

Primary Immunodeficiencies (Pi) in Senegalese Children: A Series of 30 Cases

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ABSTRACT

Background: Primary immunodeficiencies are a group of about 400 diseases of genetic origin, they are considered as rare diseases. However, above 6 million people in the world would be affected, regardless of sex, age or geographical area. Few studies have been conducted in sub-Saharan Africa. The main objective of this study was to show existence of these diseases in West Africa and difficulties to manage it. The specific objectives were to identify the different clinical patterns of PI cases, to describe their biological phenotypes and to propose management.

Method: A cross-sectional observational study over a period of 4 years and 2 months resulted in recruitment of children with either 2 or more signs among the 10 warning signs for PID or with signs described in the 10 recommendations for diagnosis of PID from African Society for Immunodeficiencies (ASID). Biological and immunological exploration were carried out in these patients. The diagnostic approach of PID for emerging countries according to the method of B. Admou and et al. was adopted.

Results: 30 cases of PID were recorded. The sex ratio was 1; with a median age at diagnosis of 24 months. The most common clinical symptoms were respiratory infections, followed by digestive and then cutaneous manifestations. 10 children had immunological confirmation. One patient had genetic confirmation of WAS. The most common category of PID was syndromic PID. Management was limited, based mainly on antibiotic prophylaxis. The death of 5 patients was recorded.

Conclusion: PI are a severe condition and certainly underestimated in Senegal. This is due to the lack of knowledge of these diseases by physicians but also to an insufficient access to diagnostic tools. The raising of the technical platform will allow better documentation of these diseases, and advocate for access to certain treatments such as immunoglobulins supplementation and bone marrow transplantation.

Keywords

Primary immunodeficiencies (PI), Children, Sub-Saharan Africa.

Introduction

Primary immunodeficiencies diseases have often been considered rare, and several diagnostic tools and approaches have been

developed to facilitate diagnosis [1-5]. However, their frequency would be rather underestimated [6,7]. Primary immunodeficiency occurs most often in the pediatric population [8].

In Africa, data on recorded PI come mainly from the Maghreb, particularly Morocco in 2014, where the establishment of a register made it possible in its first report covering a period of 15 years (1998-2012) to identify 421 PI cases in children and adults [8]. In the same year, in South Africa, the incidence of PI in pediatrics was estimated between 5 and 15 new cases per year [9]. The place occupied by these PI in childhood pathologies in Senegal is not yet clearly elucidated, it is in this context that this study was initiated.

The aim was to prove the existence of PI in children. The specific objectives of this study were to identify the different clinical patterns presented by these patients, to describe the different immunological phenotypes and to propose management.

Method

Study design

It was a multicenter (5 University Hospital Centers) observational cross-sectional study over a period of 4 years and 2 months, from October 2014 to December 2018, initiated by the immunology Laboratory of the National Blood Transfusion Center (CNTS) in partnership with 5 pediatric services. The 4-step approach of B. Admou and al. has been adopted [3]. The clinical evaluation was conducted according to a pre-established data collection form. Immunological evaluation was mainly based on lymphocyte phenotyping and serum protein electrophoresis. the immunoglobulin level measurement and the genetic study were performed abroad.

Patients

We included children aged 0 to 15 years, who had the following criteria:

Lack of evidence for secondary immunodeficiency with, in particular, negative retroviral serology in the child or mother (children < 18 months) and

- Presence of at least two of the 10 warning signs of PID, or
- The existence of signs described in the 10 recommendations for PID diagnosis proposed by the Moroccan Society for Primary Immunodeficiencies and the African Society for Immunodeficiencies ASID, 2015.

Children who did not have parental advisory, children with malnutrition related to dietary errors during diversification or weaning, and children with alternative diagnosis (e.g.: sickle cell disease, systemic diseases...) were excluded.

