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ORIGINAL ARTICLE

Selective deficiency of IgA: case series

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Abstract

Introduction: Selective IgA deficiency is the most common primary immunodeficiency, with a prevalence of 1/600 in Caucasians. Although most affected individuals are asymptomatic, symptomatic patients may present with recurrent infections, allergic diseases, autoimmune diseases and neoplasias. **Objective:** To report a case series of patients with IgA deficiency. Methods: Revision of medical records of children and adolescents with confirmed diagnosis of selective IgA deficiency, attended at the Reference center for asthma, at a pediatric hospital in Rio de Janeiro, during the last 3 years. **Results:** Four patients with selective IgA deficiency were evaluated. The mean age was 12 years, with two males. All had rhinitis/asthma. In addition to positive family history for atopy, high total IgE, peripheral blood eosinophilia, with serum levels of IgA <7mg/dL, normal IgG and IgM, and EPF negative. No patient had autoimmune diseases, neoplasms, family immunodeficiency history or consanguinity between parents. Two patients reported a history of autoimmune diseases, one of neoplasia in the family. Recurrent infections were found in two patients. At the moment, all are in use of nasal corticosteroid, one patient using oral inhaled corticosteroid and one, using bronchodilator associated with oral inhaled corticosteroid with control of respiratory and infectious symptoms. **Conclusion:** Although the evolution of IgA deficiency is benign, patients should be regularly followed for recurrent and allergic infectious conditions as observed in the patients studied.

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INTRODUCTION

Primary immunodeficiencies (PIDs) are a result of genetically determined abnormalities of the immune system, which primarily lead to an increased incidence of infections. Primary antibody deficiency is the most common PID, with a broad spectrum of clinical features ranging from asymptomatic conditions to severe recurrent infections[1]. Selective immunoglobulin A (IgA) deficiency is the most frequently observed PID, with a prevalence of 1:143 to 1:18,500 (in Caucasians, 1:600)[2] and a prevalence of 1:200 in patients with severe allergic conditions. IgA is important in mucosal immunity[3].

In individuals older than 4 years, definitive diagnosis can be made in the presence of serum levels of IgA < 7 mg/dL and normal serum immunoglobulin G (IgG) and immunoglobulin M (IgM) concentrations when other causes of hypogammaglobulinemia are excluded and there is an intact T-cell function[4,5].

In patients older than 4 years, partial IgA deficiency is defined when serum concentrations are below two standard deviations from the normal concentration for their age[6-8].

OBJECTIVE

This study aimed to report a series of cases of patients with IgA deficiency.

METHODS

In this case series, children and adolescents who were patients of an asthma reference center in Rio de Janeiro from June 2013 to August 2016 were included.

For all patients with severe respiratory conditions, recurrent infections, or both, the levels of two or more serum immunoglobulins were tested. The records of the patients diagnosed with selective primary IgA deficiency were retrospectively analyzed. Because this is a reference center for asthma, more severe patients have their immunoglobulin levels (IgA, IgM, IgG, and total IgE) routinely measured.

Exclusion criteria:

Ø Other PIDs

Ø Secondary causes of IgA deficiency (use of medications, viral infections, systemic diseases, and malignancies).

The diagnosis was made by allergists and immunologists of the asthma reference center.

The data evaluated included the following:

- Age/sex
- Personal and family history of atopy, autoimmunity, and neoplasms
- Family history of PIDs and consanguinity among parents
- Recurrent infections
- Eosinophilia (eosinophil levels > 4%) in peripheral blood, total serum IgE, sensitization to domestic mites, and parasitological stool analysis

RESULTS

Four patients with selective IgA deficiency were evaluated. Their mean age was 12 years (mean age at diagnosis: 10 years), and two patients were male. All had moderate/severe persistent allergic rhinitis and controlled asthma, with high sensitization (> 3.5 kU/L; reference value: < 0.10 kU/L) toward three species of domestic mites (*Dermatophagoides pteronyssinus*, *D. farinae*, and *Blomia tropicalis*). They also had a family history of atopy, high total IgE level, peripheral blood eosinophilia, serum IgA level < 7 mg/dL, normal IgG and IgM levels, and negative stool parasitology. None presented autoimmune diseases, neoplasms, family history of immunodeficiency, or parental consanguinity. Two patients had a family history of autoimmune diseases (diabetes mellitus and Hashimoto's thyroiditis), and one of neoplasia. Recurrent infections were found in two patients. In particular, one patient had four episodes of sinusitis and four of pneumonia, requiring hospitalization in one episode, and one episode of acute otitis media; another patient presented three episodes of sinusitis and two of pneumonia in the same year. Gastrointestinal tract infection was not reported in any patient. Further, two patients presented severe asthma. At present, all patients are using nasal corticosteroids (50 µg budesonide, one jet every 12 h); one patient is using an oral, inhaled corticosteroid (200 µg budesonide every 12 h); and another patient is using a bronchodilator associated with an oral, inhaled corticosteroid (6 µg formoterol /200 µg budesonide every 12 h) to control respiratory and infectious symptoms.

