Case Report
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Prototypic three pediatric cases of recurrent wheezing attacks associated with hypogammaglobulinemia

Abstract

Bronchiolitis and infantile asthma are the most frequent causes of typical wheezing symptoms during infancy. However, persistent wheezing symptoms resistant to β2 adrenergic-agonist and anti-cholinergic therapies should be considered for hypogammaglobulinemia. Hypogammaglobulinemia is defined when immunoglobulin isotypes are below the limit of the pre-determined set of reference ranges per age. Here, prototypic three cases of recurrent and persistent wheezing attacks during infancy associated with transient low IgG suggesting hypogammaglobulinemia diagnoses are described to raise the awareness of immunodeficiency among pediatricians. In pediatric patients with recurrent and/or persistent wheezing symptoms during infancy and beyond, especially resistant to therapy, hypogammaglobulinemia should be excluded from possible diagnoses. And if a child with hypogammaglobulinemia and experiencing life threatening infections, immunoglobulin administration should be thought.

Keywords: wheezing, hypogammaglobulinemia

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Abbreviations: THI, transient hypogammaglobulinemia of infancy; CVID, common variable immunodeficiency; IVIG, intravenous immunoglobulin; CBC, complete blood count; ESR, erythrocyte sedimentation rate

Introduction

Bronchiolitis and infantile asthma are the most frequent causes for typical wheezing symptoms in infants. Recurrent wheezing resistant to β2 adrenergic-agonist and anti-cholinergic therapies are usually investigated for hypogammaglobulinemia. In fact, recurrent viral infections including lower respiratory tract infections have been reported as associated to transient hypogammaglobulinemia of infancy (THI).[1–5] Yet, the main clinical feature in patients affected by infantile hypogammaglobulinemia remains recurrent infections. In fact, many studies THI is associated with history of recurrent wheezing consistent with diagnosis of asthma, allergic bronchitis and autoimmune disease.[5-8] Nevertheless, most of the infantile cases resolve before early childhood and achieve normal immunoglobulin levels by age of two until five without serious infections or other illness. Infantile hypogammaglobulinemia is diagnosed when immunoglobulin isotypes are below the limit of the pre-determined set of reference ranges per age. Therefore, our 3 patients described below can be accepted as hypogammaglobulinemic during infancy.[5] Hypogammaglobulinemia in early childhood is depicted among humoral immunodeficiencies, represented by a heterogeneous group of disorders in the immune system.[9]The condition can be congenital (due to a primary genetic deficiency), acquired (secondary to an underlying disease), or transient or physiological (due to an immature immune system). Physiologic hypogammaglobulinemia generally occurs between three to six months of age, a period during which maternal IgG decreases, and the infant's own synthesis remains underdeveloped.[9] THI is characterized by prolonged hypogammaglobulinemia, and this clinical picture resolves spontaneously by the second year of life; some may not resolve until subjects are four–five years old. Even some cases may develop into severe or chronic immunoglobulin deficiencies.[10,11] For instance; common variable immunodeficiency (CVID) patients have decreased serum IgG concentrations and usually manifest a decreased serum IgA and/or IgM concentrations with normal or low numbers of circulating B cells. Other conditions can also result in infantile hypogammaglobulinemia, such as IgG subclass deficiencies and excessive loss of serum immunoglobulins.[12,13]

Recurrent infections causing wheezing attacks are the most common reasons for morbidity and hospitalization in patients with hypogammaglobulinemia. Physicians often choose antibiotic prophylaxis or follow-up without any medication in therapy of these patients. Supportive therapy including antimicrobial therapy for specific (bacterial or viral) infections is generally sufficient for these kinds of hypogammaglobulinemic patients. So far, there are different opinions on the immunoglobulin replacement therapy as well.[14,15] The use of IVIG (intravenous immunoglobulin) as an alternative to antibiotic prophylaxis remains controversial also in symptomatic patients with THI. However, if a child with THI was to experience life-threatening infections, IVIG administration should be given right away.[16,17] IVIG may stop the vicious circle of infection-immunodeficiency (hypogammaglobulinemia) and should be thought as a first line therapy in highly symptomatic THI children. IVIG was also found to be more effective than antibiotics in treating viral infections associated with wheezing in infants by means of its antiviral antibody contents. IVIG significantly improves the prognosis and the quality of life of immunodeficient (hypogammaglobulinemic) patients and might routinely be used as substitutive therapy until the disorder resolves, if necessary.[14]

