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INTRODUCTION TO PRIMARY IMMUNODEFICIENCY DISEASES IN ALGERIA

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ALGIERS – ALGERIA.

Primary immunodeficiency diseases (PID) are a group of heterogeneous, rare, genetic disorders that affect specific components of immune system leading to serious complications. Affected individuals, mainly children, are susceptible to increased rate and severity of infections, autoimmune disorders and malignancies.

The study of the trends of PID epidemiology, clinical presentations, treatment and outcome has been facilitated in many countries by establishing national registries of PID. In Africa and the Middle East, there is an emerging medical literature on PID in many countries (1-4). In Algeria, there is no national PID registry at the present time, and hence, the prevalence of these disorders in our population is still unknown.

For this purpose, a group from the Algerian society of pediatrics with the collaboration of many immunologists conducted a retrospective multicenter study, including all children with PID who were diagnosed during the period from 1985 to March 1st 2015, in 13 departments of pediatrics mainly from the central region of the country with some patients from eastern and western region hospitals. PIDs were classified according to the International Union of Immunological Societies expert committee for primary immunodeficiency (5).

This study presents 409 patients (aged 0 – 17 years) with diagnosis of PID. There were 246 boys and 163 girls with a male-to-female ratio of 1.51:1. For all patients, the mean onset age was 11.95 months (0 – 120 months), the mean age at diagnosis was 37.3 months (0 – 180 months), and the mean time between the onset of symptoms and diagnosis was 24.2 months (0 – 169 months). 193 patients (47.2 %) were products of consanguineous parents, often first cousin (60 %). A family history of early death in siblings was found in 35 %. 82 children were siblings from 35 different families.
Patients are distributed into 9 categories as depicted in (figure 1). The predominant categories were combined T and B cell immunodeficiency (ID) and predominantly antibody deficiencies, equally represented with 32% each. Of combined ID category, CMH II deficiency was the most frequent condition followed by severe combined ID (SCID). Within the well defined syndromes with ID, Wiskott Aldrich syndrome and ataxia-telangiectasia were equally predominant. The most common phenotype found in the predominantly antibody deficiencies category was agammaglobulinemia condition followed by CVID. Chronic granulomatous disease (CGD) was the most common condition in the category of congenital defects of phagocyte number, function, or both. The different PID encountered among the patients of this series and their frequencies are listed in (Table I).

Patients showed a wide spectrum of clinical manifestations dominated by recurrent respiratory infections (71.3%), chronic diarrhea (35.8%), growth failure (35.5%), skin infections (26.5%), digestive candidiasis (24.8%), prolonged fever (24.5%), and recurrent otitis (24%). (Table II) reveals microbial isolates from 174 patients (42.5%).
### Table I. Different categories of PID in Algerian children

<table>
<thead>
<tr>
<th>Category</th>
<th>Number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1) Combined T – B cell ID</strong></td>
<td></td>
</tr>
<tr>
<td>- T- B- SCID</td>
<td>22 (5.4)</td>
</tr>
<tr>
<td>- T- B+ SCID</td>
<td>24 (5.9)</td>
</tr>
<tr>
<td>- CMH II deficiency</td>
<td>60 (14.7)</td>
</tr>
<tr>
<td>- CD40 ligand deficiency</td>
<td>01 (0.2)</td>
</tr>
<tr>
<td>- Omenn syndrome</td>
<td>08 (2.0)</td>
</tr>
<tr>
<td>- CD4 deficiency</td>
<td>03 (0.7)</td>
</tr>
<tr>
<td>- Others</td>
<td>14 (3.4)</td>
</tr>
<tr>
<td><strong>2) Well defined syndromes with ID</strong></td>
<td>60 (14.6)</td>
</tr>
<tr>
<td>- Ataxia-telangiectasia</td>
<td>20 (4.9)</td>
</tr>
<tr>
<td>- Wiskott Aldrich syndrome</td>
<td>22 (5.4)</td>
</tr>
<tr>
<td>- Hyper-IgE syndromes</td>
<td>16 (3.9)</td>
</tr>
<tr>
<td>- Comel Netherton syndrome</td>
<td>02 (0.5)</td>
</tr>
<tr>
<td><strong>3) Predominantly antibody deficiencies</strong></td>
<td>132 (32.2)</td>
</tr>
<tr>
<td>- Agammaglobulinemia</td>
<td>54 (13.2)</td>
</tr>
<tr>
<td>- CVID</td>
<td>35 (8.6)</td>
</tr>
<tr>
<td>- Hyper-IgM syndrome</td>
<td>14 (3.4)</td>
</tr>
<tr>
<td>- Selective IgA deficiency</td>
<td>05 (1.2)</td>
</tr>
<tr>
<td>- IgG subclass deficiency</td>
<td>04 (1.0)</td>
</tr>
<tr>
<td>- Others</td>
<td>20 (4.9)</td>
</tr>
<tr>
<td><strong>4) Diseases of immune dysregulation</strong></td>
<td>23 (5.7)</td>
</tr>
<tr>
<td>- Chediak Higashi syndrome</td>
<td>06 (1.5)</td>
</tr>
<tr>
<td>- Griscelli syndrome</td>
<td>04 (1.0)</td>
</tr>
<tr>
<td>- Familial hemophagocytic lymphohistiocytosis syndromes</td>
<td>10 (2.5)</td>
</tr>
<tr>
<td>- IPEX</td>
<td>03 (0.7)</td>
</tr>
<tr>
<td><strong>5) Congenital defects of phagocyte number, function, or both</strong></td>
<td>37 (9.1)</td>
</tr>
<tr>
<td>- Severe neutropenia</td>
<td>10 (2.5)</td>
</tr>
<tr>
<td>- Chronic granulomatous disease</td>
<td>19 (4.7)</td>
</tr>
<tr>
<td>- Leukocyte adhesion deficiency type 1</td>
<td>05 (1.2)</td>
</tr>
<tr>
<td>- MSMD</td>
<td>02 (0.5)</td>
</tr>
<tr>
<td>- TNF alpha deficiency</td>
<td>01 (0.2)</td>
</tr>
<tr>
<td><strong>6) Defects in innate immunity</strong></td>
<td>04 (1.0)</td>
</tr>
<tr>
<td>- Chronic mucocutaneous candidiasis</td>
<td>04 (1.0)</td>
</tr>
<tr>
<td><strong>7) Autoinflammatory disorders</strong></td>
<td>03 (0.7)</td>
</tr>
<tr>
<td>- Familial Mediterranean fever</td>
<td>01 (0.2)</td>
</tr>
<tr>
<td>- Hyper IgD syndrome</td>
<td>02 (0.5)</td>
</tr>
<tr>
<td><strong>8) Complement deficiencies</strong></td>
<td>04 (1.0)</td>
</tr>
<tr>
<td><strong>9) PID unclassified</strong></td>
<td>14 (3.5)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>409 (100)</td>
</tr>
</tbody>
</table>
Table II. Microbial isolates from PID patients

<table>
<thead>
<tr>
<th>Germs</th>
<th>Number</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bacterial isolates</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pseudomonas aeruginosa</td>
<td>42</td>
<td>24.1</td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
<td>55</td>
<td>31.6</td>
</tr>
<tr>
<td>Other encapsulated germs</td>
<td>47</td>
<td>27</td>
</tr>
<tr>
<td>Mycobacterium tuberculosis</td>
<td>09</td>
<td>5.2</td>
</tr>
<tr>
<td>Others</td>
<td>37</td>
<td>21.3</td>
</tr>
<tr>
<td><strong>Viral isolates</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cytomegalovirus</td>
<td>18</td>
<td>10.3</td>
</tr>
<tr>
<td>Epstein Barr virus</td>
<td>09</td>
<td>5.2</td>
</tr>
<tr>
<td>Others</td>
<td>11</td>
<td>6.3</td>
</tr>
<tr>
<td><strong>Fungal / parasitic isolates</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspergillus spp.</td>
<td>07</td>
<td>4</td>
</tr>
<tr>
<td>Candida spp.</td>
<td>57</td>
<td>32.7</td>
</tr>
<tr>
<td>Pneumocystis jiroveci</td>
<td>14</td>
<td>8</td>
</tr>
<tr>
<td>Cryptosporidium</td>
<td>11</td>
<td>6.3</td>
</tr>
</tbody>
</table>

Use of intravenous immunoglobulin (IVIG), antibacterial and antifungal prophylaxis varied according to PID category. IVIG were mainly used in combined ID (86% of patients) and predominantly antibody deficiencies (92% of patients). The use of prophylactic antibacterial and antifungal medications was required by 30.1% and 14.7% of the patients.

Bone marrow transplantation (BMT) was performed, mainly abroad, in 8 patients (3 Wiskott-Aldrich syndrome, 2 SCID, 1 CMH II deficiency, 1 CD4 deficiency, 1 CGD) at a mean age of 65 months (7 – 192 months). 2 patients (25%) died and 6 others (75%) survived.

Genetic studies were performed abroad in only 6 patients.

The global mortality in this series affected 104 children (48.5%) at a mean age of 40 months (0 – 240 months) with also 56 patients lost at follow-up (13.7%).

This study indicates that PIDs are not rare in Algeria and their number may be more important since all patients in the country don’t have equal access to special medical care. Children with recurrent infections, chronic diarrhea and growth failure should raise high index of suspicion on possibility of PID among physicians. While in the Maghreb, Tunisia and Morocco have made great progress in this area, Algeria has a large delay, especially in the therapy since the transplant of bone marrow in children is not yet used by pediatricians. This delay is caused by a bad organization of the national health system, where Pediatrics remains generalist, with lack of Pediatric subspecialties and children’s hospitals, two conditions necessary for the formation and development of Hematology, Immunology and pediatric Oncology. At the moment, strategies should be adopted to reduce mortality and morbidity of PID in Algeria by establishing national PID register and BMT program and effective cooperation with neighboring countries.

**Acknowledgments to the Algerian Study group on PID:**

References:

   J Clin Immunol; 34(4):459-68
   Les déficits immunitaires primitifs en Tunisie : étude de 152 cas.
   Arch Pediatr ; 4 : 827 – 831.
   Primary immunodeficiency diseases in Egyptian children: A single center study.
   Primary immunodeficiency diseases in children: 15 year experience in a tertiary care medical center in Qatar.
   Primary immunodeficiency diseases: an update on the classification from the International Union of Immunological Societies Expert Committee for Primary Immunodeficiency.
Primary Immunodeficiencies (PIDs) are a large group of disorders affecting the immune system, and leading to susceptibility to a broad spectrum of infections. PIDs are generally considered as rare diseases and meet little or no interest with Health Authorities. However, recent studies tended to suggest that PIDs were more common that generally thought.

Indeed, recent population-based epidemiologic studies revealed a PID prevalence of 86.3/100,000 inhabitants [1] or an incidence reaching 10.3/100,000 people-years [2] in USA. Extrapolation of these figures led us to an estimation of at least 6 million cases worldwide [3]. These prevalence or incidence suggest that PIDs are globally not rare, as they are more frequent than the global number of Tuberculosis (around 5.7 million cases) or Leukemia, already placing it as a Health Public issue and highlighting the underreport of these diseases worldwide.

In Africa, one of the most populous continents, there is a large underdiagnosis, as barely 2,500 PID patients were reported at the best of our knowledge, when estimations suggest that at least 950,000 African should live with a PID.

Moreover, these estimations are based on the classical definition of PIDs, i.e. as diseases leading to susceptibility to a broad spectrum of infections. However, recent advances proved that, besides the classical PIDs, “inborn errors of immunity” can also lead to susceptibility to only one pathogen or one narrow group of pathogens [4]. For example, it was estimated that 30-50% of severe tuberculosis in children was probably due to an inborn error of immunity. Likewise, studies tend to prove that Herpes simplex encephalitis, invasive pneumococcal or fungal disease, or even severe flu are due to a primary immunodeficiency.

Considering this new concept of PID predisposing to one type of infection, the previous estimations (6 million PID cases worldwide) would be largely underestimated. For tuberculosis alone, WHO reported a mortality of 13/100,000 inhabitants due to tuberculosis (in non-HIV people). If we consider than 40% of these deaths are due to severe tuberculosis on an underlying PID, this means that more than 360,000 cases of tuberculosis were due to an underlying defect. Another major cause of death in children of less than 5 years is acute respiratory infections (15% of deaths). Studies on community-acquired pneumonia suggested that 1-2% of these cases were due to an Antibody deficiency. So around 15,000 deaths due to pneumonia worldwide could have been underlied by an antibody defect.

Moreover, our estimations didn’t take in account the effect of inbreeding. Indeed, the epidemiologic studies were realized in USA, where the consanguinity is really low (<1%). In Africa, consanguinity rates range from 0.4-52%. In North Africa, for example, with a consanguinity around 20%, the corrected estimation would be 349/100,000 inhabitants.
(assuming that 20% of the PIDs are recessive disorders in USA). Based on this corrected prevalence, there would be 25 millions of PID cases in Africa, even reaching 26 million if we take into account severe tuberculosis or pneumonia probably due to an underlying defect.

In conclusion, these results tend to prove that Primary immunodeficiencies play a significant role in Public Health issue. Health Authorities should not dismiss this issue as being “rare” and should be more involved in unraveling the real prevalence of these disorders and improve their diagnosis and management.

References:

A SYSTEMATIC APPROACH TO THE DIAGNOSIS OF NOVEL PRIMARY IMMUNODEFICIENCIES

Craig D. Platt, MD, PhD, Raif S. Geha, MD, Janet Chou, MD

*Division of Immunology, Boston Children’s Hospital and Department of Pediatrics, Boston Children’s Hospital, Harvard Medical School.

Abstract:

There are 10,000 genes expressed in immune cells. There are about 300 different genetic causes of primary immunodeficiencies (PIDs) identified to date. Thus, potentially mutations in more than 87% novel genes that can cause PIDs remain to be discovered. Three strategies are used for identifying causative mutations in PIDs: (1) educated guesses based on known signaling pathways essential for immune cell development and function, (2) similarity of clinical phenotypes to mouse models, and (3) unbiased genetic approaches. Next-generation DNA sequencing permits efficient sequencing of whole genomes or exomes but also requires strategies for filtering vast amounts of data. We illustrated these strategies using recently identified primary immunodeficiencies to illustrate the strategies, and discuss technologies, and potential pitfalls in finding novel causes of these diseases.

Keywords: primary immunodeficiencies, whole genome sequencing, whole exome sequencing, linkage analysis, homozygosity mapping

I- Introduction:

Over the past four decades, approximately 300 molecular defects causing primary immunodeficiencies (PIDs) have been discovered through advances in immunology and genetics. Since the majority of PIDs are monogenic, whole exome/genome sequencing has expedited the discovery of pathogenic mutations, particularly when combined with classical methods of identifying genetic defects. Although there are many published examples, this review will focus on a selection of cases to illustrate benefits and limitations of a spectrum of approaches, which includes: 1) educated guesses based on known signaling pathways essential for lymphocyte development and function, 2) similarity of clinical phenotypes to mouse models, and 3) unbiased genetic approaches.

II- “Educated guess” based on known molecular pathways:

Knowledge of signaling pathways establishes a conceptual framework that links clinical phenotype and disease inheritance pattern to potential molecular defects. When the data suggests candidate genes for a PID, targeted sequencing of these genes is the most efficient approach. This has been instrumental for identifying autosomal causes of diseases that were originally discovered as X-linked disorders. A classic example involves the discovery of the defects underlying hyper-IgM syndrome. The identification of CD40 ligand on activated T cells as a critical signal for class-switching set the stage for the discovery of CD40 ligand deficiency as the cause of X-linked hyper-IgM syndrome (1). The subsequent discovery of CD40 deficiency as a cause of autosomal recessive hyper-IgM syndrome was built on the understanding of the CD40-CD40L interaction in B cell differentiation and class switching (2).

Known pathways can also guide a targeted sequencing approach to specific clinical phenotypes, such as chronic mucocutaneous candidiasis (CMC). CMC is a feature of patients with defects in the IL-17 pathway, such as those with STAT3 deficiency and a resultant lack of Th17 cells, or patients with neutralizing autoantibodies against IL-17A and IL-17F (3). This knowledge prompted the discovery of the first human mutations in the genes encoding the IL-17 receptor in patients with CMC (4). A major limitation of this approach is that hypomorphic mutations in a particular gene can lead to variable and unexpected phenotypes. For example, a mutation in CORO1A, which encodes the actin binding protein coronin-1A, was initially described as a cause of SCID (5), but has also been found to cause T cell lymphopenia and EBV-associated lymphoproliferation (6).

III- Similarity of clinical phenotypes to murine models of disease:

Mouse models demonstrate the effects of a mutation without the confounding environmental and genetic factors that affect human patients. Pathogenic mutations can be identified based on phenotypic similarities between the mouse models and patients. This approach was used to identify the first patient with a mutation in WIPF1 (7), which encodes a chaperone protein necessary for stabilizing Wiskott-Aldrich syndrome protein (WASP) (8). This case involved a girl who presented with immunodeficiency, eczema, and thrombocytopenia. Despite phenotypic features suggestive of Wiskott-Aldrich syndrome, her WAS gene sequence was normal and she had additional immune defects inconsistent with WAS: absence of T cell proliferation to anti-CD3 stimulation, defective T cell response to IL-2, and normal platelet size. These features are found in WIP-deficient mice. Targeted Sanger sequencing of WIPF1 identified a homozygous nonsense mutation as the cause of this autosomal recessive disease.

Additionally, mouse models can be used to prioritize a candidate gene list, as was the case in a family with congenital asplenia. Whole exome sequencing of three affected siblings yielded 32 candidate genes (9). Only one of these genes, NKX2-5, encoded a transcription factor essential for mouse spleen development (10). The importance of this mutation was confirmed through subsequent in vitro studies that showed that the mutation abolished NKX2-5 function (9).
A limitation of this approach is that mouse models do not always recapitulate human disease. For example, TANK-binding kinase 1 (TBK1), a serine/threonine kinase downstream of Toll-like receptor 3 (TLR3) is important for multiple antiviral and antibacterial pathways in mouse models (11), suggesting that TBK1 deficiency would manifest as broad susceptibility to viral and bacterial pathogens. However, TBK1 deficiency in humans is a risk factor only for HSV encephalitis (12). The mouse model of TBK1 deficiency therefore failed to predict the limited scope of human disease.

IV- Unbiased genetic approaches:

When knowledge of signaling pathways and animal models do not suggest candidate genes, genetic techniques have been instrumental for identifying pathogenic mutations. In the mid 2000s, next generation sequencing (NGS) revolutionized genetics by making it possible to sequence entire human genomes within days. NGS encompasses a variety of methods that simultaneously amplify and sequence millions of DNA fragments (13). Although this technology offers comprehensive sequencing data, it is challenging to distinguish pathogenic variants within the 3.2 billion bases present in the human genome (14). To further focus NGS data, sequencing can be limited to only the coding region of the genome, known as the exome. While the exome constitutes only 1% of the genome, it harbors approximately 85% of deleterious mutations (15). Whole exome sequencing (WES) identifies an average of 20,000 single nucleotide variants per exome, which can be further narrowed with the addition of older bioinformatic tools such as linkage analysis and homozygosity mapping (13).

When studying consanguineous families, homozygosity mapping is an especially effective means of narrowing the candidate gene list identified by WES. Homozygosity mapping assumes that the causative mutation for an autosomal recessive disease occurs within a locus containing clusters of homozygous SNPs specific to the affected individuals and inherited from a common ancestor (16). The elimination of synonymous variants, which alter DNA but not amino acid sequences further decreases the candidate gene list. For rare diseases, common variants with an allele frequency >1% in public SNP databases can be eliminated (13). Additionally, bioinformatics algorithms such as Polyphen-2 or SIFT can be used to identify missense mutations that may result in altered protein function (17-19). Lastly, candidate genes are filtered based on gene function and expression. Genes essential for immune function, such as those important for lymphocyte development, are prioritized; conversely, those unrelated to immune function, such as the genes encoding the olfactory receptors, can be excluded.

The combination of homozygosity mapping and WES is an increasingly common approach for identifying genetic defects underlying PID. LRBA deficiency was identified through homozygosity mapping and WES in a consanguineous family with chronic inflammatory bowel disease and a combined immunodeficiency (20). In another example, homozygosity mapping and WGS of two consanguineous parents and 1 patient identified a missense mutation in MALT1, which encodes a cysteine protease important for NF-kB activation, as a cause of combined immunodeficiency (21).
V- Pitfalls When Using an Unbiased Approach:

Although these techniques have greatly expedited the discovery of pathogenic mutations, there are limitations inherent in WES/WGS. The remainder of this review highlights some of these difficulties and discusses how recent studies have addressed them.

WES will not detect mutations in non-coding regions, as this technology primarily captures only exonic regions. Furthermore, when WGS is used, the impact of a variant in a non-coding region is frequently unclear. However, identification of a causative intronic mutation remains possible when: (1) a candidate gene is identified based on the clinical phenotype and (2) the mutation severely impairs protein expression. This was the case for the identification of intronic mutations in \textit{UNC13D}, which encodes Munc13-4, as a cause of autosomal recessive familial hemophagocytic lymphohistiocytosis type 3 (FLH3) (22). Since exonic mutations in \textit{UNC13D} were previously known to cause FLH3 (23), the authors sequenced four highly conserved \textit{UNC13D} intronic regions and detected two novel intronic mutations that abolished protein expression.

Identifying large structural variations, such as deletions, inversions, and translocations, by WES/WGS can be problematic because it can be difficult to differentiate a \textit{bona fide} deletion from a genomic interval with poor exome capture or sequencing. Fragments containing a large deletion or inversion will not align properly with the reference genome and can be missed (24). Fortunately, techniques such as array comparative hybridization have proven useful in the detection of duplications or deletions of specific loci, and have been used successfully to complement NGS data (25, 26).

Autosomal dominant diseases represent another challenge because there are approximately 69% more heterozygous than homozygous variants in any given genome (27). There is the additional challenge of proving that a heterozygous variant causes a gain of function or haploinsufficiency phenotype unlike the majority of such mutations which are silent. Effective mapping of an autosomal dominant gene requires large families to narrow the candidate gene list. To circumvent this difficulty, investigators have sequenced affected individuals from unrelated families, as was done in the study identifying heterozygous mutations in \textit{GATA2} as a cause of dendritic cell, monocyte, B and NK lymphoid deficiency (monoMAC syndrome) (28). The authors hypothesized that WES of four unrelated patients would identify the gene containing the causative variants while eliminating the majority of non-pathogenic mutations. Only one gene, \textit{GATA2}, which encodes a transcription factor important for stem cell maintenance, contained heterozygous, novel, and deleterious mutations shared by all four patients (28).

Finally, mutations with incomplete penetrance can be problematic. Filtering strategies often assume complete penetrance though this can lead to inadvertent elimination of causative variants. This was demonstrated in a study identifying an autosomal dominant mutation in \textit{TRIF}, which encodes an adaptor protein important for TLR3 signaling, as a risk factor for HSE (29). A heterozygous missense mutation in \textit{TRIF} was identified in a patient with HSE, but the patient’s mother and maternal grandfather had the same mutation without a history of HSE. The authors ultimately showed that fibroblasts from the patient and her mother had impaired cytokine production to TLR3 stimulation, which was restored by transfection with wild-type TRIF (14). This study demonstrates the importance of validating potential mutations with functional studies.
VI- Conclusions and future directions:

Advances in genetics, particularly WES and WGS, have complemented the use of educated guesses based on known signaling pathways and mouse models in the discovery of many novel defects underlying PIDs. However, these techniques primarily identify mutations in coding regions, and there is still much progress to be made. Epigenetic modifications regulating gene expression, such as DNA methylation, histone modification, and non-coding RNAs, modulate the immune system (30) and defects in these mechanisms may contribute to PIDs. NGS can be used to investigate the transcriptome to detect disease-causing splice variants leading to exon skipping, alternative splicing, and alternative start and polyadenylation sites (31). For our patients, the identification of the defects underlying PID enables genetic counseling and preimplantation diagnosis. Lastly, pinpointing these genetic defects is the foundation for the development of gene therapy as a cure.

References:

MHCII DEFICIENCY: CLINICAL AND MOLECULAR FINDINGS

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²Department of Pediatrics, CHU Blida, Algeria
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Abstract:
52 patients with MHC class II deficiency were enrolled during 10 years. That represents 20.5% of the 253 PID and 60.5% of the 86 CID diagnosed in the same period. Consanguinity was found in 64.4% of the affected families. Clinical manifestations developed by our patients are characteristic of this deficiency, they are dominated by chronic diarrhea and oral candidiasis and by recurrent lung infections. Almost all patients have typical immunological profile. HLA DR expression level was very low (<1%) for all patients, TCD4+ lymphopenia was found in 92.3% of cases, and hypogammaglobulinemia in 80.8% of cases. The genetic exploration has identified the recurrent mutation «752 del G25» in the RFXANK gene, in a homozygous state for 45 patients (86.5%) and in a heterozygous state for parents and for 63.6% of siblings confirming its founder effect in our population. The majority of patients received symptomatic treatment consisting of antibiotics and IVIG substitution. 50% of the patients died and none has received the only curative treatment represented by hematopoietic stem cell transplantation (HSCT).

Key words:
MHC II, HLA-DR, TCD4+ lymphopenia, RFXANK, deletion, founder effect

I- Introduction:

MHC class II deficiency is a rare combined immunodeficiency. The lack of MHC class II (HLA class II) expression results in a defect in both cellular and humoral adaptative immune responses [1]. This defect is inherited as an autosomal recessive trait and is caused by mutations in genes encoding essential proteins involved in the transcription regulation of HLA class II molecules. Patients suffering from this disease are classified in four complementation groups A, B, C and D, each corresponding to the defect of one of the four genes: CIITA, RFXANK, RFX5, RFXAP respectively. The first patients listed as well as the majority of reported cases are native of Maghrebian area and over 90% of them belong to complementation group B [2]. For almost all of the patients in this group, a recurrent mutation with founder effect was identified, it consists in 26 bp pair deletion named «752 del G25 or I5E6-25E6» [3]
II- Material and methods:

Patients:
We enrolled 52 Algerian patients from 45 unrelated families with MHC class II deficiency among 253 cases of primary immunodeficiency diseases (PID) diagnosed during 10 years. 27 (52%) are males and 25 (48%) are females.

Immunological investigations:
Serum levels of IgG, IgA and IgM levels were measured by nephelometry using BMD reagents. We performed immunophenotyping of T, B and NK lymphocytes by flow cytometry using monoclonal antibodies from Beckman-coulter, labeled with different fluorochromes and directed against CD3, CD4, CD8, CD19 and CD16/CD56. MHC class II (HLA DR) expression on monocytes was evaluated by combination of anti HLA DR (FITC)/ anti CD14 (RD1), and on B lymphocytes by anti HLA DR (FITC)/ anti CD19 (RD1). The evaluation of HLA DR on lymphoblasts was performed for 35 patients and required a preliminary incubation of PBMC with phytohemagglutinin (PHA) for 72 hours. 17 patients were tested for the expression of MHC class I (HLA ABC).

Genetic investigation:
This exploration included 142 subjects (52 patients, 34 couples of parents and 22 members of siblings) for whom we screened for the 752 del- G25 mutation in RFXANK gene. Genomic DNA was extracted by phenol-chlorophorm method, from whole blood or PBMC and was amplified by polymerase chain reaction using specific primers of intron5/exon 6 region of RFXANK gene. The following PCR conditions were employed: initial denaturation at 94°C for 5 min followed by 35 cycles amplification (94°C for 30 s, 61°C for 30 s and 72°C for 45 s) and final extension at 72°C for 10 min. The genetic exploration was completed by direct sequencing using Big-dye terminator (V 1.1) chemistry from Applied Biosystems reagents.