Variable

For each patient included a data collection form was established. It included general data (e.g. : age, gender, address, parental consanguinity, personal and family history...), clinical data (infections: sites, frequency, pathogen agent; skin disorders; polymalformative syndrome, delay in cord fall, tumoral syndrome,

failure to thrive, auto-immune disease), biological data (HIV test, blood cells count, blood smear, serum protein electrophoresis, immunoglobulins levels, lymphocyte immunophenotyping, genetic study), classification of PID using the IUIS classification 2017, determination of the probability score by ESID criteria, treatment and evolution.

Definitions and thresholds

Patients were classified according to the diagnostic probability of PID in 3 categories: definitive diagnosis, probable diagnosis and possible diagnosis according to ESID criteria.

Tools

Blood cells account was realized by automatons of the laboratories of the different hospitals, the immunological exploration was done by the electrophoresis analyzer and the flow cytometry in the laboratory of National Blood transfusion Center. Immunoglobulin's level and complement level have been analyzed abroad as well as molecular biology.

Statistical analysis

The data collected were recorded and analyzed using the *SPSS* software version 24. A *p* value less than 0.05 was statistically significant.

Results

A total of 30 cases of PI were recorded with an equal distribution between girls and boys. Patients were less than 5 years old in 80% of cases (26 cases) with a median age of 24 months, extremes were 1 month and 156 months.

The main source of recruitment was the hospitalization services, which accounted for 70% of cases or 21 patients. The specialized consultation was represented at 13%, exclusively represented by the pediatric dermatological consultation.

Inbreeding was found in more than a third of patients (11 cases or 36,7%) and table 1 presents the different personal and family histories of suspected cases of PID.

Table 1: Family and personal history of PID cases.

| Anamnestic data | Numbers | Frequency (%) |
|---------------------------|---------|---------------|
| Death in the sibling | 9 | 30 |
| Similar cases | 2 | 6.7 |
| Previous hospitalizations | 20 | 66.7 |
| Recurrent ENT infections | 4 | 13.3 |

Clinical patterns during PID

Respiratory and/or ENT manifestations

Pneumonia was the most frequent manifestation: 22 patients (73%). Four patients had pulmonary tuberculosis. In 9 patients with CID, pneumonia was associated with other infections: digestive, meningitis and/or skin infections.

We noted staphylococcal pleuropneumonia associated with neutrophilia of 52000/ mm³ as part of an innate PID; in a 2-month-

old infant. Bronchiectasis was found in the WAS patient at the age of 5 years.

Digestive manifestations

They concerned 10 patients, with recurrent acute gastroenteritis (4 cases) and chronic gastroenteritis (1 case). The digestive hemorrhages were found in 2 patients. This was a 13-year-old patient with Crohn's disease based on colonoscopy. These digestive signs were associated with multiple deep perineal abscesses but also skin abscesses. The second patient, aged 2 years old, had identical manifestations, however, he also had severe growth retardation which prevented him from performing his colonoscopy. These patients were suspected of CGD or Bruton syndrome, but the biological assessment was incomplete. 3 patients had persistent oral fungal infections, one of which was suspected a chronic mucocutaneous candidiasis (CMC).

Skins disorders

They concerned 8 patients (26%). Among these patients, 4 were referred by the pediatric dermatological consultation: 2 cases of hereditary angioedema, one case of Wiscott Aldrich syndrome (WAS) with eczema (Image 1) and hemorrhagic scabs on the scalp (Image 2); and 1 case of MHC class II deficiency with repeated skin abscesses. A patient with ataxia-telangiectasia syndrome presented ocular telangiectasias (Image 3). Eczema was found in 3 patients.



Image 1: Eczema in WAS; **Image 2:** Hemorrhagic scabs on the scalp of WAS patient.



Image 3: Ocular telangiectasia in ATM.

Neurological manifestations

In our study, 7 patients had neurological manifestations. Five patients presented with bacterial meningitis, 3 of whom had specific

immune exploration that was in favor of PID. We also observed a familial case of ataxia-telangiectasia syndrome in 2 sisters aged 9 and 3 years. In their family history we found 2 cases of death in the siblings. There was parental inbreeding. In addition to ataxia, both had to suffer from recurrent pneumonia, meningitis, skin abscesses, ulcerations and growth retardation with amyotrophy. The presence of ocular telangiectasia made it possible to retain the diagnosis. Biological analysis found an increase in alpha foetoproteins and a combined deficiency at lymphocyte phenotyping.