DISCUSSION

In the present study, sex distribution was found to be equal, but Weber-Mzell described a higher frequency of males (1:359 vs. 1:2,264)[3].

A table presenting normal levels of immunoglobulins (A, G, and M) and subclasses of IgG (mg/dL) for the Brazilian population according to the age range, created by Maria Fujimura and Aparecida Nagao Dias, can be found online (www.imunopediatria.org.br; in Portuguese). It is important to note that laboratories often present results in values different from those of the mentioned table, which can lead to incorrect diagnosis.

The literature indicates that most patients with IgA deficiency are asymptomatic (60%). In symptomatic patients, the most common manifestations include mild sinopulmonary infections (12%), allergy (15%–20%), autoimmunity (11%), and

association with different serious complications (2%), such as progression to common variable immunodeficiency[4].

The allergic diseases most commonly associated with IgA deficiency are allergic rhinoconjunctivitis, hives, atopic dermatitis, and asthma[2]. In this study, all patients presented respiratory allergy (rhinitis/asthma), with no other allergic manifestations; two patients had severe asthma. In all patients, laboratory examination revealed high serum total IgE levels, peripheral eosinophilia, and sensitization to domestic mites; this finding is probably justified by the fact that the patients belonged to a specialized center. In a study by Ayteki et al., 37.3% of the patients presented elevated serum IgE levels, and 70.5% had allergic diseases[2].

The literature indicates infection to be the most common clinical manifestation, followed by allergy and autoimmunity[2,4]. Sinopulmonary infections were observed in two patients (50%) and were the most common presentation of infections, which is consistent with those reported in the literature[1]. Autoimmunity, neoplasms, and severe complications were not observed in the present patients. Two patients presented two immunodeficiency warning signs (two or more incidences of pneumonia in the previous year and severe asthma). Pediatricians should be aware of the 10 warning signs of immunodeficiencies for diagnostic suspicion.

In 1996, the Jeffrey Modell Foundation (United States) created a list of warning signs that aid in the recognition of probable PIDs. These signs were adapted to the Brazilian context; the presence of more than one sign indicates the need for investigating PIDs.

The 10 warning signs of primary immunodeficiency in children:

1. Two or more incidences of pneumonia within 1 year.
2. Four or more new ear infections within 1 year.
3. Recurrent stomatitis or oral candidiasis for more than 2 months.
4. Recurrent abscesses or ecthyma.
5. One episode of severe systemic infection (meningitis, osteoarthritis, or septicemia).
6. Recurrent intestinal infections/chronic diarrhea/giardiasis.
7. Severe asthma, collagen disease, or autoimmune disease.
8. Adverse reaction to BCG and/or *Mycobacterium* infection.
9. Clinical phenotype suggestive of a syndrome associated with immunodeficiency.
10. Family history of immunodeficiency.

All patients had negative stool parasitology and no history of gastrointestinal tract infection. Patients with IgA deficiency present a higher frequency of gastrointestinal infections. The best known association is *Giardia lamblia* infection[3,5]; this is owing to the fact that IgA deficiency weakens the gastrointestinal protective barrier, which subsequently allows adherence of protozoans such as *G. lamblia* to the epithelium and proliferation, causing infection. These patients also present a higher frequency of gastrointestinal diseases such as malabsorption, lactose intolerance, lymphoid nodular hyperplasia, celiac disease, and inflammatory bowel disease[2,3]; these conditions were not observed in the present patients.

The most commonly observed autoimmune diseases include autoimmune thyroiditis, idiopathic thrombocytopenic purpura, hemolytic anemia, juvenile idiopathic arthritis, systemic lupus erythematosus, celiac disease, and diabetes mellitus. Several patients with selective IgA deficiency present autoantibodies even in the absence of the disease[2,6].

In the present study, there were no cases of parental consanguinity or family history of PIDs, which if present could suggest genetically determined abnormalities.

One case had a family history for neoplasms and two cases for autoimmunity. The literature indicates a higher frequency of autoimmunity and neoplasms in individuals with IgA deficiency and in their relatives[4,6,7].

At present, the respiratory and infectious symptoms of the present patients are controlled with medication.

A specific treatment with IgA replacement is not available as yet. In some patients with persistent respiratory tract infections, prophylactic antibiotic therapy may be necessary. Administration of intravenous gamma globulin at low IgA concentrations may be recommended to patients with deficient IgG subclasses or proven deficient humoral response[3].

Although rare, it is important to note that after transfusion of blood products (with high IgA antibody titers), serious and fatal reactions can occur because a significant proportion of patients with IgA deficiency present anti-serum IgA antibodies[3].

CONCLUSION

Although the evolution of IgA deficiency is generally benign and asymptomatic, patients should be regularly monitored because they may present severe recurrent infections and allergic conditions, as observed in the present study. Pediatricians should be aware of the 10 warning signs for PIDs to suspect the diagnosis and should refer these patients to an allergy and immunology specialist at a reference center.

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