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Case Report

Sex-Linked Agammaglobulinemia in a Pediatric Patient with Recurrent Respiratory Tract Infections

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Abstract

X-linked agammaglobulinemia, also known as Bruton`s disease, is a humoral immunodeficiency disorder caused by a mutation in the Bruton tyrosine kinase (BTK) gene resulting in defective B cell differentiation with extremely reduced numbers of mature B cells causing a severe hypogammaglobulinemia [1-4]. Bacterial infections usually begin in male infants as maternal IgG antibodies, acquired transplacentally, are lost [6] and are most likely to be diagnosed when recurrent sinopulmonary infections occur in a male infant usually younger than 1 year. This report aims the importance of consider this diagnosis in patients with recurrent sinopulmonary diseases.

Keywords: *X-Linked Agammaglobulinemia; Bruton Tyrosine Kinase (BTK)*

Introduction

X-linked agammaglobulinemia, also known as Bruton´s disease is one of the commonest Primary Immune Deficiencies (PIDs) encountered in pediatric clinical practice [5]. It is an X-linked disorder caused by a mutation in the Bruton tyrosine kinase (BTK) gene. The condition was first described in 1952 by Col Ogden Bruton, giving rise to the alternate name of Bruton agammaglobulinemia [4]. It is characterized by increased susceptibility to encapsulated bacteria (most commonly Streptococcus pneumoniae, followed by *Haemophilus influenzae* type b and *Staphylococcal* species), with absent circulating B cells in the peripheral blood, causing a severe hypogammaglobulinemia [4-6]. The incidence is reported to be around 1/200,000 male birth [2,5,6].

The onset of recurrent bacterial infections typically begins 6 -9 month after birth when maternal IgG is reduced below the protective level. Commonly the diagnosis of immunodeficiency is established before the age of 5 years, with a careful awareness the diagnosis can be made in the first year of life [2,5].

Here we report XLA case and recurrent sinopulmonary diseases. This report aims the importance of consider this diagnosis in patients with recurrent sinopulmonary diseases, to raise the awareness of these pathologies.

Case Report

A one-year-old boy who came to the allergist consultation with a history of several pulmonary symptoms. It was learned that he had previously been treated with amoxicillin and clarithromycin for bronchitis and otitis media for around 9 times, hospitalized 3 times for pneumonia. The first infection was reported around the age of 3-month-old. He was born at term with normal delivery. There was no family history of any contributory pathology.

On physical examination purulent postnasal drip was observed and fine crackles were detected by auscultation of the lungs, no respiratory distress. Patient was given oral amoxicillin/clavulanic acid, inhaled short action beta-agonist, and inhaled corticosteroid. Also was given ferrous sulfate for a 10.4 hemoglobin. Due the severity and frequency of respiratory infections an immunological screening evaluation was indicated.

A few weeks later the patient return to his control with 4 days history of fever of 39°C (102.2 F), cough and ear pain. On physical examination, purulent postnasal drip and bilateral purulent otorrhea was observe on pharynx and ear examination. Bilateral rales were detected by auscultation of the lungs. So, the patient was admitted to the hospital in order to start intravenous antibiotically treatment. Laboratory tests were as follows: hemoglobin: 10.5 gr/dl, hematocrit: 31.8 %, White blood cells: 21,270 cells/µL (neutrophils: 10.9%, lymphocytes: 69.4%), platelets: 572,000.

Patient´s grandmother brings the immunological screening evaluation, reporting a severe hypogammaglobulinemia. Results are presented in table 1.

Immunological screening test	Results	Reference range
Total IgA	0.0 mg/dl	70 - 400 mg/dl
Total IgM	15 mg/dl	40 - 230 mg/dl
Total IgG	3.0 mg/dl	700 - 1600 mg/dl
Total IgE	0.1 UI/ml	Up to 60 UI/ml
CH50	46 U/ml	31 - 60 U/ml

Table 1: *Patient´s immunological screening test results.*

Under the suspicion of a congenital hypogammaglobulinemia and in order to refine the diagnosis, a flow cytometry was indicated. Results are reported in table 2.

Flow cytometry	Results	Reference Range
Total lymphocytes	15,263 cells/µL	4000 - 10,500 cells/µL
Total LTCD3+	13797 cell/µL	
% LTCD3+	90%	54 - 76%
Total LTCD4+	5911 cell/µL	
% LTCD4+	39%	36 - 55%
Total LTCD8+	7715 cell/µL	
% LTCD8+	51%	12 - 24%
Total LCD16+56+	1173 cell/µL	
% LCD16+56+ (Natural killer)	8%	3 - 14%
Total LBCD19+	< 20 cell/µL	
% LBCD19+	0%	17 - 36%

Table 2: *Patient´s flow cytometry results.*

The screening immunological evaluation shows a patient with a persistent lymphocytosis, anemia and thrombocytosis. Likewise, we found a severe hypogammaglobulinemia. Complement function is normal. The flow cytometry shows absence of B cells with a LT and NK normal function.