During this study, their 24-month-old younger brother was included in front of recurrent pneumonia. He did not have ataxia or telangiectasia. However, a combined immune deficiency status during immune exploration has been established.

Failure to thrive

It was the main impact of the clinical manifestations of PI as observed in table 2.

Table 2: Clinical manifestations associated with failure to thrive.

| Signs linked to failure to thrive | Numbers | Frequency % |
|-----------------------------------|---------|-------------|
| Gastro-intestinal signs | 4 | 50 |
| Respiratory signs | 5 | 62 |
| Skin disorders | 5 | 62 |
| Neurological signs | 3 | 37.5 |

Others manifestations

We noted a septic arthritis of knee in one patient with suspected CGD. We found a microcephaly in a patient associated with a « bird like face » compatible with Bloom syndrome. 3 patients presented a sepsis during the evolution of their symptom.

Biologics finding

Blood counts were performed in all patients, twenty patients had lymphocyte immunophenotyping (63%) due to the lack of reagent. 17 patients (56,7%) had serum protein electrophoresis. The immunoglobulins level measurement and the determination of serum complements were performed in 4 patients. The genetic study was performed in one patient.

First-line biological exploration

Contribution of blood count to the diagnosis of PID in our study: lymphopenia was present in 21% of cases (6 patients) and was systematically related to a combined deficiency. Neutropenia was also found in 6 patients, including 1 case of congenital neutropenia. Two patients had persistent and major hyperleukocytosis above 50000/mm³ compatible with phagocytosis function abnormalities. Low platelets with small size were found in the patient with WAS

Serum protein electrophoresis was normal in 50% of cases (9 patients) and showed hypergammaglobulinemia in 42.8% of cases (7 patients); 1 patient developed hypogammaglobulinemia as part of a combined immune deficiency.

The level of immunoglobulins and the determination of serum complements (C3, C4, CH50) performed outside the country were normal.

Specific immune exploration

At lymphocyte phenotyping, CD4 T cells were decreased in one-third of cases. The decrease in CD8 T lymphocytes was found in 17.4% of cases. CD19 B lymphocyte reduction was present in 30% of cases, or 6 patients. This reduction in B cells was not isolated and was always associated with a reduction in T cells as part of a combined deficiency.

The dosage of C1 inhibitor serum supplements performed as part of a hereditary angioedema has returned to normal.

Genetic study

Molecular biology was performed in only one patient who confirmed the mutation of the WAS gene.

Etiology of primary immunodeficiencies

5 categories of primary immunodeficiencies were identified according mainly to clinical pattern, biological finding. The most common primary immunodeficiency category was well-defined syndromes (20%).

The undetermined PI (11 patients) were patients who responded to different categories of PID according to clinical pattern but, had normal or incomplete biological exploration.

The different Primary Immune Deficiencies suspected and/or confirmed according to their category are described in Table 3.

Our study included 30 cases of primary immunodeficiency (Annex). Among these patients, 10 had specific biological confirmation, including immunological confirmation. In addition to this immunological confirmation, one patient had the genetic confirmation, it was a WAS. Nine patients had a possible diagnosis of PI according ESID criteria.

Based on the PI identified in this present study, the suspected genetic transmission modes were dominated by 65% autosomal recessive followed by autosomal dominant transmission at 20% and X-related transmission at 15%.

Treatment

Thirteen patients (46.6% of cases) were started on Sulfamethoxazole/Trimethoprim antibiotic prophylaxis. Therapeutic abstention was observed in equal proportions, particularly in unclassified patients or with a possible diagnosis (ESID criteria).