III- Results:
In this study, we were able to collect 52 cases of MHC class II deficiency during 10 years. That represents 20.5% of the 253 PID and 60.5% of the 86 CID diagnosed in the same period. Consanguinity was found in 64.4% of the affected families and positive family history was reported in 48.9% of cases. The mean age at onset of symptoms is 5.2 months (range: 7 days- 22 months) and the mean age at diagnosis is 20.5 months (range: 7 days -9 years). Four patients were screened and diagnosed because of the positive family history.
Clinical manifestations developed by our patients are characteristic of this deficiency; they are dominated by chronic diarrhea, recurrent lung infections, oral candidiasis and failure to thrive. Other manifestations were developed by some patients: urinary, skin infections, chronic otitis and septicemia. Two patients had complications after vaccination with oral poliovirus vaccine; one has died after polio encephalitis and the other presented a flaccid paralysis.
Almost all patients have typical immunological profile as shown in table below.

<table>
<thead>
<tr>
<th></th>
<th>Patients tested (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CD4⁺ T lymphocytes count</strong></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>4/52 (7.7%)</td>
</tr>
<tr>
<td>Low</td>
<td>48/52 (92.3%)</td>
</tr>
<tr>
<td><strong>CD8⁺ T lymphocytes count</strong></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>24/52 (46.1%)</td>
</tr>
<tr>
<td>Low</td>
<td>11/52 (21.2%)</td>
</tr>
<tr>
<td>High</td>
<td>17/52 (32.7%)</td>
</tr>
<tr>
<td><strong>B lymphocytes count</strong></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>35/52 (67.3%)</td>
</tr>
<tr>
<td>Low</td>
<td>14/52 (26.9%)</td>
</tr>
<tr>
<td>High</td>
<td>3/52 (5.8%)</td>
</tr>
<tr>
<td><strong>NK lymphocytes count</strong></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>45/52 (86.5%)</td>
</tr>
<tr>
<td>Low</td>
<td>4/52 (7.7%)</td>
</tr>
<tr>
<td>High</td>
<td>3/52 (5.8%)</td>
</tr>
<tr>
<td><strong>IgG levels</strong></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>12/52 (23.1%)</td>
</tr>
<tr>
<td>Low</td>
<td>29/52 (55.8%)</td>
</tr>
<tr>
<td>High</td>
<td>11/52 (21.1%)</td>
</tr>
<tr>
<td><strong>IgA levels</strong></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>17/52 (32.7%)</td>
</tr>
<tr>
<td>Low</td>
<td>30/52 (57.7%)</td>
</tr>
<tr>
<td>High</td>
<td>5/52 (9.6%)</td>
</tr>
<tr>
<td><strong>IgM levels</strong></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>17/52 (32.7%)</td>
</tr>
<tr>
<td>Low</td>
<td>29/52 (55.8%)</td>
</tr>
<tr>
<td>High</td>
<td>6/52 (11.5%)</td>
</tr>
<tr>
<td><strong>HLA DR on monocytes</strong></td>
<td></td>
</tr>
<tr>
<td>&lt; 1%</td>
<td>52/52 (100%)</td>
</tr>
<tr>
<td><strong>HLA DR on lymphocytes</strong></td>
<td></td>
</tr>
<tr>
<td>&lt; 1%</td>
<td>52/52 (100%)</td>
</tr>
<tr>
<td><strong>HLA DR on lymphoblasts</strong></td>
<td></td>
</tr>
<tr>
<td>&lt; 1%</td>
<td>35/35 (100%)</td>
</tr>
<tr>
<td><strong>HLA ABC</strong></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>16/17 (94%)</td>
</tr>
<tr>
<td>Low ≈22%</td>
<td>1/17 (6%)</td>
</tr>
</tbody>
</table>

The separation of PCR products by electrophoresis in a 2% agarose gel, showed a band of 218 bp consistent with the mutated allele for 45 patients, a band of 244 bp for 7 patients corresponding to the
wild-type allele and 2 bands (wild type and mutated alleles) for all parents and for 63.6% of siblings tested (figure 2).

The direct sequencing confirmed the deletion of 26 bp encompassing the last 25 nucleotids of intron 5 and the first nucleotide of exon 6 for the patients with the mutated allele.

The majority of patients received symptomatic treatment (IVIG and antibiotics). 50% of the patients died at mean age of 32.4 months (2 to 116 months) and none has received HSCT.

IV- Discussion:

This series is one of the largest described. MHC class II deficiency seems to be more frequent in our population, thus it represents 20.6% of PID diagnosed.

Consistent with the transmission of this disease, a high consanguinity was found in our patients. The first clinical manifestations appear early in life, the mean age at onset was 5.2 months and the mean age at diagnosis was 20.5 months, these results are consistent with other series [4-5-6]. Clinical manifestations were quite similar to those previously described in other series, with chronic diarrhoea,
respiratory infections and oral candidiasis. Lived vaccines must be prohibited because they can be the cause of severe complications. That was the case for two of our patients. TCD4+ lymphopenia is very characteristic of this defect, it reflect the abnormal development of these cells into the thymus [1] and should prompt a search of MHC II deficiency after eliminating HIV infection. All of our patients showed total absence of MHC class II and none had residual expression. For the patients tested no associated MHC class I deficiency was found except for one patient who showed a moderate decrease. Hypogammaglobulinemia (decrease of 1, 2 or 3 immunoglobulin isotypes) was found in 80.8% of cases, this is consistent with the alteration of humoral adaptative immunity.

The genetic analysis has identified the recurrent mutation «752 del G25» of the RFXANK gene, in a homozygous state for 45 (86.5%) patients, in a heterozygous state for parents and for 63.6% of siblings tested confirming its founder effect in our population. Hence the screening for this recurrent mutation confirms the diagnosis, and is important for prenatal diagnosis and genetic counseling, especially because of the high consanguinity in our population which probably increases the incidence of this kind of autosomal recessive diseases.

In conclusion, MHC class II deficiency impose early diagnosis and treatment. Unfortunately, the only curative treatment (HSCT) is not available in Algeria for children with PID. Offer patients this treatment, is the greatest challenge for the coming years and the introduction of the genetic counseling is becoming a necessity in this disease, as in the other autosomal recessive diseases, especially in families where several deaths were reported in early childhood or several affected subjects were registered. That was the case for 5 families in our cohort.

References:


UPPER RESPIRATORY TRACT INFECTION IN PRIMARY IMMUNODEFICIENCY

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Background:
The upper respiratory tract is an obvious portal of entry for microorganisms and an adequately functioning immune system is required to prevent the establishment of infections in the ear, nose, and throat. Recurrent ear infection is a significant warning sign of primary immunodeficiency diseases, however, the incidence of primary antibody deficiency among children with recurrent ear infection is still unknown.

Objectives:
To estimate the frequency of primary antibody deficiencies among children presenting with recurrent otitis media (ROM > 4 times/year) and to identify other possible risk factors of ROM.

Methods:
Three hundred children (154 males and 146 females), who presented to the outpatient clinic of Children’s Hospital, Ain Shams University with ROM, were consecutively enrolled in the study over a 1-year period. According to the age of enrollment, children were classified into two groups: group A (1–6 years) and group B (>6–12 years). The demographic features of both groups were evaluated together with assessment of serum IgA level.

Results:
Of all studied patients, only two (0.7%) had a low serum IgA level for normal age-reference values. None of patients had neutropenia or lymphopenia. Iron-deficiency anemia was diagnosed in 76 cases, with higher rates among the patients in group A than group B. All patients received several courses of various empirical broad-spectrum antibiotics, but with either an incomplete course (n = 192) or a poor response (n = 49).

Conclusion:
The current study showed a relatively low incidence of IgA deficiency among children with ROM and indicated other environmental risk factors that participated in the occurrence of OM in our community.
I. Introduction:

Primary immune deficiencies (PID) comprise a heterogeneous group of genetically determined disorders that affect development and/or function of innate or adaptive immunity. Congenital deficits can affect specific immunity (humoral deficits affecting antibody production, cell deficits in T lymphocytes, combined deficits) or non-specific immunity mainly affecting polynuclear neutrophils. Immunodeficiency is characterized clinically by an increased susceptibility to infection, malignancy, and autoimmunity. The respiratory system is the major target of infections in patients with PIDs and respiratory disease is a significant cause of morbidity and mortality amongst these patients. The respiratory signs of PIDs can be divided into infectious (upper and lower respiratory tract infections and complications) and non-infectious (ILDs, bronchial abnormalities – especially bronchiectasis, malignancies, and benign lymphoproliferation). Infectious respiratory complications occur early in life whereas the non-infectious complications appear later in life usually after adolescent age. Lower respiratory airways infections are more frequent than upper airways infections. These infectious respiratory complications depend on the type of deficiency. Respiratory infections in PIDs patients are usually severe, persistent or recurrent, caused by unusual, atypical, or opportunistic microorganisms. We will describe the spectrum of respiratory disease associated with the most common forms of PID.

II. Clinical manifestations of primary immunodeficiency disorders (PIDs)

Clinical presentation and complications depend on the type of the immune defect.

<table>
<thead>
<tr>
<th>PID category</th>
<th>Main clinical features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Predominantly antibody deficiencies (CVID, XLA)</td>
<td>Recurrent pneumonia, Otitis media, Sinusitis</td>
</tr>
<tr>
<td></td>
<td>Septicemia, Meningitidis</td>
</tr>
<tr>
<td>Cellular and combined immunodeficiency disorders (SCID)</td>
<td>Opportunistic infections</td>
</tr>
<tr>
<td>Congenital defects of phagocyte (number, function or both)</td>
<td>Recurrent pyogenic, pulmonary granuloma</td>
</tr>
<tr>
<td></td>
<td>Abscesses, skin infections</td>
</tr>
<tr>
<td>Diseases of immune dysregulation (HIES)</td>
<td>Recurrent pneumonias bronchiectasis and pneumatocele formation</td>
</tr>
<tr>
<td>Complement deficiencies - Deficiencies C1 to C4</td>
<td>Autoimmune disease, pyogenic infections</td>
</tr>
<tr>
<td>- Deficiencies C5 to C9</td>
<td>Increased susceptibility to Neisseria species infections</td>
</tr>
<tr>
<td>- C3 deficiency</td>
<td>recurrent pneumonia, ENT infections.</td>
</tr>
</tbody>
</table>
III. Pulmonary disease in humoral deficits

Antibody deficiencies are characterized by low levels of serum immunoglobulins and impaired antibody production. Pulmonary changes are present in 60% of patients with primary humoral immunodeficiency.

The early diagnosis of chronic pulmonary diseases in patients with XLA and CVID is essential in preventing further infections and complications.

The most common clinical manifestation of predominant humoral deficiencies are recurrent and prolonged infections involving the respiratory tract, e.g. rhinosinusitis, otitis media, bronchitis, bronchiectasis and pneumonias.

III.1. X-Linked agammaglobulinemia

Upper and/or lower respiratory tract infections starting after 6 months of life are the most frequent clinical manifestations.

Recurrent bacterial pulmonary infections lead to the development of bronchiectasis.

Encapsulated bacteria (Haemophilus influenzae, Streptococcus pneumoniae) are the pathogens most frequently identified in these patients. Other Bacteria such as Staphylococcus aureus and Pseudomonas aeruginosa are present on damaged lungs.

In addition to bacterial infections, viral (CMV, Varicella zoster virus, adenovirus, herpes simplex) and fungal infections are less frequent. Pneumocystis jiroveci infection can occur.

High resolution computerized tomograms (HRCT) help to characterize and score typical radiographic findings such as bronchiectasis, atelectasis, bronchial wall thickening, presence of mucus plugs, air trapping, and consolidation. CT is superior to chest radiography for detecting bronchial abnormalities.

Early diagnosis, appropriate immunoglobulin replacement therapy, intensive chest therapy, and antibiotics have changed the clinical history of patients with humoral immunodeficiency.

Figure 1
6 years old boy with XLAgammaglobulinemia
Typical aspect of cylindric bronchiectasis, peribronchial wall thickening

III.2 Combined variable immunodeficiency (CVID)

CVID has a variable clinical presentation.

As in agammaglobulinemia, infections occur most frequently in the ENT area, the bronchi, and the lungs. Infections are caused by encapsulated bacteria. Sino-pulmonary infections and bronchiectasis are common complications.

These infections present later in life. The delayed diagnostic is associated with a higher risk of chronic lung disease.
Bronchial thickening and bronchiectasis are the most common and frequent respiratory finding in CVID.
Irreversible chronic bronchial obstruction and small airways disease with air trapping are often present in patient with CVID.
Patients with CVID may, in addition, develop inflammatory lung disease, often associated with multi-system granulomatous disease. The term granulomatous-lymphocytic interstitial lung disease (GLILD) has been created to describe these non infectious, diffuse lung disease complications with both granulomatous and lymphoproliferative histologic patterns.
The most common pulmonary CT findings include airway disease, ground-glass attenuation, nodules and parenchymal opacification.
In children, the non infectious diffuse lung disease occurs rarely.
CVID is associated with enhanced risk for cancer, lympho proliferative and auto immune diseases.

![Figure 2. Multiples areas of ground- glass opacities, peribronchial consolidation, peripheral nodules in an 8 years old girl with CVID.](image)

**IV. Patients with combined immunodeficiency:**

Severe combined immunodeficiency (SCID) is a syndrome characterized by the absence of T- and B-cell (and sometimes natural killer cell) function.
The loss of T cell function in patients with SCID leads to severe infections with opportunistic organisms that develop soon after the neonatal period. Other typical features are: failure to thrive, chronic diarrhea, persistent oral thrush, severe skin rashes, pneumonia, and sepsis.
Patients with combined immunodeficiency are highly susceptible to opportunistic infections with viruses, such as the herpes viruses (herpes simplex, varicella zoster), Cytomegalovirus and to *Pneumocystis jiroveci*. *Pneumocystis jiroveci* which typically produces interstitial infiltrates progressing to alveolar ones is the most common cause of pneumonia and is associated with significant mortality. CT scan should be part of the routine investigation of these patients.
V. Hyperimmunoglobulin E or job syndrome. (HIES):

The main features are ENT and pulmonary infections, eczema, recurrent subcutaneous cold abscesses, chronic skin and/or mucosal candidiasis, coarse facial features, delayed eruption of teeth.

Recurrent pneumonias may result in bronchiectasis and pneumatocele formation.

The most common infectious agent is *Staphylococcus aureus*. These infections are associated with markedly elevated serum IgE concentrations.

Surinfection of pneumatoceles by secondary organisms (*Pseudomonas, Aspergillus* and non tuberculosis species) is common. *Aspergillus* colonization will occur and prepare the way for secondary invasive infections.

VI. Chronic granulomatous disease:

The primary defect in CGD is a loss of NADPH oxidase function which is necessary to produce superoxide anions needed to kill bacterial and fungal agents.

CGD is inherited in X linked and autosomal recessive forms.

Among primary immunodeficiencies, chronic granulomatous disease (CGD) has the highest prevalence of invasive fungal diseases.

This lack of phagocytosis leads to susceptibility to severe infections including skin, lymph node, lung and liver and to catalase positive germs like bacteria *Staphylococcus aureus* and *Burkholderia* and for fungal *Aspergillus*. Pneumonia, abscess or chronic lung disease are the main respiratory manifestations.

The lung is the most common site affected by *Aspergillus fumigatus*. Invasive aspergillosis remains the major cause of morbidity and mortality in chronic granulomatous.

The aspergillus infection is suspected when persistent respiratory symptoms associated with fever last.

As clinical signs are not contributing it is recommended to monitor children with chest CT and MRI for early diagnosis.

The culture of bronchial secretions, blood culture, Bronchial alveolar lavage (BAL) or lung biopsy if available are used to highlight the pathogen.

Antibacterial (trimethoprim/sulfamethoxazole) and antifungal (itraconazole) prophylaxis has significantly reduced the rates and severity of infections in patients with CGD.

Another characteristic feature of CGD is granulomatous inflammation. CGD granulomas are typically noncaseating, composed of multinucleated giant cells, and can be found in multiple organs, including the brain, lungs, liver, spleen, and gastrointestinal tract.
VII. Work up to assess respiratory disease in PID children:

Children present with chronic cough with purulent sputum, rhonchi and rales on physical examination. Diagnostic evaluation should include:
- Personal and Familial history
- Chest X-rays
- A sputum analysis for bacterial as well as viral agents
- CT scan should be part of the routine investigation of these patients. Computed tomography (CT) plays an important role in detecting, characterizing, and quantifying the extent of lung damage. The bronchiectasis is the main radiological event. Bronchiectasis, defined as irreversible dilatation of large and medium-sized bronchi, is one of the most feared complications of the repeated pyogenic respiratory infections. Bronchiectasis is generally cylindrical, bilateral, and diffuse and commonly found in the middle or lower lobes, and less frequently seen in the upper lobes
- Pulmonary function testing
- Broncho-alveolar lavage to identify typical organisms.

VII. Conclusion:

The respiratory system is the major target of infections in patients with PIDs and respiratory disease is a significant cause of morbidity and mortality amongst these patients. The screening of respiratory symptoms and early recognition of pulmonary complication should be done on a regular basis. Thoracic CT should be included in the imaging evaluation of patients in whom the presence of a primary immunodeficiency is suspected.
### Main pathogens according to PID:

<table>
<thead>
<tr>
<th>Immunodeficiency</th>
<th>Bacteria</th>
<th>Virus</th>
<th>Parasite</th>
<th>Fungi</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agamma globulinemia</td>
<td>S. pneumoniae, Hib</td>
<td>Enterovirus</td>
<td>Giardia intestinalis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>N. meningitidis, Pseudomonas</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>aeruginosa</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>CVID</td>
<td>S. pneumoniae, Hib</td>
<td></td>
<td>Giardia intestinalis</td>
<td></td>
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<tr>
<td></td>
<td>N. meningitidis, P. aeruginosa</td>
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<td></td>
</tr>
<tr>
<td></td>
<td>C. jejuni</td>
<td></td>
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</tr>
<tr>
<td>HIES</td>
<td>S. aureus, Enterobacteria</td>
<td></td>
<td></td>
<td>Aspergillus, Candida</td>
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### REFERENCES:

MECHANISMS OF IMMUNE DYSFUNCTION IN DOCK8 DEFICIENCY

Erin Janssen and Raif Geha
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ABSTRACT:

Dedicator of Cytokinesis 8 (DOCK8) was identified as the major causative gene in autosomal recessive hyper-IgE syndrome (AR-HIES) \(^1\), \(^2\). DOCK8 deficiency is associated with atopic dermatitis, asthma, food allergies, and an unusual susceptibility to viral mucocutaneous infections. This review summarizes the various immunologic abnormalities in DOCK8 deficiency.

I- Introduction:
Dedicator of cytokinesis-8 (DOCK8) is one of eleven members of the DOCK180 superfamily \(^3\). DOCK proteins contain characteristic DOCK homology region-1 (DHR-1) and DHR-2 domains. The DHR-1 domain is important for DOCK protein targeting to membranes, through its binding of phosphatidylinositol (3,4,5)-triphosphate (PIP\(_3\)) \(^4\). The DHR2 domain binds to the Rac/Rho family GTPases, and can function as an exchange factor for these GTPases \(^5\), \(^6\). The biological functions of DOCK8 include regulation of cell migration, morphology, adhesion, and growth \(^3\). DOCK8 is expressed in all immune cells, therefore DOCK8 deficiency impairs the function of virtually all types of immune cells as discussed below.

II- T cell defects:
Total lymphocyte counts are below normal for their age group in 20% of DOCK8 deficient patients. This is primarily due to a reduction in T-lymphocyte subsets (CD3, CD4, CD8) \(^1\), \(^2\). We observed a decrease in CD4\(^+\)CXCR5\(^+\)Fas\(^+\) T follicular helper cells in DOCK8 deficient patients, consistent with the poorly sustained germinal center formation and T cell dependent antibody responses found in DOCK8 deficient mice and patients \(^7\), \(^8\). T cells from DOCK8 deficient patients also exhibit reduced proliferative responses to stimuli \(^1\), \(^2\). In the CD8\(^+\) T cell compartment, there is a striking increase in CD8\(^+\)CD45RA\(^-\)CCR7\(^-\) exhausted memory cells (T\(_{EMRA}\)). T\(_{EMRA}\) are typically increased in subjects with chronic viral infections \(^9\). DOCK8 deficiency also negatively impacts the survival of virus-specific long-term CD8\(^+\) memory T cells \(^9\), \(^10\), which may also contribute to persistent viral infections.

III- B cell defects:
In B cells, DOCK8 functions as an adaptor protein downstream of toll-like receptor 9 (TLR9) and upstream of STAT3 \(^8\), possibly explaining the interesting clinical overlap between AR-HIES and the autosomal dominant form due to STAT3 mutations. B cell numbers are normal or elevated in DOCK8 deficiency, but IgM\(^-\)CD27\(^+\) switched memory B cells and marginal zone-like IgM\(^-\)CD27\(^+\) B cells are severely decreased \(^11\). Moreover, DOCK8 deficient mice do not form germinal centers and have a deficit of marginal zone B cells \(^7\). Serum IgG (in the absence of Ig replacement) is either normal or elevated, and IgA levels are usually within the normal range. IgM is below the normal range in two thirds of the patients and declines with age. IgE levels are elevated in almost all patients \(^1\). More importantly, DOCK8 deficient patients exhibit impaired antibody responses and have poor serologic memory \(^1\), \(^8\).

IV- Natural Killer (NK) cells:
NK cell function relies on Wiskott-Aldrich syndrome protein (WASp) for filamentous actin (F-actin) accumulation at the lytic NK cell immunologic synapse (IS) \(^12\). DOCK8 activates Cdc42,
then WASp with activated Cdc42 coordinates F-actin reorganization. DOCK8 deficient patient NK cells and DOCK8 knockdown cell lines have decreased NK cell cytotoxicity, which could not be restored after IL-2 stimulation\textsuperscript{13, 14}. F-actin accumulation was impaired at the lytic IS, while overall F-actin content was unchanged in DOCK8 deficient NK cells\textsuperscript{13}. This defect may underlie and explain important attributes of the DOCK8 deficiency syndrome including the unusual susceptibility to viral infections and malignancy.

**V- Plasmacytoid dendritic cells (pDCs):**
pDCs play a key role in the innate immune response to viral infections, including the herpes simplex virus (HSV), by virtue of their capacity to produce copious amounts of type I interferon (IFN) upon activation\textsuperscript{15}. pDCs sense nucleoside-based products derived from DNA viruses through TLR9 and the TLR adaptor MyD88, a pathway that is profoundly impaired in DOCK8 deficiency. DOCK8 deficient subjects are particularly susceptible to severe viral infections, including those caused by herpes family viruses\textsuperscript{1, 2}. Flow cytometric analysis of pDCs, identified by the markers CD123 and BDCA-4, revealed a severe deficiency in the peripheral blood of DOCK8 deficient subjects. IFN-\(\alpha\) production was profoundly depressed in patients compared to control subjects, consistent with the markedly decreased number of pDCs in the former group. Furthermore, there was also decreased IFN-\(\alpha\) production on a per cell basis\textsuperscript{16, 17}. We used systemic IFN-\(\alpha\)2b therapy on two patients with severe oral herpes labialis that was refractory to therapy with acyclovir and valacyclovir\textsuperscript{17}, and one patient with unremitting warts\textsuperscript{16, 17}. All three patients successfully responded to therapy with complete resolution of the lesions. These results suggest that deficiency of pDCs may contribute to aggressive viral infections in DOCK8 deficiency, and that IFN-\(\alpha\) provides an effective rescue therapy for some of these infections.

**VI- T regulatory (Treg) cells:**
In addition to an increased infectious susceptibility and predisposition to the development of allergic diseases, DOCK8 deficient patients are prone to develop autoimmune disease, including autoimmune hemolytic anemia, vasculitis, colitis, and hypothyroidism\textsuperscript{2, 18-21}. B cell autoimmunity has been linked to defects in the central and/or peripheral B cell tolerance checkpoints that are involved in the elimination of autoreactive B cells\textsuperscript{22}. Central B cell tolerance occurs in the bone marrow, defects in central B cell tolerance have been identified in patients with BTK deficiency, which impairs BcR signaling\textsuperscript{23}, as well as IRAK4, MyD88, and TACI deficiencies, which abrogate the function of most TLRs\textsuperscript{24, 25}. After transitioning into the periphery, B cell autoreactivity is regulated at a second checkpoint, through positive and negative selection mechanisms that are not well understood. B cells that do not react with peripheral self-antigens are selected to develop into mature naïve B cells\textsuperscript{26}. The peripheral B cell tolerance checkpoint is controlled by regulatory T (Treg) cells.

DOCK8 deficient patients had increased levels of diverse autoantibodies in their plasma. We determined that central B cell tolerance did not require DOCK8 as evidenced by the normal low frequency of polyreactive new emigrant/transitional B cells in DOCK8 deficient patients. In contrast, autoreactive B cells were enriched in the mature naïve B cell compartment, revealing a defective peripheral B cell tolerance checkpoint. In addition, we found that Treg cells were decreased and exhibited impaired suppressive activity in DOCK8 deficient patients. Our data support a critical role for DOCK8 in Treg cell homeostasis and function and the enforcement of peripheral B cell tolerance\textsuperscript{27}. A defect in Treg cells may also underlie the elevated IgE levels in DOCK8 deficiency and the susceptibility of DOCK8 deficient patients to atopic diseases including asthma, eczema, and food allergy.
VII- Correction of DOCK8 deficiency by hematopoietic stem cell transplantation (HSCT):
A high success rate with corrective HSCT has been reported for DOCK8-deficient patients, especially if done early in life\(^{28-32}\). This indicates a central role for cell autonomous expression of DOCK8 in the normal function of immune cells.

VIII- Conclusion:
DOCK8 deficiency affects the function of multiple immune cells including effector and regulatory adaptive immune cells and innate immune cells. Early diagnosis is relatively simple with a high suspicion index in offspring of consanguineous marriages who present with recurrent infections, especially viral skin infections, food allergy, high IgE levels eosinophilia, low T cell numbers, and a virtual absence of memory B cells. HSCT corrects all the immune defects and is curative. Gene therapy is expected to provide an alternative for patients for whom no HLA matched donors are available.

References:


PGM3 DEFICIENCY: A NOVEL CONGENITAL DISORDER OF GLYCOSYLATION AND A POTENTIAL ROLE IN ATOPIC CONDITIONS.

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Recurrent bacterial sinopulmonary infections and skin abscesses with eczema and elevated serum levels of IgE are features of the hyper-IgE syndrome (HIES), a complex primary immunodeficiency disorder. Heterozygous dominant-negative STAT3 mutations are associated with autosomal dominant HIES and homozygous mutations in DOCK8 account for the large majority of autosomal recessive HIES.

We recently contributed to the identification of a new congenital disorder of glycosylation in autosomal recessive forms of hyper-IgE syndromes, due to mutations in phosphoglucomutase 3 gene (encoding PGM3, which is involved in the protein glycosylation pathway).

