebrospinal fluid microscopic and biochemical investigations were normal. CSF viral PCR analysis was negative. His cranial MRI revealed T2a-FLAIR hyperintense multiple focal lesions without contrast enhancement on bilateral frontoparietal lobes, dominantly left frontal lobe deep white matter. This finding revealed the suspicion of PML the interferon a-2b treatment was stopped. But control MRI repeated monthly for twice did not show prominent regression. Cranial MR angiography, venography and spinal MR imaging were normal. A control lumbar puncture was performed, and CSF analysis revealed Polyomavirus JCV DNA positivity with a copy level of 23.900 copies/mL. Anti-GAD antibody is 1.98 u/mL. After a multidisciplinary consultation with neurology and radiology departments he has recently been started on maraviroc treatment.

Progressive multifocal leukoencephalopathy is an often fatal demyelinating disease of the central nervous system that occurs almost exclusively in immunosuppressed individuals. The main approach is restoring the host adaptive immune response to improve survival. Since our patient has a primary immune deficiency disorder it is impossible to eliminate underlying immune suppressive condition. Maraviroc is one of the agents which was associated with clinical improvement in some case series. Our patient is being closely followed-up, and other treatment options are being considered.

POSTER 83 - LIVER ABSCESS IN CHRONIC GRANULOMATOUS DISEASE: A SINGLE CENTRE EXPERIENCE FROM A TERTIARY CARE CENTRE IN NORTH INDIA

AUTHORS

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Objectives: To describe the clinical features, microbiological profile, treatment measures, and outcome of liver abscess from a cohort of chronic granulomatous disease (CGD) from a tertiary care centre in North India.

Design and method: Case files of patients suffering from CGD were retrieved from the Pediatric Immunodeficiency Clinic. Out of the 48 patients with CGD, the clinical details of the patients who had liver abscess are separately analyzed. A diagnosis of CGD was confirmed using a Dihydrorhodamine (DHR) assay and a subsequent genetic analysis.

Results: Five (5) patients (10.5%) had hepatic abscess as a clinical manifestation, with a total 8 episodes. All were male and the age group varied from 4-22 years with a mean of 10 years. Most patients had their first episode of serious infection in early childhood (mean age: 3.5 years), however one patient was asymptomatic till 11 years. Mutational analysis was done in 3/5 patients out of which 2 tested positive for mutation in CYBB gene on the X chromosome while 1 remained unclassified. One patient developed 3 episodes of hepatic abscess. This patient develop third liver abscess on cotrimoxazole and itraconazole prophylaxis. However the others, who had only a single abscess, had either a difficult to treat abscess or a non resolving abscess necessitating further evaluation. 60% (5/8) of the abscesses involved the right lobe of the liver and 40% (3/8) of them were large abscesses (>5 cm in size). Staphylococcus aureus was the most common isolate (50%) out of which 3 were methicillin sensitive and one was methicillin resistant isolate. Antibiotics were given as per sensitivity with duration ranging from 3 weeks to 6 months. Three episodes of liver abscesses were particularly difficult to treat in our cohort. One patient underwent open drainage. In one patient with XL-CGD who had persistence of fever and non-resolving abscess despite 4 weeks of sensitive antimicrobials, oral prednisolone 1 mg/kg for 6 weeks followed by tapering was tried for the management along with antimicrobials for S. aureus. We noted a drastic reduction in fever following the use of prednisolone and the abscess showed decrease in size. There was no mortality in our cohort and all are on regular cotrimoxazole and itraconazole prophylaxis.

Conclusion: Liver abscess is an uncommon manifestation of CGD. Liver abscess in CGD is usually caused by S. aureus and takes longer time to resolve. Glucocorticoids can be useful for reduction of inflammation and early healing.

POSTER 85 - MYRIAD FACES OF CHRONIC GRANULOMATOUS DISEASE: ALL IN THE FAMILY

AUTHORS

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Introduction: Chronic granulomatous disease (CGD) is a genetic defect of phagocyte function resulting from mutations in genes encoding for different components of the NADPH oxidase complex. The NADPH oxidase helps in the generation of superoxide which helps in killing of intracellular microbes. X-linked CGD caused by mutation in CYBB gene is the commonest form reported among Caucasians. However, autosomal recessive forms of CGD are common in parts of the World with high rates of consanguinity and endogamy.

Objective: X-linked CGD usually affects males, but female carriers of CGD can present with clinical manifestations of the disease. In addition, female carriers of X-linked CGD are also susceptible to develop lupus. We report one such family in which in addition to the index patient, the carrier mother has lupus and the elder sister is also afflicted due to unfavourable lyonization.

Design and method: A 16 months old boy with a history of recurrent suppurative lymphadenitis and pneumonia since the age of 4 months was diagnosed with CGD. His 6 years old sister also had suppurative anterior cervical adenitis that improved with antimicrobials and healed with a scar. The mother of 2 children had polyarthritis involving small joints of hands, wrists, and knees and a malar rash suggestive of systemic lupus erythematosus (SLE).

Results: Molecular analysis done revealed that mutation was in hemizygous state (CYBB IVS 6-1G>T) in the patient. His sister and mother were heterozygous carriers for the same mutation. Dihydrorhodamine test (DHR) revealed a stimulation index of 0.7 against 132 in control. Aspirate from right cervical lymph node grew *Burkholderia cepaciae*. S.I. of 01.11, compared to 105.4 in control was noted in the sister with only 9.3% neutrophils showing right shift. A mosaic pattern was noted in the mother in the DHR (S.I.- 86.55, percentage positivity- 72.28%). Sister's b558 expression by flow cytometry showed positivity in only 11% of neutrophils and mother also showed a mosaic pattern of expression suggesting a X-linked carrier status for CGD. Antinuclear antibody by indirect immunofluorescence showed 2+ speckled positivity.

Conclusion: Manifestations of CGD can occur in female carriers for X-linked CGD due to skewed lyonization. Carriers of X-linked CGD can also develop features of SLE which might require the use of immunosuppressive medications.

POSTER 86 - MONOCLONAL GAMMOPATHY IN A CHILD WITH WISKOTT - ALDRICH SYNDROME: A RARE OCCURRENCE

AUTHORS

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Introduction: Wiskott Aldrich Syndrome (WAS) is characterized by eczema, thrombocytopenia and susceptibility to infections. Malignancy and autoimmunity are two additional important features. Monoclonal gammopathies are disorders where abnormal amounts of immunoglobulins are produced by a clone that develops from a single pro-B germ cell. It may suggest underlying malignancy or may be benign. We report a child with WAS who was found to have hypergammaglobulinemia but had no evidence of malignancy.

Case: A 5 year old boy was diagnosed to have WAS when he presented with recurrent life threatening pneumonia, eczema and persistent micro-thrombocytopenia. His Immunoglobulin levels at the time of diagnosis were: IgG-986 IgA-233 IgM-25 IgE-32. He had persistent thrombocytopenia (21x 10³), MPV was low (6.9 fl). WAS gene analysis revealed splice-site mutation (c.931+1G>A). Due to the lack of availability of matched sibling donor, Hematopoietic Stem Cell Transplant could not be performed and in view of frequent life threatening infections, he was advised cotrimoxazole along with IVIG 400 mg /kg every month. He was doing well clinically. Serial trough levels of IgG however showed consistent hypergammaglobulinemia over the next two years (Ig G levels ranging from 13.64 to 41.40 g/L). Replacement IVIG was transiently discontinued however he continued to have hypergammaglobulinemia.

A possibility of B cell lymphoma was considered. Serum electrophoresis was performed which showed IgG kappa type of M protein. CD3-11021/μl and CD19-1121-3893/μl. EBV serology was negative, EBV DNA PCR was negative. Bone marrow examination showed, non-specific reactive changes with mild excess of lymphocytes, however with no evidence of malignancy. In view of recurrent infections, he was reinitiated on replacement IVIG, he continues to have high trough IgG levels.

Discussion & Conclusion: Monoclonal gammopathy has uncommonly been described with WAS. The exact pathogenesis of this association is not known, but it is believed to be due to inadequate production of specific antibodies in this syndrome. However, this may be an early marker of underlying malignancy.

POSTER 88 - MAJOR HISTOCOMPATIBILITY COMPLEX CLASS II DEFICIENCY: DIAGNOSIS CIRCUMSTANCE

AUTHORS

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Inherited deficiency of major histocompatibility complex (MHC) class II molecules impairs antigen presentation to CD4+ T cells and results in combined immunodeficiency (CID). It's a rare primary immunodeficiency, most patient described are from North Africa. Four genes were identified: CIITA, RFXANK, RFX5 and RFXAP coding for proteins involved in the regulation of gene transcription MHC II. We present a retrospective study, between 1998 and 2016, involving 31 cases that were followed in the Clinical Immunology Unit at University Hospital of Casablanca (Morocco).

Our population was represented by a small majority of boys (sex ratio: 1.2). Parental consanguinity was noted in 26 patients (84% of the cases). Mean age at diagnosis was 2.5 years. Our patients had clinical manifestations dominated by respiratory infections (87%) and chronic diarrhea in 25 patients (80%), oral thrush have been observed in 17 patients (54%), otitis were found in 11 (35%). Finally, hematological manifestations were observed in 6 patients (19%). The immunological work up shows a CD4 + lymphopenia in 93% with absence of expression of MHC II molecules in all patients. Twenty patients had hypogammaglobulinemia. All patients were on antibioprophylaxis and intravenous immunoglobulin replacement. Only six patients received HSCT.

Our study summarizes the clinical and biological characteristics of the patients with MHC class II expression deficiency and the difficulty of treatment in the absence of bone marrow transplant unit for PID in Morocco. Hence, the interest is to multiple efforts to improve the care of patients.

POSTER 89 - TREC/KREC ANALYSIS AND THEIR CLINICAL CORRELATION IN SEVERE COMBINED IMMUNE DEFICIENCY

AUTHORS

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Severe combined immune deficiency (SCID) is an inherited disorder characterized by T-cell lymphopenia (TCL). SCID is fatal if not treated and early diagnosis is critical. SCID can be diagnosed right after birth with TREC based new-born screening. TRECs are the DNA by-products of T-cell recombination and low levels of TRECs represent TCL. Also in B-cell lymphopenia KRECs, by-products of B-cell receptor development, can be quantified. Here we analyzed TREC and KREC copy numbers of 30 SCID patients who were diagnosed by next generation sequencing (Table 1) and 14 healthy controls. For the simultaneous detection of TREC and KREC copy numbers a Real-Time PCR assay was performed on the LightCycler-96 Real-Time PCR System (Roche, USA). TREC, KREC and TRAC copy numbers were determined by extrapolating the values from a unique standard curve, which was obtained by the amplification of serial dilutions of a triple-insert plasmid (106,105,104,103,102,101), which encodes one gene copy of TREC, KREC and TRAC each. All the TREC/KREC copy numbers were below the levels of healthy controls with two exceptions. One was a compound heterozygous RAG1 deficient patient diagnosed as leaky SCID and although T-cells were detected by flow cytometry, her T cells were found non-functional after stimulation by PMA and ionomycin that causes this patient to be diagnosed as SCID. The second patient was a IL2RG mutated patient with no B-cells and KREC levels were zero as well. The results were in line with patients' immunophenotypes and the pathogenic variants that have been detected. Here we used the TREC/KREC levels to strengthen the molecular diagnosis of our PID patients that can support early diagnosis and subgroup classification of our SCID cases. This project was supported by Istanbul University Research Fund (Project no: 52575 and 20499). Sinem Firtina was funded by the Scientific and Technological Research Council of Turkey (TUBITAK) 2211-C National Scholarship Programme for PhD Students.

Type	Gene	# patients
T-B+NK+	CD3E	2
	IL7R	1
	Unknown	4
T-B+NK-	IL2RG	3
	JAK3	3
	Unknown	none
T-B-NK+	RAG1/2	7
	Artemis	2
	NHEJ1	1
	Unknown	4
T-B-NK-	ADA	3
	Unknown	none

POSTER 91 - CHRONIC GASTROINTESTINAL INVOLVEMENT IN COMMON VARIABLE IMMUNODEFICIENCY DISEASES (CVID)

AUTHORS

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Background: Acute or chronic infectious diarrhoea is the most frequent manifestation of GI in Common Variable Immunodeficiency Diseases (CVID). Non-infectious enteropathy occurs in 10 to 12 % of CVID patients and may resemble Crohn's disease, ulcerative colitis, or celiac disease. CVID-associated chronic enteropathy is a complex disorder that may include features similar to ulcerative colitis, proctitis, or severe small bowel disease.

Between 8 and 22 % of subjects with CVID develop granulomatous disease in the liver or the GI tract. Both diagnosis and therapeutic management of GI involvement in CVID are challenging.

Methods: Medical records of patients with CVID, both children and adults, referred at the University Research Hospital in Milan have been analysed.

Results: Thirty-four CVID patients, 4 children and 30 adults, have been enrolled. Median age is 33.5 years, ranged 11-70. The prospective follow-up mean time is 9 years (range 2-37). All patients are under immunoglobulins replacement therapy.

Thirteen adult patients (38.2%) reported gastrointestinal symptoms: 3 epigastric pain/dyspepsia, 7 chronic or relapsing diarrhoea and 3 both symptoms. Five patients had stool cultures positive for Salmonella, Campylobacter, Clostridium, Norovirus, and Rotavirus.

Four patients were diagnosed for gastritis (one H. pylori positive), celiac disease was diagnosed in 4, lymphocytic colitis was identified in 5 patients and ulcerative colitis in 1.

Granulomatous liver disease was found in 3 patients. Biopsy confirmed non-caseating granulomas. Two patients were found to have chronic viral infection: Cytomegalovirus and Epstein-Barr virus, respectively. The specific treatment to the isolated pathogen solved diarrhea only transiently. Two patients need chronic budesonide treatment. Gluten-free diet ameliorates symptoms in celiac disease, but diarrhoea often relapses. Two patients temporary solved symptoms with local mesalazine. All adults CVID patients are under chronic probiotics therapy.

Conclusions: Diagnosis of gastrointestinal involvement in CVID is challenging because patients can be paucisymptomatic and pathologists need specific experience to recognise CVID histologic features. Furthermore, low mucosal IgA levels may lead to luminal bacterial overgrowth. According to numerous reports about the impact of alterations of the microbiota for the pathogenesis of IBD, intestinal inflammation in CVID may also be triggered by infectious agents. Whether or not this hypothesis can be further supported remains to be determined.

Management of chronic diarrhoea is challenging too, because these patients often fail to respond to conventional therapies. The preventive use of probiotics is still controversial.

POSTER 92 - LATE PRESENTATION OF CHRONIC GRANULOMATOUS DISEASE

AUTHORS

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Objective: To describe late manifestation of Chronic Granulomatous Disease

Introduction: Chronic granulomatous disease (CGD) is a rare inherited heterogeneous disorder due to mutations in different genes encoding for different components of the NADPH oxidase system. This results in an inability to generate superoxides and severe recurrent and life threatening infections. CGD usually manifests early in childhood. The median age at diagnosis in our cohort of CGD patients was 2 years (interquartile range: 0.7, 4.5 years). However, CGD may manifest in late childhood and adulthood, this is especially true of autosomal recessive CGD with some residual NADPH oxidase function.

