Predominantly antibody deficiency: case report

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Abstract

Objectives: present a case of Inborn errors of immunity (IEI) as a potential diagnosis in pediatric patients with recurrent infections.

Description: male patient, 13 years old, since he was eight months old had recurrent diarrhea, sinusitis, otitis, abscesses and urinary tract infections. At the age of ten, he presented mastoiditis progressing to meningitis, he was admitted to a tertiary hospital, where an immunological evaluation was performed, which led to the diagnosis of Predominantly Antibody Deficiency (PAD), with suspected X-linked Agammaglobulinemia (XLA). Treatment was initiated with administration of intravenous gamma globulin 400 mg/kg every four weeks, with a significant improvement of the condition.

Discussion: usually, the diagnosis of XLA tends to be made in the first three years of life. However, in this report, although the first manifestations started at eight months of age, there was a delay of ten years before starting the treatment. In fact, the diagnosis of children and adults with IEI can be delayed if healthcare professionals are unable to find the true cause of recurrent infections. Therefore, the relevance of considering such pathologies in the presence of risk signs is highlighted, as early diagnosis being essential in treating and preventing morbidities.

Key words *Primary immunodeficiency diseases, Immunity, Infections*

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Introduction

Inborn errors of immunity (IEI) constitute of a group with more than 430 diseases that can cause various manifestations in the immune system functions. Among this universe of disorders that constitute of IEI, predominantly antibody deficiencies (PAD) and immunodeficiency combined are the most frequent, and male individuals with family consanguinity are more affected. These pathologies result in genetic defects, and their expression usually occurs at childhood, through repeated infections, such as otitis, sinusitis, stomatitis, and pneumonia. Early diagnosis is essential to institute treatment, as well as to define the best management for the IEI type, thus preventing the morbidity that is linked to the condition.[1-3]

X-linked agammaglobulinemia (XLA) is a classification of IEI in which antibody deficiency is predominant. XLA consists of absent or decreased B lymphocytes and immunoglobulins. Affected individuals are susceptible to bacterial infections by encapsulated agents and to enteroviruses. In 85% of the cases, its origin is linked to an error on the X chromosome, generating defects in the Bruton tyrosine kinase (BTK) gene, and for this reason it is called X-linked agammaglobulinemia. The error in this gene causes reduced or absent serum levels of IgM, IgG, IgA, IgE and B lymphocytes, as well as reduced size of the tonsils, spleen, adenoids and Peyer's patches. This is because BTK is expressed on all hematopoietic cell lines, with the exception of the T cells and plasma cells.[4]

In the physical examination of patients with XLA and some IEI, it is common for the tonsils and cervical lymph nodes to be small or even absent.[1] In addition, because of recurrent otitis, otoscopy often shows lesions or perforations of the tympanic membranes. As a result of upper and lower airway infections, complaints of chronic cough and purulent secretion are frequent. Crepitant lung rales are recurrent during pulmonary auscultation.

Description

A 13-year-old mixed colored skin male patient from the city of Patos, Paraíba. At eight months of age, he started with a severe diarrhea, requiring hospitalization, and since then he has had recurrent diarrhea. In the first year of life he started to present sinusitis, which became recurrent. At the age of two and three, he developed an abscess on the abdominal wall and a facial abscess, requiring hospitalization. At seven, he was hospitalized for hematuria and urinary tract infection. After that, he was stricken with otitis, whose cultures were positive for *Candida* sp. and *Staphylococcus aureus*, with an interval of five months between the situation presented.

At the age of ten, he presented mastoiditis evolving into meningitis, and was admitted to the University Hospital in the state capital, and the immunological evaluation was extended and the results of which are described in Table 1. The exams showed decreased immunoglobulins, absence of B lymphocytes, normal T lymphocytes, and NK cells with reduced levels, which led to the syndromic diagnosis of predominantly antibody deficiency (PAD), and administration of intravenous gamma globulin (IVG) of 400 mg/kg was initiated every four weeks. As mentioned above, B lymphocytes, antibody-producing cells, are absent or reduced in the presence of this syndrome, while T lymphocytes, in general, do not alterate, because they are part of the cellular immunity.

Thereafter, there was a significant improvement in the clinical and laboratorial findings, as shown in Tables 1 and 2. After initating continuous treatment with a monthly of IVG replacement, the patient presented only one episode of urinary tract infection, and the urine culture showed Escherichia coli, using ceftriaxone 30 mg/kg at home treatment. From the first manifestation of immunodeficiency until the appropriate diagnosis, ten years had passed.During this time, the patient missed one year of school due to school absences, which may also be related to the moderate degree of mixed hearing loss in the right ear, revealed by the audiological evaluation.

Thinking about other causes of immunodeficiencies, a serological test for Human Immunodeficiency Virus (HIV) was requested, the result of which was "non-reactive". For etiological confirmation of the PAD, a genetic test was requested, which confirmed the main hypothesis of X-linked agammaglobulinemia, detected by sequencing of the BTK exome in hemizygosis.