Remarkably, beside the clinical symptoms typical for HIES including eczema, most patients had a developmental delay and many had psychomotor retardation. The reported mutations in PGM3 led to an impaired biosynthesis of UDP-GlcNAc and impaired tri-antennary and tetra-antennary N-glycan structures. The impaired immunity observed did include a T-cell proliferation defect, a reversed CD4/CD8 ratio and only borderline TH17 cell numbers in some patients.

Elevation of IgE in patients with PGM3 mutations or atopic conditions might be caused by defective glycosylation of IgE or its receptors. Future studies to identify the role of glycosylation defects in patients with PGM3 mutations and atopic disease might pave the way to novel treatment options for common allergic diseases.
**CHRONIC GRANULOMATOUS DISEASE**

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I- Introduction:

Chronic granulomatous disease (CGD) is a rare primary immunodeficiency, consequential to a defect in the oxidative metabolism in phagocyte. The disorder is characterized by repeated bacterial and fungal infections, especially skin and pulmonary infections often caused by Gram positive bacteria and Aspergillus, and by granuloma formation in several organs.

II- Pathogenesis

The defect leading to CGD is a dysfunction of a membrane enzyme of phagocytic cells, NADPH oxidase involved in bacterial killing. Indeed, during infection, neutrophils pass through the capillary wall by diapedesis to reach the site of infection where they recognize the bacteria through specific receptors and phagocytose infectious microorganisms. The last step of phagocytosis uses the NADPH oxidase, characterized by several subunits (gp22Phox, gp47Phox, gp67Phox, gp91phox and gp40Phox) that is activated by releasing superoxide anions to initiate the synthesis of the remaining reactive forms of oxygen. In CGD, the bactericidal activity is defective by the presence of genetic defects in the genes encoding the proteins of the subunits of the NADPH oxidase complex.

Following the NADPH oxidase dysfunction, defective neutrophils cannot accumulate the hydrogen peroxide in the phagosomes containing the ingested microorganism (1).

Infections in the CGD are characterized by the presence of fungal and bacterial pathogens that have the common characteristic of being "catalase positive." Indeed, bacteria "catalase negative " provide to phagosome the hydrogen peroxide required for their own lysis (pneumococcus, Hemophilus).

The most common genetic form (75% of cases in the European and North American series) is the X-linked form due to a mutation in the gene gp91, this is the most severe form with early onset of symptoms and higher mortality. The recessive forms, even more rare, are due to a mutation of the p22, p47 and p67 cytosolic proteins and may be clinically mild (2-3).
III- Clinical manifestations:

- Age and mode of revelation:

In most cases, patients with CGD suffer recurrent infectious episodes since childhood. Usually the first clinical manifestation of CGD occurs in the first year of life (75%) or before the second birthday (90%), rarely during adolescence. Few cases are diagnosed during adulthood, the revelation at this age usually involves autosomal recessive forms. In the European series, the mean age at diagnostic was higher in the autosomal recessive form (8.8 years) compared to the X-linked form (4.9 years) (3).

- Infectious manifestations and pathogens:

The characteristics infections evoking a CGD are neonatal pustulosis, adenophlegmons, lung aspergillosis, locoregional BCGitis, liver abscesses and salmonella infections.

Infections are bacterial and fungal, severe and recurrent and complicated by the formation of granulomas in the tissues. The genus Aspergillus is the most frequently observed fungal agent. Bacteria involved are catalase positive bacteria including Staphylococcus aureus and enterobacteria, as well as very aggressive bacteria such as Burkholderia cepacia and Serratia marscens and Nocardia.

Lung infections are the most common and are responsible for the high mortality, including aspergillus pneumonia that tends to disseminate. They are documented in nearly 80% of cases in patient history or can be the mode of revelation. They are also severe with mortality reaching 20%. They manifest clinically by fever, cough and dyspnea. Evolution is often torpid with a msimatch between clinical and radiological features; the minimal clinical expression contrasting with the importance and variety of radiological signs: pneumonia, lung abscess, reticulonodular infiltrates, miliary and pleural effusions.

Lymph node infections were noted in 50% of cases and skin infections such as abscess or staphylococcal pyoderma are common. Hepatic features come in fourth after pulmonary aspergillosis, lymphadenitis and skin manifestations. These abscesses are often recurring. In 63% of liver abscesses, the pathogen was isolated with a predominance of Staphylococcus aureus. Osteomyelitis with Staphylococcus, Serratia and Aspergillus have been reported. The BCGitis has also been reported, with great frequency in countries where vaccination with the Bacille Calmette-Guérin (BCG) is given routinely (4-5).
- **Inflammatory manifestations:**

Inflammatory manifestations are characterized by the formation of granulomas, which are usually small and composed of multinucleated giant cells, derived from the fusion of macrophages which phagocytosed but didn’t lyse bacteria. Inflammatory manifestations can affect several systems, such as the urinary tract, where can be found stenotic granulomatous inflammatory lesions. There is also an involvement of the digestive tract with ulcerative stomatitis evoking a pseudo-Bechet, esophagitis and gastritis. Enterocolitis, clinically and histologically resembling Crohn's disease or ulcerative colitis, were the most common inflammatory complication.

Autoimmune features correspond to SLE manifestations that are more common in first-degree relatives of maternal side in the X-linked form. Indeed, the carriers are usually asymptomatic, but may have increased susceptibility to infections. Discoid lupus erythematosus or oral ulceration can be observed in these carriers.

**IV- Diagnosis:**

Reduction of nitroblue tetrazolium (NBT) is the test of choice for the diagnosis of CGD, it allows a semi-quantitative study of the function of phagocytes previously stimulated by a bacterial toxin. The lack of reduction of NBT is a negative test. Mosaic profile in the mother of the patient (50% positive cells and 50% negative) evokes X-linked CGD.

Flow cytometry (DHR test) allows much finer exploration of disease by providing a quantitative result as to the synthesis of reactive oxygen species. It allows the diagnosis of some cases of autosomal recessive CGD whose NBT test is positive due to a residual activity of NADPH oxidase.

Molecular and genetic analysis relies on the search of the missing protein in NADPH oxidase complex (gp91phox, p22phox, p47phox or p67phox) that guides the search for the mutation in one of the genes involved in the CGD (5-6).

**V- Treatment:**

Prophylactic treatment of bacterial infections is based on Trimethoprim-sulfamethoxazole combination because it has a good spectrum of activity on microorganisms encountered in the CGD. Prophylaxis of fungal infections is a core element in the management of CGD, because of the high mortality rate (30-40%)
caused by fungal infections especially infections by Aspergillus. The Itraconazole is an active antifungal on Aspergillus whose long-term safety is very good.

Treatment with interferon gamma has a role in severe infections. It is an immunomodulatory cytokine that can partially restore the activity of the NADPH oxidase.

Allogeneic bone marrow remains the only potentially curative treatment of the CGD; it is feasible only if there exists an HLA-matched donor and other treatments do not provide a good quality of life (5).

Gene therapy seems soon to be a curative treatment for CGD, especially for patients without HLA-identical donor. In the first trial, the concept of partial and transient correction of the NADPH oxidase activity after gene transfer was demonstrated without lasting clinical benefits.

With therapeutic management including anti-infective prophylaxis and the natural evolution represented by the reduction of infections with age, patients with CGD especially those diagnosed in childhood can lead a normal life. Several factors are in favor of a good prognosis including the late onset of the disease, the autosomal recessive mode of transmission, scarcity of clinical manifestations and the lack of evolution of pulmonary involvement.

VI- Conclusion:

CGD is a serious disease that must be evoked and investigated toward recurrent bacterial and fungal infections, including invasive pulmonary aspergillosis or skin or lymph node severe infections. The diagnosis is based on a body of clinical and biological arguments, including the NBT test. The diagnosis must be early to start a therapeutic treatment based primarily on anti-Aspergillus and antibacterial prophylaxis usually allowing patients to lead a near normal life. Allogeneic bone marrow transplants are successful, but their use is still limited to severe cases.

References:
Severe combined immunodeficiency (SCID) is an inherited primary immunodeficiency, which is characterized by the absence or dysfunction of T lymphocytes affecting both cellular and humoral adaptive immunity. It is one of the most severe forms of primary immunodeficiency (PID), which is life-threatening when recognized too late.

Conventionally, SCID can be classified as T−B+ and T−B− SCID with further subdivision based on the presence or absence of NK cells. However, the presentation is not always classical, and the presence or absence of NK cells may be misleading. It has become clear that clinical presentation has wide phenotype variability with considerable immunological variation. These aspects can impede the diagnosis of SCID.

Children with SCID present with high susceptibility to bacterial, viral and fungal infections in their first year of life. Persistent infections with respiratory and gastrointestinal viruses and opportunistic infections are frequent manifestations, often associated with protracted diarrhea and failure to thrive.

Engraftment of maternal T cells can lead to symptoms of graft versus host disease (GvHD), such as severe erythematous skin rash or chronic liver disease. Without hematopoietic stem cell transplantation (SCT) or gene therapy, the disease is usually lethal within the first year of life. Over 20 different molecular defects can result in the clinical syndrome of SCID. These include defects in genes involved in antigen receptor gene rearrangement (RAG1, RAG2, DCLRE1C, PRKDC, LIG4), T-cell receptor signaling (CD3D, E, G, Z, CD45, ZAP70, ORAI1, STIM1), T-cell differentiation (IL2RG, IL7R, JAK3, ADA, PNP, AK2), and the thymic development and thymic egress of T-cells (rare forms of 22q11 microdeletion syndrome, FOXN1, CORO1A).

The majority of patients with a clinical diagnosis of SCID and mutations in these genes show a severe reduction or absence of circulating T cells. However, SCID patients may also present with residual, normal or even elevated numbers of T cells.

Some SCID-causing genes affect T cell function rather than T cell development; hypomorphic mutations in SCID-causing genes may allow residual T cell development and T cells may be passively acquired by materno-fetal transfusion.

One characteristic phenotype of patients with mutations in SCID-causing genes, but residual T cell immunity, is Omenn syndrome (OS). OS is characterized by an erythematous rash, lymphadenopathy and hepatosplenomegaly, susceptibility to severe and opportunistic infections and failure to thrive. T-cell counts can be normal or even increased combined with eosinophilia and high levels of IgE.

Although hypomorphic mutations in the RAG genes account for most cases of OS, it can also be due to mutations in other SCID-causing genes, such as DCLRE1C (ARTEMIS), IL2RG, LIG4, IL7R, ADA, RMRP, the gene for chromodomain helicase DNA binding protein 7 (CHD7) and 22q11 microdeletion syndrome.
Patients may present with atypical forms of SCID or Omenn syndrome. Previously described as profound combined immunodeficiency, these patients usually survive beyond 12 months of age. Increasingly, hypomorphic mutations in genes normally associated with classical SCID are identified, thus retaining some protein function. Alternative mechanisms of demonstrating partial immunity include spontaneous gene reversion in early lymphoid progenitors.

Among the 205 cases of DIP explored in our center, in the period 2009-2015, we have diagnosed 26 SCID (12.6%) from 24 families not related. The age of patients ranged from 25 days and 22 years; 11 of them were male (42.3%). Inbreeding Parental was observed in 64, 5% of families (n = 24). The total mortality was 75%. In total, 1 patient was treated with HSCT.

Immunophenotyping of cells showed 17 patients had classical SCID, 7 patients had atypical SCID (presentation beyond the first year) and 1 patient has Omenn syndrome.

Among the 17 cases of classical SCID, Thirteen patients had T-B-NK+ phenotype (50%), including six males (46, 1%) and three patients had T- B +NK- (11, 5%), including two males. The patients with atypical SCID have low rates of T cells and 57, 1% of these patients also have a very low rate of B lymphocytes.

Our results show a predominance of T−B−NK+ SCID in our series, probably due to RAG1/2 deficiency. A molecular analysis for all cases is yet to be done to confirm this hypothesis.

The clinical presentations and the immunological phenotypes of SCID and Omenn syndrome are well defined and there are clear treatment concepts for these disorders. Diagnosis and treatment is much less clear for patients with mutations in SCID-causing genes, but milder forms of combined immunodeficiency, often termed “atypical” SCID. Due to their poorly defined clinical and immunological phenotype, these patients are sometimes diagnosed as late as in adulthood.

These variable phenotypic presentations should alert all physicians who care for patients with recurrent infections that atypical presentations may occur when genes of the immune system are mutated. Extensive molecular work up are needed for patients with atypical presentations otherwise most of these conditions will go undetected, and the full spectrum of phenotypic and genotypic heterogeneity will not be known. One effective global tool for improving diagnosis of PIDs is increasing physician’s awareness about these variable phenotypic presentations of PIDs. Continuing education of physicians from different specialties is important including those physicians who treat adolescents and adults.
References:


3- Joshi AY, Ham EK, Shah NB, Dong X, Khan SP, Abraham RS. (2012) Atypical Omenn Syndrome due to Adenosine Deaminase Deficiency Case Reports in Immunology; 2012, Article ID 919241


Complement system includes a large number of soluble proteins that are found in the circulation and in tissues and form the basis for the presence of three activation pathways: the classical, alternative and lectin. Its activation plays important roles in both adaptive T and B cell immunity as well as mediates many of the effects of antibodies (Abs) when they interact with their antigenic targets.

Under physiological conditions activation of complement is effectively controlled by the coordinated action of soluble and membrane-associated regulatory proteins. However, continuous activation of complement proteins and split products necessitates that healthy cells possess mechanisms to protect themselves from accidental destruction. An imbalance in complement, either by insufficient or excessive complement activity, can have important pathological consequences. Consequently, activation of complement presents a considerable risk of harming the host by directly and indirectly mediating inflammatory tissue destruction.

Complement deficiencies clinical manifestations are very heterogeneous. The exact manifestations depend on where in the complement cascade the defect occurs, with functions of components proximal to the defect being preserved, and those distal to the defect leading to disease. They present as recurrent infections, usually involving invasive disease caused by encapsulated bacteria, and as immune complex disease like systemic lupus erythematosus (SLE) and glomerulonephritis.

People with C3 deficiency tend to suffer from recurrent or severe invasive infection with organisms where opsonization is crucial, e.g., *Streptococcus pyogenes*, *Streptococcus pneumoniae*, and *Haemophilus influenza*. Those with deficiency of C1, C4, and C2 have a lesser opsonic defect, as they have intact alternative pathways. Deficiency of almost any complement protein, including C8 and C9, predisposes to infection with *Neisseria* species, implying that the Membran Attack Complex C5, C6, C7, C8 plays an integral role in host defense against this family of bacteria.

Factor B deficiency hasn’t yet been described. However, approximately half the individuals identified with properdin deficiency have had neisserial disease associated or not to purpura fulminans, but the remainder are asymptomatic, identified through family testing of properdin-deficient patients identified through family studies, a history of meningococcal disease was less frequent (18%) than among affected relatives of terminal complement component deficient probands (38%).

C1-inhibitor (C1-INH) deficiency is the cause of HAE, an autosomal dominant disorder that has been estimated to occur in about 1 in 100,000 individuals. HAE is characterized by recurrent episodes of subcutaneous swelling of the face, extremities, upper airway, and gastrointestinal tract that last for 48 to 72 hours. C1-INH binds irreversibly to activated C1r and C1s.
types of C1-INH deficiency exist. In the most common form of HAE (type I), the individual has one normal C1-INH gene and one that does not encode protein. These patients have low levels of C1-INH (i.e., 5% to 30% of normal). Another form of HAE (type II), the individual has one normal C1-INH gene and one that encodes a molecule that is antigenically intact but functionally inactive.

Recently, new variant of HAE predominates in women with similar symptoms with normal antigenic and function of C1-inhibitor named type III HAE. Only few patients with this disease have gain-of-function Factor XII mutation.

Other deficiencies of the complement system responsible for disease syndromes include deficiency of mannan-binding lectin (MBL), which may be responsible for susceptibility to repeated respiratory infections in early childhood, deficiencies of complement receptors causing leukocyte adhesion abnormalities, and deficiency of cellular membrane control proteins, such as decay-acceleration factor (DAF) and CD59. Only one individual with CD59 deficiency has been described. Born of consanguineous parents, this boy suffered from recurrent hemolytic anemia and cerebral infarctions. His erythrocytes and fibroblasts did not express CD59, but did express the other GPI-anchored proteins that are absent in paroxysmal nocturnal hemoglobinuria, an acquired defect in expression of GPI-anchored proteins.

Alternative pathway dysregulation assessment in order to screen for and characterize of mutations in the components of the C3 convertase (C3 and FB) or its regulators (FH, FI, MCP or CD46) has become an indispensable part of the diagnosis of the atypical Hemolytic Uremic Syndrome (aHUS), a rare thrombotic microangiopathy (TMA) that affects primarily the kidney, leading to end stage renal disease in approximately 60% of patients. On the other hand, functional analysis of these mutations helps to better understand the activation and regulation of the alternative complement pathway in physiological conditions.

Recently, perhaps the best characterized and most closely linked to the alternative pathway, Factor H Factor B and C3, is the age-related macular degeneration (AMD) disease. AMD is typically found in older individuals in a ‘dry’ form that is characterized by drusen, geographic atrophy, and the progressive loss of retinal cells, as well as a ‘wet’ form in which neovascularization and recurrent sub-retinal bleeding is the predominant clinically important finding. The close association of AMD with the alternative pathway was initially made by the original findings that AMD was associated with the deposition in drusen of many proteins from the complement, thrombotic, and chronic inflammatory.

The functional assays have the advantage that they detect abnormalities brought about by dysfunctional proteins, whereas immunochemical assays would usually fail to detect them. There are several complement deficiencies where it has been shown to be particularly important to be able to detect dysfunctional proteins, these include C1 esterase inhibitor deficiency and properdin deficiency, and for both of these special functional assays need to be carried out.

Approved complement therapeutic strategies have largely followed traditional paths involving replacement factors (C1-INH) and C5-inhibitory monoclonal antibodies (eculizumab). Antibody-
based treatments can be employed to restore the balance in the complement network in order to achieve therapeutic effects. Complement inhibition can be beneficial in pathologies where the system is hyperactivated (e.g. sepsis, transplant rejection, ischemia and reperfusion (I/R) injury) or where it is chronically activated and attacks or damages healthy tissues as autoimmune diseases.

References:


Targeted Next Generation Sequencing for Primary Immunodeficiency Disorders

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Primary immunodeficiency diseases (PIDs) are a heterogeneous group of inherited disorders comprising over 200 diseases, caused by monogenetic immune defects. Molecular genetic studies are essential diagnostic tools for PIDs; however, this gene selection is complex because of the genetic and phenotypic heterogeneity of PIDs. We developed a next-generation sequencing-based multiplexing assay that encompasses 164 PID genes with an aim to test whether an NGS-based genetic evaluation can be used as a sensitive and accurate routine diagnostic tool to facilitate genetic diagnosis. NGS using the IonTorrent PGM to screen 164 PID genes was performed on 261 patients. 122 out of the 261 patients had at least one known causal mutation at the onset of the experiment were used to assess the sensitivity of the assay. The assay was accurately able to detect the mutation of 117 out of 122 (96%) individuals with known causal mutations at the onset of the experiment with 96% sensitivity for single nucleotide variants (SNV), 92% for short indel variants and 100% for exonic deletions. This NGS assay allowed us to make a genetic diagnosis in 35 of 139 patients who lacked a genetic diagnosis at the onset of experiment; most of the cases represent atypical clinical presentations of known PIDs. Targeted next generation sequencing PID panel is a sensitive, cost-effective first-line genetic assay that can be used to screen for genetic defects in patients with suspected primary immunodeficiency disorders. The assay is helpful in solving the complex genetic approach for PIDs.
I- Introduction:

The Laboratory of Human Genetics of Infectious Diseases (HGID) has used next-generation sequencing (NGS) to tackle one of the most important clinical problems in pediatrics. Childhood infections have historically been the greatest killers of mankind. Until the late 19th century, half the population died from infection before the age of 15 years and life expectancy at birth was only about 20 years. The global burden of pediatric infections has since diminished, with the establishment of the germ theory of disease, improvements in hygiene and the development of vaccines, antibiotics and surgery. However, throughout history, for any given pathogen, severe illness has occurred in only a small proportion of infected children, and this remains true today. Adult infectious diseases occurring in the course of secondary infection or reactivation from latency often result from impaired acquired immunity. However, this “somatic”, immunological theory of infectious diseases cannot easily be applied to primary infections. The fundamental question in the field of pediatric infectious diseases is therefore that of interindividual clinical heterogeneity in the course of primary infection. Geneticists, including Archibald Garrod and Karl Pearson, proposed a “germline”, genetic theory of pediatric infectious diseases in the 1920s. Their proposal that severe infections of childhood might result from inborn errors of immunity did not immediately catch on with microbiologists and immunologists. Since the work of Ogden Bruton in the 1950s, inborn errors of immunity (primary immunodeficiencies) have been seen as rare, fully penetrant, Mendelian traits associated with multiple, recurrent, opportunistic infections in early childhood (one gene, multiple infections and familial cases). Through testing an alternative hypothesis that life-threatening isolated infectious diseases in otherwise healthy children often result from single-gene inborn errors of immunity, not necessarily displaying complete penetrance (one gene, one infection and sporadic cases), the HGID lab has discovered the first genetic etiologies of a variety of chronic and acute isolated childhood infections.
II- Mendelian susceptibility to mycobacterial diseases (MSMD) and tuberculosis (TB):

MSMD is characterized by a narrow susceptibility to weakly virulent mycobacteria. Allelic heterogeneity at nine MSMD-causing loci defines 18 different disorders, all of which feature impaired IFN-γ immunity. The lab’s most recent and surprising discovery is that of autosomal recessive (AR) ROR-γt deficiency, revealing that this transcription factor controls IFN-γ. These studies have proved clinically useful by improving the care provided to MSMD patients. They have also provided valuable immunobiological insight, by revealing that human IFN-γ immunity is more redundant than mouse Th1 immunity in host defense and by contributing to the elucidation of the basic mechanisms governing IFN-γ immunity. We began the genetic dissection of MSMD as a first step towards that of childhood TB. He discovered that AR IL-12Rβ1 deficiency displayed incomplete clinical penetrance for MSMD but could underlie severe TB in a small, non negligible fraction of otherwise healthy children without MSMD. He has thus provided the first evidence that childhood TB may result from single-gene inborn errors of IFN-γ immunity.

III- Chronic mucocutaneous candidiasis (CMC):

CMC is characterized by epithelial lesions caused by Candida albicans in otherwise healthy patients. We identified AD IL-17F, AR IL-17RA, AR IL-17RC, and AR ACT1 deficiencies as the first genetic etiologies of CMC. Patients with AR ROR-γt deficiency also suffer from CMC. Finally, he found that most CMC patients were heterozygous for gain-of-function mutations of STAT1, which impaired the development of IL-17 T cells. These patients also often display auto-immune features. He had previously shown that loss-of-function alleles of STAT1 underlie mycobacterial and/or viral disease. STAT1 is the first human gene for which allelic heterogeneity has been shown to govern such different and specific infections. Thus, CMC can result from inborn errors of IL-17, which, unlike Th17 cells in mice, is essential for mucocutaneous immunity against C. albicans, but otherwise largely redundant.

IV- Invasive pneumococcal disease (IPD):

In his search for genetic etiologies of acute infections of childhood, We have discovered the first genetic etiology of X-linked recessive anhidrotic ectodermal dysplasia with immunodeficiency (EDA-ID): hypomorphic mutations in NEMO that impair NF-κB activation. Affected children display developmental features and various infections, including IPD caused by Streptococcus pneumoniae, a common commensal organism. He then discovered hypermorphic mutations of the IkBα gene in patients with AD EDA-ID. He also discovered AR IRAK4 and MyD88 deficiencies in IPD patients without developmental defects. Human TLR- and IL-1R-dependent immunity is thus largely redundant in host defense. More recently, he discovered the first inborn errors of the LUBAC complex, with mutations in HOIL-1 and HOIP in patients with IPD and a broader phenotype, with auto-inflammation. We also discovered the first genetic etiology of isolated congenital asplenia, which underlies IPD, with heterozygous mutations in RPSA.

V- Kaposi sarcoma (KS):

KS is an inflammatory neoplasm of endothelial cell origin. Human herpes virus-8 (HHV-8), also designated as KS-associated herpes virus (KSHV), is the causative agent for all forms of KS. Despite the high seroprevalence of HHV-8 infection in the Mediterranean Basin and evidence for strong familial aggregation between mother-child and sibling-sibling relationships,
classic KS is exceedingly rare in children, with less than 40 reported cases in the last 50 years. The observation that most individuals infected with HHV-8 remain asymptomatic indicates that infection alone is not sufficient to develop KS and that other cofactors, such as impaired immunity are required. Following this notion, we identified inherited immunodeficiencies in children with classic KS and other severe infections, either preceding or concurrent with KS, AR IFN-γR1 deficiency and X-linked recessive Wiskott-Aldrich syndrome (WAS). He then discovered the first two genetic etiologies of isolated KS, with AR STIM1 deficiency and AR OX40 deficiency. Both defects impair T cell immunity. These findings provided proof-of-principle that single-gene inborn errors of immunity can underlie aggressive forms of classic KS in childhood.

VI- Herpes simplex virus encephalitis (HSE):

Some children develop HSE during primary infection with HSV-1 — an almost ubiquitous and typically innocuous virus — despite having normal resistance to other infections. HSE is the most frequent sporadic viral encephalitis in the Western world and it is not an opportunistic infection, as it is not more common in children with known inherited and acquired immunodeficiencies. We first discovered patients with HSE and an AR UNC-93B deficiency abolishing TLR3- and TLR7-9-dependent IFN-α/β responses. Consistent with the lack of HSE in children with MyD88 and IRAK-4 deficiencies, he found other children with HSE and AD and AR TLR3 deficiencies, AD and AR TRIF deficiencies, AD TRAF3 deficiency, and AD TBK1 deficiency. Using induced pluripotent stem (iPS) cells, he recently showed that these patients’ central nervous system (CNS) cells (neurons and oligodendrocytes) fail to control HSV-1. HSE therefore results from a collection of single-gene inborn errors of CNS-specific intrinsic immunity, which do not display complete clinical penetrance. HSE is the first isolated infectious disease of childhood shown to be caused by single-gene inborn errors of immunity.

VII- Severe influenza disease:

Life-threatening influenza disease in otherwise healthy children and its absence in children with known inborn or acquired errors of immunity both remain unexplained. Recently, we identified compound heterozygous mutations for two loss-of-function alleles of IRF7 in a child with life-threatening influenza during primary infection at age 2 years. She is now 7 years of age and healthy with annual influenza vaccinations. Neither the patient’s leukocytes nor her plasmacytoid dendritic cells, which are normally characterized by their high levels of constitutive IRF7 expression, produced any detectable amounts of the 19 anti-viral IFNs other than IFN-β ex vivo in response to a variety of agonists and viruses, including influenza virus. Moreover, the patient’s dermal fibroblasts and iPSC-derived pulmonary epithelial cells display increased intracellular replication of influenza virus in vitro. This cellular phenotype is rescued by wild-type IRF7 and by exogenous IFN-α2b. These findings indicate that human IRF7-dependent IFN-α/β amplification is required for protection against influenza virus, via plasmacytoid dendritic cells (innate immunity), or pulmonary epithelial cells (intrinsic immunity), or both, but is otherwise apparently redundant in host defense. They also provide proof-of-principle that severe influenza in otherwise healthy children may result from single-gene inborn errors of immunity.
VIII- Conclusion:

In the last 20 years, the HGID lab has made a number of breakthrough discoveries, identifying the first genetic causes of MSMD, TB, CMC, IPD, KS, HSE, and most recently, severe influenza disease in children with normal resistance to other infections. These studies were boosted by the advent of NGS, which enabled him to discover numerous inborn errors from 2010 onward. The novel, surprising causal relationships he has uncovered have modified the long-standing paradigm in this field. They have provided proof-of-principle that severe infectious diseases of childhood may actually result from monogenic inborn errors of immunity. These studies have important clinical implications, providing a rationale for the prevention and treatment of pediatric infectious diseases with recombinant cytokines, as exemplified by IFN-γ therapy for children with mycobacterial diseases; there is now hope to treat children with HSE or severe influenza with IFN-α. These studies have also major immunological implications. The narrow range of childhood infections associated with single-gene inborn errors of immunity reflects the considerable, but not complete redundancy of the corresponding human genes for survival in the course of primary infection in natural, as opposed to experimental conditions. Our results overall provide compelling evidence for a genetic theory of childhood infectious diseases. These studies further highlight the clinical and immunological impact of a genetic dissection of childhood infectious diseases.