Method:

Case 1: - A 12.5 year old girl, elder sibling of boy diagnosed with CGD, was symptomatic since 8 years of age with swelling following minor trauma. She was presented with fever, cough and bilateral infiltrates on chest radiograph, suggestive of Pneumonia. Recurrent lymphadenitis, cellulitis and subcutaneous abscesses had also been documented. Her first cousin was symptomatic since 1.5 years of age and misdiagnosed as ulcerative colitis.

Case 2: - A 21 years old male patient had a history of recurrent liver abscesses, pneumonia and lymphadenitis for which he had sought multiple hospital admissions since 11 years of age.

Case 3: A 21 year old female patient had a history of 3 episodes of pneumonia since the age of 20 years.

Results: Laboratory investigations of case 1 revealed hypergammaglobulinemia (Increased IgG and IgA with normal IgM) and normal lymphocyte subsets. The Nitroblue dye reduction (NBT) test was abnormal showing no reduction of dye by stimulated neutrophils. Stimulation index (SI) of neutrophils was 1.34 against 122.6 in control in the Dihydrorhodamine (DHR) flow assay suggesting a diagnosis of CGD.

NBT was abnormal in case 2 that showed no reduction of dye. DHR showed SI of 3.6 against 125.6 in control. B558 expression was found to be decreased on flow cytometry and a mutation was detected in the CYBB gene (CYBB. c.1291G>A, p.A431T) confirming a diagnosis of X-linked CGD.

DHR showed SI of 1.9 against SI of 203 in control in case 3 suggesting CGD.

Conclusion: Chronic Granulomatous disease is a disease of early childhood, but some patients with CGD can present in late childhood and adulthood. In two of our cases the SI value was more than >1.5. This could account for a late presentation due to some residual NADPH oxidase function.

POSTER 93 - PRIMARY IMMUNODEFICIENCY DISORDERS IN BANGLADESH: AN EXPERIENCE AT A TERTIARY HOSPITAL IN BANGLADESH

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Background: The clinical presentation of primary immunodeficiency disorders (PIDs) are highly variable, many PIDs present as recurrent infections and may remain undetected. Therefore, timely diagnosis of these disorders requires a high level of suspicion. There is paucity of data on PIDs from Bangladesh.

Objectives: This article provides a baseline descriptive study from a tertiary hospital on PIDs highlighting demography, clinical profiles and subtypes of different PID cases and limitations and challenges in the diagnosis.

Material and methods: It was a retrospective study conducted in the Paediatric Rheumatology and Immunology Clinic (PRIC) of Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh from July 2012 to June 2017. All the suspected cases of immunological patients attending the paediatric rheumatology and immunology clinic and admitted patients were included for analysis. The suspicion of PID was made on the basis of 10 warning signs.

Result: Twenty five PID cases were enrolled in this study. Among them Common variable Immunodeficiency disorder and Agammaglobulinemia were the majority (40% each). Selective IgA deficiency (1), Congenital C3 deficiency (), JOB syndrome and Hyper IgM syndrome were the other PIDs. Mean age was 6.5 year, Male: female ratio was 7.3:1 and mean duration of disease was 2.7 year. Limited investigations were done because of logistic constraints. Complete blood count, peripheral blood film and quantitative immunoglobulin analysis were done in all the cases. Only 5 patients had flow cytometric analysis as the service is available recently in this institute. Limitations encountered during the initial diagnosis of PID included lack of suspicion and delayed referral from GPs, pediatricians and different centers. Even now lack of genetic analysis in Bangladesh is a big diagnostic challenge in some of the PID cases.

Conclusion: The number of PID cases is gradually increasing globally. Only few PIDs cases were documented in this study. This number appears to be an underestimate due to lack of awareness about PIDs and scarcity of laboratory support. High level of suspicion is essential for timely diagnosis and referral of PID cases.

POSTER 94 - A CASE OF AUTOSOMAL RECESSIVE CHRONIC GRANULOMATOUS DISEASE CAUSED BY CYBA MUTATION WITH A HOMOZYGOUS SYMPTOM-FREE MOTHER

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Objective: Chronic granulomatous disease (CGD) is a rare primary immunodeficiency disorder due to a genetic defect in one of the components of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase complex. The CYBA gene provides instructions for making a protein called the cytochrome b-245 alpha chain (also known as p22-phox). This protein is one part (subunit) of a group of proteins that forms NADPH oxidase, which plays an essential role in the immune system. As a result, phagocytes are unable to produce reactive oxygen species to kill foreign invaders, and neutrophil activity is not regulated. A lack of NADPH oxidase leaves affected individuals vulnerable to many types of infection and excessive inflammation.

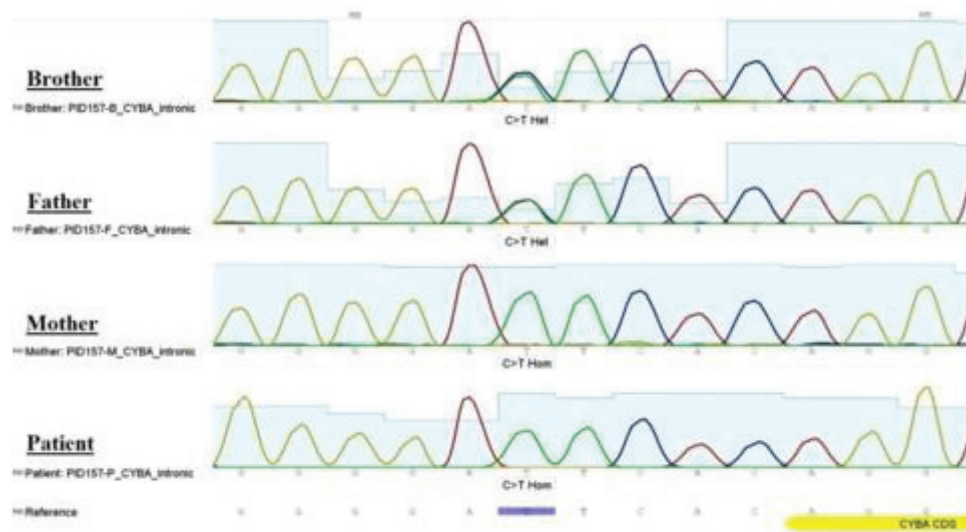
This report describes clinical and laboratory features of a child with autosomal recessive chronic granulomatous disease and her healthy mother, both with homozygous CYBA mutations.

Method: The clinical records and CYBA mutations were reviewed for analysis of symptoms in all family members especially in daughter and her affected mother.

Results: The reported case was a 5 years old girl with BCGitis diagnosed by multiple enlarged axillary and cervical lymph nodes. Her parents were first cousins and a positive family history of swollen lymph nodes was presented in her aunt and uncle.

The results of DHR123 flow-cytometry showed 39.61% of positive phagocytes after phorbol myristate acetate (PMA) stimulation with neutrophil oxidative index (NOI) of 15.5. CYBA mutation analysis showed homozygous (16 88713158 88713158 C to T) DNA change in patient. Her mother had the same homozygous mutation but never had experienced related symptoms. Other family members including her father and younger brother were both carriers and completely disease-free.

Conclusions: In this case DHR123 flow cytometric analysis helped the diagnosis of CGD and CYBA mutation analysis clarified the distribution of the gene mutation in the family members. This mutation was in accordance with the patient's clinical presentation and confirmed in patient, her healthy brother and her parents by Sanger sequencing. Although being asymptomatic in defiance of homozygous mutation of CYBA in the patient's mother is still interrogative and more genetic evaluations is recommended.



Gene	DNA Change	Protein Change	dbSNP rsID	Associated disease	Inheritance	Zygosity	Classification (ClinVar)
CYBA	16 88713158 88713158 C → T	Intronic	•	Chronic granulomatous disease, autosomal, due to deficiency of CYBA	AR	Patient: Hom Mother: Hom Father: Het Brother: Het	NR-Pathogenic

- All variants with dbSNP rsID numbers have minor allele frequencies less than 0.5% unless otherwise stated
- AD=Autosomal Dominant; AR=Autosomal Recessive; XL=X-Linked; XLR=X-Linked Recessive
- Hom=Homozygous; Het=Heterozygous; Hem=Hemizygous; WT=Wild Type
- VUS=Variant of Uncertain Significance, NR=Not Reported

POSTER 95 - AN OBSERVATIONAL STUDY ABOUT SWITCHING FROM IVIG TO SCIG ?

AUTHORS

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Intravenous administration of serum immunoglobulin G (IVIG) is the mainstay treatment for patients with PIDD and hypo or agammaglobulinemia. IVIG, maintains physiologically normal levels of serum IgG, which decreased morbidity from infections and increased survival. SCIG has important advantages over IVIg related to tolerability, ease of administration, less adverse effects and quality of life.

The aim of this study was to evaluate the patient's attitudes, satisfaction and adverse reactions(AEs) regarding to SCIG treatment while switching from IVIG to SCIG .

A questionnaire prepared which contained a list of possible AEs identified from the information leaflets from a SCIG product. A nurse, who was incharge of to teach SCIG application, called the patients and asked the questions and get the answers regarding patients satisfaction and AEs.

The study started with 16 PID patients, 3 patients tried once at hospital but they did not go on with SCIG; one patient felt inconfident regarding home-based self infusion so he preferred to receive injections at hospital because of the quality of care and follow-up, one patient had severe pain at injection area so he refused to use SCIG,, and one patient was incompatible with SCIG to IVIG .

13 patients (age Range 13-27 years) received SCIG for a mean of 1,5 years and mean duration of switch to SCIG from IVIG was 10,8 years. Patients satisfaction and adverse reactions regarding to SCIG was reviewed: The average SCIG dose was 5 grams per week, general infusion duration was within 20-30 minutes.

13 patients who are on SCIG(81%) returned to phone call. 13 of the 11 (85 %) patients had at least one AE and 2 (15%) had none. Eleven patients had only local AEs and none had systemic SE. The most common reported AE was local swelling. The second most reported AE was tingling sensation of infusion area. One patient returned to IVIG after one year therapy because of ease of administration at hospital. Twelve patients were satisfied with switching from IVIg to SCIG..A patient who was using wheel chair was very happy because of no more visit to hospital for IVIG.

Conclusion: Patients were generally satisfied from subcutaneous immunoglobulin replacement and reported better quality-of-life . Although local reactions are frequent with subcutaneous route SCIG prevented infections similar to IVIg infusions, Some adult patients are satisfied hospital-based replacement therapy and have fear of adverse effects during home-based treatment.

POSTER 96 - HEREDITARY ANGIOEDEMA TYPE I MONITORING EXPERIENCE AMONG ADULTS

AUTHORS

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In Stavropol regional center of allergy-immunology we see 5 adult patients with hereditary angioedema type I - 2 men and 3 women. Average age of patients with HAE I receiving treatment is 45+27 years old.

Regular HAE I manifestations among our patients are as follows:

Family sickness cases, presence of deadly cases due to asphyxia in families, decrease of C1 inhibitor in blood serum, abdominal syndrome, duration of attacks is 2-3 days, well Firazir tolerance. We saw a significant quality of life improvement after receiving adequate therapy for HAE I.

The peculiarities of HAE morbidity among these patients are:

1. late disease manifestation, associated with body puberty.
2. average severity of edema and abdominal syndrome.
3. frequency of HAE exacerbations - 2-3 times in 4 weeks.
4. difficult differential-diagnostical search for an underlying disease, which takes 15+5 years.
5. intermittent therapy of aminocaproic acid and deep-frozen plasma at hospital during HAE exacerbation.
6. high patient retention to systemic gluco-corticosteroid medications, administration of which is performed individually by patients during HAE exacerbation.
7. late rescue medication (Icatibant) receipt as social benefit, the fear of this medication and commitment to save Firazir.

Conclusions: early detection of HAE, timely informing of patients about their diseases, timely receipt of medication as social benefit is necessary.

Tutoring patients, their relatives and medical personnel on how to perform emergency aid during HAE exacerbation greatly improves patients' quality of life.

POSTER 97 - THE KILLER CELL IMMUNOGLOBULIN-LIKE RECEPTOR 2DS2 COULD BE A PROTECTIVE FACTOR AGAINST HEPATITIS B VIRUS INFECTION

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Background: killer cell immunoglobulin-like receptors (KIR) are transmembrane glycoproteins expressing on NK cells and a subset of T cells. The KIRs can significantly impact NK cell responsiveness in viral infection. Hepatitis B virus (HBV) infection shows heterogeneous outcome which is influenced by the host genetic background. It has been proposed that some kinds of KIRs are HBV-protective genes while some of them are susceptible genes that influence the clearance of HBV. The aim of this study was to evaluate whether each inhibitory or activatory KIR genes demonstrate an association with hepatitis virus infection in the hepatitis B families with high frequency of HBV (FHBV)

Method: KIR genotyping was evaluated in 40 patients of families with high frequency of HBV infection, more than two-thirds of members in the family are infected with hepatitis B, and 30 patients with HBV infection in whole population, (HBVW) by sequence specific primer- polymerase chain reaction (SSP-PCR). KIR gene frequencies of normal population were used from data in www.allelefrequencies.net, KIR Database, Iran KIR, Tajik et. al. All data were analyzed by two-tailed Fisher exact test.

Result: Among 16 KIRs genes 2DL4, a frame work gene, was the only gene which existed in all individuals in three groups. Furthermore, the other four framework genes; 3DL2, 3DL3, 2DP1 and 2DP3 existed in nearly all of the individuals. The patterns of inhibitory KIRs except 2DL2 were similar in three groups. Except for 2DS2 the frequencies of other activatory KIR genes including 2DS1, 2DS3 and 2DS4 were similar in all groups and the frequency of 2DS3 was the lowest among all KIR genes. The frequency of 2DS2 in FHBV was 17% lower than normal population and revealed statistically significant difference while, 2DS2 frequency in HBVW was just 3% higher than normal population and did not show any significant difference.

Conclusion: The role of 2DS2 in cytotoxicity and cytokine secretion in NK and CD28 null CD4 T cell shows that 2DS2 maybe play a critical role in HBV clearance by functional regulation of NK and subset of T cell against HBV. Although, in order to support the present results obtained in this study, assessment of KIR expression pattern and functional studies of NK/ T cells of patients from susceptible families in different population and regions are required.

POSTER 100 - CURE FOR CHILDREN WITH SEVERE COMBINED IMMUNODEFICIENCY - NOW A REALITY IN INDIA!

AUTHORS

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Objective: Hematopoietic stem cell transplantation and gene therapy are the only curative options for children with Severe Combined Immunodeficiency (SCID). In developing countries like India, definitive treatment is delayed due to lack of awareness and late referral to a transplant center. The aim of our study is to analyze the outcome of children undergoing transplantation for SCID at our centre and to study factors affecting their survival.

