Persistent Multi-Trigger Wheezing Expression of an Underlying IgA Deficiency

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Abstract

We report a child with a history of upper and lower respiratory tract infections and recurrent episodes of wheezing. The skin prick test, performed at 36 months of age, was positive for pollen. Three months before admission, the frequency of these episodes increased. The laboratory findings were normal except for immunoglobulin dosage for the following values: IgA < 5 mg/dl. Diagnosis of selective IgA deficiency was made. Symptoms, which are particularly persistent or which do not respond to treatment, could be sign not only of asthma but also of other disorders. Therefore, coexisting conditions should be evaluated whenever symptoms seem to be unusually severe or frequent.

Keywords: Asthma; Coexisting Disease; IgA Deficiency; Persistent Wheezing

Abbreviations: IgAD: Selective IgA Deficiency; ERS: The European Respiratory Society; FBA: Foreign Body Aspiration; PID: Primary Immunodeficiency

Background

Wheezing is frequent in preschool aged children, and it is a major symptom of asthma. Guidelines for the definition, assessment, and management of wheezing disorders at this age, classifying wheezing disorders on the basis of the patient’s temporal symptom pattern, were issued by the European Respiratory Society (ERS) [1]. Episodic wheeze occurs in discrete episodes, usually with no wheeze between episodes. Multiple-trigger wheezing is caused by the exposure to several triggers, smoke and allergens being the most common ones, with symptoms being present between the acute exacerbations [2]. However, wheezing may be present in other diseases, such as immunodeficiency, Foreign Body Aspiration (FBA), congenital vascular abnormalities bronchopulmonary dysplasia, cystic fibrosis, tumor, or malignancy.

IgA Deficiency (IgAD) is the most common primary antibody deficiency. Although many affected individuals have no apparent symptom, selected patients suffer from recurrent mucosal infections, asthma, allergies, and autoimmune diseases. Therefore, cases with persistent wheezing and particularly resistant symptoms, could be expression of several disease and they should be deeply evaluated in order to exclude coexisting diseases. We describe the case of a child with a history of recurrent upper and lower respiratory tract infections and asthma, experiencing increasingly frequent wheezing episodes, with a persistence of symptoms between acute episodes. The child was diagnosed with selective IgAD.

Case Presentation

A 56 months old white female was referred to us because of persistent cough and wheezing. She was born at 35 weeks of gestational age, with a birth weight of 2500 g. Pregnancy and delivery were uneventful. The mother had a history of asthma. Since the age of 2 years, the girl presented recurrent bilateral otitis media and repeated courses of oral antibiotics were executed. Eight months before admission the child experienced recurrent wheezing and cough, which was treated with bronchodilators, oral corticosteroids and antibiotics by her pediatrician. Symptoms were present between the acute exacerbations. The skin prick test, performed at 36 months of age, revealed a sensitivity to pollen. Three months before admission, the frequency of these episodes increased. On the basis of the increased frequency of wheezing episodes with incomplete healing, the child was referred to our pediatric clinic. On physical examination, pulmonary auscultation revealed crackles and wheezing in the right hemi-thorax. Oxygen saturation was 95-97% on room air.

Therefore, a chest radiography was performed. The results revealed an area of consolidation of the right lung, interpreted
by the radiologist as a pneumonia. On the basis of the clinical, anamnestic and radiological findings, the patient was admitted to our department. The initial working diagnosis was asthma in a child with recurrent upper and lower respiratory tract infections. Therefore, we started antibiotic therapy in association with bronchodilator treatment and the objectivity of lung improved during the following days. Considering the frequency of wheezing exacerbations often associated with respiratory infections, we decided to study her immunity. The laboratory findings were normal except for immunoglobulin dosage for the following values: IgA < 5 mg/dl (range 37-257 mg/dl). Diagnosis of selective IgAD was made. In the following months, the child started inhaled corticosteroid therapy. No episodes of wheezing have been reported. To date, the child performs serial controls at our center at least twice a year (Table 1).