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The aim of study is to determine the clinical and demographic features of our patients who are followed with primary immunodeficiency. The medical records of 1054 patients with primary immunodeficiency who are followed by Department of Pediatric Immunology and Allergy were evaluated retrospectively.

Six hundred forty-seven (61.4%) patients were boys and 407 (38.6%) were girls. The average age at diagnosis was 55.5 months and differed between 2 and 552 months. All of them were in the pediatric age group, except 2 patients. Regarding distrbution, 92.8% of patients (n= 980) had immunodeficiency due to antibody deficiency. The ratios of the other immunodeficiencies were severe combined immunodeficiency in 2.4% (n= 25), other well-defined immunodeficiency syndromes in 1.7% (n= 18), regulation defects of immun system in 0.9% (n=9), defects of phagocytic system in 0.2% (n= 2), complement deficiency in 0.1% (n= 1) and other immunodeficiencies in 1.8% (n= 19).

The spectrum of symptoms at diagnosis were determined as follows: recurrent upper respiratory tract infection in 54%, lower respiratory tract infection in 47%, sinusitis in 38%, acute otitis media in 25%, gastroenteritis in 9%, moniliasis in 5%, urinary tract infection in 4%, sepsis in 2%, meningitis in 1% and recurrent skin infection in 0.9%.

Parental consanguinity ratio of our patients was 37.5%. The parental consanguinity ratio of patients with severe combined immunodeficiency, phagocytic system defects and CVID were 84%, 75% and 73% respectively.

Because of the recurrent infections, prophylactic treatment of trimethoprim-sulphometaxazole was given to 379 patients (36%). Sixty-three patients (6%) had the diagnosis of chronic lung disease, and 401 patients (38%) had the diagnosis of asthma.

The incidence of primary immunodeficiency is high in Konya. We think that early diagnosis and treatment is necessary for reducing the complications.
PRIMARY IMMUNODEFICIENCY DISEASE MANAGEMENT IN TUBERCULOSIS ENDEMIC REGIONS – ARE WE AWARE ENOUGH AND HOW DOES A REGISTRY ASSIST?

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Summary:

South Africa, with one of the world’s highest tuberculosis (TB) prevalence, reported almost 300,000 new cases in 2013 (incidence 860/100,000 of the population, prevalence 715/100,000) [1]. Finding Primary Immune Deficiency Diseases (PID) within the limited resources of TB and other infectious epidemics is challenging, as infections - whether severe, recurrent, unusual or persistent (SPUR) in nature may also be the result of untreated HIV/TB/Malaria. Alternatively, SPUR infections may actually be due to a genetic deficiency of immunity, but this possibility is rarely considered as infections are usually attributed to these endemic diseases. In our setting, multiple factors such as unsafe water sources and the lack of hygienic facilities, malnutrition and co-infections, early acquisition of Epstein Barr Virus, Cytomegalovirus (as well as a host of other viruses and bacteria) add to the risk of infections in the general public, but more so in PID patients. Based on the estimated prevalence of PID patients for South Africa [2] and extrapolating from the number of TB diagnoses on the South African Primary Immunodeficiency Registry, a minimum prevalence of between 142 and 2286 of PID patients contracting TB was calculated. Increased PID awareness is critical in this and other TB endemic regions to identify patients with known or novel PID-causing mutations, who would otherwise be labeled as non-compliant with TB treatment or as repeatedly exposed in their environment.
I- Introduction:

In less resourced regions of South Africa, the health care system mostly relies on nurses and community health workers to enable broad access to healthcare within a limited health budget. Protocols and algorithms have been developed for this type of clinical practice, and basic health information is provided in the Road to Child Health Document, in addition to other guidelines for health indicators and monitoring. However, there are limitations to nurse-driven clinical care, especially for more atypical clinical scenarios and rarer medical conditions which may require specialized individual assessment.

Furthermore, the disparity of healthcare access enforced by the previous government policy of separate development is exacerbated by current vast socioeconomic differences. In previously disadvantaged communities, HIV negative infants (and presumed to be immunologically normal) appear to succumb more frequently to the infectious disease burdens which accompany HIV exposure - whether this be congenital or environmental exposure to HIV-related infections. About 6.3 million people are living with HIV in South Africa (an estimated 2.3 million are currently on treatment) many of whom are co-infected with TB and a multitude of HIV associated pathogens, which altogether inevitably contribute toward an extreme infectious environment that imposes enormous challenges for the healthy, but especially for patients living with a PID. While an excessive infectious environment may expose PID more readily, it may also obscure PID where there is a lack of awareness. The milieu of diverse exposures to infectious agents may even impact on the shaping or development of immunity in the immune competent, especially early in life, as the susceptibility to infection is greatest early and late in life [3].

Despite variable vaccine efficacy results, the universal BCG vaccination at birth is administered in South Africa, and while aimed at reducing TB risk, this is an early life threat for mycobacterial dissemination in the immune compromised host. Therefore, the dissemination of BCG in HIV negative infants suggests a genetic immune defect [4]. Mendelian Susceptibility to Mycobacterial Diseases (MSMD) is the prototype PID with regard to TB susceptibility and mycobacterial diseases. However, several other genetic deficiencies, for example NEMO deficiencies, Chronic Granulomatous Disease (CGD), Hyper IgM syndrome, and Combined Immunodeficiencies, also cause affected patients to be highly susceptible to mycobacterial infections as well as other infections. Yet, very little is known about the frequency, recurrence and complications of TB manifestations in these patients in regions with epidemic TB. Monitoring TB incidence in these patients is already compounded by the challenges of obtaining a primary diagnosis of PID in the first place. Nor is the incidence of TB infections known in PID patients who are not classically predisposed to this infectious disease – such as in those with antibody deficiencies. Hence, at present there are no guidelines on the prevention and management of TB for PID patients who are excessively exposed to TB in the high-pathogen-burden context of epidemic regions. Therefore, in addition to the recently published principles of
geographically relevant guidelines should be developed and implemented as crucial elements of PID care provision in South Africa and other TB endemic regions.

II- Methods:
A registry database for primary immunodeficiency reporting in South Africa was initiated in 2008 at the National Health Laboratory Services, Tygerberg Hospital Stellenbosch University; with ethical approval from the local Health Research Ethics Committee and as part of a consultative clinical service. Patients with presumed or confirmed genetic deficiencies, categorized according to the International Union of Immunological Societies (IUIS) criteria [6], were entered onto the database after informed consent was obtained.

A secondary objective of the registry was awareness creation as well as physician education on PID diagnosis and care. Part time secretarial assistance enabled data capture from patients across South Africa, in collaboration with two other University Hospitals in addition to the active participation of state and privately practicing paediatricians and physicians. All data are confidential and stored with password protected access on the Stellenbosch University server. Where possible, telephonic/e-mail or in-person contact is attempted every 6 months for all known live patients on the registry.

III- Results:
By means of the South African Primary Immunodeficiency Registry of 281 patients, we report on 15 patients with known TB infections (which translates to 5% of PID patients being at risk of developing TB in South Africa). Altogether, there were 28 episodes of TB, of which 3 were co-infections with *Mycobacterium avium* (*M. avium*). An additional 11 patients with Severe Combined Immunodeficiency (SCID) had 5 known episodes of BCG dissemination. Excluding the SCID group, these mycobacterial infections were linked to suspected or confirmed MSMD, but mycobacterial infections were also recorded in 2 patients with Agammaglobulinaemia, 2 patients with Common Variable Immunodeficiency (CVID), 2 patients with NEMO deficiency (who experienced 1 and 3 episodes of TB treatment respectively) and 1 patient with Interferonopathy. Persistent CNS BCGosis has been reported in one child, and localized TB infection over 7 years has been reported for intrahepatic TB in another child, not yet entered on the registry. With regard to repeat infections, 1 patient has suffered 5 episodes of TB, while 2 patients have experienced at least 2 episodes of TB. Multidrug resistant TB was diagnosed in 2 patients. Disseminated BCG in SCID patients on the registry reflects a serious threat to successful transplantation outcome (both pre- and post- transplant). Patients who were later diagnosed with CGD were mistakenly treated for unconfirmed TB of the liver, despite negative-culture findings albeit with marked improvement, at the time when the underlying genetic defect was not yet suspected. Infection with *M. avium* has posed great treatment challenges in 2 patients with bony infiltrations.
IV- Discussion:

There are no reports in the literature on screening, prevention and individualized treatment of PID patients living in TB endemic regions. Infection of PID patients with TB may be further complicated by dual infection with *Mycobacterium tuberculosis* and atypical or environmental bacteria, BCG or even MDR and XDR TB in South Africa. With an estimated prevalence of between 2850 and 45723 PID patients for South Africa [2], we can estimate that between 142 and 2286 of PID patients would contract TB. Therefore, it is imperative to have good surveillance data of PID patients as a whole and of TB diagnoses in these patients. The 15 patients reported here on a national registry, as well as the 11 SCID patients, are fundamentally the minimum estimate, as follow-up of patients on the registry is only feasible in a few.

Chronic inflammation – a hallmark of TB with granuloma formation, disseminated forms of TB, atypical infections, recurrences, and a delayed response to treatment should alert to the possibility of PID in an HIV negative patient. Through better awareness of genetic causes of TB susceptibility, the management of PID patients in TB prevalent regions can be improved; TB infections can be reduced and perhaps even prevented. While genetic susceptibility to TB does not provide sufficient rationale to account for endemic proportions of the disease, the identification of mutations in PID patients (even in single patient investigations) [7] will assist in defining new pathways and enhance our knowledge of host-defense mechanisms. Given that there are still many patients with the clinical syndrome of MSMD with no known disease-causing mutations [8], the genetic investigation of PIDs in settings with infection epidemics will most likely reveal other rare mutations for TB susceptibility and other immune deficiencies.

V- Conclusion:

Increased awareness and a high index of suspicion are required to identify the clinical phenotype of recurrent, unusual or persistent TB which needs further investigation. The high prevalence of TB in PID patients on the South African Registry, highlights the urgent need for guidelines on rapid diagnosis, appropriate prevention and surveillance of TB in all patients with known or suspected genetic immunodeficiency.

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I. Introduction:

Primary immunodeficiencies (PIDs) are an expanding group of genetic disorders affecting distinct components of the innate and adaptive immune system and resulting in recurrent and/or severe infections, autoimmunity, allergy, cancer, or autoinflammation. A commonly held misconception is that PIDs occur solely in the pediatric age group and hence, only pediatricians are involved in their management. It has become increasingly clear that many patients with PIDs survive into adulthood.

A range of factors may explain the occurrence of PIDs in adulthood. Firstly, some PIDs tend to present after adolescence, including a range of antibody disorders such as common variable immune deficiency (CVID), selective IgA deficiency, and IgG subclass deficiency (IGGSCD). The microbial spectrum of infections is usually the same with infantile forms, but we most frequently observed non-infectious complications, such as granuloma formation, autoimmunity or tumors in adults. Secondly, some patients with PIDs have a mild phenotype delaying presentation into adulthood. Examples of PIDs presenting late with atypical or attenuated phenotypes include X-linked agammaglobulinemia and atypical Severe Combined ImmunoDeficiency (SCIDs) (e.g. ADA, ARTEMIS or RAG Deficiency). Finally, and of great concern is that some patients with PIDs present in childhood with recurrent infections, autoimmune disorders, and unusual malignancies but the underlying PID passes unrecognized for many years.

II. Objective:

Although the importance of recognizing PIDs in adult patients is often the focus of review articles [1-3], primary data on this subject is sparse and is generally limited to case reports (only one series published). We describe here a series of adult patients with PIDs. This series provide unique data regarding PIDs presenting in adulthood, and serves as a timely reminder that physicians must consider the diagnosis of PIDs in their adult patients.

III. Results:

During the 6-years period between March 2009 and March 2015, forty-one (41) adult patients received the new diagnosis of a PID. Twenty-two (22) cases (53.7%) were male and 19 (46.3%) female. The mean age at diagnosis was 31 years (range: 16 – 61 years). There was a mean diagnostic delay of 11.27 years (range: 1 – 41 years). All patients were Algerian and came from across the country with no obvious predominance of a specific geographical area.

Humoral immune defects were the most common (90.2%), followed by cell-mediated (7.3%) and phagocytic defects (2.4%). The specific PIDs diagnosed in this series are shown in Fig. 1 (CVID: 32 (78.0%), X-Linked Agammaglobulinemia: 3 (7.3%), IgG subclasses deficiency: 1 (2.4%), Good’s...
syndrome: 1 (2.4%), Atypical SCID: 3 (7.3%), Mendelian Susceptibility to Mycobacteria Disease (MSMD): 1 (2.4%).

CVID is the “prototype” of PIDs in adulthood. It is a heterogeneous collection of conditions, all characterized by a primary antibody deficiency (hypogammaglobulinemia) of at least two immunoglobulin isotypes, recurrent respiratory tract infections and increased occurrence of autoimmune discords and lymphoproliferative disease. In a retrospective study [4], we analyzed 29 patients fulfilling the classical CVID definition. The mean age at diagnosis was 23 years. Recurrent upper and lower bacterial respiratory tract infections were common in almost all patients. Five patients developed autoimmune conditions and six had lymphoproliferative disease. Decreased IgG was found in almost all patients. Low IgA and IgM levels were found in 89.6% and 65.5% of cases respectively. Abnormal T and/or B phenotype was found in 75% of cases; the most common abnormalities were decreased circulating B (54.2%) and T CD4+ (41.7%) cells and inversion of the CD4/CD8 ratio (70.8%). Patients with decreased circulating B and T CD4+ cells were significantly more likely to have autoimmune cytopenias and lymphoproliferative disease.

Three cases (all males) were presumptively diagnosed with X-Linked Agammaglobulinemia (XLA) on the basis of clinical phenotype and agammaglobulinemia with no detectable CD19+ or CD20+ B cells in the peripheral circulation. No definitive genetic diagnosis has been made in these patients, although one patient had a family history of a male maternal cousin dying in childhood supporting an X-linked etiology.

IgG2 subclass deficiency was diagnosed in a 26-year-old girl with bilateral bronchiectasis and a history of recurrent respiratory tract infections beginning in childhood. IgG2 was undetectable and her IgA level was appropriate. Her symptoms have improved with monthly IVIG infusions.

Good’s syndrome, the association between thymoma and immunodeficiency, also occur in adulthood and needs to be excluded particularly in older patients with antibody deficiency. Typical features in Good’s syndrome include an absence of B cells as well as T cell abnormalities including CD4 lymphopenia, an inverted CD4/CD8 ratio and reduced mitogen induced proliferation. In a recent systematic review, the average age of patients diagnosed with Good’s syndrome was 59.1 years, although the range was 25–90 years with one pediatric case identified [5]. One suggested scheme to screen for thymoma is that all patients with antibody deficiency who are over 49 years of age with absent B cells should undergo CT scanning to exclude thymoma [6]. The patient reported in our series is a 61-year-old man with thymoma, chronic otitis, pulmonary and fungal infections, decreased IgG (0.82 g/L), IgA (<0.066) and IgM (<0.175), nearly absent B cells, inverted CD4/CD8 and impaired T cells function.

Severe combined immunodeficiency is the most severe form of primary immunodeficiency. It is caused by mutations in genes involved in lymphocyte development and function. These include defects in genes involved in antigen receptor gene rearrangement (RAG1, RAG2, ARTEMIS, PRKDC, and LIG4), T-cell receptor signalling (CD3D, E, G, Z, CD45, ORAI1, and STIM1), T-cell differentiation (IL2RG, IL7R, JAK3, ADA, and AK2). The majority of patients with a clinical diagnosis of SCID show a severe reduction or absence of circulating T cells. However, in some cases “hypomorphic” mutations in genes associated with SCIDs can also cause milder immunodeficiencies with residual, normal or even elevated numbers of T cells [7]. These “atypical” (also called “leaky”) SCIDs are often unrecognized for many years and in some cases diagnosed in adulthood. In this study, we report three patients with clinical and immunological features of atypical SCID. For one of them a mutation in ARTEMIS gene was found. Genetic evaluation (Whole Exome Sequencing) was performed by an international collaborator.
IV. Conclusion:

In conclusion, this large series of adult patients highlights the importance of considering the diagnosis of PIDs outside the pediatric age group. It is only through continued efforts to publish, present, and register PID patients that we will improve physician awareness of these rare but important conditions, ensuring patients with PIDs receive timely diagnosis and optimal management.

Figure 1: Characterization of the specific PIDs diagnosed in our series.

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IMMUNOGLOBULIN REPLACEMENT THERAPY FOR PRIMARY IMMUNE DEFICIENCIES

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The primary immune deficiencies (PIDs) are a large and ever growing group of inherited diseases that cause immunological dysfunction. The latest international classification of PIDs includes nearly 250 different disorders.¹ It has been estimated that approximately 70% of all PID patients are undiagnosed.² Lack of awareness about the PIDs by the medical fraternity and the general population, as well as limited diagnostic capacity contributes to this situation, particularly in resource-poor countries.³ Treatment options for the PIDs include implementing safe routine immunization practice, antimicrobial prophylaxis, immunoglobulin replacement therapy (IRT), other replacement therapies such as granulocyte stimulating factor, interferon gamma and long-acting adenosine deaminase, haematopoietic stem cell transplantation (HSCT), and gene therapy. The extent to which these interventions are available and accessible varies between and within countries.

The overall aims of IRT are (1) to reduce the incidence and severity of infections, particularly bacterial infections, and (2) avoid consequent organ damage that causes chronic disease such as chronic lung disease in patients with PIDs in whom there is clinically significant quantitative and/or qualitative immunoglobulin G (IgG) deficiency. The achievement of these aims will limit the deterioration in the quality of life of patients with PIDs.²

A recent survey showed that at a global level more than 15% of patients with suspected or well-defined PIDs were receiving IRT.⁴ In Africa, many governments do not fund IRT although this intervention is highly effective and life-saving.³ Furthermore, this status quo exists despite the World Health Organization having acknowledged the importance of this intervention and included human immunoglobulin in the essential list of drugs for both adults and children.⁵,⁶ African governments should be lobbied by the African Society for Immunodeficiencies, and local immunologists, physicians and paediatricians to fund this essential intervention.

Human immunoglobulin production and preparations:

Structurally and functionally intact polyvalent human immunoglobulin is prepared by fractionation of pooled plasma obtained from 1,000 to 10,000 donors. Donors are screened for hepatitis B surface antigen, HIV infection, syphilis and hepatitis C infection, and excluded if found to be infected. Each manufacturing company uses slightly different methods to purify the IgG molecules to a high degree, usually >98%.⁷,⁸ During the manufacturing process unwanted infectious agents are removed or inactivated. There has not been cases of known disease transmitted by human immunoglobulin preparations for approximately 20 years, and to date there have been no reports of transmission of pathological prions.² The large donor base ensures that all pooled human immunoglobulin products contain a wide repertoire of neutralizing antibodies, which are directed against a broad range of epitopes. Hence pooled human immunoglobulin preparations are protective against a diverse spectrum of bacteria and viruses.
Human immunoglobulin preparations are available for intravenous, intramuscular and subcutaneous administration. Although intramuscular immunoglobulin therapy may still be used in some of the milder deficiencies such as transient hypogammaglobulinaemia of Infancy, it is no longer recommended due to high rates of infusion-related reactions. Intravenous or subcutaneous administration is preferred for treating PIDs. Intravenous immunoglobulin G (IVIG) is generally available in 2 – 10% solutions. Subcutaneous immunoglobulin G (SCIG) is available in higher concentrations of 10 – 20%, permitting the administration of bigger doses in smaller volumes.

**Indications for IRT:**

Primary antibody deficiencies (PADs), combined immune deficiencies and other selective PIDs in which clinically significant quantitative and/or qualitative IgG deficiency occurs may benefit from IRT (Table 1). Lifelong IRT is required for severe PADs including diseases in which arrest in early B-cell development is demonstrated such as X-linked and autosomal recessive forms of agammaglobulinaemia, as well as other PADs listed in Table 1.

Incompletely defined PADs characterized by the presence of circulating B-cells and subnormal IgG concentration may require a 12-month trial of IRT to document the clinical response. If the response is favourable, treatment may be extended for 1 – 5 years, followed by periodic re-evaluation of the trough serum IgG concentration as hypogammaglobulinaemia may be transient and resolve spontaneously. In individuals with persistant hypogammaglobulinaemia, prolonged or lifelong IRT may be necessary. In patients with functional antibody deficiency with normal immunoglobulin concentrations, re-evaluation of their functional responses is required to determine whether long-term IRT is needed. Functional antibody responses should ideally not be checked until IRT has been discontinued for at least 6 months. Many children do not require further IRT as transient forms of functional antibody deficiency are common in children aged 2 – 5 years. When IRT is to be stopped after several months of treatment, discontinuation should take place in the warmer months to reduce the risk of respiratory viral infections. Immunoglobulin replacement therapy is not indicated for (1) selective IgA deficiency, (2) selective IgM deficiency, (3) the vast majority of infants with transient hypogammaglobulinaemia of infancy, and (4) asymptomatic individuals with one or more IgG subclass deficiencies and normal specific antibody responses.

In countries where HSCT is not available or highly restricted, many combined immune deficiencies as well as other PIDs in which IgG quantitative and/or qualitative deficiency occur, may benefit from long-term IRT (Table 1). Immunoglobulin therapy is also utilized for its immunomodulatory actions in autoimmune and inflammatory conditions such as Kawasaki disease, Gullain-Barré syndrome, idiopathic thrombocytopaenia and chronic inflammatory demyelinating polyneuropathy.

**Differences between IVIG and SCIG replacement therapy:**

Administration of human immunoglobulin by the intravenous route was the most common method of replacement during the 1980s and 1990s. Since then administration via the subcutaneous route has become common clinical practice, especially in well-resourced settings. Subcutaneously administered immunoglobulin is as effective as IVIG, exhibits better tolerability
because of fewer systemic side effects, and is acceptable to many patients and their families because of the advantages associated with home administration. Home administration require reasonably good social circumstances, specialist nursing and patient support to ensure safe administration.\textsuperscript{2,9} In well-resourced settings where both methods of replacement are widely available, the choice between IVIG and SCIG administration can be highly individualized. Several factors are considered when determining the preferred method of administration for individual patients including, the total monthly IgG dose, frequency of administration, volume and infusion rate required, number of infusion sites, the range of commercial human immunoglobulin products and/or formulations that are available, education and training of the patient and his/her family, the patient support system, and the management of adverse events.\textsuperscript{9} In resource-poor settings, sub-optimal social factors, limited community nursing support, and infrastructural challenges such as those relating to housing, and electricity and safe water supply, reduces the potential for home-based therapy. Key differences between IVIG and SCIG administration are summarized in Table 2.\textsuperscript{9,13}

**Optimizing the administration of IRT:**

This section a few practical issues relating to the management of children on IRT are briefly discussed.

*Optimal immunoglobulin dosing:* Periodic evaluation of trough or steady state IgG concentration is considered important to determine the adequacy of treatment and optimise the dosing of both IVIG and SCIG. Dose adjustment based on the trough / steady state IgG concentration should be done in conjunction with other clinical and laboratory variables including infection frequency, antibiotic usage, time lost from school, inflammatory markers and radiology / imaging.\textsuperscript{9} The trough / steady state IgG concentration is initially measured every 2-3 months and then 6-monthly.\textsuperscript{8} Although the initial minimum target is a trough / steady state IgG concentration of 5 g/L, the optimal concentration required to keep individuals free of infection varies from patient to patient, and may be greater than 5 g/L. A recent meta-analysis of 17 studies, comprising 676 patients with PIDs in whom hypogammaglobulinaemia was documented, and who received IVIG evaluated trough IgG concentration in relation to pneumonia incidence. Pneumonia incidence was 5-fold higher at a trough concentration of 5 g/L compared with 10 g/L. Furthermore, pneumonia incidence declined by 27% with each 1g/L increment in trough IgG concentration.\textsuperscript{14} A similar relationship probably exists between SCIG replacement therapy and infection risk.

*Adverse events:* Subcutaneous immunoglobulin G mainly causes infusion-site reactions. Infusion technique, and the choice of infusion sites are important factors influencing this risk. By contrast, IVIG is associated with a higher risk for infusion-related systemic adverse events including chills, headache, backache, nausea, malaise, fever, pruritis, wheezing and / or chest tightness and chest pain. Most of these manifestations occur within 2 days of the IVIG infusion.\textsuperscript{9,15,16} Reduction of the infusion rate is usually sufficient to control and prevent these events. Recurring adverse events can be modified by administering aspirin (15mg/kg/dose) or ibuprofen (5mg/kg/dose) orally, or hydrocortisone (6mg/kg/dose IV, maximum 100mg) one hour before the start of the IVIG infusion. Severe adverse events are uncommon and include seizures, aseptic meningitis, deep vein or arterial thrombosis, arrhythmias, myocardial infarction, renal failure, anaphylaxis and anaphylactoid reactions.\textsuperscript{16}
Concomitant antibiotic prophylaxis: Immunoglobulin replacement therapy is not sufficient to completely prevent recurrent infection or bronchiectasis in all patients with PADs. Patients who do experience frequent breakthrough infections despite high trough / steady state IgG concentration usually benefit from concomitant antibiotic prophylaxis with trimethoprim-sulphamethoxazole, amoxycillin or a macrolide. Additional prophylaxis should be administered before and after dental or surgical procedures.

Conclusion:

In this brief overview, some of the clinical issues and emerging trends relating to IRT were discussed. An important remaining challenge for Africa is to ensure that this essential and lifesaving intervention becomes accessible to all patients with PIDs who may benefit therefrom.