Design and Method: A retrospective analysis of data of all children who underwent hematopoietic stem cell transplantation for SCID at our hospital from Jan 2002 to Dec 2016 was done. The diagnosis of SCID was made by clinical and laboratory findings and confirmed by identification of genetic mutation in some children. The details of transplantation and complications were noted from past medical records of patients and analysed.

Results: The total number of children included in the study was 28 (male: female -2.5:1). The median age at transplantation was 7 months. The source of stem cells was peripheral blood in 14, bone marrow in 8 and umbilical cord blood in 6 children. Twelve children received graft from matched family donor, 7 received from matched unrelated donor and 4 from a haplo-identical family member. Twenty two children received reduced intensity conditioning, 4 did not receive any conditioning and 2 received myeloablative conditioning. The overall survival was 53% in our cohort. Almost all the deaths occurred within first 6 month of transplantation. Both the children whom we lost a year after HSCT had DNA repair defects. One died due to busulphan induced pulmonary fibroelastosis and the other died of severe rota-virus diarrhea. Sixty-one percent (n=10) of total deaths were due to infections (62% due to Gram negative bacterial sepsis, 25% due to cytomegaloviral infection and 12% due to Aspergillus infection). One child (7.5%) had a haplo-identical HSCT and died due to regimen related toxicity after cyclophosphamide and one (7.5%) due to graft versus host disease.

Conclusions: SCID is a medical emergency and early referral for transplantation before onset for any major infection is important for better survival. Children referred before 3.5 months had excellent overall survival and could be salvaged with HSCT without conditioning. However, when no conditioning was used before transplantation in children older than 3.5 months graft rejection was universal. Reduced intensity conditioning offer improved survival with minimum regimen related toxicity and we could offer a chance of cure for 53% of these children.

POSTER 101 - INDIVIDUALS WITH MODERATE IGG DEFICIENCY ARE SEROLOGICALLY DIFFERENT FROM THOSE WITH SEVERE IGG DEFICIENCY AND THOSE WITH NORMAL IGG.

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Objective: In neonates, IgG1 and IgG3 subclasses (IgGSc) are produced earlier than IgG2 and IgG4 and thus in a developing antibody deficiency, the IgG2 response may be lost before that of the IgG1 and IgG3. We hypothesised that the IgGSc concentrations and assessment of the response to vaccination may be altered in patients with moderately reduced serum immunoglobulins and recurrent infection compared to those with severely reduced IgG and those with normal IgG concentrations.

Design and method: Patient data were obtained retrospectively from the patient records of 136 adults that were referred to the Immunology Department, Queen Elizabeth Hospital, Birmingham for immunological investigation between 2010 – 2015 (65:71 Male: Female, median age 58 years, range 17-87).

Individuals were grouped according to IgG concentration: moderate IgG deficiency (mIgGD 4-6 g/L, n=24), severe IgG deficiency (slgGD <4 g/L, n=12) or normal IgG (>6 g/L, n=99).

Results and conclusions: The median IgA concentration in the mIgGD group was significantly higher than that in the slgGD group (1.07 vs 0.31 g/L, p=0.0006) and significantly lower than in individuals with normal IgG (1.07 vs 2.1 g/L, p=0.0013). In addition, the number of individuals in the mIgGD group with normal IgA concentrations was significantly higher than in the slgGD group (70% vs 17%, p=0.0014). The IgM concentrations were not significantly different between the three groups.

The percentage of individuals in the mIgGD group with low IgGSc concentrations was lower than in the slgGD group (71% vs 100% p=0.04) and higher than the normal IgG group (71% vs 12%, p<0.0001). The percentage of mIgGD individuals with combined IgG1-3D was lower than in the slgGD group (0% vs 42%, p=0.007) and the percentage with IgG2D and IgG3D lower than that compared to the normal IgG group (12% vs 50%, p=0.04 and 0% vs 33%, p=0.02).

The median response to pneumococcal and haemophilus vaccination was lowest in the slgGD group followed by the mIgGD group and highest in individuals with normal IgG (slgGD vs mIgGD, p=0.0009 and mIgGD vs normal IgG, p=0.046). The response to tetanus vaccination was not significantly different between the groups. The response to multiple vaccines was different across the three groups (p=0.04).

In conclusion, the IgA level, spectrum of low IgGSc concentrations, response to certain vaccines and multiple vaccines are significantly different between the mIgGD group and the groups with severe IgGD and normal IgG.

POSTER 104 - BURDEN OF IMMUNOGLOBULIN TREATMENT IN PRIMARY IMMUNODEFICIENCY DISORDERS: FINDINGS FROM AN INTERNATIONAL PATIENT SURVEY

AUTHORS

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Introduction: Immunoglobulin (Ig) replacement therapy is a common treatment for patients with primary immunodeficiency disorders (PIDs), and is administered either intravenously (IVIG) or subcutaneously (SCIG), in a healthcare facility or at home. SCIG treatment has been associated with a reduced risk of systemic adverse events compared with IVIG treatment, and improved treatment satisfaction. Little is known about patient experience with the burden of Ig treatment.

Objective: The primary objective was to describe the burden of treatment experienced by PID patients, who receive IVIG or SCIG treatment. A second objective was to describe the demographic and clinical characteristics of this population.

Methods: An online survey, designed with patient and expert input, was administered to patients in Sweden, Denmark, Norway, Italy, UK, France, Netherlands, Germany, Poland and Canada, in the local language. Adult PID patients receiving Ig treatment were identified by patient organisations and emailed the survey. The survey included 158 questions on demographics, clinical characteristics, and treatment burden. A descriptive analysis of 46 burden of treatment questions was completed, with results presented by treatment type and location.

Results: 395 (Canada: N=24, Denmark: N=36, France: N=23, Germany: N=59, Italy: N=28, the Netherlands: N=58, Norway: N=49, Poland: N=16, Sweden: N=45, UK: N=57) patients were eligible for analysis. 128 (32%) received IVIG, 266 (67%) SCIG and 1 (<1%) was unsure. 86 (22%) received their treatment in a healthcare facility and 309 (78%) at home. The mean age was 46 years and most were female (N=247, 63%). Overall, burden of Ig treatment was low, with only 60 (16%) reporting their treatment as 'always burdensome' or 'often burdensome'. 88% reported that they 'always' or 'often' wanted to continue with their Ig treatment and 87% felt that their health would get worse without their Ig treatment. Some reported that they 'always' or 'often' experienced swelling at the site of treatment (43%) or felt tired (41%). Treatment was more frequently reported as 'always' or 'often' burdensome in patients receiving IVIG than SCIG (19% vs 15%), and at a healthcare facility rather than at home (22% vs 15%).

Conclusions: This was the first international survey to examine burden of Ig treatment in PID patients. Although few patients reported that their treatment was burdensome overall, there were some areas where some patients reported higher burden. These results provide insight into how Ig treatment can impact PID patients in different ways, and highlight the importance of an individualised approach to treatment.

POSTER 106 - SUCCESSFUL PATIENT-DRIVEN SELF-ADMINISTRATIONS OF FACILITATED SUBCUTANEOUS IMMUNE GLOBULIN (fSCIG) TREATMENTS WITH MECHANICAL SYRINGE INFUSION SYSTEM AND A NOVEL ADJUSTABLE FLOW RATE CONTROLLER (AFRC)

AUTHORS

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Background: In order to meet modern patient lifestyles, fear of needles, complications at infusion sites, and adherence problems, fSCIG empowers patients by providing them with a new therapy alternative.

One challenge encountered from the use of electronic infusion systems with complex programming is the successful education of patients to comfortably perform self-treatment at home. We present results from a new at home self-administrated fSCIG using a mechanical syringe system with constant pressure (MCPS) together with an adjustable flow rate controller (AFRC), calibrated to the viscosity of the drug. The MCPS is an intuitive and easy system to operate and with a 24G high flow infusion set it is generating flow rates up to 300ml/hr. Many patients prefer to use 2 infusion sites which deliver a total flow rate of 360ml/hr, similar to the maximum flow rate used with electronic pumps.

Method: Data from fSCIG infusions was collected at two Departments of Infectious Diseases in Sweden. Patients received self-treatment education and training by an experienced nurse. A structured questionnaire was used to record data using the AFRC together with MCPS. The fSCIG training followed the Ig manufacturers' infusion ramp up recommendations.

Results: A total number of 69 fSCIG infusions were recorded. Patient age was between 25 to 81 years old (mean; 50 years). 49% of the infusions were administrated by females and 51% by males. The assessment was performed by the nurse when the patient demonstrated comfortability and confidence with self-administration. All patients reported successfully being able to adhere to the flow rate ramp up schedule. Of all infusions recorded, 93% were made totally by self-administration. Average infusion time was 87 min. With a mean performance score of 97 (out of a maximum of 100), the AFRC device connected in its MCPS shows high performance, usability and safety.

Conclusion: The results demonstrate that after receiving appropriate training, the calibrated AFRC used together with MCPS empowers patients to successfully managing home-infusion therapy by performing their own fSCIG infusions. In addition, data concerning usability and safety indicate successful use and adjustments of flow rates to preferred settings during infusion. The study shows the MCPS is easy to operate and that the AFRC connected to it meet its objectives by supporting self-administration at home. Furthermore, the system performs accurately during treatments by delivering ultimate therapeutic outcome for the patient's continual improvement of wellbeing while avoiding adverse and intolerable site reactions.

POSTER 107 - ASYMPTOMATIC GIARDIASIS IN X-LINKED AGAMAGLOBULINEMIA PATIENT WITH SEVERE LUNG DISEASE, CHRONIC GINGIVITIS AND SHORT STATURE

AUTHORS

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Background: Asymptomatic giardiasis is rarely described in X-linked agammaglobulinemia (XLA) patient. Usually, giardiasis is diarrheal disease caused by the flagellate *Giardia-Lambia*. XLA is caused by mutation in Bruton's tyrosine kinase gene resulting in arrest of B cell differentiation and antibody production. Almost all XLA patients have recurrent respiratory and many have gastrointestinal infections.

Objective: to present asymptomatic giardiasis in XLA patient with serious lung disease, chronic gingivitis, chronic conjunctivitis and short stature.

Methods: comprehensive review of medical records and BTK-gene mutation analysis was carried out.

Results: 10,5y boy with agammaglobulinemia, bronchiectasiae was transferred from regional hospital in Dec2014. Third child, from second (twin) pregnancy. Older and twin-brother healthy. Recurrent respiratory infections since age 2mo; antituberculous treatment at 2,5y. At age 5y, low serum immunoglobulin levels were detected. Diagnosed as agammaglobulinemia, bronchiectasiae, started immunoglobulin (IVIG) therapy. Inadequately treated with IVIG for 5y. When presented at 10,5y (Dec 2014): chronically sick; weight and height below 5.percentile, subfebrile, satO2 95% breathing ambient air, puls 97/min, TA 114/64mmHg, coughing, abundant purulent sputum, nail clubbing (Figure 1.), positive auscultatory lung findings, chronic conjunctivitis and gingivitis (Figure 2.). Multidisciplinary team approach was performed (immunologist, gastroenterohepatologist, infectologist, radiologist). Work up: normal inflammatory markers, mild leukocytosis. Liver enzymes (AST, ALT, GGT) were 6-8 times above normal upper limit. Other liver function tests as well as thyroid hormones-normal. Immunoglobulin levels: low IgG, absent IgA, IgM, IgE. Rtg (Figure 3) and chest CT:extensive bronchiectasiae (Figure 4). Cardiac work up, abdominal ultrasound normal. Important question remained: what was the reason for raised liver enzymes? Cysts of *Giardia-Lambia* were finally found in stool. Metronidazole treatment resulted in normalisation of liver enzymes. Genetic analysis: XLA, mutation c.1898G>A. Treatment: high doses of IVIG (now SCIG), antibiotics, physiotherapy. On follow up: significant improvement of general condition; significant improvement of body height and weight, serum level of IgG > 11 g/L; normal liver enzymes.

Discussion: Asymptomatic giardiasis is rarely described as cause of raised liver enzymes in XLA patient and should be included in differential diagnosis in such cases. XLA patients requires multidisciplinary team approach, adequate therapy with IVIG/SCIG and of associated complications.

Figure 1 Nail clubbing

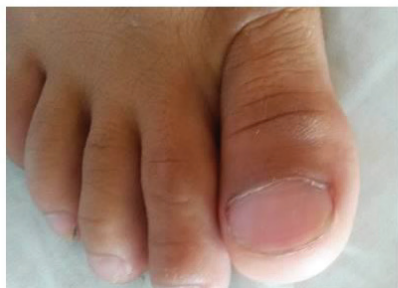


Figure 2 Chronic gingivitis



Figure 3 Chest X-ray:
bilateral bronchiectasiae

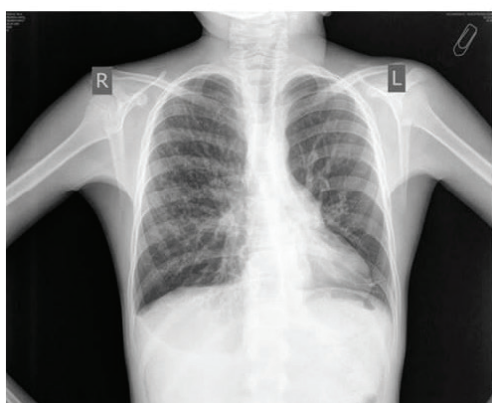
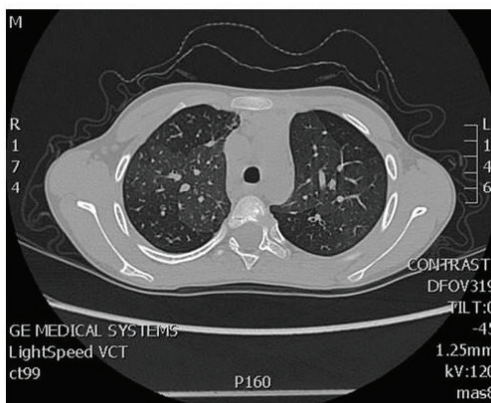


Figure 4 Lung CT:
bilateral bronchiectasiae



POSTER 108 - A GIRL WITH AUTOIMMUNE LYMPHOPROLIFERATIVE SYNDROME

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Background: Autoimmune lymphoproliferative syndrome (ALPS) is a rare genetic disease of the immune system affecting both children and adults. In the case of ALPS, mutations in the FAS gene (for death receptor) cause an abnormal buildup of white blood cells. Thus, unusually high numbers of lymphocytes accumulate in the lymph nodes, liver, and spleen, which can lead to organomegaly. ALPS cause numerous autoimmune problems such as anemia, thrombocytopenia, and neutropenia.

Aim: Here, a rare case with ALPS having intracranial hemorrhage due to chronic thrombocytopenia is reported.

