

Immunological evaluation of allergic respiratory children with recurrent sinusitis

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The objective of this study was to evaluate humoral immunity of allergic respiratory children with chronic/recurrent sinusitis. Twenty-seven allergic respiratory (persistent mild/moderate asthma and persistent allergic rhinitis) children (7–15-year old) with chronic or recurrent sinusitis were evaluated. Patients had symptoms and abnormal computer tomography scan even after two adequate treatments (long-lasting antibiotics, decongestants, and short-term oral corticosteroids). Clinical examination, sweat test, total blood cell count, measurement of serum levels of: total and specific IgE, immunoglobulins (G, M, A), IgG subclasses, antibodies to *Haemophilus influenza* type b (IgG anti-Ps Hib) and pneumococcal serotypes (IgG anti-Ps 1, 3, 5, 6B, 9V, and 14) before and after active immunization (Act-Hib® and Pneumo23®, Aventis Pasteur SA, Lyon, France), Rubella neutralizing antibody titers and human immunodeficiency virus antibodies. Specific IgE to inhalant allergens higher than class III were observed in 24/27 patients. One patient had IgA plus IgG2 deficiency and other an IgG3 deficiency. Eight and 12 of 27 patients had IgG2 and IgG3 serum levels below 2.5th percentile, respectively. Immunological responses to protein and polysaccharide antigens were normal in all patients. Although our patients have been appropriately treated of their allergic diseases, they persisted with chronic/recurrent sinusitis and 60% of them had a documented osteomeatal complex blockade. In spite of the diagnosis of IgA plus IgG2 deficiency and an isolated IgG3 deficiency, in all patients an adequate response to Ps antigens was observed. Primary and/or secondary humoral immunodeficiency seems not to be the main cause of chronic/recurrent sinusitis in patients with respiratory allergic disease.

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Chronic and recurrent respiratory infections, including sinusitis, otitis media, and pneumonias have been linked to predominantly antibody deficiencies. Immunoglobulin A (IgA) deficiency and IgG subclass deficiencies have been reported as an important role for chronic sinusitis (1–8). Among 161 primary immunodeficient patients diagnosed and followed in our Division, sinusitis was observed in 46% of them. This was the second infectious respiratory complaint reported by these patients (9).

In addition to immunodeficiency, allergic rhinitis (AR) mainly those poorly controlled, is pointed as a risk factor for sinus disease, perhaps through mechanical obstruction to normal mucus flow patterns due to mucous membrane

inflammation (edema) and osteal occlusion (3, 10–12). The sinus ostia obstruction may be secondary to infection, allergy, structural abnormalities, or nasal mucous membrane edema, which impede appropriate sinuses' ventilation and drainage (12, 13).

In this study, we evaluated humoral immunity in atopic children (asthma and AR) with chronic/recurrent sinusitis instead of the appropriate treatment of their allergic diseases.

Subjects and methods

Twenty-seven children [19 males, 7–15-year old (mean 10 yr)], regularly followed in our Division for allergic respiratory disease (persistent mild/

moderate asthma (14) and persistent AR (15)) were evaluated. Chronic sinusitis was defined if patient presented with symptoms (purulent nasal discharge and/or purulent pharyngeal drainage and/or cough and/or periorbital edema and/or headache and/or facial pain, etc.) lasting 3–8 wk or longer, independently of their severity, and recurrent sinusitis who's had three or more episodes of acute sinusitis in the last year (3, 16). All patients included had symptoms and abnormal computer tomography (CT) scans even after two adequate treatments with long-lasting antibiotics, decongestants a short-term oral corticosteroid. Sinusitis was the unique bacterial infections presented by our children during the follow-up.

After clinical examination, patients were evaluated as follow: (a) total blood cell count (TBC), (b) measurement of serum levels of total and specific IgE [inhalant allergens (house dust, *Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, and cockroach), molds (*Alternaria alternata*, *Cladosporium* sp., *Aspergillus fumigatus*), and food allergens (cow's milk, white egg, soy, peanut, wheat, fish), Pharmacia CAP system®], (c) immunoglobulin and IgG subclasses levels (compared to Brazilian normal values) (17, 18), (d) antibody levels to rubella, conjugate *Haemophilus influenza* type b and pneumococcal polysaccharide antigens. Serum samples were collected before and 6 wk after immunization with Act-Hib® and Pneumo23® (Aventis-Pasteur) vaccines. These patients had not been previously immunized for these bacteria. Rubella neutralizing antibody titres were determined only after immunization.