References:


Legends and Tables: Table 1: Primary Immunodeficiency diseases that may benefit from IRT

<table>
<thead>
<tr>
<th>I. Primary antibody deficiencies</th>
</tr>
</thead>
<tbody>
<tr>
<td>▪ X-linked agammaglobulinaemia <em>(requires lifelong IRT)</em></td>
</tr>
<tr>
<td>▪ Autosomal recessive agammaglobulinaemia <em>(requires lifelong IRT)</em></td>
</tr>
<tr>
<td>▪ Common variable immunodeficiency <em>(requires life-long IRT)</em></td>
</tr>
<tr>
<td>▪ Hyper-IgM syndromes <em>(requires lifelong IRT if HSCT is not available)</em></td>
</tr>
<tr>
<td>▪ IgA deficiency with concomitant IgG2 subclass deficiency <em>(lifelong IRT may be required)</em></td>
</tr>
<tr>
<td>▪ IgG subclass deficient patients with severe recurrent respiratory infection, particularly those with deficient specific antibody responses to protein and polysaccharide antigens <em>(lifelong IRT may be required)</em></td>
</tr>
<tr>
<td>▪ Specific (functional) antibody deficiency with normal immunoglobulins <em>(IRT is appropriate when despite antibiotic prophylaxis recurrent infections persist)</em></td>
</tr>
<tr>
<td>▪ Transient Hypogammaglobulinaemia of Infancy <em>(IRT for a limited period may be required in patients with unusually severe or frequent infections)</em></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Combined T- and B-cell immunodeficiencies</th>
</tr>
</thead>
<tbody>
<tr>
<td>▪ Severe combined immunodeficiency <em>(IRT is required prior to HSCT and during the post-HSCT immune reconstitution phase)</em></td>
</tr>
<tr>
<td>▪ Other combined immunodeficiencies <em>(long-term IRT is beneficial, especially in settings were HSCT is not available)</em></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Examples of selective PIDs in which IgG qualitative and/or quantitative deficiency occur</th>
</tr>
</thead>
<tbody>
<tr>
<td>▪ Wiscott-Aldrich syndrome</td>
</tr>
<tr>
<td>▪ Ataxia-telangiectasia with IgG or IgG subclass deficiency</td>
</tr>
<tr>
<td>▪ X-linked lymphoproliferative syndrome</td>
</tr>
</tbody>
</table>
Table 2: Differences between IVIG and SCIG administration

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>IVIG administration</th>
<th>SCIG administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pharmacokinetic profile</td>
<td>Infusion into the bloodstream achieves immediate high concentration, but falls off towards the end of each 3- or 4-week cycle</td>
<td>Ig reaches the bloodstream at a slower rate after being transported from the subcutaneous tissues via the lymphatics, weekly infusions results in consistant plasma concentration</td>
</tr>
<tr>
<td>Loading dose</td>
<td></td>
<td>100 mg/kg/day on 5 consecutive days avoids the need for an initial IVIG loading dose</td>
</tr>
</tbody>
</table>
| Dose & interval for regular infusions | Usually 400 mg/kg every 3 – 4 weeks  
Patients with bronchiectasis or chronic gut disease require a starting dose of 600 mg/kg every 3 – 4 weeks | 100 – 150 mg/kg every week |
| Infusion rate                       | Maximum rate: 3 - 5 mL/kg/hour                                                       | For 16% products maximum rate: 10 – 20 mL/hour  
For 20% products, maximum rate : 15 – 25 mL/hour |
| Infusion volume                     | Volumes are seldom limited except in patients with cardiac or renal disease           | Volumes are limited by what can be comfortably tolerated, and varies according to the age of the child; usual maximum of 20-25 ml per site in children |
| Infusion time                       | Generally, 4 - 6 hours required to complete an infusion                               | Usually 1-2 hours are required to complete a weekly infusion |
| Number of infusion sites            | Infusion administered via a single intravenous canula                                | Weekly infusions can be given usually in 1 – 2 sites, but up to 6 sites may be required |
| Systemic side effects               | More frequent than SCIG administration; largely dependant on the rate of infusion     | Less frequent than IVIG because of slow attainment of peak bloodstream immunoglobulin G concentration |
CO1/ SEVERE COMBINED IMMUNODEFICIENCY : RESULTS OF A MULTICENTER STUDY IN ALGERIA.

Cherif N.1, Tahiat A. 2, Touri N. 3, Kedji L.4, Inouri Y. 5, Djidijk R. 2, Benhalla K.N.6

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4. Service de Pédiatrie CHU Bab El oued. Algeria
5. Service de Pédiatrie HCA Ain Naadja. Algeria
6. Service de Pédiatrie CHU Beni Messous A. Algeria

Introduction:
Severe combined immunodeficiencies (SCIDs) are a heterogeneous group of genetic disorders with common clinical phenotypes presenting in early infancy with serious or recurrent infections and failure to thrive. This group is characterized by defect in differentiation of T and/or B lymphocytes and susceptibility to infections since birth.
For more than 40 years, allogeneic hematopoietic stem cell transplantation (allo-HSCT) has provided curative therapy for these disorders.

Methods :
This is a retrospective, multicenter study that included all primary immunodeficiencies followed in 13 pediatric departments in several regions of Algeria since 1985. The data were collected from pre-established forms including demographic data, clinical and biological findings, treatment and outcomes. Statistical analysis was performed with Epi Info 6.

Results:
During this 30 year period, we identified 409 children with PID among which 60 patients with SCID (14.7 %).
The median age at the onset of the first infection was the 2nd month of life. Six patients (10%) had positive family history for SCID. One infant (1.7%) had T-B-NK- SCID phenotype, 20 patients (33.3%) had T-B-NK+ SCID phenotype, 9 children (15%) had T-B+NK- SCID phenotype, 15 patients (25%) with T-B+NK+ SCID phenotype.
Mutation analysis revealed one child with c.75delC (p.K26RfsX36) mutation in Cernunnos gene, 1 had deficiency of recombinase-activating gene (RAG1) and 1 had RAG2 deficiency. The others have not been explored.
Fifteen patients (25%) had unknown phenotype and remained without known underlying genetic defect.
Two patients (3.3%) who underwent hematopoietic stem cell transplant (HSCT) survived, while 29 (48.3%) died between 3 and 12 months after diagnosis was made. Eleven were lost-to-follow up.

Conclusions :Severe combined immunodeficiency (SCID) is the most severe form of inherited primary immunodeficiency and is a pediatric emergency. Delay in recognizing and detecting SCID can have fatal consequences and also reduces the chances of a successful allo-HSCT. Screening for SCID at birth would prevent children from dying before HSCT can be attempted and would increase the success of HSCT.

CO2/ CLINICAL ASPECTS AND OUTCOME OF HYPER IGE SYNDROME IN ALGERIA.

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Introduction:
Hyper-IgE syndrome is a rare and complex primary immunodeficiency disorder, characterized by various clinical manifestations mostly eczema, skin and lung infections and a high serum concentration of IgE. There are two forms: autosomal dominant and autosomal recessive.

Methods:
This is a retrospective, multicenter study that included all primary immunodeficiencies followed in 13 pediatric departments in several regions of Algeria since 1985. The data were collected from pre-established forms including demographic data, clinical and biological findings, treatment and outcomes. Statistical analysis was performed with Epi Info 6.

Results:
During this 30 year period, we identified 409 children with PID among which 16 patients with hyper-IgE syndrome (3.9%).
Our study has objectified a male predominance (68.8%). Inbreeding was found in 31% of cases. The mean age of onset of clinical events was 12 months with a mean age at diagnosis of 52 months and a diagnostic delay of 43 months. The clinical presentation included skin infections in 81% of cases, eczema (62%) and recurrent pulmonary infections in 68.8%. The diagnosis was based on a very high level of IgE. However, no genetic study was done. Bacteria were isolated in 69% of cases with Staphylococcus in 81.8%. Concerning the treatment, 62.5% of patients received repeated intravenous antibiotic and 25% sequential antibiotic therapy; 12.5% had received curative anti-viral treatment. The trimethoprim-sulfamethoxazole prophylaxis was prescribed in 19% and immunoglobulin infusions intravenously in a third of cases. The evolution was marked by lobectomy in a patient and the death of another patient at the age of 18 months following a severe infection.

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

CO3/ CLINICAL, IMMUNOLOGICAL AND MOLECULAR CHARACTERIZATION OF DEDICATOR OF CYTOKINESIS (DOCK8) DEFICIENT TUNISIAN PATIENT.

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Introduction:
Deficiency of dedicator of cytokinesis (DOCK8) is a primary immunodeficiency characterized by viral and recurrent sinopulmonary infections, elevated serum IgE, eosinophilia and high incidence of food allergy. Mortality is high at a young age. Autosomal recessive mutations in DOCK8 gene are responsible for many cases of autosomal recessive hyper-IgE syndrome. Most of these mutations are large deletions.

Purpose:
We present the clinical, immunologic and molecular characteristics of a patient with DOCK8 deficiency.

Patient and methods:
An 8 year-old girl, born to first degree consanguineous parents, with a history of recurrent pneumonia and bronchiectasis since the age of 18 months. This patient had skin infections caused by Molluscum contagiosum, a feature frequently associated to DOCK8 deficiency. She had high serum IgE levels (6581 IU/L) and hypereosinophilia. Genomic DNA was extracted from whole blood, total RNA was prepared from Epstein-Barr virus (EBV)-transformed B cell lines and cDNA was synthesized using the reverse transcription kit. DOCK8 gene was amplified from genomic DNA and cDNA using specific primers.

Result and discussion:
The lymphocyte phenotyping shows an increase of naïve B lymphocytes and a decline of switched and unswitched memory B lymphocytes which are in favor of DOCK8 deficiency. Molecular analysis shows the failure of cDNA fragments amplification, suggesting the absence of DOCK8 transcripts due to genomic deletion. This result was confirmed by the lack of PCR products for the first 43 exons of DOCK8 gene. This is in accordance with the literature, since the majority of DOCK8 mutations are large deletions.

Conclusion:
Herein, we report a large deletion of DOCK8 gene which would probably abolish the protein expression. It will be interesting to determine if this deletion is restricted to DOCK8 gene or affects other contiguous genes.

CO4/ HEMATOPOETIC STEM CELL TRANSPLANTATION IN OMENN SYNDROME

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**Introduction:**
Omenn syndrome (OS) is a rare autosomal recessive disorder characterized by severe combined immunodeficiency (SCID) typically associated with the triad of erythrodermia, hepatosplenomegaly, and lymphadenopathy. In the absence of hematopoietic stem cell transplantation (HSCT), OS remains a fatal disorder due to increased susceptibility to infections with a high lethality early in life despite intensive supportive care. We report our experience of allogeneic HSCT in four patients with OS who were transplanted in the period between 1999 and 2015.

**Patients and Methods:**
Four patients among 17 patients with OS were transplanted in our center from 1999 to 2014. All patients fulfilled clinical criteria of OS.

**Results:**
They are three boys and one girl. The median age of diagnosis was 4 months. The clinical presentations include failure to thrive, ichthyosiform erythroderma and infiltration of lymphoid tissues in all patients. All patients developed recurrent infections. Hyper eosinophilia and/or raised IgE level was observed in the four patients. The immunological study showed T cell lymphopenia and B cell lymphopenia in all cases. HLA genoidentical HSCT was performed at an average age of 3 years; 2 of them died respectively at 19 days post HSCT by acute respiratory distress and 20 months post HSCT by chronic graft versus host disease. Two patients had good engraftment and are alive respectively two years and 7 years after HSCT.

**Conclusion:**
OS is a combined immunodeficiency with heterogeneous clinical and immunological phenotype. Evolution is usually fatal outside the HSCT. Despite genoidenical donor, survival was 50%.

**CO5/ A FAMILY WITH ICF: A NEW SPECTRUM OF THE DISEASE.**
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2- Department of Bone marrow transplant, Great Ormond Street Hospital, London, UK.
3- Department of Paediatric Gastroenterology, Great Ormond Street Hospital, London, UK.
Background:
Immunodeficiency, Centromeric instability, Facial anomalies (ICF) syndrome is a rare autosomal recessive disease presenting with hypo-/agammaglobulinemia, developmental delay, and facial anomalies. Centromeric instability is the cytogenetic hallmark of the disorder which results from targeted chromosomal rearrangements related to a genomic methylation defect. Herein we discuss a family with ICF syndrome with novel clinical presentation widening the spectrum of clinical phenotype.

Case report:
Two siblings of consanguineous Kuwaiti parents were diagnosed with ICF at the age of 3.5 (girl) and 2 (boy) years old, respectively. Both presented at birth with symmetrical growth retardation. The girl required nasogastric tube feeding due to severe hypotonia. Global developmental delay with dysmorphic features were noted at birth and brain MRI showing cystic encephalomalacia. Progressive intermittent neutropenia, macro-thrombocytopenia and normocytic anaemia were noted, and examination of the bone marrow was hypocellular with dysplasia in megakaryocytes and myeloid series. Since infancy, both children have had recurrent ear and lung infections, together with intractable diarrhoea and chronic excretion of Sapovirus. Endoscopy revealed a severe panenteric inflammatory enteropathy, which caused severe malnutrition in both children exacerbating their developmental delay. They required prolonged parental nutrition in combination with immunosuppressive therapy. A variable degree of bilateral sensorineural hearing loss was noted in both patients. Café-au-lait spots and joint hyper-extensibility was seen in the boy. Immunological investigations revealed B lymphopenia with significantly decreased IgM and IgA, but normal T cell number and function. Cytogenetics and chromosomal breakage studies were normal. Mitogen stimulated lymphocytes showed decondensation, breaks and multiradial interchanges in the pericentromeric region of chromosomes 1 and 16, defining the diagnosis of ICF. No mutation was identified in either of the known ICF genes (DNMT3B and ZBTB24). Results from whole exome sequencing are pending. Due to intractable enteropathy and dependence on parental nutrition, the girl underwent a reduced intensity conditioned stem cell transplant (Campath/Treosulphan/Fludarabine) at the age of 4 years. Unfortunately, she developed a severe capillary leak syndrome in response to conditioning and died prior to stem cell infusion. In the absence of a fully matched donor, the boy, currently 5 years old, is managed conservatively with parental nutrition, sirolimus and anti-infectious prophylaxis.

Conclusion: These cases reveal an extended clinical phenotype for ICF type 3 (genetically undefined), including features of bone marrow failure, severe enteropathy, sensorineural hearing loss and sensitivity to alkylating chemotherapy.

CO6/ WISKOTT-ALDRICH SYNDROME: A VARIABLE DISEASE


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5. Service d'Epidémiologie CHU Blida, Algeria
Background:

Wiskott–Aldrich Syndrome (WAS) is a rare X-linked Primary Immunodeficiency (PID) that affects 1–10 out of a million male individuals. WAS is an X-linked immunodeficiency disease with a characteristic clinical phenotype that includes thrombocytopenia with small platelets, eczema and recurrent infections. Thrombocytopenia associated with small platelet volume is a key diagnostic indicator. So far, a wide spectrum of the WAS gene mutations have been identified causing a wide spectrum of disease severity.

Objective:
Describe clinical and biologics characteristics as well as outcomes of patients with WAS in Algeria.

Method:
This is a retrospective, multicenter study that included all primary immunodeficiencies followed in 13 pediatric departments in several regions of Algeria since 1985. The data were collected from pre-established forms including demographic data, clinical and biological findings, treatment and outcomes. Statistical analysis was performed with Epi Info 6.

Results:

Twenty-two children have been diagnosed with WAS. Mean age at first symptoms was 3.5 months (1-9), mean age at diagnosis was 16 months (2-50), consanguinity rate is 15% and positive family history is present in 38% of patients. The clinical symptoms are: recurrent or severe pulmonary infections (59%), chronic severe diarrhea (27%), eczema (95%) and mucosal bleeding (68%). All children have low mean platelet volume and thrombocytopenia with an average rate of platelet of 38 000/mm3, 23 % have a platelet count < 20,000. Fifty-nine percent have platelet count between 20,000 and 50,000. Only 3 patients had thrombocytopenia comprised between 50,000 - 100,000. The triad of eczema, thrombocytopenia and recurrent infections was present in 17 children (81%). Genetic confirmation was made only for 3 patients. Two patients had complications such as autoimmune vasculitis, autoimmune anemia and arthritis. Eight children received multiple courses of IV antibiotherapy, 6 children had IV IG therapy every 3 weeks, 3 children with severe WAS underwent allogeneic hematopoietic stem cell transplantation with good results, 4 children were lost to follow-up, 5 died.

Conclusion:
Wiskott–Aldrich Syndrome has a heterogeneous clinical expression. In addition to the severe forms that must quickly benefit from treatment with hematopoietic stem cell transplantation, less severe forms must be carefully monitored.

CO7/ WISKOTT - ALDRICH SYNDROME IN A SENEGALESE CHILD: A CASE REPORT

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2. National Blood Transfusion Centre
3. Faculty of Science of the University Gaston Berger Health- St. Louis Senegal
Introduction:

Wiskott-Aldrich syndrome (WAS) is a X-linked recessive genetic disease, due to a mutation in the gene that regulates WASp the actin cytoskeleton. This is a rare disease characterized by a triad of immune deficiency, eczema and microcytic thrombocytopenia.

Objective:

Our objective is to report a case diagnosed and treated in the Senegalese context.

Observation:

PMG, male, was hospitalized at the age of 7 months at the Centre Hospitalier National d'Albert Royer Children of Dakar for bloody diarrhea and eczema with bleeding excoriations. From a non-consanguineous marriage, he is the third in a family of three children; one male had similar manifestations and died at the age of 4 months. He was hospitalized for a neonatal infection at two weeks of life, for pneumonia at the age of 3.5 months, and for decapitated bacterial meningitis at 5.5 months. Furthermore, he presents recurrent ENT infections and chronic diarrhea. Laboratory tests showed a microcytic thrombocytopenia (43,000/mm³; MPV 5.47fl), a CD4 and CD8 lymphopenia and increase in IgA and IgG. These anamnestic, clinical and biological features enabled us to retain the diagnosis of Wiskott-Aldrich syndrome, pending confirmation by genetic testing not available in our context. P.M.G. was followed in dermatology and pediatrics with a treatment with antihistamines, emollients of oral corticosteroids and iterative transfusions of platelet concentrates. The outcome was favorable for eczema, but the platelet count remains low.

Conclusion:

Wiskott-Aldrich syndrome should be considered in the association of a microcytic thrombocytopenia with eczema and recurrent infections. If confirmation requires genetic testing, guidance is essentially clinical in front of recurrent infections and/or severe autoimmunity or neoplasia. The management is multidisciplinary and cure is the transplantation of hematopoietic stem cells.

CO8/ ATAXIA TELANGIECTASIA : CLINICAL AND MOLECULAR PROFILE IN MOROCCO.

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3. Laboratoire de Biochimie-Immunologie, Université Mohamed V- Agdal, Rabat
Ataxie Telangiectasia (AT) is a primary immunodeficiency characterized by a clinical triad gathering progressive cerebellar ataxia, oculocutaneous telangiectasia and recurrent respiratory tract infections. The causal gene, ATM (Ataxia Telangiectasia Mutated), coding for a protein involved in DNA repair, explains the increased risk of malignancy in AT patients. This work aims to discuss the clinical, immunological and molecular profile of AT patients in Morocco, as well as demonstrating the value of genetic counseling in this disease.

Between 1998 and 2014, 45 patients, issue from 33 unrelated families, have been diagnosed as AT. Mean age at diagnosis was 6.88 years (9 months-12 years) and mortality reached 46.6% with a mean age at death of 11.5 years. Male patients represent 46% and parental consanguinity was reported in 63.3% of families, with 7 multiplex families (at least 2 affected children). All patients presented with ataxia, ocular telangiectasia and a variable immunodeficiency. Only 24 patients, from 20 families, benefit from a molecular analysis. We found 14 different mutations in this sample, which 7 have never been reported. The c.5644C>T mutation was the most common in this cohort.

Outcome has been marked by death in 21 patients (46.6%), due to respiratory failure on bronchiectasia (9 cases), neoplasia (4 cases) and tuberculosis (2 cases).

The fatal outcome of this disease and possibility to perform a prenatal diagnosis open the debate on how to approach these families, considering religious and ethical issues.

CO9/ ATAXIE TELANGIECTASIE : A PROPOS D’UN CAS FAMILIAL
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2.Laboratoire de Bactériologie et de Virologie. Unité d’Immunologie. Hopital Aristide Le Dantec

INTRODUCTION:
L’ataxie télangiectasie ou syndrome de Louis Bar est une maladie génétique à transmission autosomique récessive. Elle se manifeste par une triade classique : ataxie – télangiectasie
oculaire- infections à répétition. Cette affection est associée à un déficit immunitaire primitif. Le
gène responsable (ATM) est localisé sur le bras long du chromosome 11.

**OBSERVATION:**
Une fillette de 8 ans était hospitalisée dans le service de Pédiatrie de l’hôpital Principal de Dakar
du 14 avril au 23 avril 2014 pour un retard staturo-pondéral et un retard du développement
psychomoteur. Le tableau évoluait depuis l’âge de 18 mois. La marche autonome n’avait jamais
été acquise. Elle présentait des troubles de l’équilibre, une incapacité à se tenir debout sans
appui. Des épisodes répétés de rhinobronchites et de dermatoses récidivantes survenaient. Un
scanner cérébral, prescrit au cours d’une consultation, était revenu normal. Des séances de
kinésithérapie motrice avaient été prescrites. Devant l’absence d’amélioration clinique, les
parents s’étaient orientés vers les tradithérapeutes.

On retrouvait, dans les antécédents familiaux, une notion de consanguinité parentale de premier
degré. Elle était quatrième d’une fratrie de six enfants. Deux décès étaient survenus dans cette
fratrie : le premier en période néonatale et le second chez la sœur cadette âgée de 3 ans. Une
ataxie - télangiectasies avait été diagnostiquée chez cette dernière dans le service du 1er avril au
23 avril 2014. Cette sœur cadette avait été admise dans un tableau d’anémie sévère avec
hépatosplénomégalie et des télangiectasies oculaires. L’ataxie était peu marquée. Elle avait
présenté une anémie hypochrome microcytaire à 4,8 g/dL, une hyperleucocytose à
polynucléaires neutrophiles et une élévation de la CRP à 149,2 mg/L. Le taux d’alpha-
foetoprothène était de 211,7 ng /ml (N : 0-12 ng/mL). La sérologie rétrovirale était négative. Une
hémoculture avait isolé un streptocoque non groupable. L’électrophorèse des protéines sériques
avait montré une hypergammaglobulinémie. L’IRM cérébrale montrait des lésions de
démyélinisation diffuse. L’évolution initiale avait été favorable. Admise de nouveau le 7 juillet
2014 dans un tableau de convulsions fébriles en rapport avec une méningite à pneumocoque,
elle décédait dans les 24 heures. Notre patiente présentait sur le plan clinique : une ataxie
cérébelleuse, des télangiectasies oculaires, des lésions du cuir chevelu évocatrices d’une dermite
séborrhéique et des lésions croûteuses ulcéro-nécrotiques des membres inférieurs. La biologie
révélait une hyperleucocytose à prédominance neutrophile, une augmentation de la CRP à 46,9
mg/L. Le taux de l’alpha-foetoprothène était de 1161 ng /ml (N = 0-12). La sérologie rétrovirale
était négative. Le prélèvement de pus de l’abcès du cuir chevelu montrait un staphylocoque
aureus sensible à l’oxacilline. L’immunophénotypage montrait un déficit en lymphocytes T à
1,006.109/L (N=1,2-2,6) soit 45,4% (N= 60-76) et un déficit en lymphocytes B à 0,026.109/L
(N= 0,27-0,86) soit 1,19 % (N= 13-27). L’électrophorèse des protéines sériques montrait une
hyper-alphaglobulinémie. L’IRM cérébrale était normale. Un vaccin anti-pneumococcique était
prescrit à la sortie.

**CONCLUSION:**
L’ataxie-télangiectasie est une maladie rare dont la prise en charge est lourde en Afrique
Subsaharienne. Elle est, à l’instar des autres déficits immunitaires primitifs, sous diagnostiquée
dans nos régions. La médecine moderne donne peu de réponses thérapeutiques satisfaisantes
dans le contexte de pays en voie de développement. L’accès aux immunoglobulines représente
dès lors une perspective thérapeutique pouvant améliorer le pronostic vital des enfants atteints.

**CO10/ CHRONIC GRANULOMATOUS DISEASE IN ALGERIAN CHILDREN**

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Introduction:

Chronic Granulomatous Disease (CGD) is an inherited disorder of the innate immunity, affecting the phagocytic cells. The majority of cases of CGD in the western world is X-linked while autosomal CGD is more common in the Middle East.

Methods:

This is a retrospective, multicenter study that included all primary immunodeficiencies followed in 13 pediatric departments in several regions of Algeria since 1985. The data were collected from pre-established forms including demographic data, clinical and biological findings, treatment and outcomes. Statistical analysis was performed with Epi Info 6.

Results:

During this 30-year period, we identified 409 children with PID among which 19 patients with CGD (4.6 %) including 14 boys. Mean age at diagnosis was 50 mo ± 40 with a median of 36 and an interquartile range (IQR) of (17.5 – 84). The median time between the onset of symptoms and diagnosis was 18 mo with an IQR of (2- 36). Inbreeding was found in 52.6%. In the family history, death in infancy was noted in 47.4% of siblings with a PID identified in 23% which was CGD in 3/4. Vaccination complications found in 23.5% were all due to BCG (1 BCGitis and 3 adenitis). The median age at first manifestations is 7 mo with an IQR (2- 36). Symptomatology is dominated by respiratory manifestations such recurrent pulmonary infections in 87.5%, chronic abscesses, adenitis, prolonged fever and skin infections in respectively 62.5, 56, 56 and 44%. We noted 18% of meningitis and osteoarthritis. The impact on growth was important since failure to thrive was present in 50% of children. After elimination of acquired immunodeficiency (HIV), testing by the NBT test helped confirm the diagnosis of CGD. Susceptibility to infections met in this type of deficiency was confirmed: Staphylococcus aureus in 44% of pyogenic infections. The fungal infections were caused by Aspergillus (71%) and Candida albicans (29%). A unusual finding in CGD was the presence of a single CMV infection. The only genetic study done was that of the child who has had a bone marrow transplant, which carries a mutation in CYBB. For the treatment, 93.7% of patients have had repeated courses of IV antibiotherapy (ATB) and sequential ATB was given in 44.44%. The curative antifungal therapy was used in 85.7% of patients using either fluconazole, voriconazole or amphotericin B. Seventy-five percent of children had a trimethoprim-sulfamethoxazole prophylaxis and 58% an antifungal prophylaxis with voriconazole essentially. We noted 70% of complications such as aspergillosis, liver failure and bone involvement. In this series, only one patient had a bone marrow transplant at the age of 6 years with a good evolution after a follow-up of 8 years. We found 53% of deaths from infection at a median age of 6 years. At the latest news, children have a median age of 9.3 years.

CO11/ CHRONIC GRANULOMATOUS DISEASE IN LIBYA:
CLINICAL AND LABORATORY STUDY OF 35 PATIENTS

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Introduction:

Chronic granulomatous disease (CGD) is a rare primary immunodeficiency disease, characterized by failure to activate the respiratory burst in the phagocytes. CGD is inherited as autosomal recessive or x-linked recessive trait. Patients with CGD have a greatly increased susceptibility to severe infections, early in childhood at different sites. There is a paucity of data from Libya on CGD; we aimed to study CGD in Libyan children, to evaluate the diverse multisystem clinical manifestations of CGD and their prevalence as well as the outcome.

Materials & Methods:

Our study was retrospective; it included pediatric patients with a diagnosis of CGD seen in immunology department at Pediatric hospital in Benghazi, between 2007 and 2013. Their diagnosis was confirmed by Nitroblue Tetrazolium test.

Results:

We reviewed the records of 35 patients: 66% were male, 94% had onset of disease <1 year of life, and 60% of their parents were relatives. Reticuloendothelial system was involved in 94% followed by skin (91.4%), respiratory (83%), gastrointestinal (68.6%) and bone (28.6%). Ninety-one percent had hepatosplenomegaly and 80% suffered from suppurative lymphadenitis. Skin abscesses were seen in 75%, perianal fistula in 30% and BCGitis in 20). Pneumonia was the main respiratory problem (83%), followed by aspergillosis (22.8%), bronchiectasis (14%) and pulmonary abscess in 5.7%. Despite aggressive antimicrobial therapy, 43% was died.