The Case: 14-year-old- girl of ALPS presented to our clinic with deterioration in general condition and generalized tonic-clonic seizure. Other than first-degree cousin marriage, nothing remarkable was in her family history. Past medical history started with persistent moniliasis, recurrent bronchitis and dermatophyte infections around 6 months of age. At five years of age, she suffered from epistaxis, hematuria and pneumonia. When she was 8-year-old, she had her first intracranial hemorrhage and evaluated for lymphadenopathy, splenomegaly, and thrombocytopenia during admission. Her physical examination showed huge splenomegaly till groin, ongoing dermatophyte infection and rhonchi and rales heard in lung auscultation. Abdominal and thorax CT showed paraaortic lymphadenopathy and bronchiectasis. Bone marrow aspiration demonstrated normal findings. Laboratory evaluation showed platelet: 33.100 /mm³, IgG:3.259 mg/dl, positive direct Coombs test, and >7.86% double negative T (CD4-CD8-) cells. With these clinical and laboratory findings, she was diagnosed with ALPS. She has been treated with IVIG for the last several years and was doing fine. When she was admitted last time, she was unconscious and pupils were fixed dilated. CBC revealed that platelet was 23.600 /mm³. PT, aPTT, and INR were normal. Chest X-ray was normal. Eye examination indicated intracranial hemorrhage. Due to profuse bleeding, brain CT could not be done. Although she was given platelet and erythrocyte suspensions plus IVIG, she died of active bleeding.

Conclusions: Although one of the causes of death could be intracranial hemorrhage in ALPS, this case draws our attention to see fatality even with the platelet count of 23.600/mm³. We think that use of immunosuppressive agents and/or splenectomy to overcome thrombocytopenia should be given priority in these kinds of patients.

POSTER 109 - A PATIENT WITH RECURRENT HERPES INFECTION: CASE REPORT

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Background: Herpes simplex virus type 1 (HSV-1) infections in a child is frequently seen. However, recurrent HSV-1 infections could be related to various congenital immunodeficiencies. Our aim is to present our case and discuss the reasons for recurrent HSV-1 infections.

The case presentation: 4.1/2-year-old male patient had his first herpetic vesicles around eyebrow and on right eyelid when he was 2 years and eleven months. After 4 months, our patient reapplied to pediatric infectious diseases department because of recurrent vesicles on his face. A single vesicle on his right cheek was detected in his examination. Laboratory findings demonstrated normal CBC, routine biochemistry, sedimentation rate and immunoglobulins. Anti-HIV, anti-EBV-VCA IgM/G, anti-EBV-EBNA IgM/IgG, anti-HSV-1 IgM / IgG, anti-HSV-2 IgM/ IgG, anti-Parvovirus B-19 IgM/ IgG antibody, anti-toxoplasma IgG/IgM, anti-Rubella IgM/IgG and anti-CMV IgM titers were all negative. Anti-CMV IgG was only found to be positive. Oral Acyclovir treatment was started after diagnosing him with recurrent herpes infection. During 2 months of oral acyclovir treatment, vesicles appeared both on left cheek and beneath right eye again. On the physical examination; enlarged lymph nodes were detected up to 2x2 cm in right central cervical area. There was not any hepatosplenomegaly and axillar lymph node. His second cervical ultrasonography showed 26x11 mm gryphotic cortex, lost hilus and oval shaped multiple lymph nodes in left intraparotis and bilateral submandibular areas suggesting chronic lymphadenitis. There were not any atypical and malignant cells in his peripheral blood smear. Pulmonary radiography examined normal. Additional laboratory findings showed that anti-CMV IgM/IgG: positive, anti-CMV IgG avidity: 0.92 (high avidity), anti- rubella IgG: positive, anti-HBs: negative, anti-HSV-1 IgM/IgG: positive, but anti-HSV-2 IgM/ IgG were negative. Total IgE was 12.8 kU/l, inhalation and food allergen scanning tests were negative. C3, C4 levels and IgG subclasses were normal. Flow cytometry depicted normal T and B cell counts, but borderline low NK cells. TLR-3 expression, DOCK8 expression and STAT1 phosphorylation were normal. Response to TLR-7 ligand was low. Type I IFN signal transduction was found to be normal. NK cytotoxicity assay was normal.

Conclusions: Further laboratory investigations into our patient's NK cell and functions are ongoing thru cooperation with experts in abroad. Sometimes to find out the reason causing recurrent HSV-1 infections in a child could be troublesome.

POSTER 110 - EXTENDED LYMPHOCYTE IMMUNOPHENOTYPING FOR IMMUNODIAGNOSIS OF RECURRENT INFECTIONS OCCURRING IN THE ABSENCE OF PRIMARY IMMUNODEFICIENCY

AUTHORS

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

Design and method: SLI and ELI was applied in 25 children aged 1-9 years, presenting PID-unrelated RI. The control group consisted of 18 healthy subjects. The determinations were made from EDTA-collected fresh whole blood, using 8-color methodology.

The data acquisition and analysis of results was performed with Becton-Dickinson equipment: FACSCanto II flow cytometer, compensation microspheres (Anti-Mouse Ig, κ/Negative Control Particles Compensation Set), FACSDiva 6.1 software.

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

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

The study was funded by grant of Romanian Ministry of Education and Research, Core project 22N 03 04/2016.

POSTER 111 - HOW TO SELECT OPTIMAL NEEDLE LENGTH FOR SUBCUTANEOUS IMMUNE GLOBULIN INFUSIONS (SCIG)

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Background: To avoid local skin reactions when giving SCIg infusion, it is important to select the optimal needle length to obtain the correct infusion depth. Today, there are no tools or guidelines available to help select the optimal needle length. Instead, the practice is through clinical experience and tradition. One of the most common questions among health care providers is related to which needle length should be used.

Objective: To create guidelines for needle length selection when administering SCIg infusions.

Methods: Questionnaires were used to gather patient data from three different infusion treatments to assess the patients' subcutaneous fat layer and develop a correlation between them and optimal needle length. Data was collected on:

- 1) body mass index (BMI),
- 2) skin depth measure using a caliper,
- 3) gripping skin by hand, and 4) the patient's selection of own body shape using the three somatotypes; Endomorph, Mesomorph and Ectomorph.

Results: 57 patients reported outcomes from 166 infusions. BMI in relation to subcutaneous fat layer on different locations on the same patient's body is highly variable. Patients' measurements show that the skin depth can be very different on the stomach versus on the thighs. We found it to sometimes be slightly challenging for the patient to assess own body shape and to use a caliper to measure subcutaneous fat layer.

Conclusion:

- The creation of a guideline is still an ongoing process. We have found factors that need further research which affect selection of the optimal needle length for SCIg.
- BMI is not precise enough for selecting needle length.
- Measuring subcutaneous fat layer requires skill in the method to effectively support the selection of the optimal needle length for SCIg therapy. It should be made by a trained health care professional prior to the selection of needle length to use.
- Same patient might need different needle lengths for thighs versus abdomen.

POSTER 112 - INCIDENCE OF DRUG LEAKAGE WHEN GIVING SUBCUTANEOUS IMMUNE GLOBULIN (SCIG) AND FACILITATED SUBCUTANEOUS IMMUNE GLOBULIN (FSCIG) TREATMENTS – IS IT MORE FREQUENT THAN EXPECTED?

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Introduction: During our study on guidelines for selecting the optimal needle length for SCIg and fSCIg infusions, we found a higher rate of drug leakage from infusion sites than expected. Patients haven't spontaneously mentioned occurrence of leakage prior to the study. There are several parameters to consider when selecting the optimal needle length to avoid local site complications. Drug leakage at the site is one of the contributing factors.

Objective: To investigate patients' experiences and local site complications when administrating SCIg and fSCIg.

Method: Questionnaires were used to gather patient data from 3 different infusion treatments. To assess patient's local site complications, we asked participants to report any leakage of drug during and/or directly after treatment, when removing the needle from the infusion site.

Result/Discussion:

57 patients reported outcomes from 166 infusions. Interesting findings in relation to the high incidence are:

- 34 patients reported experience with drug leakage during or directly after treatment.
- 30 placed the needle by themselves and 4 were placed by a nurse.
- 48% of all 166 infusions reported occurrence of drug leakage.
- Of the three body shapes, the endomorph infusions reported 61% with drug leakage, which is a higher incidence compared to the other two groups.

We suspect there are several factors contributing to leakage of drug such as technical skills, selection of infusion site(s), optimal needle length, dressing used, dose and volume per site, subcutaneous fat layer, infusion rate, and pump used.

Conclusion: Today, patients don't spontaneously report leakage. This must be investigated to improve treatment therapy and be a part of the standard follow up with active patient evaluations to be made by health care professionals. The practice is through clinical experience in which longer needles are typically recommended. Patients with an endomorph body shape might need extra attention, since this particular group shows a tendency for more problems with leakage. Today there are limit guidelines available and further research is needed.

POSTER 113 - CRYPTOCOCCAL INFECTIONS IN CHILDREN ASSOCIATED WITH PRIMARY IMMUNODEFICIENCY DISEASES: EXPERIENCE FROM CHANDIGARH

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Objective: Cryptococcal infections have been described in children with certain immune deficient states like HIV infection, diabetes mellitus and malignancies. Cryptococcal infections including disseminated cryptococcal infections have been reported in immunocompetent children. However, these children should not be termed as immunocompetent only because no apparent immunodeficiency could be demonstrated in them. At best, these children may be called as “apparently immunocompetent”.

Methods: We describe 3 cases with cryptococcal infections. Evaluation led to the finding of a myriad of immunodeficiencies in some of them.

Results:

Case 1: 3 year boy, presented with fever and pain abdomen for 3 months. Had jaundice 1 month back. Examination revealed generalized lymphadenopathy, jaundice and hepatomegaly. Investigations showed anemia, conjugated hyperbilirubinemia with elevated alkaline phosphatase and gamma glutamyl transferase. Biopsy from axillary lymph node revealed multiple necrotizing granulomas and numerous refractile fungal yeasts in giant cells, histiocytes and in necrotic tissue confirming to the morphology of Cryptococcus. A diagnosis of disseminated cryptococcosis was concluded. Evaluation for underlying immune defect revealed elevated serum immunoglobulin E (>10,000 U/L) with reduced Th17 cells (0.9% as compared to 2.1% in age matched control) and p-STAT3 (10.9% as compared to 30.8% in control).

Case 2: 4 year boy, presented with fever, rash and pain abdomen for 6 weeks. Examination showed cervical and axillary lymphadenopathy, hepatosplenomegaly and discrete umbilicated lesions over trunk and limbs. FNAC from cervical lymph node showed granulomatous inflammation and numerous intracellular and extracellular round to oval capsulated organisms consistent with Cryptococcus. Search for immune deficiency was unrewarding. With a diagnosis of disseminated cryptococcosis, Amphotericin B and flucytosine are initiated. On follow-up, skin lesions were healing and organomegaly disappeared.

Case 3: 4 year boy, presented with fever, headache, seizures and altered sensorium for 1 month. Investigations: Ultrasonography of abdomen showed altered echo texture of liver with multiple hypo-dense lesions in spleen. Cerebro-spinal fluid (CSF) examination showed Cryptococcus on India-ink staining. CSF as well as blood culture revealed Cryptococcus neoformans. A diagnosis of disseminated cryptococcosis was arrived at. Further evaluation showed reduced expression of IL12RB1 on lymphocytes (10.0% as compared to 46.4% in age matched control). This was one of the uncommon causes of disseminated cryptococcal infection.

Conclusions: A diligent search for underlying immune defect in children with cryptococcal infections may result in uncovering of rare or novel immune defects.

POSTER 114 - CHARTING THE BEST COURSE FOR A PATIENT WITH CHRONIC GRANULOMATOUS DISEASE WITH COMPLEX PERIANAL FISTULA

AUTHORS

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The patient is currently a 2year 1months old Chinese boy, diagnosed with Chronic granulomatous disease since October 2015 (at 5months old). His main problem for discussion is in the management of his complex perianal fistula.

He first presented at the age of 4months old with irritability and respiratory distress. QX completed 12 days of antibiotic therapy, despite no positive cultures. A 2nd admission followed 4 days after discharge, this time around treated for nosocomial pneumonia requiring multiple changes to antibiotic therapy. It was at this point that consultation and subsequent diagnostic investigation of Dihydrorhodamine flow cytometric assay was carried – which showed a very low respiratory burst response to PMA.

QX had recurrent Klebsiella infection started since the age of 9months old, whereby he presented with fever with raised CRP and positive urine culture of Klebsiella initially sensitive to Ciprofloxacin and carbapenems. Since then, he has been admitted on an almost monthly basis with each admission duration ranging from 2 to 4 weeks for prolonged intravenous antibiotic therapy due to either persistent ear infection or urinary tract infection. Due to the recurrent infections, an extensive workup to delineate other causes of recurrent urinary tract infection was also done, including ultrasound bladder to look for a rectovesical fistula – which all yielded negative results. It was not until he was 1year 8months old when it was noted that he had a perianal swelling, with one episode of pus discharge that he was suspected to have a perianal fistula. An MRI done at the age of 1 year 11months showed presence of a complex perianal fistula. Discussions with the paediatric surgery either of three options – either a fistulectomy, a colostomy with fistulectomy or a colostomy alone and allow for the perianal fistula to heal by secondary intention.

On a side note, HLA typing of parents and his elder sister revealed no suitable match for transplant. A search for a matched unrelated donor in the local bone marrow registry was also unsuccessful. Molecular study for his underlying CGD is not available in our local facilities and the option of administering interferon gamma to improve his neutrophil function is cost prohibitive.

I am forwarding this case for discussion with the international community with regards to their experience in managing such a complication in a patient with CGD.

POSTER 115 - HYPER IGE SYNDROME: OFTEN A MISSED DIAGNOSIS IN COUNTRIES WITH LIMITED FACILITY FOR MOLECULAR ANALYSIS

AUTHORS

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Hyper-IgE syndrome (HIES) is a primary immunodeficiency (PID) clinically characterised by eczema, recurrent staphylococcal skin abscesses and recurrent lung infections, with laboratory findings of eosinophilia and markedly elevated levels of IgE. Most cases are sporadic, but 2 types of HIES, an autosomal dominant (AD-HIES, also known as Job syndrome) and autosomal recessive (AR-HIES) have been described. In countries such as Malaysia, where molecular analysis for PID is limited, high index of suspicion is required in children presented with chronic eczema and recurrent pyogenic infections (especially with *Staphylococcus aureus*). Furthermore, the diagnosis of HIES has been difficult to confirm until both somatic and immunologic features exist.