IgG anti-Ps Hib were determined by an enzyme-linked immunoassay (19), and levels $\geq 0.15 \mu\text{g/ml}$ for non-immunized children and $\geq 1 \mu\text{g/ml}$ to those vaccinated were considered protectors (20, 21). IgG anti-pneumococcal to serotypes (Ps) 1, 3, 5, 6B, 9V, and 14 were determined by a modified enzyme-linked immunosorbent assay (ELISA) protocol (22), and adequate response was arbitrarily defined as a post-immunization antibody concentration $\geq 1.3 \mu\text{g/ml}$ or with a minimum 4-fold increase over the baseline (pre-immunization) value (22). Antibodies to human immunodeficiency virus (HIV) and sweat test were also done in all patients.

Results

All patients had been treated for asthma and AR according to their diseases' severity, and had received a 21-day treatment with antibiotics

(cephalosporin) plus oral decongestants and a 5-day period of oral corticosteroids. Nocturnal cough (25/27), purulent nasal discharge (16/27), and headache (11/27) were the most frequent symptoms reported by these patients. Purulent post-nasal drip was observed in 26/27 patients during clinical examination. All patients were well nourished and had normal weight to stature adequacy.

Sodium and chloride in sweat and TBC count were normal. HIV antibodies were negative in all children.

Serum total IgE levels ranged from 24 to 2001 kU/l (geometric mean 1103.2 kU/l) and all patients had a positive specific IgE to inhalant allergens (24/27 $\geq$ class III). Serum specific IgE to molds and food allergens were negative in all patients.

IgA serum levels were lower than percentile 3 in 5/27 patients, and bellow 7 mg/dl in one of them (patient No. 6, Fig. 1). High IgM serum levels were observed in 17/27 (63%) patients and high IgG serum levels in 7/27 (26%) patients. IgG1 subclass serum levels were bellow normal age-matched controls in 3/27 patients and higher in 3/27 (Fig. 2). IgG2 serum levels bellow 50th

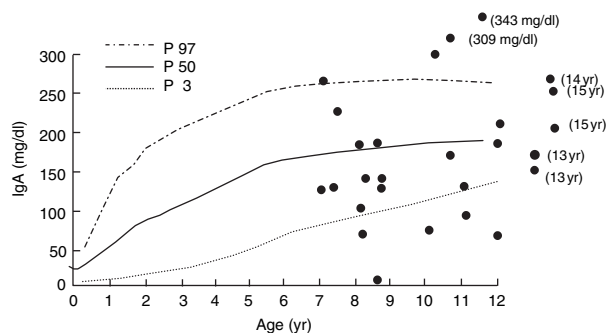


Fig. 1. IgA serum levels of children with respiratory allergy (asthma and allergic rhinitis) and recurrent sinusitis compared to Brazilian normal references (18).

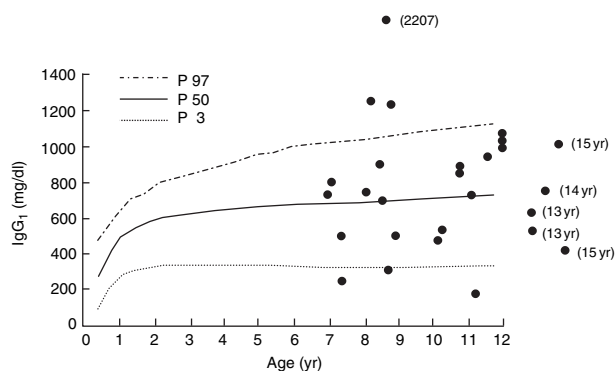


Fig. 2. IgG1 serum levels of children with respiratory allergy (asthma and allergic rhinitis) and recurrent sinusitis compared to Brazilian normal references (18).