Conclusions:

This study is one of the largest series on CGD from North Africa and Arabic region reflecting the different modes of inheritance, as well as the wide and variable clinical manifestations of CGD. Awareness of CGD features may aide in early detection and management.
Introduction:

Primary immunodeficiency disorders (PIDs) include more than 200 disorders that affect the development or the function of the immune system or both. PIDs are classified into eight major categories. Diseases of immune dysregulation are one of these categories which include: Familial Hemophagocytic Lymphohistiocytosis (FHL), Autoimmune Lymphoproliferative Syndrome (ALPS), Griscelli syndrome (GS) and Chediak-Higashi syndrome (CHS).

Methods:

This is a retrospective, multicenter study that included all primary immunodeficiencies followed in 13 pediatric departments in several regions of Algeria since 1985. The data were collected from pre-established forms including demographic data, clinical and biological findings, treatment and outcomes. Statistical analysis was performed with Epi Info 6.

Results:

During this 30-year period, we identified 409 children with PID among which 20 patients were diagnosed with diseases of immune dysregulation (4.9%). Mean age at diagnosis was 11 months (1-72). There were 10 boys and 10 girls. The distribution of patients according to each category was: FHL in 10 cases (50%), CHS in 6 cases (30%) and GS in 4 cases (20%). The rate of consanguinity was 80%. At time of diagnosis, patients showed a wide spectrum of clinical manifestations: pulmonary infection (40%), skin infection (20%) and failure to thrive (30%). Partial albinism was seen in patients with GS and CHS (35%). Manifestations of autoimmunity were observed in one patient. During follow-up, recurrent infections were frequently seen nearly in 35 % of patients. Twelve patients (60%) developed an accelerated phase of the disease with hepatosplenomegaly, cytopenia, bone marrow infiltration and hemophagocytosis. Antimicrobial prophylaxis was used in 7 patients (35 %) and 4 patients (20%) received intravenous immunoglobulin replacement therapy. Other therapy included cyclosporine and corticoids. Nine patients (45%) died during the study period. The median age at death was 5 months. Fulminate infection and failure to thrive were the commonest causes of death.

Conclusion:

Our cohort represents a sample of Algerian children having a rare variety of PID with high rate of mortality. Allogeneic bone marrow transplantation from an HLA-matched sibling is the therapy of choice and should be performed early.
CO13/ EPSTEIN-BARR VIRUS-INDUCED LYMPH PROLIFERATIVE DISORDER: CLINICAL CHARACTERISTICS AND THERAPEUTIC OUTCOME
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Introduction:

Epstein-Barr Virus (EBV)-induced Lymphoproliferative disorder (LPD) is most frequently seen in patients receiving immunosuppressive treatment after organ transplantation (post-transplant lymphoproliferative disorder), but can also arise in primary immunodeficiencies such as the Wiskott-Aldrich syndrome (WAS).

Objective:

To describe clinical features and therapeutic outcome of an EBV-induced LPD in two patients followed within the National Center of Bone-Marrow Transplant of Tunis.

1st observation:

Y.M, a two-year old boy with WAS, revealed at the age of 13 months by a massive hematemesis, associated to Kaposi’s sarcoma and a cerebral EBV-induced LPD. Clinical signs were dominated by intracranial hypertension. The CT scan showed an intracerebral tumor with an important ventricular compression and an early cerebral engagement. Biopsy revealed larges CD20+ cells and EBV. This cerebral lesion did not respond to systemic and intrathecal treatment with specific anti-CD20 (Rituximab) immunotherapy. A better response was obtained with intrathecal and systemic Methotrexate. Finally, the patient received an allogeneic bone marrow transplantation as a treatment of its WAS with T immunodeficiency responsible for both: Kaposi’s sarcoma and EBV-induced LPD. He remains clinically free of LPD at 12 years.

2nd observation:

J.H, a five-year old girl with chronic granulomatous disease, revealed at the age of two years, by recurrent skin infections. She received a bone marrow transplantation at the age of five years from a 4/6 HLA identical donor and conditioned with Fludarabine, Busulfan and antilymphocyte globin. Nine months later, she consulted for fever and anorexia. The clinical signs were cervical lymphadenopathy, hepatic and splenic enlargement. The laboratory tests showed a pancytopenia, a hypofibrinogemia, high serum ferritin level and raised triglyceride due to a macrophagic activation syndrome, a B lymphocyte proliferation, and a positive EBV PCR (328,679 DNA copies /ml) in relation with a post-transplant EBV-induced LPD. A therapy with four weekly doses of 375 mg/m2 of Rituximab and corticotherapy was undertaken with a transient good evolution, death occurred 4 months later.

Conclusion :

Frequent quantitative monitoring of EBV reactivation is necessary to an early diagnosis in transplanted patients and also in combined immune deficiency. Rituximab is a promising new tool for the treatment of post transplant lymphoproliferative disease.
Introduction:

The complement system is a major effector of the innate and adaptive immunity. The hereditary defects in fractions of the complement, essentially those of the common way (C5-C9), constitute susceptibility factors of purulent meningitis, in particular meningococcal meningitis.

Purpose:

To study the clinical and biochemical characteristics of three children having a hereditary complement deficiency.

Results:

This is about 2 sisters and a boy, whose mean age at the time of diagnosis is 7.2 years. Two children had a history of relapsing meningitis. These patients appeared in a clinical picture of purulent meningitis. The meningococcal origin was confirmed in 2 cases. The level of C5 was collapsed in the 2 sisters’ sera and the level of C7 was decreased in the boy's. The evolution was favorable in 3 cases.

Conclusion:

The description of these three cases shows that the genetic defects in complement is not rare; it is clinically characterized by forms of meningitis of fickle severity.
Purpose:
Primary immunodeficiencies are a heterogeneous group of genetic disorders affecting distinct components of the innate and adaptive immune system. The laboratory plays a critical role in the diagnosis of these conditions given their frequently overlapping signs and symptoms. Based on our experience, we aimed to highlight the role of flow cytometry (FC) in the diagnosis of primary immunodeficiencies.

Methods:
This study was conducted on 205 patients. Different membrane and intracellular staining were performed using a six-color cytometer (BD Biosciences, U. S. A).

Results:
Applied in the setting of possible immune deficiency, this technology can in some cases clarify a diagnosis and in other settings help to direct additional testing to establish a diagnosis. In our laboratory, FC is routinely used to: (1) detect the absence/decrease of a specific cell population/subpopulation, such as T cells/naive T cells, in the diagnosis of severe combined immunodeficiencies (SCIDs) or the presence/increase of a specific cell population/subpopulation such as alpha beta double negative T cells in the diagnosis of autoimmune lymphoproliferative syndrome, (2) screen for altered expression of a specific membrane protein such as HLA-DR for the diagnosis of MHC class II deficiency, (3) screen for altered expression of a specific intracellular protein such as Bruton tyrosine kinase (Btk) in the diagnosis of X-linked agammaglobulinemia and (4) evaluate certain functional immune characteristics such as dihydrorhodamine (DHR) FC assay in the diagnosis of chronic granulomatous disease (CGD). In addition to its diagnostic role, FC has proven to be useful in the classification of common variable immunodeficiency patients into subgroups according to B-cell subsets, which has clinical implications.

Conclusion:
FC have emerged as a critical tool in the evaluation and diagnosis of PIDs. The application of FC provides rapid results and in many cases clarifies the likely diagnosis, directs further immunologic studies, and/or can be linked to clinical phenotype.
Agammaglobulinemia is a rare primary immunodeficiency characterized by absent peripheral B cells and severe hypogammaglobulinemia. About 80-85% of patients have mutations in BTK, the gene responsible for the X-linked agammaglobulinemia (XLA). Underlying mutations for half of the remaining patients only are identified. The affected genes are required for the pre-BCR assembly or its signaling cascade and encode for the μ heavy chain, Igα, Igβ, λ5, BLNK, p85δ and E47 respectively.

Consanguinity is a hallmark of North African and Middle Eastern populations reaching more than 50% in some areas. High prevalence of consanguineous marriages contributes to the increased occurrence of autosomal recessive primary immunodeficiency diseases. In this context, we aimed to investigate the molecular basis of agammaglobulinemia in a highly consanguineous North African population. We initially excluded the XLA in 10 out of 50 male patients after BTK gene sequencing. Thus, our study population included 10 male and 13 female patients presenting with early onset of bacterial infections, agammaglobulinemia and very low or absent circulating B cells. These patients were assigned to the autosomal recessive form of the disease and screened for mutations in genes encoding for the pre-BCR complex (IGHM, CD79A, CD79B, IGLL1 and Vpre-B).

Sequence analysis of IGHM gene revealed the presence of a homozygous complex mutation in one patient, consisting of 2-pb insertion and 5-bp deletion at codon 378. This mutation leads to a frameshift and a premature stop codon at position 379 (p.V378AfsX379). A second mutation (c.549delC) was identified in two patients within the same family. This mutation causes a frameshift and premature stop codon at position 205 (p.T183TfsX205).

Mutational analysis of CD79A gene in two siblings showed the presence of a novel nonsense mutation (c.383G>A), representing the sixth mutation reported worldwide.

In conclusion:
XLA is present in 63.5% of our cohort population. The autosomal recessive forms are more frequent as compared to European series. This is probably due to high prevalence of parental consanguinity. Molecular basis remains unknown in the majority of patients, for whom whole exome sequencing is ongoing.
CO17/CLINICAL, IMMUNOLOGICAL AND GENETIC FEATURES OF ALGERIAN PATIENTS WITH LEUKOCYTE ADHESION DEFICIENCY TYPE I

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Introduction:
Leukocyte adhesion deficiency type 1 (LAD-1) is a primary immunodeficiency of phagocytes, inherited as an autosomal recessive trait. It is characterized by recurrent bacterial and fungal infections, omphalitis and/or delayed umbilical cord separation and persistent leukocytosis. It is caused by the lack or low expression of β2 integrin (CD18). The disease is categorized as severe form with less than 2%, and as moderate form with 2–10% of normal CD18 glycoprotein expression.

Objectives: We report the clinical, immunological and genetic features of 5 Algerian patients with LAD-1, three of them belonging to the same family.

Material and methods: This is a retrospective, multicenter study that included all hospitalized followed in 9 pediatric departments in several regions of Algeria. The data were collected from pre-established forms including demographic data, clinical and biological findings, treatment and outcomes. The expression of CD18 was evaluated on granulocytes by flow cytometry using monoclonal antibodies directed against CD18 and labeled with FITC. Genomic DNA was purified from whole blood samples using salting-out method. All coding exons of CD18 gene (ITGB2) were amplified using the primers pairs that hybridized to intronic sequences that flank the exons. Direct sequencing of PCR products was performed using the Big-Dye 3.1 kit and an Applied Biosystems 3130®sequencer (Applied Biosystems).

Results: The five patients enrolled belong to 3 unrelated families that are consanguineous (first cousins), 4 boys and 1 girl. All of them developed the first symptom (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 for all patients (21,000 to 83,000/mm3). The CD18 expression on granulocytes was <1% of the normal value for all the patients which allowed us to classify them in the severe form. For the first patient, the sequencing identified two heterozygous missense mutations: c.533C>T in exon 6 and c.1358G>A in exon 11. A homozygous nonsense mutation, c.562C>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 exon 10 (c.1101C>A) and 11 (c.1323 T>C) for two families that showed the same deleterious mutation. All of these genetic abnormalities have been described before. 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: Our patients suffer from severe form of LAD I 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 but usually fatal clinical evolution.
CO/18 PARTIEL FACTOR I DEFICIENCY DUE TO DOUBLE HETEROZYGOTE MUTATIONS IN A PATIENT WITH ATYPICAL HEMOLYTIC UREMIC SYNDROME

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Background:

Mutations and polymorphisms in alternative pathway components, complement regulator molecules FH and MCP but also in FI have recently been associated with atypical hemolytic uremic syndrome (aHUS). It’s a disorder characterized by hemolytic anemia, thrombocytopenia and acute renal failure. In this study, we report one patient with different heterozygous mutations in FI gene who developed severe aHUS at different time points in his life.

Patient and methods:

A.W. is a 4-year-old boy with no history of recurrent infections. He presented at 3 years and 7 months with thrombotic microangiopathy syndrome with proteinuria and acute renal failure. Specific blood tests including hemoglobinemia, platelet count, lactate dehydrogenase and antigenic dosages of C3 and C4 by nephelometry laser and Factor B, Factor H and Factor I by Radial immunodiffusion (Binding Site) were performed for him. Genomic DNA sequencing by direct sequencing of all CFI and CFH genes was performed.

Results and discussion:

Tests results showed anemia, thrombocytopenia, elevated lactate dehydrogenase and creatinine and positive proteinuria. He also showed normal expression of MCP and C4 concentration. However, we found decreased amount of C3 and very low Factor I concentration. Double heterozygote p.K358N and p.Q427P mutations in factor I gene associated to 2 very rare polymorphisms of Factor H in CFH: p.S890I (rs515299) and p.V1007L (rs534399) have been identified. Literature reports that complete FI deficiency results in consumption of C3 due to uncontrolled activation of the alternative pathway. Such patients have a high susceptibility to recurrent pyogenic infections and may develop glomerulonephritis or systemic lupus erythematosus. In contrast, some individuals with heterozygous mutations in FI are healthy, as in the case of the patients’ unaffected parents. Our patient seems to have intermediate phenotype due to the presence of double heterozygous mutations leading to decrease FI amount.

Conclusion:

Most mutations are single heterozygous and certain patients may have more than one mutation and/or risk-associated polymorphisms in these factors. We described the first patient with a double heterozygous mutation in CFI suffering from severe aHUS phenotype.
A SIMPLE ASSAY FOR THE MOLECULAR DIAGNOSIS AND THERAPY MONITORING IN THE IMMUNODEFICIENCY OF FACTOR H-RELATED ATYPICAL HEMOLYTIC UREMIC SYNDROME


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Introduction:

In contrary of the others immunodeficiencies, the “atypical” form of Hemolytic Uremic Syndrome (aHUS) shows no particular relationship with infection. In 40% of cases, the affected protein is the complement regulator Factor H (FH): 30% due to mutations and 10% because of anti-FH autoantibodies. A clinical course of aHUS characterized by progression to end-stage renal failure and recurrences after transplantation seems to be associated to patients with factor H mutations. Here we describe the detailed protocol for a rapid test to analyze the functional defect associated with FH-related abnormalities from a 34 years-old women case report.

Methods:

The Complement components C3, C4 and factor B were quantified in all samples by nephelometry laser (Beckmann Image 800, USA). The characterization of the underlying complement factor H defect was performed by a Hemolytic assay with nine plasmatic serial dilutions, based on spontaneous lysis of non-sensitized sheep erythrocytes in contact with patients’ plasma, described by Lubka T. Roumenina (2014).

Results and discussion:

We performed the hemolytic assay on the plasma from one patient with aHUS, the plasma with a known Factor H deficiency as a positive control, one patient with typical HUS, and 30 control individuals. All patients have C3 and C4 levels within the normal range of variation, except the aHUS one where C3 was decreased. The hemolytic assay shows that aHUS patient and the positive control having a mutation in factor H present a high level of lysis (above 60% of total lysis), and that it is significantly different from the lysis observed in typical HUS patient and in control individuals.

As Lubka T. Roumenina et al (France), A. Massart et al (Belgium) and P. Sánchez-Corral et al (Spain), we illustrate that a control plasma do not lyse sheep erythrocytes under the conditions of this assay, while sera from the aHUS patients lyse the sheep erythrocytes in a dose-dependent manner.

Conclusion:

We believe that the simplicity of the hemolytic assay for factor H described here makes it a useful tool for the prompt diagnosis and the treatment by plasma therapy of factor H-related aHUS.
CO20/FIRST REPORT ON PRIMARY IMMUNODEFICIENCY DISEASES
IN LIBYAN CHILDREN

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Introduction and objectives:
Primary immunodeficiency diseases (PIDs) are a group of rare diseases characterized by variable genetic immune defects mostly observed in infants and children. Recognition of PIDs in Libya is only recent and no studies describing the spectrum of PIDs have been reported. We aimed to determine the spectrum of PIDs in Libyan children and to determine diagnostic facilities and treatment availability.

Material and methods:
This study included pediatric patients with diagnosis of PIDs whom seen at department of immunology of pediatric hospital in Benghazi, Libya through 2007 - 2013. To confirm the diagnosis of PIDs, the following tests were performed for patient with features suggestive of immunodeficiency: complete blood count, serum Immunoglobulin and complement assays and flow cytometry. Other tests were guided by the clinical features of the patient. HIV infection was excluded in all patients.

Results:
Our study included 62 PIDs patients, majority (90%) presented before the first year of life. Males constituted 55%. Positive family history of PIDs was recorded in 60% and positive consanguinity in 58%. Phagocytic defects (61%) included chronic granulomatous disease (56%), neutropenia (3%) and leukocyte adhesion defect (2%). Well-defined syndromes with immunodeficiency (21%) included Hyper-IgE syndromes (8%), ataxia telangiectasia (6.5%), Wiskott–Aldrich syndrome as well as DiGeorge anomaly (3%). Agammaglobulinemia (8%), and one case of common variable immune deficiency, transient hypogammaglobulinemia of infancy and hyper IgM syndrome constituted the humoral defect (13%). Two siblings with Chediak–Higashi syndrome were representing diseases of immune dysregulation. One case of epidermodysplasia verruciformis was an example of innate immunity defect.

Conclusions:
This study is the first in Libya to provide an overview of PID in children; congenital phagocyte defects were the commonest PID with majority of cases being CGD. Many immune deficiencies could not be identified due to lack of diagnostic facilities and life of many PIDs patients could not be saved due to absent or delayed therapy. Physicians’ education, better diagnostic facilities as well as international collaboration are needed to improve PIDs diagnosis and management.
Background:
Common variable immunodeficiency disorders (CVID) are the most frequent symptomatic primary immune deficiency with a prevalence of approximately 1/50,000 to 1/25,000. CVID represents a heterogeneous group of disorders characterized by a defect in antibody production and recurrent bacterial infections. Several studies about CVID in both adult and children have been published but publications concerning exclusively CVID in children are infrequent.

Objectives:
Our objective was to determine the clinical manifestations, the immunological characteristics and the outcome of Algerian pediatric CVID patients.

Methods:
This is a retrospective, multicenter study that included all primary immunodeficiencies followed in 13 pediatric departments in several regions of Algeria since 1985. The data were collected from pre-established forms including demographic data, clinical and biological findings, treatment and outcomes. Statistical analysis was performed with Epi Info 6. CVID was diagnosed using standard criteria including low level of serum IgG, IgA, and/or IgM greater than 2 SD from the normal mean, low levels of circulating B cells and exclusion of other defined causes of hypogammaglobulinemia.

Results:
During this 30-year period, we identified 409 children with PID among which 35 patients with CVID (8.6 %). Twenty-three (66%) were female and 12 (34 %) were male. Consanguinity was found in 29 % of cases. The median age at onset was 3 years. The median age at diagnosis was 6.7 years. The median delay between first relevant symptoms of immune deficiency and detection of dysgammaglobulinemia was long: 4.5 years; 33 patients had recurrent infections (94%); low respiratory infections (80%) were the most common type; bronchiectasis was present in 11 patients (31%). The second most common manifestations were chronic diarrhea (37%) and otitis (26%); growth failure was found in 11.5 % of patients. Autoimmune diseases were found in 8 cases (23%) of CVID: 2 autoimmune anemia, 2 autoimmune thrombocytopenia, 1 Evans syndrome, 2 autoimmune hepatitis and malignancy in 1 case. Twenty patients were reported to be alive, whereas 4 (11 %) were deceased. The average of follow-up is 5.6 years.

Discussion:
This is an original study of an exclusively pediatric population. The results do not completely match the published studies with both children and adults. As might be expected, we found a broad range of clinical manifestations, including acute and chronic infections and autoimmune disease. But we have not fulfilled all the ESID diagnosis criteria. Because the cause of the CVID is unknown, there is no universally accepted definition of the disorder; various diagnostic criteria have been proposed. Our study did not use criterion A (age of onset >4 years) of the ESID but instead validated the diagnosis after age 2 years and subsequently might include some children with transient hypogammaglobulinemia. Despite that, the long term follow-up seems to confirm our diagnosis.

Conclusion:
Our study emphasizes the importance of clinical symptoms. CVID can be challenging in both diagnosis and treatment, especially in childhood. Regardless of which criteria are used, it is essential that sound clinical judgment is exercised when diagnosing and treating these patients.
CO22/ CLINICAL AND BIOLOGICAL FEATURES OF COMMON VARIABLE IMMUNODEFICIENCY IN MOROCCO

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The common variable immunodeficiency (CVID) is the most frequent symptomatic primary immunodeficiency (PID). It is a heterogeneous group of disorders characterized by a defective antibody production. The main features include respiratory tract infections and their associated complications, enteropathy, autoimmunity and lymphoproliferative disorders. This work is an evaluation of data collected in the Moroccan registry of PID from 1999 to 2015. All patients with diagnosis of CVID were included.

We analyzed data on 29 patients. Twenty one patients were reported alive whereas 6 were deceased and 2 had been lost to follow-up. The sex ratio (M/F) was 0.93. The median age was 9.35 years old (extremes: 2 - 18 years old). Parental consanguinity was reported in 18 patients and three patients reported similar cases in their family. Mean age at onset was 6.29 years (+/- 6.5 SD) while mean age at diagnosis was 13 years old (+/- 12.31 SD). Clinical manifestations were varied but dominated by recurrent infections involving mainly respiratory, ENT and digestive in all our patients. Almost a third of cases (10 patients) had autoimmune manifestations: autoimmune cytopenias and autoimmune hepatitis. We found a tumoral syndrom in 6 cases (splenomegaly). One patient died of a brain tumor (type germinoma). All patients with CVID had a low IgG level. Decreased levels of IgA and IgM were found in 68% and 59 % respectively. Sixteen patients benefited from a lymphocyte subpopulations phenotyping. Only 2 patients of them had a disturbed immunophenotyping (moderate decrease in CD4).

We tried to find a significant relationship between the variables of this work. For clinical manifestations, splenomegaly was associated with autoimmunity in most of the cases; and among them were the two patients with a low CD4 count. Patients with bronchiectasis were found to have a significantly lower IgG values (mean = 0.12 g/L) than those without (mean = 1.18 g/L).

Our patients with CVID are similar to those reported in the literature by their clinical and biological heterogeneity. Proper classification of these patients is essential for defining homogeneous groups and guide molecular characterization. Many ways to improve the diagnosis and classification of CVID have been proposed over the past decades. Currently, serum immunoglobulin levels and flow cytometry showing numeric B-cell subgroup deficiencies are the gold standard for CVID diagnostics and classification.
Introduction:
The African Society for Immunodeficiencies (ASID) is now 7 years-old and gathers more and more members. Through this period, ASID established several projects as the International PID Registry, the ASID website, the ASID newsletter and the A-project. It was time to ask for a feedback from our members on what they think about our projects and what they expect from ASID.

Methods:
We developed 4 mini online surveys (no more than 10 questions) for each activity: the website, the eLetter, the A-project and the Registry. The links for these surveys was sent to a mailing list collected from ASID registered members on the website and attendees to the A-projects. No incentive was offered and two reminders were sent. Responses were collected between January 11th and February 18th.

Results:
On 147 mails sent, 11 bounced back as the address was incorrect. However, only 16 responses were collected at most (Response rate of 11.8%). Responders came from 9 different countries, which are already known as implied in Primary Immunodeficiencies. Globally, responders were satisfied with our products: 69% liked the website design and more than 60% liked the contents; more than 80% were satisfied with the A-projects; more than 70% were satisfied with the newsletter; and all responders (9) were interested in the patient registry. Moreover, responders reported 403 PID patients diagnosed in the last 5 years. Some responders also provided valuable ideas to improve our projects.

Conclusion:
As the answering rate was low, which is unfortunately common in Africa, drawing conclusions is hardly possible. However, it seems that ASID members are globally satisfied with our activities and some have good suggestions to improve our Society. ASID should strive to imply more active members in the decision-making process and highlight the importance of each member.
CO24/ PID ALERTS’ SYMPTOMS IN CHILDREN

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Introduction:
Primary Immunodeficiencies (PID) represent a group of 250 inherited diseases that lead to recurrent, severe or uncommon infections. Specific features of these infections could help in early detection. We aimed in this survey to compare presentation of three most frequent groups of PID [predominantly antibody deficiencies (PAD), congenital defect of phagocyte (CDP) and combined T and B cell immunodeficiencies (CID)] in Clinical Immunology Unit of Department of Pediatrics in Ibn Roshd Medical School, Casablanca, Morocco.

Patients and methods:
It was a retrospective, descriptive and analytical survey conducted on children that were treated for primary immunodeficiency with accurate immunological diagnosis. The study was performed from January 2012 through December 2013. The inclusion criteria were accurate diagnosis of PAD, CID or CDP. Diagnoses were made upon clinical suspicion and antibodies dosage (A, G, M and E), whole blood count, lymphocyte subpopulation count (CD3, CD4, CD8, CD16, CD19 and DR) and bacterial oxidative capacity by nitroblue tetrazolium reduction test. Data were collected from primary immunodeficiencies’ registry and patients’ medical records. The variables studied were related to socio-demographic data (age at diagnosis, gender, consanguinity and familial similar cases), clinical presentation (referral reason, underlying disease, complications) and type of deficiency (PAD or CID or CDP). Data were analyzed with SPSS software. Comparison of proportions was performed using chi-square test and a p-value < 0.05 was considered as statistically significant.

Results:
During the study period, 82 PID were diagnosed and 51 met inclusion criteria with a rate of positive cases at 62.2%. Among these, PAD, CDP and CID accounted respectively for 29.4% (n = 15), 35.3% (n = 18) and 35.3% (n = 18). The sex ratio was 1.7. The mean age at diagnosis was respectively 6.9, 5.2 and 1.1 years in PAD, CDP and CID. The family history was informative in 19.6% of cases and consanguinity existed in 50%. The main clinical presentations were pneumonia, diarrhea, oral thrush and skin lesions. There was a significant association between PAD and pneumonia (p = 0.0011) and CID and diarrhea and oral thrush (p = 0.0078). The relationship between CDP and skin lesions was less strong (p = 0.1454) but skin manifestations were frequently reported in CDP.

Conclusion:
Early detection of PID is possible and should be the rule since specific treatment options are available. Any repeated or severe or uncommon infection must be considered as PID until investigation appears negative. Pneumonia, diarrhea and skin lesion are the most associated in these condition. Nevertheless, HIV infection should be excluded.
CO25/ AGAMMAGLOBULINEMIA IN ALGERIAN CHILDREN: A SERIES OF 54 CASES.

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Introduction:
Primary immunodeficiencies (PIDs) in children include a large number of genetic abnormalities affecting adaptive or innate immunity. Agammaglobulinemia represents one of the main causes.

Methods:
This is a retrospective, multicenter study that included all primary immunodeficiencies followed in 13 pediatric departments in several regions of Algeria since 1985. The data were collected from pre-established forms including demographic data, clinical and biological findings, treatment and outcomes. Statistical analysis was performed with Epi Info 6.