In the management of bacterial infectious complications, antibiotic therapy was systematic with the use of 3rd generation

cephalosporins in 53.8% of cases (16 patients), followed by antituberculosis drugs in 6 patients (23.1% of cases) and penicillin in 4 patients (15.4%). Second generation of cephalosporins were used in 2 patients or 7.7% of cases. Intravenous infusion of immunoglobulins was offered to our patients; however, this treatment was not effective due to lack of resources.

A therapeutic approach using hematopoietic stem cell transplantation was not available during our study.

Evolution

We recorded 5 cases of death, including 2 in the same family. All the deceased patients had a combined immunodeficiencies.

We did not find a statistically significant association between definitive and probable diagnosis of PID and some qualitative variables such as inbreeding, previous hospitalizations and age.

Discussion

This was a pioneering study on PI in children in Senegal, with multicenter and prospective recruitment allowing longitudinal follow-up for subsequent studies in this population.

The limits; were related to the sample size of 30 cases, which was a constraint in the analysis of the associated factors. The second limitation was biological exploration, which was not uniform in our patients. Indeed, not all patients had a complete immunological assessment due to lack of reagents; the exploration of innate immunity could not be carried out, in particular the exploration of functional abnormalities of phagocytosis.

30 patients were enrolled over a 4-year period, with an average of 7.5 cases/year. In Morocco, the first report of the PI registry over a 15-year period identified 401 cases of PI with a mixed sample including adults and children [8]. In South Africa, the incidence of PI in pediatrics was estimated at between 5 and 15 new cases per year, which was superimposed on the data found in our study [9].

Male predominance in primary immunodeficiency has been found in several studies [8,10,11]. This could be related to the existence of PI related to the X. In our study, we noted a sex ratio of 1 probably related to the size of our study sample and the prevalence of autosomal recessive diseases in our cohort.

We found parental inbreeding in 30% of cases. This inbreeding is found in 43.2% in Morocco, in 20.9% of cases in Europe [8,12] while in Asia parental inbreeding was noted in less than 3% of cases [13]. The influence of inbreeding in autosomal recessive

Table 3: PID Classification of cases.

| Combined immunodeficiencies (CID) | CID with associated syndromic features | Congenital defect of phagocyte number, function or both | Defects in intrinsic and innate immunity | Complement deficiencies |
|-----------------------------------|--|---|--|---------------------------|
| SCID (1) | WAS (1) ATM (3) | Congenital neutropenia (1) CGD (1) | CMC (1) | Hereditary angioedema (2) |
| CMH class II deficiency (3) | Bloom or NJS (1) Hyper IgE (1) | LAD (1) Cyclic neutropenia (1) | IL12/INF γ deficiency (1) | |

transmission PI has been demonstrated. In our study, in addition to this parental inbreeding, we noted a predominance of autosomal recessive transmission PID.

The median age at diagnosis was 24 months. In France, the median age was 3.3 years (39 months) according to the French National PI Registry in 2010, which included both children and adult patients [14].

The study by Bousfiha et al. in Morocco found the same median age of 2 years as our study. [8] We did not assess the diagnostic delay in our patients because it was poorly defined by the parents. However, in 60% of the cases, we found one to several previous hospitalizations, which could indirectly indicate the diagnostic delay.

Several clinical manifestations have been described, the main one being respiratory and/or ENT infections (22 patients) followed by digestive manifestations, then growth retardation and dermatological manifestations in equal parts. These results were superimposed on those found in a meta-analysis conducted in Europe [16].

Non-infectious manifestations have been dominated by dermatological conditions that affect 40% to 70% of patients diagnosed with primary immunodeficiencies [17,18]. The C1inhibitor assay performed in one of the patients with hereditary angioedema returned to normal, however this does not rule out the diagnosis of hereditary angioedema [19]. In our study, these skin manifestations were associated with a definitive or probable diagnosis in 3 out of 4 cases.