The patient was diagnosed as a congenital hypogammaglobulinemia, specifically as a X linked agammaglobulinemia (AGX) and referred to a third level health care center in order to finish the evaluations and start prompt treatment with parenteral immunoglobulin.

Discussion

Primary immunodeficiency diseases (PIDs) are a heterogenous group of monogenetic disorders of the immune system, resulting in recurrent and/or severe infections, autoimmunity, autoinflammation, or malignancies [7].

PIDs generally are considered rare, but recent studies have shown that they are more common that previously been estimated, affecting 1 - 2% of the population [8].

Campaigns have been created by different foundations and medical associations around the world to increase awareness regarding the diagnosis of primary immunodeficiency diseases, in order to establish a rapid diagnosis and a prompt treatment, diminishing the complications risk and the mortality rate.

Criteria have also been developed by the Jeffrey Modell Foundation (JMF) for warning signs, both in children and adults, that the immune system may be faulty (Table 3). The criteria are important reminders of signs that may indicate defects in the patient's immune system.

Pediatrics	Adults
• Four or more new ear infections within 1 year	• Two or more new ear infections within 1 year
• Two or more serious sinus infections within 1 year	• Two or more new sinus infections within 1 year, in the absence of allergy
• Two or more months on antibiotics with little effect	• One pneumonia per year for more than 1 year
• Two or more pneumonias within 1 year	• Chronic diarrhea with weight loss
• Failure of an infant to gain weight or grow normally	• Recurrent viral infections (colds, herpes, warts, condyloma)
• Recurrent deep skin or organ abscesses	• Recurrent need for intravenous antibiotics to clear infections
• Persistent thrush in mouth or fungal infection on skin	• Recurrent, deep abscesses of the skin or internal organs
• Need for intravenous antibiotics to clear infections	• Persistent thrush or fungal infection on skin or elsewhere
• Two or more deep-seated infections including septicemia	• Infection with normally harmless tuberculosis-like bacteria
• A family history of PID	• A family history of PID

Table 3: *Warning signs of primary immunodeficiency disease.*

Table adapted and modify from [9].

The patient presented 5 warning criteria at the time of his first consultation, criteria was enough to create an IDP suspicion. Under the probability of having a patient suffering a PID, guidelines indicated start with a basic immune screening evaluation that includes complete blood count with differential, serum immunoglobulin levels (IgA, IgG, IgM and IgE) and total complement hemolytic activity.

The more recently available genetic investigation is a definitive tool for diagnosing PIDs; however, DNA analysis takes time and is expensive. Flow cytometry may serve as a bridge between conventional immunological testing and DNA sequencing, offering rapid and accurate results based on single cell analysis [10].

Flow cytometry is a routinely available laboratory method to study cells in suspension, including peripheral blood, bone marrow, cerebrospinal fluid, and other body fluids or tissue suspensions. The clinical application of flow cytometry evolved as a tool for enumeration of CD4+ T cells in the blood of patients with HIV infection and to characterize hematologic malignancies. More recently, the role of flow cytometry has broadened to include the study of disorders of the immune system, including PID [11].

Patient flow cytometry evaluation indicated absence of circulating B cells associated with a severe reduction of all serum immunoglobulins. The sum of laboratory findings helps us to confirm our PID suspicion, more specific an XLA.

XLA accounts for 85% of cases of congenital agammaglobulinemia. As described before XLA patients presents recurrent sinopulmonary infections associated to encapsulated bacteria (*S. pneumoniae* and *H. influenzae*), as well as gastrointestinal infections by *Giardia lamblia*. T-lymphocyte function is normally maintained, and they can eliminate fungi and most viruses competently [12].

XLA treatment is based in the use of intravenous or subcutaneous immunoglobulins (IVIG or SCIG) and antibiotics to clear infections. Despite advances in immunoglobulin therapy, there remain obstacles. Commercial products contain virtually no IgA or IgM, important immunoglobulins that play a major role in protecting the mucosal surfaces. Without adequate replacement of these isotypes, the patients continue to experience frequent mucosal infections, increasing the risk of serious complications such as bronchiectasis and chronic rhinosinusitis. In the Italian cohort of 73 XLA patients, Plebani., *et al.* reported 37 episodes of pneumonia requiring hospital admission over a median follow-up of 7 years [13]. Winkelstein., *et al.* in the US cohort of 201 XLA patients reported frequent rates of otitis, sinusitis and pneumonia [14].

Mortality rates are drop approximately to 1% vs historical reports of 17 - 25%, as a result of more timely diagnoses and prompt treatment [15].

Conclusions

Clinicians need to keep PIDs in mind as part of differential diagnosis in children with recurrent respiratory infections, particularly associated to severe presentations, failure to thrive and persistent diarrhea.

XLA is characterized by the absence of circulating B cells and severe reduction of all serum immunoglobulins due to mutations in the BTK gene. Prompt detection of these patients allows an early treatment with IVIG or SCIG, diminishing complications and the rate of infections and mortality.

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