We report 4 cases of HIES (2 unrelated female patients with AD-HIES and 2 male siblings with possible AR-HIES). Apart from the elevated IgE level and eosinophil numbers, cases 1 and 2 presented with distinctive musculoskeletal and connective tissue abnormalities consistent with Job syndrome. Case 1 has recurrent pneumonias, neonatal onset of eczema and recurrent staphylococcal skin infections. She also has bronchiectasis, pneumatoceles and recurrent otitis media with a history of tuberculous liver abscess. Case 2 presented with recurrent furunculosis and scalp abscesses which grew *Staphylococcus aureus*. Both cases were initially investigated for a possible diagnosis of chronic granulomatous disease. Cases 3 and 4 who were born to non-consanguineous parents, presented with recurrent wheezing episodes secondary to pneumonia. They also have eczema which repeatedly infected with *Staphylococcus aureus* and *Streptococcus pyogenes*. Both of them were diagnosed to have asthma and investigated for atopy, which then revealed elevated levels of total IgE and specific IgE against house dust mite and increased eosinophil numbers. Interestingly, Case 3 has markedly increased IgE towards Der p1 and Der f1 but low IgE to Blo t1, whereas Case 4 has increased IgE to Der p1 and Blo t1 but low towards Der f1. Case 3 also has skin infection with *Molluscum contagiosum* virus which was initially treated as scabies, while case 4 has recurrent skin infection/abscesses over the plantar aspect of his right foot initially treated with antibiotics but later complicated with fungal infection. We then compare the clinical presentations, laboratory findings and therapeutic aspects of HIES in these 4 cases. In general, therapies include prolonged antibiotic therapy for acute infections, and early surgical intervention (in whom required) to attain resolution of symptoms. The primary goal of treatment is to prevent further infections with antibacterial with or without antifungal prophylaxis.

POSTER 116 - IGG3 SUBCLASS DEFICIENCY AS A PREDICTIVE MARKER OF MORTALITY IN PATIENTS ADMITTED TO ICU

AUTHORS

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Objective: Pneumonia is fourth common cause of death and patients admitted to ICU due to pneumonia still shows high mortality despite improvements in treatment. Among immunoglobulins (Ig), IgG is the most abundant in human serum, which further divides into IgG1, IgG2, IgG3 and IgG4. IgG3 antibody is thought to have mechanisms against viral and atypical pathogens in upper and lower respiratory infections. In this study, we were to find relationships in mortality and level of IgG subclasses in patients admitted to medical ICU.

Design and Methods: The patients admitted to medical ICU from September 2016 to February 2017 due to pneumonia were enrolled in this study. The patients were diagnosed as either community acquired pneumonia (CAP) or hospital acquired pneumonia (HAP) transferred from other medical centers and were intubated or applied high flow nasal cannula. Levels of serum IgG and IgG1, IgG2, IgG3 and IgG4 subclasses along with serum IgE, IgA and IgM were measured within 48 hours of admission to ICU. The results of laboratory tests were compared between survivors and non-survivors after 28-days.

Results: Thirty-one patients were enrolled, 21 survivors and 10 non-survivors. The mean age of patients was 75.9 vs 8.97. APACHE-II score was 23.7 and 19.2 in non-survivor and survivor patients, respectively. Serum levels of IgG1 (557.15 vs 93.36 vs 476.85 vs 63.34), IgG2 (432.54 vs 133.36 vs. 32.74 vs 46.56), IgG3 (69.09 vs 46.48 vs 28.68 vs 11.74) and IgG4 (30.62 vs 17.04 vs 9.54 vs 6.01) was higher in survivors compared to non-survivors, which only IgG3 was clinically significant ($p=0.018$). (Table 1 and Fig.1.)

Conclusions: Non-survivors of pneumonia admitted to ICU showed slightly lower levels of IgG3, which serum IgG3 level at the time of admission may be a prognostic factor of mortality in pneumonia patients admitted to ICU.

Table 1. Comparison of serum immunoglobulins between non-survivors and survivors.

	Non-survivor (n=10)	Survivor (n=21)	P-value
Total IgG (mg/dL)	673.00±355.85	1229.37±520.41	0.347
Total IgE (mg/dL)	134.06±172.47	202.74±331.14	0.127
IgG1 (mg/dL)	476.85±64.34	557.15±93.36	0.112
IgG2 (mg/dL)	332.74±46.56	432.54±133.36	0.245
IgG3 (mg/dL)	28.68±11.74	69.09±46.48	0.018
IgG4 (mg/dL)	9.54±6.01	30.62±17.04	0.09

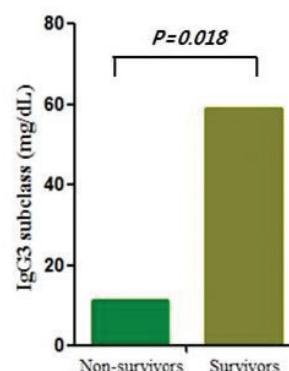


Fig. 1. Comparison of IgG3 subclass levels between non-survivors and survivors.

POSTER 117 - SEVERE COMBINED IMMUNODEFICIENCY: MALAYSIA'S FIRST SUCCESSFUL HLA-IDENTICAL HAEMATOPOIETIC STEM CELL TRANSPLANTATION IN A 1½-MONTH-OLD CHILD

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Severe Combined Immunodeficiency (SCID) is the most severe forms of primary immunodeficiency (PID) and considered as a paediatric emergency because survival depends on expeditious stem cell reconstitution. Therefore, early diagnosis is crucial before the child develop any infections. SCID in Malaysia is a cause for great concern. The number of SCID in Malaysia is increasing; since 2010 we are seeing at least 1-2 cases per year compared with 6 cases within 18 years period (1992-2010). However, it is frequently not suspected by primary physicians, even at the referral centres, hence delayed in diagnosis. This is due to several reasons which include, lack of recognised family history, absence of distinguishing physical or classical characteristic and their variability, lack of awareness among paediatricians on early suspicion and lack of available facilities to work up towards a diagnosis (distant from primary hospital). In addition, complications of BCG vaccination, especially disseminated infection and its most severe forms are known to occur in SCID patients. Prior to this, almost all (100%) of SCID in Malaysia made a demise between 4 to 15 months. Here, we describe a patient with a very early diagnosis of SCID, who was monitored and investigated soon after birth following the death of his 3rd male sibling at the age of 8 months due to severe sepsis with coagulopathy secondary to SCID. The BCG vaccination was withheld, intravenous immunoglobulin was started, antibiotic and antifungal prophylaxes were commenced and he was kept in an isolation room. Instructions were given as not to transfuse unirradiated blood products and not to feed him with breast milk until maternal CMV status was known. As soon as he was confirmed to have T-B+NK- SCID, he was immediately transferred to the bone marrow unit. At the age of 1½ month, he received HLA-identical haematopoietic stem cell transplantation (HSCT) from his first male sibling. Three months post transplant, his immune parameters have markedly improved and lymphocyte numbers have normalised.

POSTER 118 - IMMUNE DYSREGULATION, POLYENDOCRINOPATHY, ENTEROPATHY, X-LINKED (IPEX) SYNDROME: THE FIRST CASE REPORT FROM INDONESIA

AUTHORS

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Background: Immune dysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX) syndrome is a rare primary immunodeficiency (PID) due to mutation in the transcription factor of FOXP3, the important gene of T regulatory cells. IPEX presents in early life with a triad of autoimmune enteropathy, autoimmune endocrinopathy, and atopic dermatitis.

Objective: To report the first case of IPEX syndrome in Indonesia.

Case: We present a male infant with classic manifestations of IPEX syndrome. Patient was diagnosed with atopic dermatitis, with positive specific IgE of white egg, chicken, cow's milk, and shrimp at 2 months old. At 5 months old, patients admitted to PICU due to severe respiratory distress and hyperglycemia. Patient was diagnosed as diabetic ketoacidosis on type I diabetes mellitus.

At 22 months old, patient had intractable watery diarrhea, severe malnutrition, and sepsis. The genetic examination showed that he had hemizygous in-frame deletion mutation at exon 8 of FOXP3 gene c.748_750del, which confirmed IPEX syndrome. The same mutation in heterozygotic state was found in the mother. After the infection was controlled, he was given immunosuppressive therapy with prednisone. The diarrhea was controlled and patient went home after 4 months of hospitalization. We added cyclosporine, however we have to discontinue the cyclosporine due to severe anemia. Currently he is stable on prednisone. He gains his weight, no diarrhea nor infections.

Conclusion: IPEX syndrome should be considered in male infants with type 1 diabetes mellitus, chronic diarrhea, and atopic dermatitis. Genetic testing plays an important role to have definitive IPEX diagnosis.

POSTER 120 - ADVERSE REACTIONS TO IVIG IN PRIMARY IMMUNE DEFICIENCY PATIENTS; MARMARA EXPERIENCE

AUTHORS

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Background: Reactions to intravenous immunoglobulin (IVIG) replacement in primary immune deficiency (PID) patients mostly occur in the first 72 hours following administration. We hereby present IVIG reactions in our PID patients.

Materials and Methods: Adverse reactions to 433 IVIG infusions in 87 (26F,61M) PID patients were followed prospectively. Mean age of patients was 12.2±6.1 years (median:12.9, min:1.5, max:33.4 years).

Results: Mean IVIG dosage was 510 mg/kg (min:280 mg/kg, max:830 mg/kg). Mean infusion duration was 5 hours and 8 minutes (min:3 hours, max:6.5 hours). Rate of adverse reactions to IVIG was 5%. Adverse reactions were classified as follows: mild 42% (n:18), moderate 0.7% (n:3) and severe 0.2% (n:1). Fever (n:9, 2.1%), headache (n:6, 1.4%), tremor (n:4, 0.9%), rash (n:1, 0.2%), pruritus (n:1, 0.2%) and abdominal pain (n:1, 0.2%) were most common mild reactions. Moderate reactions were wheezing (n:1, 0.2%) and hypertension (n:2, 0.5%). Anaphylaxis (n=1) was the only severe reaction observed. Patients experienced any reaction or not did not statistically differ in their current age, age at onset, age at diagnosis, IVIG dosage, infusion count, duration and premedication need. Patients received premedication in only 11.5% of IVIG infusions (n=50) which were as follows; antihistaminics (n=45, 10.4%) and antipyretics (n=5, 1.2%).

Conclusion: Rate of adverse reactions to IVIG in PID patients was found to be 5% which were mostly mild and rarely moderate reactions in our cohort. Demographic characteristics, IVIG dosage or duration of our patients did not predict an adverse reaction to occur.

POSTER 121 - RAPID SCIG INFUSION IN PRIMARY IMMUNE DEFICIENCY PATIENTS; MARMARA EXPERIENCE

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Background: Immunoglobulin (Ig) replacement treatment is necessary in decreasing the severity and frequency of infections in primary immune deficiencies (PID). Ig may be administered by im, iv or sc routes. We hereby describe our rapid subcutaneous Ig (SCIG) infusion in PID patients.

Materials and methods: Rapid SCIG infusions between June2014-August2016 are prospectively recruited. Demographic data of patients, SCIG dosage, interval, duration and location of infusion and side effects were evaluated.

Results: Sixty-three (30F, 33M) PID patients (0-65 years (11.9 ± 10.5)) receiving SCIG at 10% concentration were enrolled. Mean SCIG dosage was 6.8 ± 2.45 grams (min:5, max:12.5), dosage interval as 11.2 ± 6.65 days (min:7, max:21) and volume per site as 31 ± 9.45 ml (min:25, max:50). Duration of infusion varied from at least 15 to 25 minutes. Every dose was infused 2-3 sites (periumbilical, thigh and upper-arm). No systemic severe reactions were observed during any SCIG infusions whereas local pain, induration, pruritus and redness were observed which were common and totally relieved in minutes.

Conclusion: Ig replacement therapy via rapid SCIG infusions is safe, effective, comfortable, easy to administer and individually tailored option for PID patients.

POSTER 122 - INITIATION OF 20% SUBCUTANEOUS IMMUNOGLOBULIN THERAPY IN PATIENTS WITH PRIMARY IMMUNODEFICIENCY NAÏVE TO IG THERAPY

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Rationale: Immunoglobulin replacement is prescribed for patients with antibody defects and is available in intravenous and subcutaneous forms. Data on the use of SCIG in patients' naïve to Ig therapy is limited.

Methods: We retrospectively identified fourteen subjects who received 20% subcutaneous immunoglobulin (SCIG) therapy for primary immunodeficiency without first receiving a loading dose of IVIg.

Results: Fourteen subjects aged 7 to 67 years were identified: 4 with CVID, 5 with hypogammaglobunemia, 2 with hypogammaglobunemia with poor pneumococcal response, and 3 with selective antibody deficiency. Mean pre IgG level was 497 mg/dl (range 324-1290 mg/dl). Three subjects required dose adjustments over the first 3-4 months of therapy; the remaining eleven subjects had therapeutic IgG levels after 12 weeks of therapy and no dose adjustment was necessary. No serious bacterial infections were noted for any subject. No serious adverse reactions were noted for any subject.

Conclusion: SCIG can be safely and effectively administered to primary immunodeficient patients who have not received a loading dose of Ig therapy. IgG levels as well as number of infections need to be monitored in order to determine individualized doses.

POSTER 124 - SHOULD PENICILLIOSIS BE CONSIDERED AS A SIGN OF PRIMARY IMMUNODEFICIENCY DISEASE: A CLINICAL CASE REPORT

AUTHORS

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Penicillium marneffei is the only dimorphic member of the genus and is an emerging pathogenic fungus that can cause fatal systemic mycosis. *Penicillium marneffei* disseminates hematogenously to other locations. *Penicillium marneffei* infections most commonly involves the skin, lungs, bone, bone marrow, joints, lymph nodes, pericardium, liver and spleen.

Case report: We report one 3-year-old boy who came to our hospital on March, 2016 because of prolonged high fever, coughing and skin papules lesions with central necrosis in the face and neck. The patient had suffered from many episodes of media otitis, severe pneumonia, meningitis. The papules culture and blood culture showed *Penicillium marneffei* infection. HIV test was negative. He was treated with Amphotericin B for two weeks and discharged.

The patient come to our hospital second time after one year. This time he suffered from high fever, pneumonia, lymphadenopathy, without skin lesions. Laboratory studies showed a hemoglobin concentration of 6.8g/dL, leukocyte count of 3370/mm³, with a differential count of 10% neutrophils and 60% lymphocytes, and platelet count of 204,000/mm³. Chest X-ray showed reticular infiltration. Ultrasonography of the abdomen demonstrated diffuse hepatosplenomegaly and enlarged paravertebral lymph nodes. FNA of left axillary lymph nodes was performed, the aspirate revealed the presence of *Penicillium marneffei*. His blood culture and bronchial lavage fluid result also revealed *Penicillium marneffei*. A diagnosis of disseminated *Penicillium marneffei* infection has been made. Second time HIV test was still negative. His immunological test showed low serum IgG level (20mg/dL; normal range: 295- 1156mg/dL), normal serum IgA (440mg/dL; normal range: 27- 246mg/dL) and high serum IgM level (1150 mg/dL; normal range: 37- 224mg/dL). Lymphocyte subset showed normal T-cell (CD3: 8045/μl), B- cell (CD19: 650/μl) and NK-cell (CD56: 260/μl) . The patient was diagnosed disseminated Penicilliosis/ primary immunodeficiency disease. He was treated with Amphotericin B for 6 weeks and IVIG infusion at dose 800/mg/kg.

Conclusion: Penicilliosis is a severe disease which can cause death to children. Penicilliosis should be considered as an indicator for underlying immunodeficiency in HIV- negative individuals. Immunological investigations should be performed, especially in those with recurrent infections.