As for personal history, the mother reported prenatal care, and the patient was born at 40 weeks of gestational age and weighed 3,435 kg. The fall of the umbilical stump occurred on the eighth day. He received all the vaccines from the *Programa Nacional de Imunização* (National Immunization Program) and no adverse reaction was reported. Exclusive breastfeeding lasted until three months of age.

As for autoimmune and allergic diseases and other comorbidities, only vitiligo was reported. He was hospitalized seven times in all, with a maximum of 22 days in one hospitalization. Intensive care was required during hospitalization for meningitis.

There is no consanguinity in the family history, however the death of his mother's brother at the age of 16 from recurrent infections contributed to the diagnosis.

Table 1

Parameter dosages for immunological evaluation performed before and after initiation of intravenous gamma globulin therapy (IVG)

Parameters	Results					Reference values
	6 months before initiating IVG	5 months before initiating IVG	1 week before initiating IVG	3 months after initiating IVG	1 year after initiating IVG	
IgG	70 mg/dL	70 mg/dL	<0.01 mg/dL	752 mg/dL	1,156 mg/dL	540 – 1,822 mg/dL
IgM	15 mg/dL	8 mg/dL	2.97 mg/dL	8 mg/dL	1.97 mg/dL	41 - 183 mg/dL
IgA	15 mg/dL	19 mg/dL	0.25 mg/dL	15 mg/dL	1.22 mg/dL	40 - 350 mg/dL
IgE (K/UL)	-	< 2 K/UL	-	-	25 K/UL	< 140 KU/L
NK Cells CD56/CD16	-	-	-	-	2.6%	4.2% - 16.1%
	-	-	-	-	84/mm³	116-443/mm³
IgG for Rubella	-	-	< 5.0 IU/mL	-	-	NR < 5.0 IU/mL
IgG for Measles	-	-	< 5.0 U/mL	-	-	NR < 5.0 U/mL
B lymphocytes CD19	-	-	0%	-	-	9.5 – 20.3%
	-	-	0.00/mm3	-	-	234 - 952/mm³
CD3 T lymphocytes	-	-	94%	-	-	41.1-77.4%
	-	-	4,232/mm³	-	-	1,240 – 2,619/mm³
CD4 T lymphocytes	-	-	42%	-	-	28.5 - 46%
	-	-	1,880/mm³	-	-	566.4-1292.5/mm³
CD8 T lymphocytes	-	-	47%	-	-	17.1 – 32.3%
	-	-	2,101/mm³	-	-	390-1,024/mm³
CD4/CD8 ratio	-	-	0.90%	-	-	0.3 – 3.5%

NR =- Non Reactive; IVG = Intravenous Gamma globulin.

Table 2

Blood counts performed before and after initiation of intravenous gamma globulin (IVG) therapy.

Parameters	Results		Reference Values
	1 week before initiating IVG	3 months after initiating IVG	
Red Blood Cells	4.94 millions /mm³	5.20 millions /mm³	4.1 – 5.5 millions /mm³
Hematocrit	35,7%	40%	36 - 48%
Total leukocytes	16,900 /mm³	9,400 /mm³	3,600 – 11,500 /mm³
Neutrophils	67%	21%	30 - 60%
	11,323/mm³	3,660 /mm³	1,500 – 7,200/mm³
Lymphocytes	23%	27%	30 - 60%
	3,887/mm³	4,606 /mm³	1,200 – 6,000/mm³
Eosinophils	0%	0%	1 - 5%
Platelets	371,000 /mm³	244,000 /mm³	150,000 – 450,000/mm³

Discussion

As mentioned above, the clinical manifestations of IEI begin during childhood, although in some cases they may occur after the second or third decade of life. The mentioned patient presented his first manifestations quite early, at eight months of age. In general, the diagnosis of congenital agammaglobulinemia (CA) tends to be made most commonly in the first three years of life.[5] However, in this report, the boy went through a debilitating ten-year path to a suspicious diagnosis. Indeed, the diagnosis of children and adults with IEI can be delayed if health care professionals cannot find the true cause of the recurrent infections. This has been reported in other cases in the literature.[5,6]

The spectrum of infections in IEI is one of the main factors for the suspicion of the diagnosis in children during their early years of life, as well as being a parameter for

follow-up during the treatment.[4] In this sense, the male patient may have the diagnostic hypothesis for XLA considering when there are recurrent infections during early childhood, a pathological family history positive for PADs, the occurrence of hospitalization before the age of five, and vaccine reaction, especially after vaccination with live attenuated virus. The patient had all these conditions, except for the vaccine reactions. The *Sociedade Brasileira de Imunizações* (SBIm) (Brazilian Society of Immunizations) has available in its arsenal for children from zero to five years of age the following live attenuated virus vaccines: Oral Poliomyelitis, Monovalent Rotavirus, Pentavalent Rotavirus, Yellow Fever, MMR (measles, mumps, and rubella), Varicella, and Dengue.[7] These vaccines should be avoided in patients with suspected or diagnosed for XLA.