Table 1: Clinical characteristics of the patient.

| Patient |   |
|---------|---|
| Age (months) | 56 |
| Sex | Female |
| Age of onset of infection | 2 |
| Type of infections | Otitis media + Pneumonia + |
| Associated disease | Allergy + |
| Serum IgA levels (mg/dl) | < 5 (range 37-257 mg/dl) |

Discussion

One third of all children aged 0 to 3 years have an episode of wheezing, and almost 60% of them stop wheezing by the age of 6 years. It is estimated that 50% of 6-year-old children have had at least 1 episode of wheezing [3].

Brand and colleagues described wheezing in terms of its temporal pattern as episodic (viral) or multiple-trigger wheezing [1]. In our case, the child’s history led to a diagnosis of multi-trigger wheezing, with symptoms between the acute episodes. Several factors could be predictors of persistent wheezing and/or asthma after preschool age. Maternal asthma, prematurity and low birth weight, early allergic sensitization, which were present in our child, seemed to play an important role in persistent asthma [4-6]. Therefore, the clinical persistence and worsening could be interpreted as a sign of the underlying persistent wheezing disorder. In this perspective the persistence of symptoms and the lack of response to treatment must lead to further investigations to exclude the presence of coexisting diseases [1].

Others diseases, such as immunodeficiency, FBA, cystic fibrosis, bronchopulmonary dysplasia, congenital vascular abnormalities, tumor, or malignancy can cause wheezing disorders. The child was diagnosed with selective IgAD. IgAD represents the most common Primary Immunodeficiency (PID). The incidence of IgAD varies from 1:143 to 1:18,500 depending on ethnic origin [7]. IgAD is defined as a serum IgA of less than 7 mg/dl, with normal serum IgG and IgM levels in patients older than 4 years with otherwise normal immune system [8]. IgA is the most abundantly produced isotype in humans. IgA and IgA receptors play a significant role in vivo in maintaining the integrity of immune responses in systemic and mucosal compartments [9]. However, the function of serum IgA in the systemic immune response has not been clearly understood. A fundamental defect in IgAD is the failure of IgA bearing B lymphocytes to mature into IgA secreting plasma cells, but the reason for this defect is unknown. Patients with IgAD have a wide range of clinical presentations, even though the vast majority of patients (85-90%) are asymptomatic.

Symptomatic patients with IgAD suffer from recurrent sinopulmonary infections, gastrointestinal infections and disorders, allergies, autoimmune conditions, and malignancies. The most symptomatic IgAD patients have recurrent respiratory tract infections. These infections are often caused by viral pathogen, while bacterial infections are relatively uncommon. Patients with IgAD have an increased frequency of gastrointestinal diseases including giardiasis, malabsorption, lactose intolerance, nodular lymphoid hyperplasia, celiac disease, and inflammatory bowel disease. Allergic disorders appear to be common in patients with IgAD, the most common being allergic rhino-conjunctivitis, urticaria, atopic dermatitis, and asthma, in particular among younger patients [10]. In subjects with IgAD and allergies asthma, as in our child, is often much more resistant to treatment, probably because of recurrent respiratory infections [11]. Autoimmune disorders are common among IgAD cases.

The main autoimmune disorders are autoimmune thyroiditis, Idiopathic Thrombocytopenic Purpura (ITP), hemolytic anemia, Juvenile Idiopathic Arthritis (JIA), systemic lupus erythematosus, Celiac Disease (CD), and Diabetes Mellitus (DM). The association of IgA deficiency and malignancies have been reported in sporadic cases, particularly at older ages. Those are usually of lymphoid and gastrointestinal origins. Our case confirms that nonresponding wheezing in preschool aged children is a particular condition, which may be related to a coexisting disease. Therefore, in cases with symptoms, which are particularly persistent or which do not respond to treatment, other suspected disorders should be confirmed or excluded by thorough investigations. In particular, in a child with wheezing and recurrent upper and lower respiratory tract infections, IgAD should be considered, both to better define the disorder, and to organize the appropriate follow up.

Competing Interests

All authors declare that they have no conflict of interest.
Authors’ Contributions

All authors read and approved the final manuscript.

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