Allergol Immunopathol (Madr). 2016;44(4):376–381

Allergologia et immunopathologia

Sociedad Española de Inmunología Clínica, Alergología y Asma Pediátrica

www.elsevier.es/ai

ORIGINAL ARTICLE

Response to pneumococcal polysaccharide vaccine in children with asthma, and children with recurrent respiratory infections, and healthy children

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Received 12 November 2015; accepted 29 January 2016
Available online 30 May 2016

KEYWORDS
Asthma;
Antibody deficiency syndrome;
Pneumonia;
Pneumococcal polysaccharide vaccine;
Recurrent respiratory infections

Abstract
Background: To analyse specific immune response to the 23-valent pneumococcal polysaccharide vaccine by measuring pneumococcal antibodies in children with asthma and with respiratory recurrent infection (RRI) as compared to healthy children.
Methods: The study included 60 children, divided into three groups: 20 with asthma, 20 with RRI, and 20 healthy controls. Post-vaccination specific IgG antibodies against 10 pneumococcal serotypes (S1, S3, S4, S5, S6B, S9V, S14, S18C, S19F, and S23F) contained in the 23-valent pneumococcal polysaccharide vaccine (PPV) were measured. A specific IgG concentration $\geq$1.3 μg/mL was considered a protective response to the vaccine. For statistical analysis, levels of specific IgG antibodies against each of the 10 pneumococcal serotypes were compared across the three groups of children using the x^2 test.
Results: All of the children showed antipneumococcal antibody levels >1.3 μg/mL for over 70% of the serotypes, considered within the normal range of response. Average IgG antibody levels and percentages of children protected were statistically comparable among the three groups studied.
Conclusion: The asthmatic children without RRI had pneumococcal antibody levels and percentages of serotype-specific protection to PPV comparable to those of healthy children. Asthmatic children with recurrent infections should be evaluated for specific antibody deficiency (SAD). Because asthma patients are at high risk for invasive pneumococcal infections, it would be worthwhile to explore systematic administration of PPV in children over the age of two years who have not received a pneumococcal conjugate vaccine, considering the positive response to PPV reported here.

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http://dx.doi.org/10.1016/j.aller.2016.01.003

Introduction

In subjects with recurrent respiratory infections older than two years and with normal serum immunoglobulins, response to the pneumococcal polysaccharide vaccine (PPV) is used as diagnostic test for selective antibody deficiency (SAD).[1] In a prior study, we found a strong association between asthma and this primary immunodeficiency (PID).[2]

Certain disorders involve elevated risk for invasive pneumococcal disease, due to deficient immunological response to encapsulated agents. Groups at greatest risk include children under the age of two years, sickle cell anaemia carriers, patients with functional or surgical asplenia, and patients with primary or secondary immunodeficiencies. Other high-risk groups are patients with diabetes, with nephropathy, with chronic heart disease, with chronic pulmonary damage, and others over the age of two years who are recommended to receive the 23-valent PPV.[3] Children with asthma are also at high risk for invasive pneumococcal infections.[4] Asthma is one of the most common chronic diseases in children, affecting from 1% to 25% of various populations studied, and its prevalence seems to be rising.[5] In Chile, studies have reported a prevalence of 7% in a population of children aged 6–7 years and 23% in children aged 13–14 years.[6]

It has been found that patients with asthma have a 2.4-fold greater risk of developing an invasive pneumococcal infection than their healthy counterparts.[4] Even those with mild asthma have a risk 1.7 times higher than that of the general population, while those with severe asthma have a risk 2.6 times higher.[4,7]

Children with asthma are at particularly elevated risk for invasive pneumococcal infections when the clinical presentation of the asthma is severe or requires corticosteroid treatment.[4] Studies of patients with severe pneumococcal infections confirm that asthma patients are at higher risk for pneumonia and positive *Streptococcus pneumoniae* sputum culture.[8] Children with asthma develop pneumonia at a rate higher than that of the general population. According to a U.S. study of over 500 children under the age of 18 years, asthma patients acquire pneumonia more frequently than children without known risk factors.[9] Asthmatic children treated with inhaled corticosteroids also have higher rates of oropharyngeal colonisation with *S. pneumoniae*.[10]

In many reports, approximately 50% of primary immunodeficiencies are antibody deficiencies,[11] and more than 10% of children with recurrent respiratory infections have selective antibody deficiency (SAD).[12,13] The frequency of this condition in asthmatic children has not been established, but it is noteworthy that a large proportion of children with recurrent respiratory infections are asthma patients. Associations between asthma and allergic illnesses with other types of primary immunodeficiencies have been reported.[14]

The objective of this study was to assess the specific immune response measured through pneumococcal antibody levels, to administration of 23-valent polysaccharide pneumococcal vaccine (PPV) in asthmatic children older than two years without recurrent respiratory infections and normal immunoglobulin concentrations, and to compare the response to PPV in children with respiratory recurrent infections without immunodeficiency, and in healthy children.

Patients and methods

Prospective, controlled clinical study of 60 children divided in three groups from an urban area (Santiago, Chile):

Group A: Twenty patients between 2 and 15 years old, random included, with a diagnosis of GINA-defined mild-to-moderate, well-controlled asthma, without history of recurrent respiratory infections, selected from a primary care office.
Group B: Twenty patients between 2 and 15 years old, with a history of recurrent respiratory infections, selected from the Immunology Unit of Dr. Exequiel Gonzalez Cortes Hospital (Santiago, Chile), according to at least one of the following criteria: six or more episodes per year of respiratory infection; one or more episodes per month of respiratory infection during the winter period; or three or more lower respiratory tract infections.[15] Children were excluded if there was another cause of recurrent respiratory infection, such as immunodeficiency, local anatomical damage resulting in localised pneumonia, or concomitant neutropenia.
Group C: Control group of 20 children between 2 and 15 years old, with no history of pathology, selected randomly from the same primary care office as Group A.

Parents of all participating children provided written informed consent, and the study was approved by the Ethics Committee of the University of Chile.

Patients were excluded for previously-diagnosed primary or secondary immunodeficiency; local anatomical defect (cause of recurrent localised pneumonia); concomitant neutropenia; pathology such as cystic fibrosis, nephropathy, cardiac disease, chronic respiratory disease, sickle-cell anaemia, functional or surgical asplenia, or diabetes; or inability to obtain the informed consent of parents.

Baseline immunological studies were performed for serum IgG, IgM, and IgA, complement C3, and IgG subclasses, as well as haemogram with absolute lymphocyte and neutrophil count. All children included had normal immunoglobulin concentrations and normal immunological laboratory parameters in order to excluding hypogammaglobulinaemia and other primary and secondary immunodeficiencies.

All children received the 23-valent PPV (Pneumo 23®, Sanofi Pasteur), containing 25 μg of each of the 23 polysaccharides included in the formulation. The IgG-class anti-polysaccharide pneumococcal antibody levels for 10 serotypes (S1, S3, S4, S5, S6B, S9V, S14, S18C, S19F, and S23F) were measured using third-generation ELISA techniques as standardised by the Centers for Disease Control (CDC),[16] at study enrolment (T1) and 45–60 days post-vaccination (T2). Antibody concentration equal to or greater than 1.3 μg/mL of specific IgG for each serotype was considered a normal protective response.

For statistical analysis, serological response was measured as the concentration of specific IgG antibody against each of the 10 pneumococcal serotypes in the three groups (children with asthma, children with recurrent respiratory infections, and healthy children), using x^2 for the geometric mean titres expressed in micrograms per ml of blood in each