The laboratorial tests performed to initiate the investigation of CA aimed to confirm the existence of the immunological defect, thus, they must contain blood count, dosage of immunoglobulins (IgM, IgG, IgA and IgE) and titling of antibodies generated in response to the vaccines belonging to the vaccination framework in force. The second stage of testing should contain a cytometry flow in order to phenotype and count the lymphocytes.In the present case, after immunological evaluation, a reduction in serum levels of immunoglobulins and B lymphocytes was noted, as well as the absence of antibodies against rubella and measles, and the presence of normal serum levels of T-lymphocytes. Moreover, the confirmation of the diagnosis can be made by genetic testing that confirms variants in the BTK gene, or, if genetic testing is not available, a confirmed family history of XLA.[4] Since it was not possible to confirm the family history, a genetic test should be requested, which identifies, the hemizygosis, in the BTK gene, the variant ChrX:101.356.055 G>T, promoting the substitution of the aspartate amino acid in codon 521 by glutamate (p.Asp521Glu).Based on this confirmation of X-linked agammaglobulinemia, the patient was classified according to the International Classification of Diseases (ICD-10) as D80.0.

Aspartate at position 521 is highly conserved in diverse biological species, and "in silico" pathogenicity prediction computer programs suggest that its replacement by glutamate is potentially deleterious. Approximately this variant is absent among 181,000 X chromosomes in population-based individuals and has been previously described in the medical literature in association with the agammaglobulinemia condition.[8,9] It is worth noting that genetic testing is not essential to initiate the treatment in being suspected of IEI. In the present case, such a test was performed only about two years after initiating therapy.

From the syndromic diagnosis of PADs, several etiologies can be considered. Among patients with circulating B cells below 2% of the total of lymphocytes and with undetectable or very low antibody levels, about 85 to 90% have XLA, due to mutations in the BTK gene, and 5% of them have immunoglobulin M heavy chain deficiency, a condition whose clinical manifestations are more severe compared to XLA. Patients in this case are at greater risk for pseudomonas sepsis, arthritis, skin abscesses, chronic diarrhea, and enteroviral infections in the central nervous system (CNS).[10,11]

In the common variable immunodeficiency (CVID), there is reduced serum levels of at least two immunoglobulin isotypes, associated with normal or reduced amounts of B cells. It is usually diagnosed between the third and the fifth decade of life, and when it begins in childhood, it is usually associated with medium otitis, growth deficit, and developmental delay.[10]

Treatment for IEI depends on the disease diagnosed and can be definitive or supportive. The therapeutic options are still under study and aim to prevent and treat infections, stimulating the immune system, and treating the cause of immunodeficiency. Given the diagnostic hypothesis, human immunoglobulin replacement is the main therapeutic method in patients with IEI in almost 75% of this disease group.[12] Administration can be done intravenously (IVG) or subcutaneously (SCIg), but in urgent cases, IVG is the route used. Intravenous immunoglobulin replacement has a dosage range from 400 mg/kg/dose to 800 mg/kg/dose by administrating every 21 to 28 days. The dose and interval can be adjusted to decrease the incidence of infection. For subcutaneous replacement, it is recommended that therapy should be initiated using 100 to 200 mg/kg/dose every seven days.[12,13] Immunoglobulin treatment should be continuous.

After initiation of immunoglobulin therapy, it is expected that severe infections, such as sepsis, meningitis, and cellulitis would be reduced; however, it is common for patients to continue to have chronic and/or less severe infections, such as sinusitis, urinary tract infections, and otitis.[2] Since the suspected diagnosis of XLA, the mentioned patient initiated immunoglobulin replacement with intravenous administration of IgG every four weeks, achieving considerable improvement of the symptoms.

Prophylaxis antibiotic is another therapeutic method that aims to reduce the risk of complications and is patient-specific.In the case in question, it has not been necessary to use this resource so far.

An alternative therapy for IEI is hematopoietic stem cell transplantation (HSCT), known as bone marrow transplant, which consists of replacing altered cells

with hematopoietic stem cells from healthy donors.It is a curative treatment option for specific cases of IEI, but its indication should be individualized and should consider the risks of future disease progression versus the risks of transplantation, such as graft versus host disease.In general, HSCT is not indicated for patients with XLA.[14]Gene therapy, finally, constitutes a promising possibility of cure for patients with IEI, since it corrects the genetic alterations of the individual´s hematopoietic stem cells, restoring B-lymphocyte function, without the need to wait for compatible donors and with less risk of rejection.[14]

Based on the discussion of this case report, it can be stated that the diagnosis of IEI is still a challenge for health professionals, as many cases take years to receive the appropriate treatment. Therefore, it is recommended that future research study the main factors that prevent the early diagnosis of such diseases.Concomitantly, it is of fundamental importance that health education work be carried out in this sense, in order to train more and more professionals and, consequently, avoid complications resulting from the disease, reduce hospitalizations and health expenses, as well as promote a better quality of life for affected individuals.

Author´s contribution

Morais LJ: study design, data collection and analysis, manuscript writing and revision;

Silva BBM: data collection and analysis, manuscript writing;

Brito LAC, Lemos LAP, Lustosa MSL, Carneiro RRD and Aragão TG: data collection, manuscript writing;

Lima RCPC: study design, data analysis, manuscript revision;

Nóbrega VM: study design and supervision, data analysis, manuscript revision.

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