POSTER 125 - ?AUTOIMMUNE LYMPHOPROLIFERATIVE SYNDROME TYPE III: A CASE REPORT

AUTHORS

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Introduction: Autoimmune lymphoproliferative syndrome is a disorder of lymphoid system regulation characterized by chronic splenomegaly, lymphadenopathy and autoimmune phenomena especially immune-mediated cytopenias. Autoimmune lymphoproliferative syndrome should be considered in differential diagnosis of any patient with unexplained Coomb's positive cytopenias, hypergammaglobulinemia, generalized lymphadenopathy and splenomegaly. The confirmation of the diagnosis should be based upon genetic analysis and detection of the affected genes involved in Fas pathway.

Case report: The authors report a 6-year-old boy when he was first hospitalized for chronic generalized lymphadenopathy, splenomegaly and hepatomegaly. On examination he had discreet facial dysmorphism, otapostasis and clinodactyly fifth fingers of both hands. He had several enlarged, nontender lymph nodes involving cervical, submandibular, axillary and inguinal areas and a huge spleen were detected. In laboratory findings boy had elevated aminotransferases, reduced IgA levels and chronic CMV infection. According to flowcytometry of peripheral blood and immunophenotyping of lymph node tissues which revealed increased numbers of CD3+CD4-CD8-T lymphocytes and increased vitamin B12 levels autoimmune lymphoproliferative syndrome was suggested for him. But no mutations were detected in studied genes (CASP8, CASP10, FADD, FAS, FASLG, ITK, KRAS, MAGT1, NRAS, CTLA4). Lymph node biopsy was performed one time. Indicated treatment with systemic corticosteroids followed by a decrease in the size of lymph nodes and spleen. Three years after diagnosis boy regularly controlled as outpatient.

Conclusion: This case highlights the importance of comprehensive diagnosis in children with evidence of lymphoproliferation in order to prove rare diseases especially autoimmune lymphoproliferative syndrome.

Keywords: Autoimmune lymphoproliferative syndrome, Lymphadenopathy, Splenomegaly

POSTER 128 - MYCOPHENOLATE MOFETIL FOR TREATMENT OF SEVERE THROMBOCYTOPENIA IN PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS AND AUTOSOMAL RECESSIVE HYPER-IGE SYNDROME, A CASE REPORT

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Objective: To know the outcome of immunosuppressant treatment for Autosomal Recessive Hyper-IgE Syndrome (AR-HIES) patient with autoimmune disease.

Design and Method: This is a case report of adult patient with AR-HIES treated with mycophenolate mofetil for severe thrombocytopenia related to secondary Antiphospholipid Syndrome and Systemic Lupus Erythematosus.

Results: Male, 44 years old came to clinic with chief complain papular eruptions appeared at lower abdomen which spread and enlarged to external genitalia and perianal since 6 months. There were also dome-shaped papules with central umbilication on his face and multiple papules on the hand and feet. There were history of recurrent eczema and allergic rhinitis. No history of anal intercourse or sexual intercourse other than with his wife. From history and physical examination, he was diagnosed with giant condyloma acuminata, verrucae vulgaris, mollusum contagiosum, and scabies. He was treated with topical trichloroacetic acid (TCA) 90% for condyloma, cryotherapy and salicylic acid 40% for verrucae, potassium hydroxide 10% for mollusum contagiosum, and permethrin 5% for scabies. High risk human papilloma virus (HPV) were found positive. Laboratory results showed mild anemia, thrombocytopenia (28000/microL), eosinophilia (1306/microL), normal ferritin level, non-reactive Anti-HIV, non-reactive TPHA, reactive VDRL with titer 1:1, decreased CD4 (178 cells), normal CD8 (435 cells) and increased IgE (3484 ng/mL). From these results, we considered the patient had AR-HIES that predispose him to chronic viral infection. Further work up for thrombocytopenia revealed negative HBsAg and anti-HCV, positive antinuclear antibody test (titer 1/1000 with coarse speckled pattern), positive anti-dsDNA (189.5 UI/ml), strong positive for lupus anticoagulant, high positive ACA IgG, and positive Beta 2 GP IgG. Considering these results, the patient was diagnosed with secondary antiphospholipid syndrome related to systemic lupus erythematosus. Because we planned to do skin biopsy, we decided to treat the thrombocytopenia with mycophenolate mofetil 500 mg twice daily. After 6 weeks, platelet increased to 112000/microL. We planned to taper down the dose faster than standard treatment for patients without underlying immunodeficiency. During treatment there were no signs of new infection. The condyloma acuminata resolved faster than predicted, not only at lesions treated with TCA 90%.

Conclusions: Dysregulation of immune response and chronic viral infection make patients with AR-HIES prone to develop autoimmune diseases. Immunosuppressive treatment, when needed for autoimmune condition in patient with primary immunodeficiency, must be carefully given and monitored.

POSTER 130 - DO CHILDREN WITH RECURRENT INFECTIONS GROW WELL?

AUTHORS

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Introduction: The analysis of patient's body weight and height is used to evaluate the child's health condition and it's growth. In order to obtain objectivity of these parameters you should use the centile charts.

The aim: Estimation of physical growth of children with recurrent respiratory infections, in relation to healthy children.

Methods & Materials: Retrospective study has included 137 children with recurrent respiratory infections, who were divided into 2 groups: 61 children with primary immunodeficiency (PI) with clinical and laboratory disorders and 76 children with clinical symptoms but without laboratory and immunological confirmation of PI. 70 children were a control group. Based on data, the following parameters were analysed: birth body weight and length; body weight (BW) and height during hospitalization. Then this data was evaluated in relation to polish centile charts.

Results: During hospitalization 20% of patients with PI had their body weight and height below 3rd percentile. Almost every third child with diagnosed PI had his or her body weight below 3rd percentile at the day he/she was born. Based on their BMIs during hospitalization, 21,31% were underweight and 11,48% overweight. Among children with RRI (without laboratory immunological disorders) 7% had BW below 3rd centile and 13% had height below 3rd centile. 17% of children with recurrent respiratory infections were underweight and every fourth was overweight.

Conclusions: Results of the study indicate on influence of recurrent infections on physical development. It should be remembered that underweight and low height in developmental age always require to search for its cause and may be one of the PI syndromes.

POSTER 132 - MEASURING TREATMENT SATISFACTION IN PATIENTS WITH PRIMARY IMMUNODEFICIENCY DISEASES RECEIVING IMMUNOGLOBULIN INFUSIONS

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

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

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

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

POSTER 133 - PENTAGLOBIN USE EXPERIENCE AMONG PATIENTS WITH GENERAL VARIABLE IMMUNODEFICIENCY

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General variable immunodeficiency (GVI) belongs to primary immunodeficiencies with low level or absence of IgA, IgG and IgM in blood serum.

Starting from 2012 we saw a 36 year old patient, white, Caucasian, who has GVI from the age of 36 and had typical clinical manifestation of this disease. Immunologic research of humoral status showed a total absence of IgA, IgG and IgM immunoglobulines in this patient blood serum.

Before 2012 the patient had a full absence of any clinical GVI manifestations. She performed vaccinations on schedule and had rare intercurrent diseases. The patient had 3 pregnancies, all of them resulted in the act of natural delivery with no pathology. All the children are intact from the moment of birth and do not have any signs of immunodeficiency.

After GVI diagnosis confirmation, the patient, using the social benefits, received IgG in the dose of 0.8 g per kg on a monthly basis. The patient well tolerated the medication. But in 2015 the Ministry of Healthcare of Stavropol region purchased Pentaglobin and the patient crossed over to this medication. It is worth noting that there was a risk to give Pentaglobin to this patient due to absence of IgA in blood serum, so 60mg Prednisolone was administered. But this patient is tolerating medication well and still receives it in the prescribed dose without pre-medication.

Conclusion: GVI can have late manifestation and can be compensated for a long period of time. The risks of administering enriched immunoglobulines are reasonable due to development of anaphylactic reaction to IgA risks, but in the absence of IVIG, IgG can be an alternative as a lifetime therapy for patients with GVI.

POSTER 134 - HEALTH-RELATED QUALITY OF LIFE OF NORWEGIAN ADULTS WITH PRIMARY IMMUNODEFICIENCY

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Objective: Primary immunodeficiency diseases (PID) are characterized by recurrent or persistent infections which may impact the patient's qualitative experience or "quality of life" (QoL). QoL encompasses physical, psychological and social aspects of well-being. The aims of our study were to expand the limited systematic knowledge on the QoL of adults with PID in Norway, and to test a validated QoL instrument.

Design and method: We distributed a questionnaire that combines the World Health Organization Quality of Life questionnaire (WHOQOL-BREF), and the Common Variable Immune Deficiency Quality of Life questionnaire (CVID_QoL). The latter was developed by Quinti et al. (2016) and tested on Italian patients. The Centre for Rare Disorders (CRD) translated the CVID_QoL to Norwegian in accordance with the authors' guidelines.

Our sample consisted of 34 adults (25 women, 9 men; M = 48.8 years) with primary immunodeficiency, who attended a course organized by the CRD. Thirty-two patients had antibody deficiencies, with CVID as the largest group (N = 15). Thirty-three patients were receiving immunoglobulin replacement therapy.

Results: The Norwegian participants had significantly higher scores on the CVID_QoL than the patients in the study by Quinti et al. (2016), indicating lower quality of life. The distribution of scores was compared between the samples. In our study, tiredness was experienced often or always by 79% of the sample (47% in Quinti et al.), and 59% reported being often or always afraid that their health might worsen (29% in Quinti et al.). We calculated Cronbach's alpha for the three dimensions of the CVID_QoL: a) Emotional functioning, alpha = 0.90; b) Relational functioning, alpha = 0.79; c) Gastrointestinal and skin symptoms, alpha = 0.72; identical values were reported in the study by Quinti et al. (2016). The CVID_QoL-dimensions "emotional functioning" and "relational functioning" correlated strongly with all subscales on the WHOQOL-BREF: physical health, psychological domain, social relationships, and environment (range -0.570 to -0.850). The dimension "gastrointestinal and skin problems" did not correlate with the WHOQOL-BREF.

Conclusions: A group of Norwegian patients with PID reported significantly lower quality of life than the Italian patients in a study by the developers of the CVID_QoL, Quinti et al. (2016). The two samples also rated the impact of the symptoms differently. Cronbach's alpha was identical in the two CVID_QoL studies. In our study, two of the three dimensions in the CVID-QoL correlated strongly with the WHOQOL-BREF.

POSTER 137 - NEUROBLASTOMA AMPLIFIED SEQUENCE (NBAS) MUTATIONS; THE SPECTRUM OF DISEASE

AUTHORS

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Background: NBAS is a highly conserved gene which is thought to play a role in the Golgi-Endoplasmic reticulum retro-grade transport of vesicles. Germline mutations in NBAS were first associated with human disease in 2010. Homozygous mutations were reported in SOPH (short stature, optic nerve atrophy, and Pelger–Huët anomaly of granulocytes) syndrome in 33 Yakut patients. Bi-allelic/heterozygous mutations in NBAS were described in patients with recurrent episodes of acute liver failure, probably caused by IL-6 receptor mediated liver necrosis. Hypogammaglobulinaemia was found in a number of patients with NBAS loss-of-function mutation.

Objective: Here we report the clinical phenotype of two sisters with novel NBAS mutations who have a longstanding follow-up of over twenty years.

Patients and Methods: Two sisters known with achromatopsia, dwarfism and recurrent respiratory tract infections due to hypogammaglobulinaemia were referred in 1994. Clinical phenotypes are summarized in the table below. Patient 1 developed B-cell non-Hodgkin's lymphoma in 2013 for which she was successfully treated with chemotherapy and rituximab. Patient 2 developed an inflammatory osteoarthritis, for which she consecutively received DMARDS, rituximab and recently an interleukin-6-receptor inhibitor.

Results: Patient 1 had B-lymphocytes in and above the normal range since June 1994 until chemotherapy was started. T cell analysis revealed CD8+ T cell lymphocytosis. In Patient 2, B lymphocyte numbers were reduced under the reference values since 2006. Patient 2 also showed persistent CD4+ and CD8+ T cell lymphopenia. T-cell receptor repertoire analysis revealed a persistent oligoclonal expansion in peripheral blood and lymph nodes in both patients. Whole exome sequencing of both patients revealed three variants in NBAS; a nonsense mutation in exon 1 and two missense mutations in exons 8 and 13. The role of NBAS mutations in relation to hypogammaglobulinemia is currently under investigation.

Conclusion: NBAS mutations are causing a multisystem disorder involving bone, liver, retina and the adaptive immune system. Understanding the role of NBAS in the human immune system, especially in B cell development and function may provide new insights in the pathophysiology of hypogammaglobulinemia.

Table: Clinical phenotypes of two sisters with novel NBAS mutation

Clinical features and laboratory abnormalities	Patient 1	Patient 2
Age (years)	55	52
Race	Caucasian	Caucasian
Consanguinity	none	none
Stature	Dwarfism	Dwarfism
Skeletal dysplasia	+	+
Vitiligo (achromatism)	+	+
Liver disease	-	+
Pelger-Huët anomaly	+	+
Hypogammaglobulinemia	+	+
Bronchiectasis	+	-
Recurrent viral infections	+	+
Unspecified pruritis	-	++
Achromatopsia	+	+
Arthritis	-	+
Neoplasms	B-NHL	-

POSTER 138 - HEALTH RELATED QUALITY OF LIFE IN PATIENTS WITH COMMON VARIABLE IMMUNODEFICIENCY RECEIVING IMMUNOGLOBULIN REPLACEMENT THERAPY

AUTHORS

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Introduction: Health related Quality of Life (HRQoL) studies in patients with Common Variable Immunodeficiency (CVID) receiving immunoglobulin replacement therapy are scarce in The Netherlands. HRQoL examination is a tool that may contribute to a more personalized approach in the treatment of patients with CVID.

Objectives: We measured the HRQoL in patients with CVID, requiring immunoglobulin replacement therapy and compared them with the normative data of the Dutch population and with patients with cancer in order to determine the burden of disease.

Method: Sixty-five adult patients, (>18 years) diagnosed with CVID and receiving immunoglobulin replacement for at least six months, were invited to participate in a cross-sectional study. Patients were asked to complete the RAND-36, a generic validated questionnaire measuring HRQoL and a questionnaire about the demographic characteristics. Also the impact of disease related variables were investigated.

Results: Forty patients with CVID were included in the study and completed the RAND-36 form. Patients with CVID had lower scores in all dimensions of HRQoL compared with the normal Dutch population and significant lower scores in social functioning and general health, compared with patients with cancer. On the other hand, patients with CVID had significant higher scores in physical and emotional profiles than patients with cancer. The dimension general health is the most striking abnormal finding and low in all age ranges. Men have a significantly higher score in physical functioning than women, but significantly lower on vitality. There is no significant correlation shown in all HRQoL dimensions and IgG trough levels.

