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Research Article

Primary Immunodeficiencies in Children: Follow-Up and Outcome

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Abstract

Introduction: Primary Immune Deficiencies (PID) of rare, under-determined diseases particularly in sub-Saharan Africa. Our aim was to share the results of the follow-up of these patients.

Patients and Methods: We conducted a descriptive and analytical cross-sectional study at the Albert Royer National Children's Hospital in Dakar, in collaboration with other pediatric departments and the Immunology laboratory of the National Blood Transfusion Center. We included all patients received with suspected PID, from 2014 to 2021, after ruling out HIV infection. The diagnostic criteria were the recommendations of the Moroccan Society of Immunology. We did not include patients with incomplete data. A complete blood count was performed in all patients. Further explorations were carried out depending on the orientation. The data was analyzed with Excel 10.

Results: Out of 32 patients registered, 16 were included in a follow-up consultation (50%). The sex ratio was 0.6 and the mean age at diagnosis was 51.1 months. Inbreeding was observed in half of the patients (8/16). The warning signs were mainly infectious (11/16). The other symptoms were dermatological, such as eczema and warts (3/16), but also neurological, type ataxia (3/16). Anemia was observed in 12/16 children, lymphopenia in 4/16 children. Protein electrophoresis was performed in 10/16 children, immunoglobulin weight determination in 4/16 children and lymphocyte immunophenotyping in 10/16 patients. The main PIDs diagnosed were congenital neutropenia (3/16), severe combined immune deficiencies or SCID (3/16), ataxia-telangiectasia (3/16), hypogammaglobulinemia (2/16), verruciform epidermodysplasia (2/16), Wiskott-Aldrich syndrome (1/16), chronic granulomotous disease (1/16), Evans syndrome (1/16). The course was marked by relapses-remissions in 6/16 patients and discontinuation of follow-up in (5/16 patients). Bronchiectasis was observed in 2 patients, with secondary bacterial and fungal infections and digital hypocratism. One hundred percent mortality was observed in carriers of SCID and ataxia-telangiectasia.

Conclusion: PIDs are suspected based on atypical clinical signs. Confirmation is difficult in low income countries. The development is marked by a risk of complications or death, hence the need to strengthen clinical-biological collaboration.

Keywords: *Primary Immune Deficiencies; Sub-Saharan Africa*

Introduction

Primary Immunodeficiencies (PID) are rare under-determined diseases because they are unknowed by physicians and families are also not able to do some biological complementary exams that are not usually available. In Developed Nations, the frequency is around 1/5,000 births/year [1]. In Africa, the prevalence is 107,730 births/year [2]. These diseases are more described in North African populations. In Sub-Saharan Africa, only few cases are reported because they are under diagnosed. In Senegal expected cases are around 1/100000 biths/year.

Aim of the Study

Our aim was to share the results of the follow-up and outcome issue of PID patients in a Children Hospital.

Patients and Methods

We conducted a descriptive and analytical cross-sectional study at the Albert Royer National Children's Hospital in Dakar, Senegal. It was a collaborative study with other pediatric departments particularly Principal Hospital, Dermatology Unit, and the Immunology Unit of the National Blood Transfusion Center. We included all patients received with suspicion of PID, from 2014 to 2021, after ruling out HIV infection. We used the clinical diagnosis criterias with the 10 warning signs of Primary Immunodeficiency of Jeffrey Modell Foundation and the recommendations of the Moroccan Society of Immunology. We did not include patients with chronic diseases and those with incomplete data. Family and personal history was specified. Clinical examination was completed by complementary investigations. A complete blood count (CBC) was performed in all patients. Others explorations were carried out depending on the orientation. It was mainly biology (protein electrophoresis, immunoglobulin weight dosage), microbiology (bacterial and fungal exam), immunology (Direct Coombs test, lymphocyte immunophenotyping), imagery (chest –ray, scanner), histology and genetic.

The follow up was assessed during appointment in basal state or during emergencies. The data was analyzed with Excel 10.

Results

In our study, 32 patients were registered and 16 were included in a follow-up consultation (50%). The sex ratio was 0.6 and the mean age at diagnosis was 51.1 months. Consanguinity was observed in half of the patients: 50% (8/16). The warning clinical signs were mainly infectious (11/16). The other symptoms were dermatological (3/16), such as eczema and warts (Figure 1-3), hematological such as telangiectasia (3/16) and neurological, like ataxia (3/16).