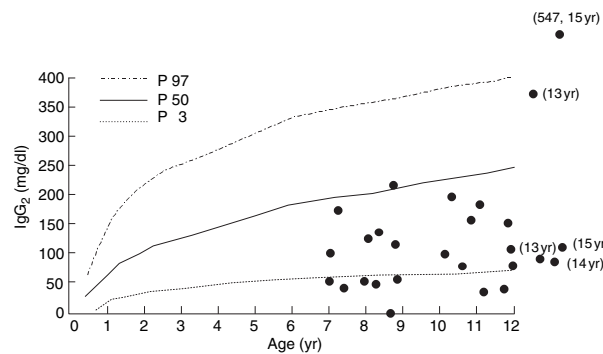


Fig. 3. IgG2 serum levels of children with respiratory allergy (asthma and allergic rhinitis) and recurrent sinusitis compared to Brazilian normal references (18).

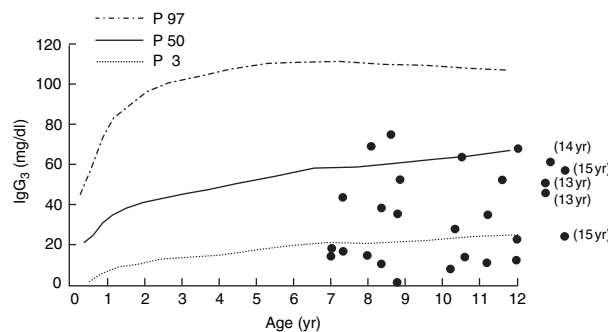


Fig. 4. IgG3 serum levels of children with respiratory allergy (asthma and allergic rhinitis) and recurrent sinusitis compared to Brazilian normal references (18).

percentile of normal age-matched patterns occurred in 25/27 and below 2.5th percentile in 8/27 patients (patient No. 6 was 0 mg/ml, Fig. 3). IgG3 serum levels were above 50th percentile of normal age-matched controls in 3/27 and below 2.5th in 12/27 patients (patient No. 8 was 0 mg/ml, Fig. 4), and IgG4 in 7/27 patients. Low levels of two or more IgG subclasses were observed in 7/27 patients. There was an IgA plus IgG2 deficient patient (No. 6) and an IgG3 deficient patient (No. 8).

Rubella neutralizing antibodies were absent in 6/27 patients. Despite recurrent infections and age, 11/27 patients had Hib antibody serum levels below 1.0 $\mu\text{g/ml}$ before immunization (geometric mean 1.49 $\mu\text{g/ml}$). After immunization, all of them presented levels > 1.0 $\mu\text{g/ml}$, and some of them reached extremely high values (range 3.8–1088 $\mu\text{g/ml}$; geometric mean = 127.8 $\mu\text{g/ml}$) and a mean fold increase of 84.9 (range 3.4–1433.6).

Antibodies to pneumococcal antigens (Table 1) were measured before and after immunization. Mean levels higher than 1.3 $\mu\text{g/ml}$ were observed for all analyzed serotypes before immunization, and an increase was observed after immunization in all patients, including patients Nos 6 and 8. Adequate antibody levels (> 1.3 $\mu\text{g/ml}$) for the all six analyzed serotypes were observed in 22/27 patients, and for five serotypes in the others five patients. Serotype 14 promoted the higher levels of specific antibody (Table 1).

Discussion

The prevalence of chronic sinusitis in children is variable and difficult to be considered. A cohort study with children followed from birth to 8 yr of age documented to be 13.1% the prevalence of sinusitis, 78% of them with AR associated (23). AR, mainly persistent, is pointed as an important sinusitis pre-disposing factor. The extended airway mucosa edema secondary to allergic inflammation, damage of mucociliar clearance and osteomeatal complex obstruction induces retention of sinus secretion, hypoxemia and bacterial proliferation. Sinus X-ray alterations were documented in almost 80% of persistent AR patients and in 16.7% of those with seasonal AR (24, 25).

In children, chronic sinusitis and persistent AR symptoms may overlap. CT scans have been recommended by several authors to diagnose and evaluate paranasal sinuses involvement (26).