Conclusion: This study underlines the importance of quality of life research in patients with CVID. Patients with CVID have a lower HRQoL, especially a significantly low score on the dimension general health. Identification of patients at risk for a poor HRQoL provides an opportunity to introduce a more individualized therapy.

POSTER 141 - MUTATION OF IL12RB1 REVEALED BY BCGITIS: ABOUT 4 CASES

AUTHORS

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BCGitis is a local or regional inflammatory reaction due to infection with the vaccine bacteria, BCG. Disseminated BCGitis is a very serious and sometimes fatal complication occurring in one third of cases in children with primary immune deficiency, notably the syndrome of Mendelian Susceptibility to Mycobacterial Disease (MSMD), which is caused by defects in antimycobacterial immunity mediated by IL12/IFN γ axis. Those patients are predisposed to poorly virulent mycobacteria, such as bacillus Calmette-Guerin (BCG) vaccines and environmental mycobacteria (EM) and to Salmonella. Ten genes have been found to be mutated in children with this syndrome: IFNGR1 and IFNGR2, STAT1, IL12p40, IFN γ and IL12RB1, IKBKG, CYBB, IRF8 and ISG15.

IL12RB1, encode the β 1 chain of IL-12 receptor, expressed on NK and T cells, the stimulation of this receptor causes the synthesis and release of IFN γ , which plays an important role in antimycobacterial immunity.

In a retrospective study, we found 4 cases of children with BCGitis, from the clinical immunology unit of pediatrics 1. The IL12/IFN γ axis was explored by both the wholeblood assays and the sequencing of the coding regions of candidate genes. The 4 cases came from 4 different families, 1 boy and 3 girls. The average age at diagnosis is 5 months. All cases present BCGosis and one presented, several infections due to salmonella enteritidis: pericarditis, recurrent dysentery with colic infiltration. They were diagnosed with MSMD based on the results of immunological studies, and genetic analyses. Results show homozygous mutations of the same gene, IL12RB1. All patients receive four antiTB antibiotics with good evolution in two cases.

Vaccination by mistake of immunocompromised newborns, especially patients with MSMD, is an exposition to a high risk of BCGitis, and other complications. Morocco is greatly concerned by this situation, since vaccination is mandatory in neonatal period, where immune deficiencies are often unknown, and because of the high rate of consanguinity, increasing the number of genetic pathologies.

In general, this pathology has good prognosis, patients with defects in IL12R signaling pathway can be treated with antibiotics and recombinant human IFN γ ; for patients suffering from complete defects in IFN γ R signaling, the hematopoietic stem cell transplantation (HSCT) is the only curative option to date. An accurate molecular diagnosis is indeed crucial to determine the optimal treatment strategy for individual patients.

Keywords: Mendelian Susceptibility, Mycobacteria, BCGitis, BCGosis

POSTER 142 - AUTOIMMUNE LYMPHOPROLIFERATIVE SYNDROME (ALPS) : A PRIMARY IMMUNODEFICIENCY

AUTHORS

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Background: ALPS is a rare pathology characterized by immune dysregulation due to a defect in lymphocyte apoptosis. clinical manifestations may include lymphadenopathy, splenomegaly, cytopenias and increased risk of lymphoma .

Patients and methods : 5 patients reviewed in our clinical immunology unit, between 2010 and 2016
They were object of Clinical and biological investigations.

Results: We describe 5 cases, 1 girl and 4 boys, collected in the clinical immunology unit. consanguinity in two cases, the median age at presentation is 4 years and median age of clinical manifestations onset is 24 months. Splenomegaly is present in all patients, and accompanied by hepatomegaly in 60 % of cases. Lymphadenopathy is reported in 80%. CBC show cytopenia of one or more lineages in all patients. An other patient is followed since the age of 12 months for hemophilia A minor.

Furthermore, all these patients had an elevated level of circulating Double Negative T cells, hypergammaglobulinemia, and direct coombs test positive, the level vitamin B 12 was high in 60 %.

Treatment modalities are directed at the chronic and persistent lymphoproliferation and autoimmunity, corticosteroids and other immunosuppressants like MMF were the principal therapy. Unfortunately, all the patients have failed to show regression of splenomegaly and hepatomegaly, there cytopenia has been persistent. One of them showed resolution of cytopenia and organomegaly with a positive response to sirolimus.

conclusion: These cases reemphasize the fact that pediatricians should include a rare diagnosis such as ALPS.

POSTER 146 - CORRELATION BETWEEN SERUM AMOUNTS OF TOTAL IGE, C3 AND C4 LEVELS IN PATIENTS SUFFERED FROM IGA DEFICIENCY WITH AND WITHOUT ALLERGIC RHINITIS SYMPTOMS

AUTHORS

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Correlation between serum amounts of total IgE, C3 and C4 levels in patients suffered from IgA deficiency with and without allergic rhinitis symptoms

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Abstract: IgA deficiency association with the development of allergic disorders especially allergic rhinitis (AR) as well as the relation with the serum amounts of total IgE and C3 and C4 levels have led us to the design a study to determine whether serum IgE, C3 and C4 levels of children of IgA deficiency were related to with or without allergic rhinitis (AR) symptoms or not. In this cross sectional analytic descriptive study total serum IgE levels and serum concentration of C3 and C4 were measured by ELISA method in 64 children under seven years old suffered from serum IgA level less than 0.05 mg/ml with and without allergic rhinitis who were referred to the Children Ali Asghar Hospital of Zahedan city, Zahedan-Iran. 76.7% of patients were suffered from allergic rhinitis. The results showed that there was significant difference in high levels of total IgE levels (>185 IU/ml) and no significant difference in mean serum of C3 and C4 levels between group of AR patients and normal subjects of the same age. Furthermore, in patients with the absence of AR disease, 63.6% of them had significantly lower amount of serum C3 levels. Therefore our study showed that low amount of IgA, was strongly associated with the symptoms of AR and high levels of IgE.

POSTER 147 - A GAIN OF FUNCTION STAT3 MUTATION LEADING TO TUBERCULOSIS, AUTOIMMUNE AND LYMPHOPROLIFERATIVE MANIFESTATIONS

AUTHORS

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Introduction: STAT proteins are a family of transcription factors that mediate cellular response to cytokines and growth factors. STAT3 gain of function (GOF) mutations have been correlated to early onset lymphoproliferation and multi-organ autoimmunity together with increased risk of infections.

Case presentation: A 4 year-old girl, with a history of failure to thrive since the first year of life, delayed motor milestones and diagnosis of leishmaniasis (+ve PCR) was admitted for prolonged fever, hemolytic anemia, mediastinal lymphadenopathy, hepatosplenomegaly, and nonspecific rash. Imaging investigation revealed organizing pneumonitis-pleurisy and pericarditis. There was no response to antibiotics, ascitis and optic neuritis were added and the clinical condition was deteriorated. Acute phase proteins were elevated and TB was diagnosed at the 3rd month of the hospitalization by PCR in ascitic fluid, mediastinal lymph node and gastric fluid. Immunological work-up revealed no IFN-gamma production. A disorder downstream of IL-12 receptor was postulated. Anti-TB treatment and rIFN-gamma were administered without improvement. Prednisolone was initiated in the 5th month of disease with remission of fever and recurrence during all efforts of steroid tapering. On the 8th month of disease she developed hyperpyrexia and severe mucocutaneous necrotic lesions and was admitted at the ICU with respiratory, renal and heart failure and Posterior Reversible encephalopathy syndrome. Treatment with rIFN-gamma was withdrawn. Whole exome sequencing revealed a GOF mutation of the STAT3 gene [c.454C>Tp.(Arg152Trp)]. Prolonged administration of high dose steroids led to complete resolution of clinical manifestations and radiological findings; but hepatopathy insisted. Anti-il6 treatment (tocilizumab) was started together with gradual steroid tapering. After 11 months due to elevated liver enzymes, anti-TB treatment was discontinued. The patient is under close follow-up.

Conclusion: This case underlies the wide range of clinical manifestations of STAT3 mutations. Further studies are needed to clarify whether decreased IFN-gamma production contributes to intracellular infections.

POSTER 149 - FUNGAL PNEUMONIA IN A CHILD WITH CHRONIC GRANULOMATOUS DISEASE COMPLICATED WITH HEMOPHAGOCYTOSIS

AUTHORS

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Chronic granulomatous disease (CGD) is a genetic disorder of phagocyte function. It is characterized by recurrent and life-threatening bacterial and fungal infections and granuloma formation. The most common pathogens are *S.aureus*, *Serratia marcescens*, *B.cepacia*, *Aspergillus*, *Candida albicans*, *Nocardia* and *Salmonella*. Its clinical presentation is variable, clinical signs and symptoms of CGD usually occur in early infancy. In this case even if diagnosis of CGD is made early because of his brother has CGD, he had no any serious infection and hospitalization until nineteen year of age. He present with fungal pneumonia complicated with hemophagocytosis.

19-year-old boy with CDG admitted with non-productive mild cough for two month, mild fever for one month especially last week it reach to 39°C and become continuous. His repeated physical examination was normal, laboratory examination show leucocyte count 11.3007 mm³, C-reactive protein 55 mg/dL, sedimentation 114 mm/hour, chest radiograph showed peribronchial infiltrates. He was hospitalized, ampicillin-sulbactam was initiated. Computed tomography of thorax showed focal nodular opacities, cavities and halo sign on superior apical segment on right lung, galactomannan was positive. Intravenous voriconazole was initiated. Although voriconazole, teicoplanin and meropenem given in appropriate dose and time, his fever continued bicytopenia developed, ferritin and trigliserid levels increased. Bone marrow aspiration was done and hemophagocytic cells were observed. With diagnosis of hemophagocytosis IVIG was administered two times with 400 mg/kg/dose/day, but clinical response was not enough. Therefore steroids was initiated at 1 mg/kg/dose, after steroid treatment his fever was subside he clinically and laboratory recover, steroid treatment was continued to 14 days. Voriconazole treatment continued for 21 days, than it given as oral maintenance therapy and he was discharged. Although sign and symptoms of the CGD usually occur in early infancy, rarely it occurs late in adult age, and can be very serious and complicated.



POSTER 151 - THE DIFFICULTY IN DIAGNOSING CHRONIC GRANULOMATOUS DISEASE IN BRAZIL

AUTHORS

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Objective: To show a difficulty in diagnosing Chronic Granulomatous Disease in Brazil, due to the precariousness of places that perform the DHR test (dihydrorhodamine oxidation test), necessary for diagnosis.

The process that leads to the diagnosis of Chronic Granulomatous Disease is difficult, since it is a disease which diagnosis takes an average of 2 years and this delay is related to a poor prognosis. In Brazil, published case reports show children diagnosed between 5 and 10 years of age.

This work is based on a literature review and it was possible to realize that the most common manifestations of the disease are pneumonia, adenitis, cutaneous abscess, hepatic abscess, osteomyelitis. In addition, patients with Chronic Granulomatous Disease may have several chronic conditions caused by problems of incomplete resolution of infection or recurrent infections.

Diagnosis of primary immunodeficiencies is often time-consuming due to poor clinical knowledge of these diseases, which increases the risk of complications and death secondary to infections. Many cases are misdiagnosed, resulting in inadequate therapeutic measures.

The diagnosis of Chronic Granulomatous Disease is due to a history of severe and recurrent infections of early onset, and it is necessary to make the DHR (dihydrorhodamine oxidation test) for the diagnosis of Chronic Granulomatous Disease, however, it is difficult to have access to this test (DHR) in Brazil and in the state of Bahia, which has about 15 million inhabitants and only one place that does this exam, Hospital das Clínicas which is a research institution, where patients with suspected Chronic Granulomatous Disease need to be referred to a specific Ambulatory and then they are referred for DHR exam.

POSTER 152 - LATE ONSET COMMON VARIABLE IMMUNODEFICIENCY PRESENTING AS CYTOMEGALOVIRUS ASSOCIATED DEMYELINATION: A CASE REPORT**AUTHORS**S. MARIA ¹, E. YUNIHASTUTI ¹, R. ESTIASARI ²**AFFILIATIONS**¹ Allergy - Clinical Immunology Division, Internal Medicine Department, Faculty of Medicine University of Indonesia, Jakarta, INDONESIA, ² Division of Neuroinfection and Immunology, Neurology Department, Faculty of Medicine University of Indonesia, Jakarta, INDONESIA**Introduction:** Primary immunodeficiency is a rarely thought of diagnosis on adult patients. Our case highlights Common Variable Immunodeficiency (CVID) as a form of late diagnosis of primary immunodeficiency on adults.**Case Presentation:** A 39-year-old male was referred to our hospital for further evaluations. The patient was hospitalized repeatedly due to fever since 1.5 years prior to admission and his condition only improved after three weeks of antibiotics treatment. He also complained about gradual deterioration of motoric and cognitive functions. He grew weaker and less responsive to communication and often developed seizures while sleeping. Two days prior to admission, the patient had a seizure for 1.5 hours before becoming unconscious. A history of recurrent infections during childhood and adolescence periods was denied. He had non-consanguineous parents. On physical examination, we found GCS E3M5Vtube, severely ill, tachycardia 120 times/minute, normal temperature, breath rate 20 times/minute, rales in both lungs, frequent twitching, bilateral hemiparesis, and clonus on both upper and lower extremities. No visible abnormality on face and skin. Other physical examinations were unremarkable. Brain MRI showed multiple hyper intense T2 lesions in white matter with gadolinium enhancement lining the lesion. Cytomegalovirus (CMV) DNA was isolated from CSF and EEG revealed generalized slowing. From these finding we assumed CMV-associated demyelination. Despite the positive CMV DNA in his CSF, series of serum IgM and IgG to CMV remained negative. We also found normal lymphocyte count (1047 cells/uL), low CD19 in lymphocyte subset panel (absolute 38 cells/uL, percentage 4%), normal C3 and C4 levels, and normal IgG, IgM, and IgA levels with slight increase of IgE level. He was diagnosed with Common Variable Immunodeficiency. After the first admission to our hospital, he was repeatedly hospitalized due to respiratory and urinary tract infections. We gave IVIG 400 mg/kg IV every three weeks. There was no significant improvement on his neurological functions, but recurrent bacterial infection could be prevented with IVIG therapy.**Tabel 1. Complete blood count**

	Result						Normal Range
	10/10/2016	2/5/2016	03/12/2016	30/01/2017	18/02/2017	02/05/2017	
Hb	14.2	12.5	14.2	12.9	13.8	14.3	13.0 – 16.0 g/dl
Ht	42.5	36.7	43.3	39.7	41.9	44.2	40.0 – 48.0 %
WBC	15,210	12,980	21,680	6,790	13,900	9,810	5,000 – 10,000 /ul
Platelet	418,000	276,000	324,000	272,000	289,000	274,000	150,000 – 400,000 /ul
Diff count							
Bas	0.1	0.3	0.4	0.6	0.7	0.8	0 – 1 %
Eo	0.0	2.8	1.4	7.2	3.6	2.9	1 – 3 %
Neu	89.2	78.5	89.0	63.6	79.4	79.3	52.0 – 76.0 %
Lymph	5.6	13.2	3.8	20.2	11.0	12.1	20 – 40 %
Mo	5.1	5.2	5.4	8.4	5.3	4.9	2 – 8 %

Tabel 2. Normal Immunoglobulin and Complement Levels

Immunoglobulin	Result	Normal Range
IgE	355.4	<240 ng/mL
IgG	1450	700 – 1600 mg/dL
IgA	157	70 – 400 mg/dL
IgM	44	40 – 230 mg/dL
C3	164	90–180 mg/dL
C4	34.6	10.0–40.0 mg/dL

Tabel 3. Persistent low level of CD19 B cell

Lymphocyte Subset	Result						Normal range
	26/05/2016	12/07/2016	18/08/2016	09/1/2016	13/12/2016	03/01/2017	
Lymph CD45+ abs cnt	1564	1815	1451	1047	2018	1472	1000 – 4000 cells/ul
CD3+ %	81	71	65	80	59	72	55 – 84 %
CD3+ abs cnt	1263	1289	948	834	1198	1062	690 – 2540 cells/ul
CD8+ %				56	38	50	31–60 %
CD4+ abs cnt				585	749	718	410 – 1590 cells/ul
CD3+ CD4+ %	42	47	46				31 – 60 %
CD3+ CD4+ abs cnt	650	847	663				410 – 1590 cells/ul
CD8+ %				23	17	19	13 – 41 %
CD8+ abs cnt				242	358	295	190 – 1140 cells/ul
CD3+ CD8+ %	19	23	17				13 – 41 %
CD3+ CD8+ abs cnt	293	411	248	38			190 – 1140 cells/ul
CD19+ %	4	4	4	4	2	3	6 – 25 %
CD19+ abs cnt	57	67	63	38	41	49	90 – 660 cells/ul
CD16+ %				17	38	23	5 – 27 %
CD16+ abs cnt				174	755	345	90 – 590 cells/ul
CD16+ CD56+ %	29	22	28				5 – 27 %
CD16+ CD56+ abs cnt	446	396	413				90 – 590 cells/ul

Conclusion: Clinicians must be aware of adult onset Primary Immunodeficiency of which Common Variable Immunodeficiency is the most common. Late recognition of this disease may cause severe morbidity and mortality.