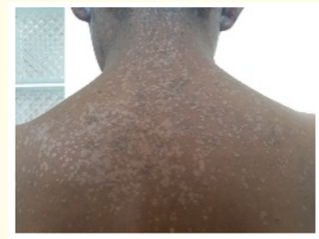

Figure 1: *Warts in the back.*

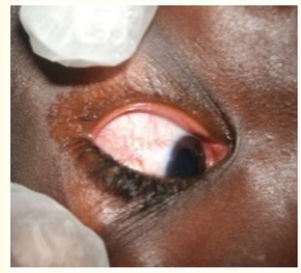

Figure 2: *Ocular telangiectasias*

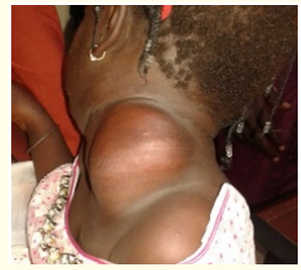

Figure 3: *Adenitis.*

Biologically, anemia was observed in 12/16 children (75%). Others cytopenias are represented in figure 4.

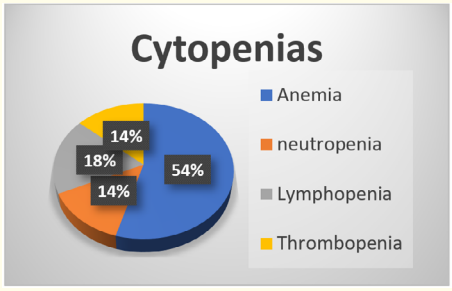

Figure 4: *Cytopenias.*

Direct Coombs Test was positive in 1 patient. Protein electrophoresis was performed in 10/16 children, immunoglobulin weight determination in 4/16 children and lymphocyte immunophenotyping in 10/16 patients. Others investigations showed hypogammaglobulinemia, hight level of alpha foeto-protein rate, isolation of bacterias (*Staphylococcus aureus*) and fungal pathogens (*Candida albicans*).

The main PIDs diagnosed were:

- Congenital neutropenia (3/16) with white cells: 3410/mm^3 and neutrophiles: 670/mm^3;
- Severe combined immunodeficiencies or SCID (3/16), phenotype T_ B_ NK+ with lymphopenia: T CD3: 22% (332/mm^3), LCD19: 2% (30/mm^3), NK normal: 44% (664/mm^3);
- Ataxia-telangiectasia (3/16), with lymphopenia TCD3 and BCD19 and hight level of αFP: 1161 ng/L, (1161 ng/L);
- Hypogammaglobulinemia (2/16), with lymphopenia: 2500/mm^3 low level of immunoglobulin, IgG: 4.2 g/l, IgA: 0.14 g/l, IgM: 0.75 g/l;
- Verruciform epidermodysplasia (2/16), PNN = 540/mm^3, typical histological aspect;
- Wiskott-Aldrich syndrome (1/16) with thrombopenia: 43,000/mm^3 and decrease mean platelet volume (MPV): 5.47Fl;
- Evans syndrome (1/16) with anemia: 6.3 g/dl, thrombocytopenia: 1000/mm^3, direct Coombs test positive;
- Chronic granulomatous disease (1/16) with white cells: 28,700/mm^3 PNN: 13,490/mm^3.

Discussion

The organization of PID diagnosis and cares is not easy in resource limited countries. In collaboration with pediatricians, dermatologists, biologists and immunologists, we put in place a trace of a cohort of PID patients. In this study, we share the experience of the follow-up.

Ataxia-Telangiectasia was found in 3 sibling from the same family. It is a rare autosomal recessive disease affecting neurologic and immune system. The diagnosis is based on a clinical triad: ataxia, telangiectasia and immunodeficiency. In Morroco Jedane reported 27 cases between 2008 and 2012 (4 years), from 22 unrelated families [3]. In our study the sex ratio was 0.6 and the mean age at diagnosis was 51.1 months (4.26 years) for all the cohort. In Morroco, it was 5.51 years. All of our patients presented ataxia, ocular telangiectasia and recurrent infections because of immunodeficiency. The more common infections was respiratory tract infections and skin infections. Alpha foetoprotein serum level was also elevated. Consanguinity was observed in half of our patients (8/16) but was higher in Jedane study, around 81.8% [3]. According to Barbouche, these diseases are more common in North African populations because of the high prevalent of consanguinity [4]. Three others patients presented severe combined immunodeficiency (SCID) with phenotype T_ B_ NK+ in one of them. It is a heterogeneous group of rare primary immunodeficiencies.