Results:
During this period, we identified 409 children with PID among which 54 patients presented Agammaglobulinemia (13.2 %).
We found 42 males and 12 females (sex ratio: 3.5). The mean age at diagnosis was 49 months and ranged from 2 and 168 months. The inbreeding rate was 37% and family history of deaths in infancy were found in 31.5%. The clinical manifestations were mainly respiratory (75.9%), digestive (33.3%), cutaneous (25.9%), ENT (25.9%), osteoarthritis (22.2%) or prolonged fever (14.8%). Patients received infusions of immunoglobulins (IVIG) monthly (23%) or every 21 days (66 %), with mean dose of 400mg/kg. This substitution was regular in 40.7% of cases, well tolerated in 98 %. During follow-up, 28.6% of children were infected by Staphylococcus, Pseudomonas or encapsulated bacteria. Bronchiectasis was found in 28% of cases. Three children died (5.6%) from sepsis (2 cases) or severe malnutrition (1 case).
Genetic analysis is still ongoing. So far, known mutations within the B cell–specific Btk gene were identified as well as novel mutations that will be described elsewhere.

Conclusion:
Agammaglobulinemia is the leading cause of humoral PID. In recent years, the availability of replacement therapy (IVIG) has improved the fate of these patients, with improved quality of life and life expectancy.
CO26/ AGAMMAGLOBULINEMIA, NON-BRUTON TYPE

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Introduction:
Agammaglobulinemia is a primary immunodeficiency disease. Affected children had blockade in the maturation of B-cells in the bone marrow which leads to low or absent serum immunoglobulin levels [1]. There are three types: X-linked, early onset, and late onset. In X-linked agammaglobulinemia (Bruton’s agammaglobulinemia), there is a mutation in Bruton tyrosine kinase (BTK) gene which is responsible for about 90% of early onset agammaglobulinemia with low or absent B cells. Late onset agammaglobulinemia is usually due to common variable immunodeficiency. The other type is early onset non-Bruton agammaglobulinemia, which is mostly due to autosomal recessive/dominant inheritance [2-4]. In autosomal recessive agammaglobulinemia, the child usually suffers from infections in the first few years of life (the clinical features are similar to that seen in children with X-linked agammaglobulinemia) and has low serum immunoglobulin levels and absent B lymphocytes in the peripheral blood [5]. Our aim was to describe the clinical presentation of two cousins with non-Bruton agammaglobulinemia.

Case reports:

Case 1: 6 years old boy born from consanguineous parents who presented since the age of 4 months with recurrent lung infection and recurrent bilateral purulent conjunctivitis. His sister was also affected (figure 1).

Case 2: 7 years old girl who had recurrent lung and sinus infections since the age of 3 months. Her sister died at age of one year due to recurrent lung infections.

Clinical examination of both children revealed no palpable lymph nodes, tonsillitis nor organomegaly. The laboratory investigations of both cases showed absent B lymphocytes (CD19+) with low serum level of immunoglobulins (IgG, IgM and IgA) in comparison to reference ranges for age. These cousins represent form of early onset non-Bruton agammaglobulinemia; most probably autosomal recessive, as we noted the parental consanguinity and the presence of two affected females in the kindred. Intravenous \( \gamma \)-globulin was given monthly for both cases. During follow up, patients were still developing infections. Serum trough levels of IgG were found to be suboptimal. Thus the dose of Intravenous \( \gamma \)-globulin was increased. Once the optimum level was reached, the recurrent conjunctivitis in the first case as well as the chronic sinusitis in the second case improved.

Conclusion:
Children with non-Bruton agammaglobulinemia usually develop recurrent infections in early months of life, and low IgG trough level due to insufficient \( \gamma \) globulin infusions can lead to recurrent and persistent infections.

Recommendation:
Agammaglobulinemia should be considered in the differential diagnosis of children with recurrent infections in the early months of life. Monitoring of serum IgG trough level is essential until optimum levels are achieved to prevent further morbidities.
Figure 1: Family pedigree of both cases

References:
CO27/COMMON VARIABLE IMMUNODEFICIENCY-ASSOCIATED GRANULOMATOUS-LYMPHOCYTIC INTERSTITIAL LUNG DISEASE (GLILD): A CASE REPORT.
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Department Pediatric  University Hospital Mustapha Pacha Algeria

Introduction:
Common variable immunodeficiency (CVID) is characterized by hypogammaglobulinemia, defective antibody responses and recurrent infections. Granulomatous disease occurs in 8 to 22% of patients with CVID.

Methods:
We report the case of a nine-year-old girl born to non consanguineous parents. Her family history is unremarkable. She has a history of granulomatous liver disease that began at the age of three years. Since then, she developed recurrent ear, nose and throat (ENT) and airway infections due to several pathogens including Pneumocystis, chronic respiratory symptoms and diffuse abnormalities on chest radiography and reticulonodular lesions on computed tomography (interstitial lung disease). She developed also organomegaly (lymphadenopathies and splenomegaly). The diagnosis of sarcoidosis has been suggested. Nevertheless, the immunological tests revealed a common variable immunodeficiency (CVID) with a low serum IgG and IgA concentrations, a normal IgM concentration, a poor antibody response to protein and polysaccharide antigens, decreased level of CD19 (7%) and a normal number of T cells (except CD8+T cells). The patient was diagnosed as having common variable immunodeficiency (CVID) associated with granulomatous and interstitial lung disease.

Discussion:
A disseminated granulomatosis is often secondary to sarcoidosis. However, an immunodeficiency disease, in particular CVID, should be further explored because it requires a specific management. The recent description of this entity probably explains the delay in diagnosis in our patient. Beside the increased susceptibility to recurrent and chronic infections, patients with CVID also have an increased incidence of auto-immune disorders and malignancies. Thus, they require a regular follow-up.

Conclusion:
In all cases of disseminated granulomatosis, the diagnosis of CVID should be suggested. Granulomatous disease is a relatively unusual complication of CVID and is still poorly recognized. In children who appear to have granulomatous disease, recurrent infections should lead to an evaluation of at least immunoglobulin levels to provide specific treatment as early as possible. This will ultimately reduce the risks associated with severe infection and reduction of quality of life caused by chronic infectious disease.
Posters
P01/ ACUTE DISSEMINATED ENCEPHALOMYELITIS IN A BOY WITH BRUTON'S DISEASE

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Introduction:
Acute Disseminated Encephalomyelitis (ADEM) is a rare condition of acute demyelination of the central nervous system that is most common among immunocompetent children secondary to an infection or vaccination. This monophasic disease has a good long-term prognosis when it is promptly treated with corticosteroids and immunosuppression. We report the case of a child followed for Bruton's disease who presented with an impaired alertness with bilateral uveitis.

Observation: Seddik, 5.5 years, whose parents were first-cousins, is followed for Bruton's disease since the age of 1 year and treated with monthly IV immunoglobulins. Last infusion was received 6 months before admission. Seddik presented progressive drowsiness worsened after 5 days by bilateral ptosis with diarrhea, vomiting and fever. At admission, the child was drowsy. Neurological examination detected difficulty to stand with a negative Romberg, conserved overall muscle strength and no coordination disorder. Deep tendon reflexes were normal and superficial and deep sensitivity is preserved. He presented cranial pairs with anisocoria, bilateral ptosis and oculomotor III nerve deficit. Brain scanner is normal, biochemistry shows glycorrhachia at 0.6 g/L, cervicospinal fluid proteins at 0.38g/L, and chlore at 117meQ/L. Culture was negative. PCR for CMV, HSV and enterovirus were negative. CRP is negative. Complete blood count showed anemia (HB: 8.9 g/L), with 14000 WBC (PNN: 5300; Lymphocytes: 7300, monocutes: 1560) and thrombocytosis (666000 / mm3). He showed a granulomatous uveitis and synechia in the crystalline. Fundus oculi examination showed hyalitis with papilledema and inferolateral retinal detachment. Unilateral granulomatous uveitis exploration was negative. Brain MRI found a rhombencephalitis. The child was treated with steroids bolus, local antibiotics, ocular corticosteroids and intraocular antiviral aciclovir. There was improvement in consciousness from D3 of bolus treatment and improvement of ptosis. Control examination showed marked improvement of anterior uveitis, and recovery of binocular vision 4 months after. Comment: Acute disseminated encephalomyelitis (ADEM) is an autoimmune demyelinating disorder with inflammatory lesions of the central nervous system, probably due to viral antigens or vaccines. This rare pathology includes multiple sclerosis, optic neuropathy, acute transverse myelitis and neuromyelitis optica. Three-quarters of cases, where fever is associated with the onset of neurological disease, involve post-infectious and post-immunization encephalomyelitis. It can occur at any age, although it is more common in children. Few information are available instead about the incidence in immunodeficient patient but the prognosis is better if treatment with steroids is taken early.
P/02 BONE MARROW TRANSPLANTATION IN GRISCELLI SYNDROME

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Introduction:

Griscelli syndrome is a rare autosomal recessive disorder characterized by hypopigmentation of the skin and light silvery-gray hair albinism with immunodeficiency starting in infancy that usually causes death by early childhood. There are three types of this disorder, which are distinguished by their genetic cause and pattern of signs and symptoms. The only real treatment for the hemophagocytic lymphohistiocytosis (HLH) of which Griscelli syndrome is a part is bone marrow transplantation.

Observation:

We report the case of an 8-month-old boy suffering from Griscelli syndrome revealed by HLH that manifested by fever, hepatosplenomegaly, pancytopenia, hyponatremia, hypertriglyceridemia, elevated LDH, hyperferritinemia and hypofibrinemia and complicated by HLH in the central nervous system without meningitis. The infant was treated by corticosteroids, cyclosporine and four infusions of anti-lymphocyte serum. Bone marrow transplantation with geno-identical donnor was performed 3 months later. The conditioning consisted of a combination of Bisulvex, Etoposide and Endoxan. He received 5.39x106 CD34 cells / kg. Engrafment held to day+16 after transplantation. The chimerism at D+30 was 96% of donor DNA. Moreover, the infant has a grade II cutaneous GVHD well managed with corticosteroids and a favorable evolution of a veino-occlusive disease. Two years after transplantation, he has no signs of HLH and good neurological development.

Conclusion:

Bone marrow transplantation in Griscelli syndrome must be of early indication to prevent the serious complications, especially the occurring of neurological impairment.
Hyper IgM syndrome is characterized by a decrease or lack of serum IgA and IgG with normal or increased IgM. Several genetic mutations were defined that affect the interaction between T and B cells required to produce Ig A and G. There are two main forms: X-linked and autosomal recessive. Clinical manifestations are dominated by recurrent infections (pulmonary, ENT, digestive ...), especially with opportunistic pathogens, autoimmunity and lymphoproliferation.

Our study reports 16 cases of hyper IgM followed in our department since 1995. There are 6 boys and 10 girls with 11 patients reporting a parental consanguinity. The mean age at diagnosis is 4.5 years (5 months to 12 years). The clinical manifestations were dominated by respiratory infections (13 cases), including 6 cases of bronchiectasia and two CMV pneumonia. Chronic diarrhea was observed in 4 patients with cryptosporidiosis. ENT infections were noted in 6 cases. One patient had three episodes of meningitis and another one BCGitis. A lymphoproliferative syndrome was observed in 9 patients: hepatomegaly (4), splenomegaly (5) and lymphadenitis (2). All patients had low IgG and IgA and 11 patients had high levels of IgM [3.10 to 10.75]. Five patients had thrombocytopenia.

Genetic study was performed in 5 patients, confirming a CD40L deficiency in one patient and an Ataxia Telangiectasia in another. Seven deaths were reported.

Unlike Europe, where X-linked hyper-IgM syndrome (HIGM1) is the most common, this Moroccan series shows the frequency of autosomal recessive forms in our context as suggested by the inbreeding rate, the frequency of female and the predominance of phenotypes with lymphoproliferation.
P04/ CHEDIAK-HIGASHI SYNDROME: CASE REPORT AND REVIEW OF THE LITERATURE.

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Introduction:
Chédiak-Higashi syndrome (CHS) is an extremely rare autosomal recessive disease, characterized by partial oculocutaneous albinism, blonde hair, severe immunodeficiency, presence of abnormal large cytoplasmic granules in leukocytes and other granule containing cells. Most patients undergo a variable period of recurrent infections before going into the accelerated phase consisting of a lymphoproliferative syndrome. Primary presentation in the accelerated phase is unusual. We report a Libyan female infant with CHS in accelerated phase at presentation.

Case report:
Our patient was born at full term to consanguineous parents after normal pregnancy. She presented at the age of two years with progressive abdominal distension associated with fever and loss of appetite for 1 month. Parents and 6 siblings have neither fair skin nor blond hair. One sibling with fair skin and silvery hair died due to similar disease at the age of 1.5 year.
On examination, she had fair skin and blond hair with photophobia and nystagmus. Her weight and height were at 3rd percentile. Chest was clear. Abdominal examination revealed hepatosplenomegaly. Ophthalmic examination showed pale retina and bilateral papilledema. Lab investigations results were anemia (Hb= 6 mg/dl), platelet= 27×10⁹/L, WBC= 6×10⁹/L with neutropenia, normal RFT, elevated liver enzymes and hypergamaglobulinemia.
Microscopic examination of Wright-stained blood and bone marrow films showed giant granules of leukocytes and their precursors respectively whereas large clumped melanosome were seen in hair examination; confirming the diagnosis of CHS. On the basis of the clinical presentation, hematologic and cytological findings, a diagnosis of accelerated phase of CHS was made. Molecular testing could not be performed due to unavailability.

In conclusion:
We report a rare case of CHS, to the best of our knowledge, she is the first case reported from Libya. It is an unusual case in that the first presentation was in the accelerated phase at 2 years of age. As bone marrow transplantation is the only cure to the disease, early diagnosis is required before the accelerated phase has developed. Genetic counseling and family education about the disease and the recurrence risk in the subsequent pregnancy is needed.
Le syndrome d’activation macrophagique primitif est rare et survient sur un terrain prédisposé. Son diagnostic est parfois difficile surtout chez un jeune nourrisson. Nous rapportons l’observation d’un nourrisson de sexe féminin âgé de 3 mois fille unique de sa famille, issue d’un mariage consanguin de 1er degré admise dans notre formation pour prise en charge d’un choc septique, ayant dans les antécédents, un icterus prolongé apparu à J3 de vie, avec des rectorragies de moyenne abondance à l’âge d’un mois et demi, ce qui a nécessité plusieurs consultations sans bilan. L’examen retrouve un nourrisson conscient avec un faciès particulier, cheveux gris, yeux gris, fébrile à 39°C, pâle, en mauvais état hémodynamique et neurologique (TRC allongé, tachycardie, extrémités froides, marbrures généralisées) et qui présente un icterus généralisé cutané-muqueux sans syndrome tumoral. Le patient a été mis sous antibiothérapie et remplissage vasculaire.

Le bilan initial a révélé une pancytopénie avec anémie à 6g/dl normochrome normocytaire, une thrombopénie à 10 000/mm3 et une neutropénie à 300/mm3, la CRP était à 30 mg/l, le bilan infectieux réalisé était stérile. Une insuffisance hépatocellulaire avec un TP à 21% et TCK à 50, une cholestase : bilirubine totale à 140 mg/l et la Bilirubine directe à 110 mg/l, une hypoglycémie à 0,15 g/l, une hyponatrémie à 120 mmol/l et hypoalbuminémie à 19 g/l, Le medullogramme n’était pas concluant avec présence de blastes ou cellules atypiques. L’échographie abdominale a objectivé : hépatosplénomégalie avec des adénopathies multiples abdominales complétée par une TDM thoraco-abd: HSMG avec un discret épaississement pleural.

L’évolution a été marquée par la persistance des lésions erythémateuses généralisées et de la fièvre. Le patient a reçu plusieurs transfusions CG et PLQ avec correction des troubles métaboliques sans amélioration clinique et apparition d’une splénomégalie, de lésions ulcéronécrosantes au niveau de la région fessière, et des Convulsions apyrétiques. Un Ionogramme sanguin fait en urgence a montré une hyponatrémie à 120 mmol/l, une hypochlorémie à 87 mmol/l, un taux du LDH 925ui/l, une ferritinémie élevée à 1200 ng/l, un taux de triglycérides élevé à 3,3g/l.

Le syndrome activation macropahagique sur un griscelli probable a été retenu. Le nourrisson a été mis sous antibiothérapie à large spectre avec correction des troubles métaboliques, bolus de corticothérapie, perfusion d’immunoglobulines. Une biopsie du cuir chevelu et biopsie cutanée des lésions crouteuses ont été réalisées, l’étude génétique n’a pas été réalisée faute de moyens. Et l’évolution était marquée par le décès.
Introduction:
Mucocutaneous candidiasis occurs either in isolation or alongside other symptoms in patients with various primary immunodeficiency diseases (PID). The primary purpose of this study is to identify PIDs with susceptibility to candidiasis and a secondary goal is to determine the critical pathways in human immunity against Candida species.

Patient and methods:
This retrospective study was conducted on 140 patients.

Results:
Among the 140 PIDs, oral and mucocutaneous candidiasis were observed in 19 (13.6%) patients who can be divided in two groups. The first group (n=13) include patients with T-cell defects: SCID (n=6), DiGeorge Syndrome (n=1), MHC Class II Deficiency (n=5), and DOCK8 deficiency (n=1). The second group (n=6) is very heterogeneous with regard to the nature of the immunodeficiency, but has a common feature that is neutrophil defect: congenital neutropenia (n=1), chronic granulomatous disease (n=1), hyper-IgM syndrome (n=1), X-linked agammaglobulinemia (n=2) and Chediak—Higashi syndrome (n=1). The present work highlights the role of T-cell, in particular TH17 cells and neutrophils in host defense against Candida species. TH17 cells secrete IL-17 and IL-22, which promote activation and recruitment of neutrophils. Neutrophils mediate microbial killing through phagocytosis, degranulation, and neutrophil extracellular traps.

Conclusions:
The delineation of the critical pathways in human host defense against Candida species will not only lead to an improved risk stratification in affected patients (eg, by means of genetic counseling) but will also lead to improved novel therapeutic management strategies by strengthening the IL-17/IL-22 axis in patients at risk for or already having overt disease.
Background:

Idiopathic CD4 deficiency is a rare primary immunodeficiency with varying clinical presentations severity. Here, we report 2 cases.

Case 1:
M. Ayoub presented at the age of 3.5 months with recurrent infections, namely bilateral pneumonia, forehead and scalp skin infections at the age of 4 months, recurrent skin abscesses, invasive pneumococcal infection following an acute otitis media at 17 months. This clinical picture involving repeated and severe infections with multiple germs (Pseudomonas aeruginosa, Staphylococcus aureus, Streptococcus pneumoniae) raised the hypothesis of a primary immunodeficiency. Full immunological testing performed found an isolated deficiency of CD4+ T cells with CD4+ value 500 cells/mm3. The child was treated with several courses of IV antibiotics relayed by prophylactic treatment combining Trimethoprim -Sulfamethoxazole and oral penicillin and IVIG infusion every 21 days.

Case 2:
Salim was hospitalized at the age of 3 years for Pseudomonas aeruginosa lung infection. He previously had several infections: pyelonephritis at 12 months, ear infection at 17 months and Staphylococcus aureus lung infection at 2.5 years. His brother was also hospitalized many times for infections and died at the age of 17 months in an array of post measles viral encephalitis. Complete immunologic exploration found CD4 deficiency (CD4: 5 % or VN: 30% to 40 %) and absence of any alternative explanation for the CD4 lymphocytopenia. The HLA family study found HLA-compatible sister allowing Salim to benefit from a bone marrow transplant with a good evolution.

Conclusion:
Idiopathic CD4+ T cell lymphocytopenia (ICL) is a rare and heterogeneous clinical syndrome defined by persistent CD4+ T cell lymphopenia in the absence of infection with HIV-1 or any other cause of immunodeficiency.
Background:
Congenital neutropenia is a rare primary immunodeficiency (PID) disorder, including heterogeneous types of diseases. Neutropenia is usually permanently or intermittently severe (<500/mm3). There are two main forms of hereditary neutropenia: severe congenital neutropenia and cyclic neutropenia. Currently, in light of recent genetic data, it is possible to distinguish severe congenital neutropenia based on the gene that is involved, but nearly 40% still have unknown mutations.

Objective:
To determine the frequency and characteristics of congenital neutropenia in Algeria.

Methods:
This is a retrospective, multicenter study that included all primary immunodeficiencies followed in 13 pediatric departments in several regions of Algeria since 1985. The data were collected from pre-established forms including demographic data, clinical and biological findings, treatment and outcomes. Statistical analysis was performed with Epi Info 6.

Results:
There were 10 patients with neutropenia, 5 males and 5 females. The median age at diagnosis was 18 months. Four patients were progenies of consanguineous marriages, and in 2 cases we noted infant death in the family history. The median age at onset of the disease was 3.5 months. The most frequently observed signs were repeated pulmonary infections (7), chronic oral and digestive candidiasis (5), prolonged fever (4) and otitis (4). The median absolute neutrophil count was 500 cells/mm3.

The diagnosis of neutropenia was specified in two cases: a cyclic neutropenia in one case and Kostmann syndrome in another. Five patients received repeated antibiotics and 4 were on trimethoprim-sulfamethoxazole prophylaxis. Growth factors (G-CSF) were given to 6 patients, but the terms were not specified. One patient died at the age of 24 months of unspecified cause, and 5 patients were lost-to-follow up. For the remaining 4 cases, the mean age at last visit was 70 months.

Comments:
In this study, 2.4% of the children with primary immunodeficiency had congenital neutropenia. The diagnosis remains unclear for the majority of the patients. Genetic testing was not available. The patients are at risk for bacterial or fungal infections and it is crucial to prevent recurrent infection. The growth factors (G-CSF) have greatly improved the prognosis of severe congenital neutropenia. Currently available, they must be used in the most severe forms. However, this treatment must be conducted and controlled by a pediatric hematologist because the patients are at risk of developing leukemia. Hematopoietic stem cell transplantation is the sole option for patients who experience severe infections despite G-CSF therapy. In conclusion, progress must be made in the diagnosis and management of these disorders in our country.
INTRODUCTION:
Primary Immunodeficiencies (PIDs) are a heterogeneous group of diseases resulting from genetic abnormalities in the development and / or maturation of immune cells. Although PID and autoimmunity seems to be the two opposite ends in the immune response, they are often linked in reality.

MATERIAL AND METHOD:
We report here 35 PID patients presenting autoimmune manifestations, collected from 1997 to 2014.

RESULTS:
This as about 35 patients, 19 cases (56%) are from consanguineous marriages. Mean age at diagnosis was 8 years old for PID and 6 years for Autoimmune disease (AID), AID diagnosis was made earlier than PID in 15 cases and AID were variable and sometimes multiple in the same patient.
AID found in our patients were autoimmune neutropenia in 12 patients, autoimmune hepatitis in 4 patients, ITP in 4 patients, Evans syndrome in 3 patients, alopecia in 3 patients, juvenile idiopathic arthritis in 3 patients, AIHA in 2 patients, myopathy in 2 patients and celiac disease in 2 patients.
For PID, 7 of our patients have CVID, 7 cases had autosomal recessive agammaglobulinemia, 5 cases of hyper IgM syndrome, 4 cases of SCID, 2 cases of Wiskott-Aldrich syndrome, 2 cases of Bruton's disease, 2 cases of ALPS, a case of selective IgA deficiency, a case of MHC II deficiency, a case of ataxia telangiectasia and one case of APECED.

DISCUSSION:
Association of PID and AID can be explained by the disruption of the mechanisms responsible for the maintenance of tolerance, this loss of tolerance is multifactorial and depends on the immune system abnormality that caused the PID.

CONCLUSION:
PID and automimmunity are related and there are PID-related autoimmune manifestations. Therapeutically, these AID remain a major problem in the absence of standardized protocol.
P10/ LES MANIFESTATIONS DERMATOLOGIQUES DES DEFICITS IMMUNITAIRES PRIMITIFS

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Introduction :
Les présentations cliniques des déficits immunitaires primitifs (PIDs) sont très hétérogènes. Les
manifestations cutanéo-muqueuses sont fréquentes et entrent parfois dans les critères
diagnostiques de certains PIDs. Elles ne sont pas spécifiques, parfois sévères néanmoins souvent
au second plan.
Nous rapportons les différentes manifestations dermatologiques rencontrés dans une série de 17
patients porteurs de PIDs

Patients et méthodes :
C’est une étude prospective menée au service de pédiatrie de l’hôpital AlFarabi en 4 ans depuis
2010, portant sur les patients présentant des PIDs.
Le diagnostic était porté sur les critères de l’IUIS Expert Committee on PrimaryImmunodeficiency
Nous avons éliminé chez tous les patients une infection par l’ HIV et nous avons exclu les
candidats recevant un traitement immunosuppresseur.
Des explorations spécifiques ont été demandées en fonction de l’orientation clinique.

Résultats :
Sur 17cas de DIP recensés, 80% avaient des affections cutanéomuqueuses, celles-ci étaient
révélatrices du déficit immunitaire dont 35% des cas.
Elles étaient représentées principalement par des dermatoses infectieuses dans 83,3% des cas
faite d’infections mycosiques dans 40%, bactériennes dans 40%, mycobactérienne et virales dans
10% chacune. Nous avons notés également deux cas d’érythrodermie

Conclusion :
Dans le contexte marocain la forte consanguinité est à l’origine d’une fréquence particulièrement
élevée des maladies héréditaires en l’occurrence des DIP.
Les manifestations dermatologiques ne sont pas rares au cours de ces maladies leur connaissance
permettra réorienter ou aider au diagnostic.
P11/ PRIMARY IMMUNODEFICIENCIES AND NEOPLASIA IN MOROCCO

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Introduction:
The association of neoplasia and immunodeficiency is now well established. This relationship has been well studied in patients who received chemotherapy preparatory organ transplantation (6% of cases) and in patients with severe immune deficiency associated with HIV infection (Kaposi's sarcoma in 14% of cases and non-Hodgkin lymphoma in 3% of cases). In PID, estimates of the overall risk range from 1.8 to 13 SRI (standardized incidence ratio) according to studies.

Material and methods:
We report 10 cases of primary immunodeficiency complicated by cancer, collected in two centers (Rabat and Casablanca).

Results:
This is about 7 boys and 3 girls. Mean age at diagnosis of neoplasia was 10.2 years. PID diagnosis was revealed by the neoplasia in 5 cases. There were 4 cases of Ataxia Telangiectasia, 2 cases of Common variable immunodeficiency, one case of selective IgA deficiency, one case of Bloom syndrome, one case of Severe combined immunodeficiency and one case of Hyper IgE syndrome. Neoplasia associated to these PID were 3 cases of Non-Hodgkin lymphoma, 2 cases of Hodgkin disease, 2 Burkitt lymphoma, one LAL, one LAM type 1 and one germinoma. Except for the Selective IgA deficient patient who showed complete remission after 2 months of treatment, other patients don’t respond to the treatment and 7 patients died during the chemotherapy.

Conclusion:
These observations of neoplasia associated to PID highlight the requirement to investigate the eventual immunodeficiency in any patient presenting a neoplasia, and vice versa to monitor each PID patient for these complication, as well as the difficulties encountered to manage these complications.
Background
Ataxia telangiectasia (AT), an autosomal recessive disorder, is a multi-systemic syndrome caused by a genetic abnormality; a mutation of ATM gene located on chromosome 11.