POSTER 154 - DIAGNOSIS OF PRIMARY IMMUNODEFICIENCY DISEASES AT THE MAJOR GREEK CENTER DURING THE LAST SIX YEARS

AUTHORS

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Introduction: Primary immunodeficiencies (PID) are a large group of heterogeneous, genetic and rare diseases, presenting with increased risk of infections, allergy, autoimmune and lymphoproliferative manifestations.

Aim: To estimate the diagnostic delay in PID patients, who were referred to our center in the period 2011-2016.

Methods: Data from medical records of PID patients who were diagnosed in our center during 2011-2016 were reviewed. The diseases were classified by the nine major groups of PID according to the International Union of Immunological Societies (IUIS) expert committee. Patients with unclassified Immunodeficiency, Selective IgA deficiency and Transient Hypogammaglobulinaemia of Infancy were not included.

Results: 56 (36 male/ 20 female) patients diagnosed with PID were distributed in the following categories:

	No. of Patients	Percentage	Mean Diagnostic Delay (months)	Range (months)
Immunodeficiencies affecting cellular and humoral immunity	9	16%	8.6	0-48
Combined immunodeficiencies with associated or syndromic features	14	25%	19.44	0-108
Predominantly antibody deficiencies	12	21.4%	58.54	0-184
Diseases of immune dysregulation	8	14.3%	35.1	0-132
Congenital defects of phagocyte	7	12.5%	67.7	0-288
Defects in intrinsic and innate immunity	5	8.9%	36	0-120
Autoinflammatory disorder	1	1.8%	2	
Complement deficiency	2	3.6%	78	24-120

Conclusion: The last 6 years, 9.3 patients per year had been diagnosed with a certain Primary Immunodeficiency in our center. The actual rate have been estimated at about 10 patients/year excluded unclassified PID, SIgA deficiency and Transient Hypogammaglobulinaemia of Infancy. The diagnostic delay, resulting from the clinical heterogeneity of the disease, varies even in Combined Immunodeficiencies. It seems that the severity of the clinical manifestations and complexity implies the early investigation and diagnosis. The increase of knowledge, the awareness and the education of physicians will contribute to the early diagnosis of PIDs with significant improvement of the prognosis and the quality of life.

POSTER 155 - COMMON VARIABLE IMMUNODEFICIENCY : ABOUT 25 CASES

AUTHORS

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Common variable immune deficiency (CVID) is a primitive immune deficiency of humoral immunity characterized by hypogammaglobulinemia, responsible for recurrent bacterial infections. It presents a great clinical heterogeneity, which will be illustrated by the observations that will be reported.

Methods: A retrospective multicenter study of the clinical manifestations of patients meeting the criteria for CVID.

Results: There are 25 patients, 13 males and 12 females. CVID is diagnosed in 18 patients before 15 years and in 7 patients after 15 years, one of them at 56 years. Sixteen of our patients are from consanguineous marriages.

Diagnosis was made in the presence of repeated infections (mainly pneumonia in 21 cases, including 11 cases of bronchiectasis, and ENT infections in 10 patients), and / or chronic diarrhea (15 cases).

All our patients have profound hypogammaglobulinemia, with B lymphocytes present.

Nine of our patients show autoimmune manifestations, sometimes multiple (4 cases of autoimmune hemolytic anemia, 4 cases of idiopathic thrombocytopenic purpura, 1 case of alopecia plaque and 1 case of primary biliary cirrhosis). Eight patients have splenomegaly.

One patient presented systemic granulomatosis, and two patients, with sarcoidosis. A neoplastic complication occurred in a patient, germline type.

All our patients are treated by immunoglobulin infusion and antibiotic prophylaxis. Six of our patients died.

Conclusion: This series illustrates the great diversity of clinical manifestations related to CVID, responsible for difficulty and delay in diagnosis.

POSTER 156 - FREQUENT AUTOINFLAMMATORY DISEASES IN MOROCCO : FAMILIAL MEDITERRANEAN FEVER AND MEVALONATE KINASE DEFICIENCY :ABOUT 8 CASES

AUTHORS

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Autoinflammatory syndromes are hereditary diseases caused by mutations in genes involving the innate immunity, they have a common clinical profile of recurrent fevers intersected with irregular intervals and a biological inflammation during crisis periods. From these diseases, Familial Mediterranean fever (FMF), mevalonate kinase deficiency (MKD), are the most reported.

In this study, we report eight cases with four FMF and four MKD at A. Harouchi Children Hospital.

Four girls were diagnosed and genetically confirmed FMF with an average age of 9 years (5-12 years) from consanguineous union, have fever associated with abdominal pain, arthralgia and arthritis, as well as rashes, present in 3 cases. MKD was diagnosed for three girls and one boy with an average age of 6.75 years (2-14 years). The main clinical presentation is represented by febrile periods during 2 to 3 days, separated by an asymptomatic interval. Febrile episodes are associated with adenopathies in all cases and splenomegaly in three cases. Arthralgias are present in all patients and complicated with arthritis in 3 cases. Abdominal pain was noted in 50% of patients. The polymorphic rash is found in 3 cases. The diagnosis was first based on a clinical profile associated with an increased excretion of urinary mevalonic acid in 3 cases and genetic test finding V337I heterozygous mutation in one case. All patients had inflammatory biological syndrome.

POSTER 159 - EFFECT OF CHRONIC PHYSICAL STRESS ON IMMUNE SYSTEM

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Background: Physical stress affects most people in some way, but prolonged exposure to physical stress can negatively affect all body systems including immune system. Chronic stress suppresses the immune system and its functions, which can lead to an increase in the susceptibility to infections and cancer.

Objective: Investigating the effect of chronic physical stress on some parameters of immune system.

Patients and Methods: This study has been carried out on 50 patients subjected to chronic physical stress, and 20 healthy persons of matched age and sex as a control group. Serum cortisol level (fasting, morning), IgG, IgM, IgA, C3 and C4 were measured, in addition to CBC and leucocyte differential count.

Results: There was a positive correlation between cortisol level and chronic physical stress, and a negative correlation between chronic stress and IgG and IgA levels. Results also revealed a statistical significant increase in WBCs count in the case group.

Conclusions: Chronic stress has a deleterious effect on immune system.

Key words: Chronic stress, immune system, immunoglobulins, complement.

POSTER 165 - SENEQA: STUDY ON THE UTILISATION OF HYQVIA (10% NORMAL IMMUNOGLOBULIN AND RECOMBINANT HUMAN HYALURONIDASE) IN ELDERLY PATIENTS

AUTHORS

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Background: HyQvia is a dual-vial unit consisting of recombinant human hyaluronidase (rHuPH20) and 10% normal immunoglobulin (IgG) solution. IgG provides the therapeutic effect and rHuPH20 facilitates dispersion and absorption of the IgG, increasing its bioavailability. In the registration study, HyQvia was effective, safe, and bioequivalent to intravenous IgG at the same administration intervals, with fewer systemic reactions. HyQvia received market authorization in the European Union in July 2013 for the treatment of patients with primary (PID) and secondary (SID) immune deficiencies. In the USA, HyQvia was approved in September 2014 for adult patients with PID.

Aims: To assess the suitability of HyQvia in elderly patients with PID or SID.

Methods: The SENEQA study is a retrospective chart review of elderly patients in several institutions in the Netherlands and Germany. Collected parameters comprise patients' disease characteristics, previous and current immunoglobulin G (IgG) replacement regimens, self-administered versus assisted infusions, infusion parameters, serum IgG levels, infections, and pharmacoeconomic parameters. Detailed information on the most recent HyQvia application is documented. Patients are eligible for participation if they have provided written informed consent, are at least 65 years old, have PID or SID, and received at least 1 HyQvia infusion in the past. No explicit exclusion criteria have been specified to avoid selection bias. The goal is to enrol a minimum of 10 patients. Currently, 9 patients have been enrolled; the first enrolled in November 2016. Database lock is expected end of May 2017.

Conclusions: SENEQA is expected to provide real-life data on HyQvia in elderly patients, complementing data from the controlled trial.

POSTER 166 - CASE REPORT: SUCCESSFUL TREATMENT OF LEUKOCYTE ADHESION DEFICIENCY TYPE 1 SYNDROME AND RECURRENT PYODERMA GANGRENOSUM WITH ALLOGENEIC STEM CELL TRANSPLANTATION

AUTHORS

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Objective: Here we report a case of a 30-year old man with moderate and incomplete leukocyte adhesion deficiency type I syndrome (LAD-1) with therapy-resistant recurring pyoderma gangrenosum, including failed treatment with cyclosporine, prednisolone, methotrexate, azathioprine, infliximab and adalimumab, in which we demonstrate that allogeneic stem cell transplantation is a possible curative treatment for this condition, with a successful outcome in this patient.

Design and method: The patient underwent a bone marrow transplantation ($2,6 \times 10^8$) total nucleic marrow cells/kg; $1,7 \times 10^6$ CD34+ cells/kg) with a matched unrelated donor in August 2016, following a conditioning regimen of fludarabine 30 mg/m² and treosulfan 14 g/m² once daily i.v. for 5 and 3 days, respectively, as well as anti-thymocyte globulin 6 mg/kg i.v. distributed in 4 days. Following transplantation, the patient received immunosuppressive treatment with oral cyclosporine (target concentration 150-200 ng/ml).

Results and conclusions: Hematopoietic engraftment occurred day +21 with an absolute neutrophil count of $0,5 \times 10^9$ /L, after receiving treatment with 300 µg G-CSF for 5 consecutive days. The patient displayed a state of complete chimerism day +26. A successive healing of the patient's skin lesions followed, with no new lesions observed by the patient's treating dermatologist 2 months post-transplantation. However, in December 2016 the patient exhibited a mixed chimerism, confirming transplant rejection 4 months post-transplantation. The patient has nevertheless to this date, 9 months post-transplantation, remained in complete remission from pyoderma gangrenosum. A re-transplantation was planned in March 2017 with the same donor, but had to be postponed due to detection of asymptomatic invasive pulmonary aspergillosis, which is currently being successfully treated with oral posaconazole. The onset of invasive fungal infection highlights the necessity of re-transplantation for curative treatment of both the patient's LAD-1 and pyoderma gangrenosum conditions. The patient is currently planned to undergo re-transplantation in August 2017, after which new results shall be available as a supplement.

POSTER 170 - 22Q11.2 DELETION SYNDROME THE CAUSE OF PHYSICAL DEVELOPMENT DISORDERS – CASE REPORT

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22q11.2 deletion syndrome (DiGeorge syndrome) is the most common chromosome microdeletion disease occurring in approximately 1:3000 births. The main symptoms of DGS are: congenital heart disease, an immune deficiency, characteristic facial features, palatal abnormalities and learning difficulties. The disease is characterized by full penetration and very variable expression. Which means that any person with a mutation causing this syndrome will have some symptoms but they are incredibly diverse.

The patient was a male born with congenital heart disease (VSD, PDA) and facial abnormalities. At first, fed with a nasogastric tube, in spite of poor suction and swallowing reflexes, was gaining weight. In the 4th week of life, pulmonary banding and ligation-PDA were performed. Postoperative course complicated by respiratory failure, probably on the background of diaphragm relaxation appendicular necrosis. At 2 months old, after genetic counseling, suspicion of the 22q11.2 microdeletion syndrome was suspected. In the following months, symptoms of heart failure were observed. In 5 months of life, the boy was reoperated. In 6 months of life, based on the FISH study DGS was diagnosed. In the following months of life several respiratory failure occurred in the course of respiratory tract infection. At 9 months of age the boy was operated again - Nissen fundoplication and gastrostomy was established. From 8 to 19 months of age, healed for treatment IVIG.

The case report shows that patients with DGS require constant multi-specialty care.

POSTER 171 - LABORATORY DIAGNOSIS OF PRIMARY IMMUNODEFICIENCIES: WHICH TEST, WHICH METHOD?

AUTHORS

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Primary immunodeficiencies (PIDs) represent a large group of conditions, characterized by an inborn error of immune system. Clinically, patients generally present susceptibility to a broad or narrow spectrum of pathogens, but can also present autoimmunity, inflammation, neoplasia,...

Diagnosis is based on the confrontation of clinical signs and biological results. Clinical immunology laboratories have a central role in the diagnostic approach and the choice of test panel and method is important to pinpoint the right diagnosis. The availability of age-related reference value is also necessary for a good interpretation of laboratory results.

Our aim is to present the required tests for first-line and second-line investigations in PID diagnosis, with the advantages and pitfalls of each method proposed on the market. Depending of the resources, three levels of panels can be offered, from the most basic ones (HIV serology, CBC and protein electrophoresis) to the most specific ones (molecular biology, extended lymphocyte count,...).

Cooperation between national and international laboratories is the success key to answer the needs of physicians for improved diagnosis and appropriate management.





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