Table 1. Immunoglobulin G (IgG) anti-pneumococcal serotypes (Ps, geometric mean) before and after immunization with Pneumo23®, before/after ratio (arithmetic mean) and patients with adequated immunological response * (total n = 27)

Pneumococcal serotype	IgG anti Ps ($\mu\text{g/ml}$)		Before/after increase (range)	Adequated response (%)
	Before (range)	After (range)		
1	2.02 (0.68–10.9)	3.30 (1.1–38.4)	2.12 (0.48–10.97)	100.0
3	2.95 (1.2–10.7)	2.60 (1.2–13.1)	0.92 (0.5–1.7)	100.0
5	4.47 (0.89–22.7)	5.78 (2.0–23.9)	1.44 (0.56–3.37)	100.0
6B	2.37 (0.44–12.3)	3.24 (0.9–16.7)	1.74 (0.61–7.59)	88.9
9V	1.69 (0.44–6.4)	2.96 (0.79–7.7)	2.28 (0.3–9.55)	92.6
14	5.81 (1.7–22.0)	16.10 (4.6–148.9)	5.58 (0.5–36.5)	100.0

*Post-immunization level ≥ 1.3 mg/ml or 4-fold increase of baseline value.

Cough, purulent post-nasal drip, and purulent nasal discharge were the predominant symptoms observed in our patients and 60% of them maintained an obstruction of the osteomeatal complexes after treatment with antibiotics.

Primary immunodeficiencies have been diagnosed among patients with chronic/recurrent sinusitis, in variable proportions up to 17% (2, 7, 8, 27). Common variable immunodeficiency, IgA deficiency, IgG subclasses deficiencies mainly IgG3 deficiency were the most reported (2, 3, 6). Among patients with predominantly humoral immunodeficiencies, chronic sinusitis has been documented in up to 60% (6, 9, 28–31).

The prevalence of IgG subclasses deficiency is variable depending on the methods and criteria used in its diagnosis. One of our patients was documented as an IgA plus IgG2 deficient patient (No. 6). Three patients presented low levels of IgG1 and 12/27 of IgG3 levels.

In patients with chronic/recurrent sinusitis alterations of IgG3 levels have been reported by several authors although not unanimously (7). The reasons for these findings are unknown (2–5). Lower levels of IgG subclasses during an infectious episode may be interpreted of two manners: consumption increase or insufficient production. Among our patients high IgG1 levels were observed in three and of IgG2 in one. IgG3 is important in the defense against *Moraxella catarrhalis* and *Streptococcus pyogenes* M component infections, commonly associated to bacterial sinusitis (16). In this subclass are founded, more frequently, antibodies to protein antigens. So, IgG3 deficient patients would be more predisposed to virus upper airways infections and possible evolution to sinusitis. Other possible explanations for such observation are: $\gamma 3$ codifying gene deletion associated to impairment of IgG3 production with preservation of the other subclasses, increased consumption and reduced half-life (32).

In spite of low levels of IgG1 and IgG3 presented by some of our patients they had an appropriate response to the anti-hemophilus type b conjugated vaccine, and antibodies to Rubella were present in 80% of them. *Streptococcus pneumoniae* has been pointed as one of the more frequent etiological agents of sinusitis. A recent study documented pneumococcal serotypes 3 (13%), 19F (11%), 6B (9%), and 23F (9%) as the most involved in recurrent sinusitis (33). *Streptococcus pneumoniae* was identified in 66.6% of patients with AR and sinusitis previously evaluated (34). IgG2 subclass antibodies are important in the defense against polysaccharide antigens and its deficiency may predispose to

infections with encapsulated microorganisms. All of our patients had an appropriate response to 23-valent pneumococcal vaccines. Serotype 14 was that presented the more intense response, as has been observed by others (27).

Finocchi et al. evaluated humoral immune defects in apparently 67 non-atopic patients with recurrent infections and in 55% a humoral defect was diagnosed (35). More than 60% referred upper respiratory infections but some had other associated infectious episodes. Forty-one of 44 patients had a normal functional response to *H. influenzae* after immunization (35). As all our patients were atopic children they cannot be compared to those of Finocchi, since in atopic patients with AR and sinusitis, there is a chronic inflammatory activity in the respiratory mucosa, which is not observed in non-atopic patients with immunodeficiencies.

In conclusion, although our patients have been appropriately treated of their allergic diseases, they persisted with chronic/recurrent sinusitis and 60% of them have a documented osteomeatal complex blockade. Although, among all our patients there were two with primary immunodeficiency (IgA plus IgG2 deficiency and IgG3 isolated deficiency), all of them had increased levels of anti-pneumococcal and anti-hemophilus antibodies after immunization. Our data reinforces the concept that humoral immunodeficiency in respiratory allergic children is not the main cause of chronic/recurrent sinusitis, and a more aggressive anti-inflammatory treatment of the AR might be necessary.

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