Due to a lack of reagents, immune and genetic biological investigations were not uniform. Hemogram is a simple and inexpensive test that provided useful information for referral to a given DIP, as the hemogram found neutrophilia in 20.8% of cases compatible with phagocytosis abnormalities such as suspected chronic septic granulomatosis and another case of phagocytosis abnormalities (LAD: Leukocyte Adhesion Deficiency) was suspected in the presence of a delayed cord fall in a context of neonatal infection associated with hyperleukocytosis at 39860 elements/mm³. Functional tests for phagocytosis to confirm the suspected types of PI should be available. Lymphopenia was in all cases associated with combined PI and confirmed by lymphocyte phenotyping. The humoral deficiency represents the most frequent PI in the world. The immunoglobulins level measurement was only performed in 2 patients in our study and returned normal.

In 2014, Brodzski N and al. [15] showed that among 15 patients who had a PI with specific immune exploration, seven patients had genetic confirmation. Therefore, although this genetic confirmation is the definitive diagnosis, specific immune exploration should be accessible because it allows a diagnosis of PI with a probability of more than 85% of having the same diagnosis in 20 years and makes it legitimate to start treatment.

We did not find a statistically significant association between definitive and probable diagnosis of PI and some qualitative variables such as inbreeding, previous hospitalizations and age. However, a meta-analysis has shown the association between autosomal recessive PI and parental inbreeding [20]. The small sample size of our cohort may explain this discrepancy. Nevertheless, longitudinal monitoring and continued recruitment would expand the cohort to highlight the different factors associated with these PIDs in our country.

Conclusion

Primary immunodeficiency in children is a reality in hospitals. They are still underestimated. The use of simplified tools such as the 10 warning signs, phenotypic classification will facilitate diagnosis for clinicians as well as the availability of some biological explorations. Continued recruitment will make possible to refine the epidemiological profile and advocate for access to certain treatments such as intravenous immunoglobulins or bone marrow transplants.

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Annex: Summary table of cases of PID