Materials and methods
This is a retrospective, multicenter study that included all primary immunodeficiencies followed in 13 pediatric departments in several regions of Algeria since 1985. The data were collected from pre-established forms including demographic data, clinical and biological findings, treatment and outcomes. Statistical analysis was performed with Epi Info 6.

Results:
During this 30-year period, we identified 409 children with PID among which 20 patients with AT (4.9%).
No sex predominance was found (sex ratio: 1.3). Inbreeding was noted in 70% of cases.
Age at diagnosis was 78 ± 39.9 months (1-132 months) and the mean age at the onset of symptoms was 31.2 ± 28.7 months. The delay of diagnosis was 44 ± 35.9 months
Common symptoms observed were ataxia, noted in 80% of cases, ocular telangiectasia in 75% of cases, recurrent pulmonary infections in 65% of cases, ENT infections in 40%, bronchiectasis in 30%, hypotrophy in 20% and chronic diarrhea in 20% of cases.
Immunological exploration revealed IgA deficiency in 40% of cases, low IgG levels in 15% and increased IgM levels in 35%. The management was not uniform. Seven patients (35%) received sequential antibiotic therapy and 4 patients (20%) had immunoglobulin infusions.
Nine patients are alive, three died and 8 patients were lost-to-follow up. Autoimmune anemia was observed in one patient. No case of neoplasia was found.

Conclusion:
AT diagnosis was made in all of our patients on the combination of clinical findings (ataxia, and/or ocular telangiectasia and/or recurrent pulmonary infections) and biological analysis that shows immune deficiencies. No genetic study has been done.
The clinical and immune heterogeneity explains the observed delay in diagnosis and differences in care between patients.
Introduction:
Common variable immunodeficiency (CVID) is the most common symptomatic primary immunodeficiency in adults. CVID represents a heterogeneous group of primary antibody deficiency, characterized predominantly by decreased antibody production; low or normal B-cell numbers and a broad clinical spectrum, mainly showing recurrent respiratory tract infections accompanied sometimes by increased susceptibility to autoimmunity and lymphoproliferative diseases.

Objectives:
Our purpose is to evaluate the immunological abnormalities that characterize patients with CVID in Algerian patients.

Methods:
This is a retrospective analysis of 32 patients with CVID, diagnosed according to the classic diagnosis criteria. Immunological features were performed, including serum levels of IgG, IgA and IgM and lymphocytes subpopulation phenotyping.

Results:
There were 16 (50%) males and 16 (50%) females. Mean age at onset of disease was 19 years, and mean age at diagnosis was 31 years. Average delay in diagnosis was 12 years. Recurrent infections (100%) especially bacterial respiratory tract infections (84%) were the most common manifestations. For immunological features, 90.62 % of patients have decreased levels of IgG, 93.55% and 86.66 % have low levels of IgA and IgM, respectively. We found reduced B cell numbers in 66.66 % of patients and decreased T CD4+ cell numbers in 48.27 % of them. Autoimmunity disease was present in 25 % of the patients; haemolytic anemia and autoimmune thrombocytopenic purpura were the most common manifestations. In addition, 31.5% developed lymphoproliferative disease. These two manifestations seems to be more common in patients with low circulating B and TCD4+ cells. No correlation had been found between the number or the severity of infection’s episodes and the immunological features.

Conclusion:
These results suggest that in almost all adults’ patients, the defects in B and/or T-cells may account for CVID; and confirms the heterogeneity of CVID. An extended analysis of patients with CVID is necessary to define homogeneous groups of patients and to characterize specific molecular abnormalities in each group.
Introduction:
Chronic mucocutaneous candidiasis (CMC) is characterized by severe persistent or recurrent infections of skin, nails and mucosae by Candida fungi, especially Candida albicans. The research for the molecular basis of this genetic predisposition remains valid.

Objective:
The aim of this study is to know this particular entity to establish a clinical and biological description and understand the immunological and molecular basis.

Materials and Methods:
This is a descriptive retrospective multicenter study of hereditary immunodeficiencies involving 410 cases including 4 cases of CMC who have been compiled on the basis of predetermined data sheets.

Results:
This is about 3 male children; the mean age at diagnosis was 11.3 months (ET 1.52). Median age at diagnosis was 8.5 months (ET 0.7). Inbreeding was found in 25% of cases. The mean age of the first clinical signs is 6 months (ET 5). Clinical manifestations were represented by pulmonary disease, chronic or recurrent candidiasis skin, mucous membranes and gastrointestinal candidiasis; and chronic diarrhea; 75% of our patients had low weight (<-2 DS). Immunological balance found CD3 decreased in only one case. The CD4, CD 19, NK, HLA-DR, CH50 and NBT test are normal in the entire cohort. No autoimmune disease was found.
All patients had proven infections of Candida and received curative antifungal treatment and antifungal prophylaxis.
One child died with sepsis at the age of 18 months. The genetic study in this child identified a STAT1 gain-of-function mutation. The genetic study of 2 other patients is ongoing.

Conclusion:
Our patients have a particular type of inherited immunodeficiency characterized by a genetic susceptibility to Candida infections. All identified causes are associated with a defect in the immune-dependent IL-17. CMC can be syndromic or isolated (chronic mucocutaneous candidiasis diseases) like in our 4 patients, heterozygous mutation gain-of-function STAT 1 being the most common genetic cause. However, despite genetic advances, a large proportion of patients with no identified genetic defect remains.
P15/ HEMATOPOIETIC STEM CELL TRANSPLANTATION IN HEREDITARY DEFECTS OF PHAGOCYTES

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Introduction:

Hereditary defects of phagocytosis are accompanied by recurrent tissue infections with pyogenic bacteria (abscess) and by fungi. These infections can be serious and fatal. The only way to fight against this evolution is the bone marrow transplantation.

Patients and methods:
We report the results of hematopoietic stem cell transplantation in 3 patients affected with hereditary defects of phagocytes and followed at the Pediatric Immunohematology unit of the National Bone Morrow Transplantation Center of Tunis.

Results:

Three cases of hereditary defects of phagocytes were compiled with 2 girls and a boy. We found one case of LFA-1 deficiency, one case of severe congenital agranulocytis and one case of chronic granulomatous disease. The median age at hematopoietic stem cell transplantation was 65 months [8 months to 13.5 years]. Two conditioning regimen were used: Busilvex and Endoxan on the first two patients and Bisulvex, Fludarabine and anti-lymphocyte globulin on the other patient. Engraftment occurred on only two patients with an average of 22.5 days [17 days and 28 days]. The patient having LFA-1 deficiency died before engraftment due to severe sepsis. Post-transplant complications were one case of acute GVHD and one case of hepatic veno-occlusive disease.

Conclusion:

Bone marrow transplantation in hereditary defects of phagocytes should be initiated as soon as possible to preserve the prognosis of patients with recurrent severe infections. As this disease is not a frequent indication of hematopoietic stem cell transplantation, its modalities remain questionable.
P16/ ATYPICAL CHEDIAK-HIGASHI SYNDROME WITH HYPERPIGMENTATION

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**Background:**

Chediak-Higashi syndrome (CHS) is a rare autosomal recessive immunodeficiency caused by mutations in CHS1, a gene coding a putative lysosomal trafficking protein. CHS is typically characterized by infantile-onset hemophagocytic syndrome, immunodeficiency, and oculocutaneous albinism. A small number of reports of rare forms of CHS with hyperpigmentation exist. The accelerated phase characterized by a massive hemophagocytic lymphohistiocytosis is lethal unless allogeneic bone marrow transplantation is performed.

**Case report:**

A case of Chediak Higashi syndrome is reported in a four year-old boy who presented with recurrent fever and repeated ENT infections, hyper pigmentation of sun exposed areas and the iris, gray hair since the age of six months and hepatosplenomegaly with cholestasis. Cytopenia and finally a neurologic dysfunction with ataxia, seizures and movement disorders developed. Parental consanguinity was present. Laboratory evaluation revealed a Hemophagocytic lymphohistiocytosis (HLH), with abnormal giant granules in neutrophils in peripheral blood and bone marrow, microscopic hair analysis revealed the presence of typical pigment aggregates.

**Results:**

Uncommon hyperpigmentation of sun exposed areas may be the initial symptom in the Chediak Higashi syndrome. Early diagnosis of CHS is easy with a simple, quick and non-invasive careful examination of a peripheral blood smear. Prognosis is poor in the childhood because of the development of an accelerated phase which is lethal unless bone marrow transplantation is performed.

**Conclusions:**

Chediak Higashi Syndrome is usually characterized by oculocutaneous albinism, but it can be revealed by an hyperpigmentation of skin exposed areas and the iris.
P17/ COMEL-NETHERTON SYNDROME: ABOUT 2 CASES

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Background:

NETHERTON syndrome is a rare autosomal recessive disorder due to a mutation of SPINK5 gene (5q31-q32). It is characterized by congenital ichthyosiform erythroderma, hair anomalies (trichorrhexis invaginata), atopic manifestations, recurrent bacterial infections and delayed growth, hyper IgE and/or hyper IgA.

Methods:

This is a retrospective, multicenter study that included all primary immunodeficiencies followed in 13 pediatric departments in several regions of Algeria since 1985. The data were collected from pre-established forms including demographic data, clinical and biological findings, treatment and outcomes. Statistical analysis was performed with Epi Info 6.

Results:

First case: A girl aged 5 months from a consanguineous couple, with a family history of death at young ages and onset of symptoms at age of one month with recurrent pulmonary infections, chronic diarrhea, skin infections, congenital ichthyosis, severe stunting and high IgE levels.
Second case: A girl of 36 months from a non-consanguineous couple with a family history of 3 deaths in infancy, who presents since the age of one month bronchopulmonary infections, recurrent skin infections, ichthyosis with fragile hair thinning, severe malnutrition and high IgE levels.

The diagnosis was based on clinical and immunological data. Treatment was symptomatic and the outcome was favorable in the second case, the first was lost-to-follow up.

Conclusion:

Netherton syndrome is a genetic disease in which prenatal diagnosis is possible, hence the importance of genetic counseling.
Background:
In case of selective IgA deficiency (IgAD), there is no reliable screening test for celiac disease (CD).

Objective:
To evaluate the usefulness of endomysial IgG and transglutaminase IgG tests for the diagnosis of CD in IgAD.

Methods:
Anti-endomysium IgA and IgG antibodies (IgG -EMA), and transglutaminase IgG (IgG anti-tTG) were assayed in 51 IgAD / CD patients; and 25 healthy controls. We used direct immunofluorescence on monkey esophagus to research EMA IgG while ELISA was used for IgG anti-tTG.

Results:
In 11 IgAD / CD patients, IgG –EMA and IgG-anti-tTG were positive while IgA antibodies against these antigens were negative. Three IgAD / CD patients produce IgG-EMA product but not anti-tTG IgG. Healthy controls were negative for IgG-EMA while one of the 25 healthy controls was positive for anti-tTG IgG.

Conclusions:
IgG-EMA and anti-tTG IgG tests can be useful for identifying IgAD / CD patients.
P19/ HYPER IGE SYNDROME: ABOUT TWO CASES

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Introduction:

Hyper-immunoglobulin E syndromes (HIES) are rare primary immunodeficiencies characterized by high serum levels of IgE (>2000 IU/ml), eczema, cold staphylococcal skin abscesses and recurrent lung infections. To date, there are three molecularly defined subgroups: autosomal dominant form (AD-HIES) associated with heterozygous mutations in STAT3, and two autosomal recessive forms (AR-HIES) associated with TYK2 mutations or DOCK8 mutations.

Objectives:

We report clinical and biological findings in two males with hyper IgE syndrome.

Materials and methods:

Immunological investigation included:
- Nitroblue-tetrazolium (NBT) assay on whole blood.
- Measurement of serum levels of total IgE by chemiluminescent immunometric assay
- Measurement of serum levels of IgG, IgA and IgM by a nephelometry assay.

Results:

The two patients are from two unrelated families. The age at onset of clinical manifestations was 5 months for one patient and 4 years for the other. The patients suffer from recurrent pulmonary infections and skin abscesses as well as eczema, one of them had oral candidiasis. The NBT assay performed showed normal reduction. Determination of immunoglobulin concentrations revealed a significant increase in IgE levels (>2000 IU/ml).

Conclusion:

Given the association at young age of eczematoid dermatitis, recurrent respiratory infections and a marked hyper-IgE, hyper-IgE syndrome should be considered. However, we need to identify the genetic mutations involved in order to understand more about the disease and to better understand the link between clinical features of our patients and type of the mutation.
IRA4K deficiency is a rare primary immunodeficiency associated with increased susceptibility to invasive infections, especially to pyogenic bacteria, Pneumococcus and Staphylococcus. In contrast, patients appear to be resistant to infections caused by most other bacteria, viruses and parasites.

We report the case of a male child, 9 years old, from consanguineous parents, with good psychomotor development but short stature (-2 SD). He has been admitted for several hospitalizations since the age of 40 days, for severe bacterial infections (lymphadenitis, purulent meningitis, urinary tract infection, upper lobar pneumonia, multiple hepatic abscesses, multiple soft tissue abscess and abscess under cold mandibular). The immunological tests showed negative retroviral serology, normal levels of immunoglobulin A; G; M, normal lymphocyte subsets, and normal reduction of nitroblue tetrazolium (NBT test). However, we noted a high level of IgE (suggesting the diagnosis of hyper IgE syndrome). Later, the genetic study confirmed the IRAK4 deficiency (homozygous mutation in the patient and heterozygous in the mother). The child was put under antibioprophylaxy and anti-pneumoccocal vaccination with good evolution (no severe infectious episodes). Since the age of 6 years, the child has episodes of scalp tinea, isolating a Trichophyton violaceum, relapsing despite correct treatment.

The association of IRAK-4 deficiency with bacterial skin infections were more frequently reported in the literature that the fungal infections. This raises the importance of a thorough clinical examination (including dermatological) in any patient followed for IRAK4 deficiency.
Introduction:
The hyper-immunoglobulin D syndrome (HIDS) is a rare autosomal recessive autoinflammatory disease. PIDs are classified into eight major categories. Autoinflammatory disorders is one of these categories. HIDS is linked to a mutation in the gene encoding mevalonate kinase (MVK), enzyme involved in the biosynthesis of cholesterol, this mutation results in an abnormally high mevalonic acid in urine.
Clinical picture is typical, it combines monthly febrile episodes lasting only a few days, cervical lymphadenopathy, digestive disorders with abdominal pain, oral or vaginal sores, a non specific inflammatory syndrome with increased IgD levels (> 140 mg / L).

Material and methods:
Three patients with suspected periodic fever were explored. The dosage of immunoglobulin (IgG, IgA, IgM, IgD) was performed by radial immunodiffusion and by laser nephelometry.

Results:
We report the cases of three patients with hyper IgD, two boys and a girl all from unrelated families. The mean age at onset of symptoms was 3 years and the mean age at diagnosis was 5.5 years. Clinical manifestations are dominated by prolonged fever and recurrent lung infections. Two of the three patients also had abdominal pain and urinary tract infections, and finally a patient had mouth sores. Immunoglobulin (IgG, IgA, IgM) level was increased for two or three isotypes and IgD assay revealed high level (140 mg / L).

Conclusion:
Although they are not frequent, periodic fever or inflammatory fevers are increasingly individualized. Through these three cases, we stressed that it is important to search for hyper-IgD syndrome in prolonged and isolated fever with early onset in the childhood, and it would also be preferable to dose mevalonic acid in urine for diagnosis confirmation.
Late-onset combined immunodeficiency (LOCID) is a rare, severe disorder, defined by low or normal T cells count with impaired proliferative T cell functions. The infectious dermatitis may suggest or reveal a combined immunodeficiency by its progressive and extensive course.

We report a case of a patient followed for LOCID and having chronic warts.

A girl aged 13 years, with parental consanguinity and a history of several hospitalizations for pneumonia complicated by bronchiectasia, hodgkin disease treated at the age of 11 years and arthralgia, had chronic warts on hands and face for 5 years. Clinical examination noted a failure to thrive ( -3SD), tachypnea, clubbing, otitis, but no hepatosplenomegaly. Complete blood count showed mild anemia (11.5 g / dl), normal lymphocytes and neutrophils (2000 and 8500 / mm3 respectively) and normal platelets. Immunoglobulin assay initially showed normal levels then a gradual decrease and hypogammaglobulinemia. Lymphocyte subsets count showed essentially CD4 lymphopenia (390). The diagnosis made was LOCID complicated by neoplasia, bronchiectasia and chronic widespread warts.

The evolution was marked by the onset of a fatal neurological complication, probably infectious.

LOCID, combining a cellular and humoral deficiency, is responsible for severe opportunistic infections. Warts are viral skin infections favored by certain viruses such as human papillomavirus, and are generally observed in cellular immunodeficiencies.
**P23/ SEVERE COMBINED IMMUNODEFICIENCIES WITH RAG 1 AND 2 MUTATIONS: ABOUT 2 CASES AND A LITERATURE REVIEW**

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**Purpose:**
Mutations in recombination activating genes 1 and 2 (RAG1 and RAG2) cause a spectrum of severe immunodeficiencies which can lead to different phenotypic expression of a given genotype. Our aim is to report clinical and immunological characteristics of 2 patients with RAG mutation and to discuss the broad of phenotypes.

**Methods:**
We report two cases of severe combined immunodeficiencies due to RAG mutations with a review of the literature.

**Results:**
The first case is a 6 months-old boy. He presented with a chronic diarrhea and recurrent respiratory infections. He was diagnosed with T-B-NK+ SCID; genetic study in the child revealed homozygous deletion mutation in the RAG1 gene. The child is now 1 year old and is still alive.
The second patient who was 3 months old, also presented as a typical SCID at the age of 20 days with a chronic diarrhea, multiple abscesses and hepatomegaly. The immunological tests confirmed the phenotype T-B-NK+ while the sequencing of RAG 1/2 genes noted a mutation in RAG2 gene. He is lost-to-follow up.
Unfortunately, none of our patient can have bone marrow transplantation.

**Discussion:**
Severe combined immunodeficiencies are genetically determined defects of adaptive immunity. A default of somatic rearrangement in genes of antigen receptor in T and B cells, an essential step in the differentiation and diversification of T and B lymphocytes, leads to the absence of T cells associated with the absence of B cells in contrast to the normal presence of NK cells, corresponding to the phenotype T(-) B(-) NK(+). Indeed, the rearrangement V(D)J of T and B lymphocytes during B and T cell development process is highly dependent on the presence of the activator genes RAG1 and RAG2 so that mutations RAG1 or RAG2 genes lead to a spectrum of manifestations as it is reported in our two observations.

**Conclusion:**
Mutations in recombination activating genes 1 and 2 (RAG1 and RAG2) cause a spectrum of severe immunodeficiencies ranging from classical T- and B- cell severe combined immunodeficiency and Omenn syndrome to an increasing number of peculiar cases.
P24/ SELECTIVE IGA DEFICIENCY: RESULTS OF A MULTICENTER STUDY.

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Introduction:
Selective IgA deficiency is the most common primary immunodeficiency in the world with a prevalence estimated at 1/500. Individuals with selective IgA deficiency are mostly asymptomatic, but some have an increased frequency of bacterial infections, mainly ENT, gastrointestinal and bronchopulmonary infections.

Methods:
This is a retrospective, multicenter study that included all primary immunodeficiencies followed in 13 pediatric departments in several regions of Algeria since 1985. The data were collected from pre-established forms including demographic data, clinical and biological findings, treatment and outcomes. Statistical analysis was performed with Epi Info 6. The diagnosis of selective IgA deficiency has been considered if the child was symptomatic with IgA <0.06 g / l.

Results:
During this 30-year period, we identified 409 children with PID among which 5 patients had a Selective IgA deficiency (1.2%). We noted a male predominance (sex ratio = 1.5). The median age at diagnosis was 48 months, with a range from 12 to 84 months. The mean time to diagnosis was 37 months (0-72 months). The mean age at onset of symptoms was 11 months (1-18 months). The clinical features were identified in order of frequency: recurrent broncho-pulmonary infections, chronic ear infections, bronchiectasis, chronic diarrhea and failure to thrive. Two patients were treated by sequentially antibiotics and the other 3 patients received antibiotics at request, 3 of 5 patients had presented bacterial infections during their follow-up.

Conclusion:
Patients with selective IgA deficiency are mostly asymptomatic, but when the deficit is severe it is causing serious complications that can be life-threatening, hence the importance of screening and early treatment of these patients.
Introduction:

Mendelian susceptibility to mycobacterial disease (MSMD) is a rare disorder predisposing apparently healthy individuals to infections caused by weakly virulent mycobacteria such as bacilli Calmette–Guerin (BCG), environmental mycobacteria, and poorly virulent Salmonella strains. This syndrome consists of impaired antimycobacterial immunity (IL12/INF-g axis) constituting a new immune deficiency and outlining its major role in mycobacterial immunity. These diseases include a primary immunodeficiency caused by mutations in 7 autosomal genes (IFNGR1, IFNGR2, IL12B, IL12BR1, STAT1, ISG15, and IRF8) and an X-linked gene (NEMO).

The genes involved display a high level of allelic heterogeneity, accounting for a number of distinct genetic disorders which vary in their mode of inheritance and clinical presentation.

Methods:

We identified two cases in two unrelated patients through the observations of young children with a disseminated infection due to Mycobacterium tuberculosis. They were born to parental consanguinity and they had no familial history of mycobacteriosis or salmonellosis.

Results
Case 1:
29 months-old boy who was referred to our hospital with clinical symptoms suggestive of LCH. However, during the medical process the initial LCH diagnosis was rejected and he was diagnosed with Mendelian Susceptibility to Mycobacterial Disease with AD-STAT1 deficiency. He died due to severe malnutrition and sepsis.

Case 2: 40 months-old girl. The white blood cell, lymphocyte, and NK cell counts were normal, including those of the subpopulations with CD3, CD4, CD8, CD19, and CD16/56. The serum immunoglobulin levels were within normal ranges. The patient was diagnosed with MSMD. She was treated successfully with antitubercular agents, including isoniazid, rifampicin and pyrazinamide.

Conclusion:
The description of the molecular and immunological basis of this syndrome has allowed us to explain the pathophysiology of antimycobacterial immunity and is essential to understand and manage these diseases.
**Introduction:** Good’s syndrome (GS) is the association of thymoma with immunodeficiency. It is a rare cause of combined T and B cells immunodeficiency in adults. The clinical characteristics of Good’s syndrome are: increased susceptibility to respiratory tract infections and opportunistic viral infections. The most consistent immunological abnormalities are hypogammaglobulinaemia and low or absent B cells. Defects in cell mediated immunity are important causes of morbidity and mortality in this disorder.

**Case report:** We report a case of a 61-year-old man with thymoma, admitted to our hospital because of chronic otitis and mycotic cutaneous lesions. Viral serological tests HBV, HCV and HIV were negative, immunological tests reveal significantly decreased levels of IgG (0.82 g/L), IgA (<0.24) and IgM (<0.175), a lack of B cell lineage (30 Elt/mm3), T (CD4+) cell lymphopenia (980 Elt/mm3), abnormal CD4+/CD8+ T cell ratio and impaired function of T cells. After resection of the thymoma, blood tests reveals the persistence of immunodeficiency.

**Conclusion:** This immunological profile associated with thymoma allowed to confirm the diagnosis of Good’s syndrome in this case.
Background:
Omenn syndrome (OS) is a rare form of severe combined immunodeficiency. Its transmission is autosomal recessive. It was brought back for the first time by OMENN in 1965. Its incidence is still unknown.

OS includes a severe combined immunodeficiency, lymphadenopathy, hepatosplenomegaly and a generalized erythroderma associated with alopecia.

Biologically, B cells are mostly absent, T cells counts are normal to elevated, and IgE high. Hypereosinophilia is also observed.

Skin biopsy reveals an acanthosis and a parakeratosis with hematoxyline-eosinia staining. The diagnosis of certainty is brought by the genetic study.

The treatment is based on IVIG substitution and immune suppressors, but the only cure is allogeneic hematopoietic stem cell transplantation.

Aims of the study:
Describe epidemiologic, clinical, biologics characteristics and outcomes of patients with OS.

Method:
A Multicenter retrospective study was conducted, by the Algerian Society of Pediatrics, in 13 pediatric hospital departments. Data are collected from medical records by the mean of a standardized questionnaire.

Results:
Eight children have been diagnosed with OS. Sex ratio is 1/1, consanguinity rate is 75% and positive family story is present in 100% of patients. Mean age at first symptoms was 1 month (0-3), while mean age at diagnosis was 2 months (0-4).

The clinical symptoms are: skin manifestations (100%) with alopecia (75%) and generalized erythrodermia (50%), recurrent or severe pulmonary infections (62.5%), chronic severe diarrhea (62.5%), hypotrophy (50%) and septicemia (50%).

All children had low B cells count and 50% had high T cells count. Immunoglobulin was low in 62.5% of cases. IgE level was high in all the patients tested. Only one child realized a skin biopsy which reveals an acanthosis and a parakeratosis with hematoxyline-eosinia staining. The triad of alopecia, generalized erythrodermia and low B cells count was present in 4 children (50%). None of the 8 patients had a genetic confirmation.

Five children received multiple courses of IV antibiotherapy, 4 children received IV antifungal therapy, and 4 children had IV immunoglobulin therapy every 3 weeks. None of the 8 patients had an allogeneic hematopoietic stem cell transplantation, 6 died with a severe infection.

Conclusion:
Omenn syndrome is a rare form of severe combined immunodeficiency characterized by heterogeneous clinical symptoms, mainly skin features. The diagnosis must be done early. Without allogeneic hematopoietic stem cell transplantation, the forecast is bad and the outcome of the disease is fatal in the first year of life.
Introduction:
Chronic granulomatous disease (CGD) is caused by genetic defects in the genes that encode the components of the nicotinamide adenine dinucleotide phosphate (NADPH) oxidase enzyme complex. These defects result in an inability to produce superoxide anions required for killing of bacterial and fungal organisms. The nitroblue Tetrazolium (NBT) test can be an accurate method for CGD screening but is not quantitative without using a relatively large blood volume, can often lead to misdiagnosis as a result of poor cell handling, and may not be suitable for X-linked carrier screening in all settings. The dihydrorhodamine (DHR) flow cytometry based assay is the more commonly used diagnostic screening-test for CGD in reference laboratories and larger medical centers.

Patients and methods:
Over a period of six months from November 2014 to April 2015, nine patients with suspected CGD were screened by DHR flow cytometry assay. This test is based on the principle that nonfluorescent DHR 123 when phagocytosed by normal activated neutrophils (after stimulation with PMA- phorbolmyristate acetate) can be oxidized by hydrogen peroxide, produced during the activated neutrophil respiratory oxidative burst, to rhodamine 123, a green fluorescent compound, which can be detected by flow cytometry.

Results:
Among the nine patients analyzed, two had reduced/absent oxidative burst. Both patients were born to non-consanguineous parents. The first patient, a six-years-old boy, whose results has showed complete lack of oxidative burst (E.coli= 0%, fMLP= 0% and PMA=0%), presented with clinical picture of phagocytes defect (bacterial and fungal recurrent infections), and may have the X-linked form of the disease. The second one is a seven years-old girl. She presented with abdominal lymphadenopathy (with necrosis). The DHR test showed a partial oxidative burst (E.coli= 5%, fMLP= 0% and PMA=38%) as would be expected in the autosomal recessive (AR) form of CGD.

Conclusion:
The DHR test allows a rapid and sensitive diagnosis of CGD and can provide an indication of the likely underlying molecular defect (X-linked vs. AR form).