Here we report prototypic three cases of recurrent and persistent wheezing attacks during infancy associated with transient low IgG suggesting hypogammaglobulinemia diagnoses should be excluded.

Case 1

A twenty four month young girl was affected by respiratory tract infection with coughing and persistent wheezing. Anamnesis reported wheezing symptom and breathing difficulty for two months. Her symptoms persisted despite of therapy with antibiotics, nebulized salbutamol and budesonid therapy. Her medical history revealed previous nine wheezing attacks. In the family history, her father suffers asthma. Laboratory findings showed normal routine biochemistry, complete blood count (CBC) and sedimentation rate (ESR). Chest X-ray showed normal findings. Echocardiography was normal. The pH-metry for reflux investigation was normal. Sweat test was normal. In the serological evaluation: low immunoglobulin G (IgG) levels (358mg/dl) for her age was detected at two different times where IgM, IgA and IgE levels were normal. After diagnosis of hypogammaglobulinemia, IVIG was given to her at 500mg/kg/dose. Later, her symptoms did improve and not recur for the last 5months.

Case 2

An eight month young girl suffers coughing and wheezing. At two months of age, she had urinary and upper respiratory tract infections. Despite antibiotic therapy, wheezing persisted for 2 months and wheezing severity increased not responding to β2-adrenergic agonist therapy. Thereafter, hospitalization for seven days resolved symptoms. However, she came back to hospital due to recurrence of her symptoms in next 10 days. In her medical history, grandmother and her cousins had asthma. Physical examination revealed breathing difficulty. Although salbutamol, ipratropium, antibiotherapy (clarithromycin) and anti-reflux therapies were given, her symptoms did not improve for two weeks. At the 15th day of admission, she was given IVIG at 500mg/kg/dose. Later, her respiratory system symptoms did not recur for the last several months. Once she was evaluated for persistent wheezing attacks during admission, biochemistry, CBC, ESR tests were normal. Chest X-ray and echocardiography showed normal findings. In her serological evaluation: low IgG level for her age (279 and 304mg/dl) was detected at two different times. IgG subgroups, IgM, IgA and IgE levels were normal.

Case 3

A twenty months young boy was brought to us due to complaints of having frequent viral lower respiratory tract infections (bronchiolitis). He was experiencing recurrent wheezing attacks almost every week in the last six months. In past medical history, he was diagnosed with trisomy 21 and hypothyroidism at the 3 months of age. He went thru an operation for atrio-venticular septal defect. Physical examination revealed dyspnea, tachypnea and wheezing. Crackles were heard on the chest auscultation. Abdominal, cardio-vascular and the rest of the examination were normal. When he was evaluated for frequent wheezing attacks in our outpatient clinic, routine biochemistry, CBC and ESR were normal. Chest X-ray showed normal findings. In his serological evaluation: low IgG level for his age (256 and 300mg/dl) was detected twice. IgG subgroups, IgA, IgM and IgE levels were within normal. He was given IVIG at 400mg/kg/dose. For the last three months, he did not have any lower respiratory tract infection.

Conclusion

The awareness of immunodeficiency among pediatricians has been greatly improved. Recurrent respiratory tract infections are major infections in these patients. THI is a relatively common disorder among infantile hypogammaglobulinemia. In patients with recurrent and/or persistent wheezing symptoms during infancy and beyond, especially resistant to therapy, hypogammaglobulinemia should be excluded from possible diagnoses.

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Conflicts of interest

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