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ORIGINAL ARTICLE

Specific antibody deficiency with normal immunoglobulin concentration in children with recurrent respiratory infections

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Abstract
Background: Response to polysaccharide antigens is a test to evaluate the immunological competence of children with recurrent respiratory infections (RRI) of unknown cause and no other immune system abnormality. In order to detect specific antibody deficiency (SAD), a group of children with RRI without other immunodeficiency were prospectively studied.
Methods: We included 20 children (12 male), age range 3–14 years, with six or more annual episodes of respiratory infections (RI); one or more monthly episodes of RI during the winter months; or three or more annual episodes of lower RI. The children were immunised with 23-valent polysaccharide anti-pneumococcal vaccine, and ELISA was used to measure anti-polysaccharide IgG antibody levels for 10 pneumococcal serotypes at baseline (T0), and 45 days (T1) and one year post-immunisation (T2). Post-immunisation response above 1.3 μg/ml for more than 50% of the serotypes was considered normal for children 2–5 years, and for more than 70% of the serotypes in children older than 5 years.
Results: At T1 19/20 children showed a normal response for their age, and only one patient showed a deficient response, suggestive of classic moderate SAD. At T2, 8/20 patients showed deficient responses, suggestive of impaired persistence of specific antibodies. There was a noteworthy association between deficient response and asthma and allergic rhinitis.
Conclusions: We propose first ruling out local or systemic causes, then performing serum immunoglobulin IgM, IgG, IgA, IgE and IgG subclass levels, and finally measuring response to polysaccharide pneumococcal antigens for detection of SAD.

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Introduction

Recurrent childhood infections, especially respiratory tract infections, are a common cause of morbidity and medical visits.[1,2]

During the first years of life, the immune system remains immature, and some components of the innate and adaptative responses are deficient. In young children, serum immunoglobulin levels are low and local antibody and cellular immune responses are underdeveloped. Children under the age of two are incapable of producing anti-polysaccharide antibodies.[3,4]

Recurrent or persistent infections, as well as infections due to unusual or opportunistic pathogens, are sometimes a symptom of primary immunodeficiency (PID).[5] Most children with recurrent infections have a normal immune response. Therefore, it is an important clinical challenge to identify the children with recurrent infections who may have PID, as an early diagnosis leads to better treatment, improves prognosis, and allows the opportunity for timely genetic counselling. Furthermore, reliable guidelines for ruling out the possibility of PID can help avoid unnecessary testing.[6]

In many reported case series, the most common paediatric PID is associated with predominantly antibody deficiencies.[7] In children, there are four clinical entities that make up the majority of PID cases: selective IgA deficiency, IgG subclass deficiency, transient hypogammaglobulinaemia of infancy, and selective antibody deficiency with normal immunoglobulins. This set of syndromes share certain common characteristics, such as most patients have completely normal cellular immunity, phagocytic function, and complement levels; the illnesses are characterised by recurrent bacterial respiratory infections (rhinosinusitis, otitis, bronchitis, and pneumonia); their molecular basis is poorly known; very few require intravenous immunoglobulin; and the long-term prognosis is generally favourable.[8]

Children over two years of age who suffer repeated respiratory infections (otitis media, sinusitis, pneumonia) due to capsular pathogens, requiring frequent antibiotic treatment, should be tested for defective anti-polysaccharide antibody response to screen for specific antibody deficiency if they have normal immunoglobulin and IgG subclass levels and no other identified immunodeficiency.[9]

The objective of this study is to evaluate the response to polysaccharide capsular pneumococcal antigens, in order to screen for selective antibody deficiency with normal immunoglobulin (SAD) in children with recurrent respiratory infections.

Materials and methods

Participants were prospectively enrolled patients, aged more than two years to younger than 15 years, who visited the Immunology Unit of the Dr. Exequiel Gonzalez Cortes Hospital (Santiago, Chile) with recurrent respiratory infections (RRI), defined as the presence of at least one of the following criteria: six or more episodes of respiratory infection per year; one or more episodes of respiratory infection per month during the winter; or three or more episodes of lower respiratory tract infection.[10] Written informed consent was obtained from the parents prior to enrolment, and the protocol was approved by the local Ethics Committee.

Children were excluded if there was another identified cause for the recurrent infections, such as previously diagnosed primary or secondary immunodeficiency, local anatomical defect or other cause of recurrent localised pneumonia, congenital pulmonary airway malformation, immotile cilia syndrome, neutropenia, immunosuppressive treatment, illness such as cystic fibrosis, sickle cell anaemia, functional or surgical asplenia, malnutrition, diabetes, nephropathy, or chronic cardiac or respiratory disease. Furthermore, children were excluded if they had received pneumococcal polysaccharide or conjugate vaccine, intravenous immunoglobulin, or transfusion prior to the study. Patients were also excluded if there was no authorised guardian available to provide informed consent.

A complete blood count with differential was performed for absolute neutrophil and lymphocyte counts. The initial immunological study included measurement of serum immunoglobulins G, M, A, and E, complement C_3, and IgG subclass. All values were classified as normal if they fell within two standard deviations of the average for the age group. IgG anti-polysaccharide antibodies for 10 pneumococcal serotypes (S) (S1, S3, S4, S5, S6, S9, S14, S18C, S19F and S23F) were measured in serum samples of the patients, using third-generation ELISA calibrated and pre-absorbed according to the technique standardised by the CDC.[11] Measurements of antibodies were performed prior to immunisation (T0) and 45 days post-immunisation with 23-valent pneumococcal polysaccharide vaccine (Pneumo23®, Pasteur Merieux) 0.5 ml im (T1). Post-immunisation response was considered normal if values were above 1.3 μg/ml for over 50% of the serotypes in children aged two to five years and over 70% of the serotypes in children older than five years. Measurement of anti-polysaccharide pneumococcal antibodies was repeated 12 months post-immunisation (T2). Diagnosis of SAD was based on clinical history of infections, and normal IgG, IgM, IgA serum concentration, and IgG subclass levels, but abnormal IgG antibody responses to polysaccharide pneumococcal vaccine.

Data for the study were entered into program Stata 12.0. Log-transformed values for pre-immunisation and post-immunisation pneumococcal antibody titres were used to minimise the effect of a few very high values and to calculate the geometric means. Comparisons of patient groups were done with Wilcoxon test and Mann–Whitney test. Significant difference was considered with p value < 0.05.

Results

The study included 20 patients (12 males), with an average age of eight years (range three to 14 years). Eight patients were diagnosed as SAD according with their abnormal antibody response to polysaccharide vaccine. These eight patients have at least three bacterial acute pneumonias not associated with asthmatic exacerbations, and other bacterial acute respiratory infections such as otitis, rhinosinusitis and pleuropneumonia. One patient (male, seven years old) had a septic shock associated with pleuropneumonia. The main clinical characteristics of these eight patients