The prevalence is higher in populations with high rates of consanguinity [5]. The main diagnosis criteria is lymphopenia, with the lack of autologous T lymphocytes. In Senegal we don't have many datas because this kind of diseases had never been reported. In Morocco, 96 cases was reported from 1998 and 2019 with 66% of consanguinity. The clinical manifestations commonly observed were recurrent respiratory tract infection. The phenotypes T−B−NK+ was more common: 44.5% [5]. Congenital neutropenia was diagnosed in 3 patents. This PID is defined by neutrophiles level under 1500/mm^3, without any secondary cause. In one of our patient, a history of asphyxia was found with recurrent abcess. CBC showed leuco-neutropénie with white cells: 3410/mm^3 and neutrophiles: 670/mm^3. The main classification identify the primitive congenital neutropenia with many genes (*ELA2, HAX1, G6CPC3, GFI1, WASP*) and syndromic congenital neutropenia in genetic or metabolic disease [6]. One patient caried Wiskott-Aldrich syndrome, an X-linked recessive disorder characterized by a classic triad: immunodeficiency, eczema, thrombocytopenia with increased risk of autoimmune disorders and malignancies. Our patient was the only alive child of of a non-consanguineous couple. His two older siblings died before two years old in the same conditions (severe infections, eczema and bleeding). In the newborn, he had neonatal infection, rectal bleeding. As an infant, he had pneumonia, bacterial meningitis and chronic diarrhea [7]. The CBC showed microcytic thrombocytopenia: 43,000/mm^3 with Mean Platelet Volume (MPV): 5.47Fl. It is a pathognomonic finding in patients with mutations of the WASP gene [8]. He presented also lymphopenia, predominant on CD4+ and CD8+ T lymphocytes an increase level of IgA and IgG. Molecular genetic studies showed a duplication of cytosine in the hemizygous state at intron 2: c.273 + 11dupC, referenced as a polymorphism with no effect on protein synthesis and a hemizygous mutation at exon1:Exon1:c.37C>T(p.Arg13*) [7]. Chronic granulomatous disease was found in one of our patients but with only a clinical diagnosis. Specific biological explorations (NBT test and DHR test) are not available in our condition. This PID is characterized by an inability of phagocytes to produce reactive oxygen species (ROS), which are required to kill some microorganisms [9]. Patients suffer from recurrent bacterial and/or fungal infections from the first year of life. Our patient was the only one of 3 siblings. But one multiplex family, with three affected siblings, was identified [10]. Two infant presented hypogammaglobulinemia but only one was is followed. Bruton Disease is the main cause of agammaglobulinemia caused by Bruton's tyrosine kinase (BTK) gene defect. It is the first described (1952) and the prototype for primary immune deficiencies [10]. Confirmation diagnosis requires molecular analyse and it is not yet possible for this infant. The phenotype is characterized by dramatically reduced or absent mature B lymphocytes (less than 2% of total lymphocytes) and a profound deficiency in all immunoglobulin isotypes. The consequences are high susceptibility to severe and recurrent bacterial infections mainly, respiratory tract infections. In our study, the infant presented recurrent otitis after 7 months old.

Outcome

The course was marked by relapses-remissions in 6/16 patients and discontinuation of follow-up in (5/16 patients). Bronchiectasis was observed in 2 patients with digital hypocratism, secondary bacterial and fungal infections. Recurrent bliding was observed in Wiskott-Aldrich syndrome and the eczema is resistant to therapy. Many secondary bacterial infections was noted with *Staphylococcus aureus*, *Streptococcus, Pseudomonas aeruginosa* Bacilli de Koch, fungal infections with *Candida albicans* and viral herpes infections, posing a therapeutic challenge, mainly in Wiskott-Aldrich syndrome. Antibiotic therapy improve the prognostic to some patients but lack of compliance induce high risk of complications. In our condition, immunoglobin of replacement is not yet available. Overall mortality was 37.5%, but in patients carrying SCID and ataxia-telangiectasia the mortality rate was One hundred percent. In Morocco, it was 37% in Ataxia and 84% in SCID which requires bone marrow transplantation.

Conclusion

PIDs are the new approach of infectious diseases. They are suspected on atypical clinical signs. Confirmation is difficult in low income countries. It is critical to continue investigation of these diseases in order to better understand the underlying mechanisms and to improve patient care. The follow-up is marked by a high risk of complications and death. Hence the need to strengthen clinical-biological collaboration in order to provide a clinical and immunological description and to assess changes in the patients cares. In our cohort, syndromic PID are more common in the patients but prognosis is reserved with SCID and ataxia.

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