

# Primary Immune Deficiencies (PID): Diagnosis Challenges

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## Abstract

**Background:** Primary Immune Deficiencies (PID) are rare, under-determined diseases particularly in sub-Saharan Africa. The diagnosis is often suspected with uncommon clinical signs. Infections are the main diagnostic circumstances in infants. Confirmation is often difficult because some additional examinations are unavailable in many of our countries. **Aim:** Our aim was to share the challenge of diagnosis and treatment in PID. **Case Presentation:** It is about two infants, a boy and a girl, with early several infections. Both of them presented a hypo-gammaglobulinemia and to the boy, the immuno-phenotyping lymphocyte showed a decreased level of lymphocytes CD19. We are looking for genetic confirmation but it is not easy. The treatment of these infants requires a substitution for life of immunoglobulin which is unavailable in our countries. **Conclusion:** PID are suspected with atypical clinical signs. Confirmation genetic diagnosis is difficult in low income countries. To improve the follow up, we need to strengthen clinical-biological collaboration.

## Keywords

Primary Immune Deficiencies, Hypo-Gammaglobulinemia, Infants

## 1. Introduction

Primary Immune Deficiencies (PID) result from dysfunction of an immune response [1] [2]. They are suspected of early, severe, recurrent infections. Sometimes it is about unusual infections locations, opportunistic germs or adverse

clinical manifestations after immunization. These situations require further investigations, in order to confirm diagnosis and manage patients. Across two young infants' cases, we share the difficulties linked to the diagnosis and treatment of these diseases in low income countries.

## 2. Case Presentation

### 2.1. Case 1

A 5-month-old, female was referred to our hospital for exploration of a hypogammaglobulinemia. It was discovered following the appearance of suppuration at the injection site after each immunisation session. The mother reported a lack of healing after the first immunization with Calmette-Guerin Bacille (BCG) injection. Induration had appeared, followed by ulceration and then suppuration, around the age of 4 months. He had no fever and any other impaired general condition. The same symptoms were observed after each immunization injection with Expanded Program on Immunization (EPI). The course was chronic, more than two months, despite local surgical care. This infant, was fed with breast milk and artificial milk and presented liquid and frequent stools. She was the third in a family of three living children, with no parental consanguinity or similar cases in the siblings. Physical examination found a weight: 9.5 kg; size: 64 cm; head circumference: 43.5 cm; arm circumference: 16 cm and temperature: 36°C. She presented an ulcer in the process of healing in BCG injection site, and post-immunization inflammatory swelling of the right thigh. The laboratory investigations showed a negative HIV serology, a normal complete blood count and a hypo-gammaglobulinemia: 7.9% (age normal range: 11% - 18%). An immunoglobulin weight assay and lymphocyte immunophenotyping were requested, but could not be performed. The bacterial investigation in the ulceration was negative. The chest x-ray was normal, and the ultrasound of the induration showed oedematous infiltration of fatty tissue in the right thigh, non-inflammatory right iliac lymph nodes, without detectable collection. She received local cares with antiseptic and antibioprohylaxy. The parents stopped the disease monitoring since the COVID-19 pandemic beginning. According to the mother, the infant feels better.

### 2.2. Case 2

A seven-month-old male infant is referred for purulent, recurrent, chronic otorrhea, since the age of 4 months, in a context of intermittent fever. He had several outpatient consultations, with symptomatic treatment. He had also diarrhea episodes while teething. He was fed breast milk and artificial milk, with diversification from 6 months. Psychomotor development was normal and immunization was correct. He was the second with two siblings, without similar cases. There was a third degree parental consanguinity. Physical examination found weight: 9 kg; size: 73 cm; head circumference: 45.5 cm; arm circumference: 14 cm; temperature: 36.6°C. It had the rales crackles and bilateral bron-

chitis. We found no lymph nodes and no organomegaly. Additional examinations showed moderate, hypochromic microcytic anemia (Hb: 10.9 g/dl; TCMH: 25.5 pg; MCV: 78fl; moderate hyperleukocytosis: 12,000/mm<sup>3</sup>, lymphopenia: 2500/mm<sup>3</sup> and normal platelet count. There was hypogammaglobulinemia: 5.4% (standard: 8% - 15%); a decrease of IgA: 0.14 g/l (normal: 0.27 to 0.86). The immune-phenotyping lymphocyte showed a decrease of lymphocytes CD19: 350/mm<sup>3</sup> (Normal: 610-2600). The bacterial investigation in the ulceration was negative. The Bruton Disease is suspected but has to be confirmed with genetic examination which is not available. For the managing, the treatment of this infant requires a substitution for life of immunoglobulin which is unavailable in our countries. We propose the immunization, prophylaxis against bacterial infections and monitor the temperature.

### 3. Discussion

Primary Immune Deficiencies (PID) are rare but not exceptional diseases. More than 300 genetic disorders have been identified, particularly in children [3] [4]. The prevalence is underestimated in the world, particularly in Africa [4]. Actually, 2500 patients have been diagnosed in Africa while at least 65,000 patients are expected [5]. In the National Albert Royer Children Hospital in Dakar, 32 patients are registered, in collaboration with the National Blood Transfusion Center. These two infants reported are a boy and a girl, with parental inbreeding about the boy (infant 2). In fact, transmission occurs most often in the autosomal recessive mode, which means that these pathologies are more common in areas with a high rate of consanguineous marriages [6]. In infants the main symptoms are early infections. The diagnosis is suggested when these infections are uncommon, with a recurrent chronic course. In our two infants, it was purulent otitis and post-immunization suppuration. In our countries, PID are still poorly understood by physicians, making their diagnosis difficult and delays care. To improve their diagnosis in our country, we organised training sessions for physicians, a few years ago [4]. However, availability of immunological investigations and genetic tests are the main challenge to confirm the diagnosis and manage the treatment. The parents of one of the two infants were able to achieve immunological explorations while the others were not. These difficulties increased morbidity and mortality due to social problems of parents themselves [7]. The hypothesis of a hypogammaglobulinemia in early childhood seems likely in infant 2 because of lymphopenia B. It appears in infants with bronchial infections after 6-month-age, while maternal IgG disappears. Bruton's disease is more likely in this infant, due to gender and age. Genetic analysis is underway. The sex-linked gammaglobulinémie (Bruton) manifests as pulmonary or digestive infections, meningitis, after the 6th month. It is recessive X-linked disease. The diagnosis is suggested with the absence of B lymphocytes and serum immunoglobulin. The treatment involves a substitution of immunoglobulin lifetime, antibiotics for secondary bronchial infections and chest physiotherapy.

The disease progresses to bronchiectasis, chronic sinusitis and attacks. Antenatal diagnosis is possible by looking for the btk gene in Xq22. Infections are not the only DIP revelations modes that can be expressed as allergy, inflammation of autoimmunity or neoplasia [8]. In these two infants, there were no other non-infectious manifestations. They were referred by pediatricians trained with the support of the African Society for Immunodeficiencies (ASID) and Moroccan Society for Immunodeficiencies [9]. About the management, it depends on the type of PID. The main treatment is anti-infectious drugs, immunoglobulins, graft hematopoietic stem cell. Some treatments are often unavailable or inaccessible [10]. That's why, the best strategy remains primary prevention or targeted neonatal screening [11].

#### 4. Conclusion

The hypogammaglobulinemia results from a humoral deficiency. There is one of the most common primary immune deficiencies. All pediatricians should be able to suggest the diagnosis to save lives. However, the challenge is the availability of several additional examinations which improve the diagnosis and contribute to managing the follow-up.

#### Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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