| Age /Gender | Personal and family history | Clinical patterns | Biologics finding | Type of PID/ IUIS Classification 2017 | Diagnostic/ ESID criteria |
|---------------|--|--|---|---------------------------------------|---------------------------|
| 16 month, M | 2 death in the siblings, no parental consanguinity, 3 previous hospitalizations | Eczema Pneumonia, otitis, méningitis, malnutrition, gastroenteritis | Lymphopenia, thrombopenia, hypogammaglobulinemia, low CD4, CD8 and CD19 | WAS | Definitive |
| 48 month, F | Parental consanguinity, 1 previous hospitalization / Pneumonia | Pneumonia | Hypergammaglobulinemia normal CD4,CD8,CD19 level | Unclassified | |
| 36 month, F | Recurrent skin abscess | skin abscess requiring intravenous antibiotic therapy | Neutropenia: 130/mm ³ , hypergammaglobulinemia, normal CD3, CD4, CD19 and high CD8 | Congenital Neutropenia | Probable |
| 132 month, F | None | Multifocal Tuberculosis | Hyperlymphocytosis, hypergammaglobulinemia, high CD3, CD4, normal CD8 and CD19 | Deficiency of IL12/IFN γ axis | Possible |
| 120 month, F | Parental consanguinity, 2 death in the siblings, 1 previous hospitalization | Gastroentéritis | White blood cell level normal, hypogammaglobulinemia, low CD4 and CD19, normal CD8 level | CMH class II deficiency | Probable |
| 108 month, F | Parental consanguinity, 2 death in the siblings, 1 previous hospitalization | Ataxia, Pneumonia, Méningitis, Malnutrition | Hyperleucocytosis, low CD4, CD3, CD8, and CD19 | Ataxia-télangiectasia (ATM) | Probable |
| 36 month, F | Parental consanguinity, 2 death in the siblings | Ataxia-télangiectasia, Pneumonia, Méningitis | Neutropenia, lymphocytosis, anaemia | Ataxia-télangiectasia (ATM) | Possible |
| 26 months, F | Oral antibiotic therapy for about 2 months | Pneumonia | Hyperleucocytosis Hypergammaglobulinemia | Unclassified | |
| 1 month, M | None | Gastroenteritis, malnutrition | Leucopenia, lymphopenia, hypogammaglobulinemia, low CD3, CD4, CD8, CD19 | SCID | Probable |
| 14 month, M | 1 previous hospitalization | Pneumonia, sepsis | Neutropenia ; lymphopenia | Unclassified | |
| 24 month, M | 2 previous hospitalizations | Inflamatory bowel disease, Malnutrition | Hyperleucocytosis, | Predominantly antibody deficiency | Possible |
| 48 month, M | None | Pneumonia, gastroentéritis | Serum protein electrophoresis, CD3,CD4, CD8, CD19 : normal | Unclassified | |
| 14 month, M | None | Angioedema | C1 inhibitor level : normal | Hereditary Angioedema | Possible |
| 48 month, M | 1 previous hospitalization | repeated pneumonia | Blood count, Serum protein electrophoresis (SPE), Immunophenotyping: normal | Unclassified | |
| 24 month, M | 2 previous hospitalizations, parental consanguinity, 4 death in the siblings including 2 for Ataxia-télangiectasia | Pneumonia | Hyperlymphocytosis, CD3, CD8 normal; low CD4, CD19 | Ataxia-télangiectasia | probable |
| 14 month, M | 1 previous hospitalization, parental consanguinity, 1 death in the siblings | Pneumonia | Hyperlymphocytosis, normal SPE, normal CD3, CD8 ; low CD4 | CMH class II deficiency | probable |
| 10 month, F | 1 previous,hospitalization, parental consanguinity, 1 death in the sibling | Pneumonia | Normal blood count Lymphocyte phenotyping : normal | Predominantly antibody deficiency | |
| 11 months, F | 2 previous hospitalizations | Skin abscess, Gastro-enteritis, Malnutrition | Hyperleucocytosis, normal level CD3 , CD8, low CD4 | CMH class II deficiency | probable |
| 44 months, F | 1 previous hospitalization | Pneumonia, Malnutrition, microcephaly | Hyperlymphocytosis | NJS/ Bloom syndrom | Possible |
| 24 months, F | 1 previous hospitalization | Pneumonia, thrush, Malnutrition | NFS, normal Ig level, normal immunophenotyping | Unclassified | Qx<Q1ZA |
| 24 months, F | Recurrent otitis, 4 previous hospitalizations | Skin abscess, Méningitis, Sepsis, Pneumonia, septic arthritis | Hyperleucocytosis | CGD | Probable |
| 24 months, F | 2 previous hospitalizations | Thrush, Gastro-entéritis | hyperlymphocytosis, high level of IgM, h IgG and normal IgA ; high level of CD3, CD4, CD8 and normal CD19 | CMC | Possible |
| 156 months, M | 2 previous hospitalizations | Inflamatory bowel disease | Hyperleucocytosis | CGD | Possible |
| 132 months, F | 1 hospitalization, recurrent ENT infections | Méningitis | Hyperleucocytosis, Complement level : C3, C4, CH50 normal | Unclassified | |

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|--------------|--|--|---|-----------------------------------|-----------------|
| 2 months, M | None | Abscess, angioedema | Hyperleucocytosis | Hereditary Angioedema | Possible |
| 10 months, F | 3 previous hospitalizations | Pneumonia, Sepsis, Malnutrition | Normal white blood count, Normal CD4 and CD8 level | Predominantly antibody deficiency | Possible |
| 34 months, M | 1 hospitalizations, parental consanguinity | Severe Eczema, Malnutrition, thrush | Hyperleucocytosis, Normal level of CD3, CD4, and CD8. | Hyper IgE syndrom ? | Possible |
| 84 months, F | Reccurent tonsilittis | Pneumonia, Atopy | Leuconeutropenia | Cyclic Neutropenia | Possible |
| 1 months, M | 1 hospitalization, 1 death in the sibling, consanguinity | Umbilical cord fall delay (21j), neonatal infection/ prematurity | Hyperleucocytosis Normal lymphocyte phenotyping | LAD | Possible |
| 2 months, M | 2 death in the sibling | pleuro-pulmonary staphylococia | hyperleucocytosis, Neutrophilia | Unclassified | |