

IgG subclass specific antibody response in recurrent bronchitis

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Abstract

The IgG subclass specific immune response against pneumococcal type 3 polysaccharide antigen before and after immunisation in healthy children and children with recurrent bronchitis was studied. Recurrent bronchitis was defined as three or more episodes a year, during at least two consecutive years, of bronchopulmonary infection, productive cough with or without fever, and/or diffuse rales by physical examination. Twenty five patients and 15 healthy children were selected.

The patient group had lower concentrations of IgG₁ and IgG₂ specific pneumococcal antibodies compared with healthy children, regardless of whether or not the total IgG₂ concentration was low. The children with recurrent bronchitis showed a greater increase in IgG₁ and IgG₂ antibodies after immunisation than the controls.

It is concluded that children with recurrent bronchitis show a decreased humoral immune response to pneumococcal type 3 polysaccharide antigen. This finding suggests that a defect in the humoral immune response against polysaccharide antigens is an important cause of recurrent bronchitis in childhood.

A high incidence of IgG₂ subclass deficiency is reported in children with recurrent upper and lower respiratory tract infections.¹⁻⁶ Antibodies against polysaccharide antigens are mainly found in the IgG₂ subclass.⁷⁻¹⁰ Polysaccharide antigens are the main antigenic determinants of encapsulated bacteria such as *Haemophilus influenzae* and *Streptococcus pneumoniae*; the latter is a major cause of recurrent respiratory infections. In IgG₂ deficient children, the humoral immune response after immunisation with a polysaccharide antigen is significantly decreased.¹¹⁻¹⁴ Ambrosino *et al* reported a patient with recurrent bacterial pneumonia, normal concentrations of immunoglobulin classes and subclasses, but a significantly decreased immune response against polysaccharide antigens.¹⁵ This suggested a functional disorder in humoral immunity. Recently some authors observed a decreased antibody response after immunisation with a polysaccharide antigen in children with recurrent infections without any immunoglobulin class or subclass deficiency.¹⁶⁻¹⁸ Therefore we were interested in the serum concentrations of IgG subclass specific antibodies against type 3 polysaccharide antigen before and after immunisation in children with recurrent bronchitis.

Patients and methods

PATIENTS

Because a formal definition of recurrent bronchitis in childhood is lacking, we defined it as three or more episodes a year, during at least two consecutive years, of bronchopulmonary infection, productive cough with or without fever, and/or diffuse rales by physical examination. In order to avoid the inclusion of mainly asthmatic patients, wheezy or dyspnoeic children were excluded and children had to be at least 3 years old. Asthma as the aetiological factor in recurrent respiratory symptoms is usually recognised clinically by 3 years.¹⁹

According to this definition 25 children (15 boys) (mean age 57 months, range 36-105) were selected. Thirteen patients were attending the outpatient department of the paediatric respiratory clinic at the University Hospital, Ghent; 12 were residents in an asthma centre at De Haan, Belgium.

Respiratory symptoms were first seen at the mean age of 7 months. The mean annual rate of episodes of respiratory symptoms was 10. In 84% of the children, fever was a constant sign during symptom episodes. Sixty percent of the patients had recurrent pneumonia and in 72% there was no seasonal occurrence of symptoms. There was a family history of chronic bronchitis in a first degree relative in 36% of the children, with atopy and/or asthma in 56%. There was a combination of both chronic bronchitis and asthma in more than one first degree relative in 12%. Adenoids and tonsils were removed in 48% and 28% of the patients respectively.

In 40% of the patients total IgE serum concentrations were higher than 2 SD above the mean for age.²⁰ Eight percent showed one or more positive radioallergosorbent tests. Sweat tests gave negative results in all children. Ciliary function was examined on bronchial biopsy specimens or nasal swabs in 15 children. The immotile cilia syndrome was diagnosed in one patient. Gastro-oesophageal reflux was found in four of the 15 children tested. Forty eight percent of the patients showed persistent abnormalities on radiographs of the thorax. Persisting radiological signs consisted of atelectasis or infiltration of the right middle lobe and/or lingula. Bronchoscopy was performed in 12 children and *H influenzae* was cultured from bronchoalveolar lavage fluid in two patients. Severe signs of chronic bronchitis were found in all of the patients (that is, hypersecretion, pale mucosae, hypertrophic submucosal glands, longitudinal mucosal folds). Six of the nine children in whom a bronchography was done showed bronchiectasis.

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A control group of 15 children, mean age 71 months (range 36–144), was enrolled. The parents of 640 children in an infant and elementary school were informed of the study and asked for their cooperation. All control children were selected after they had returned a questionnaire in which the proneness to upper and lower respiratory tract infection was evaluated. Only children with two or fewer yearly episodes of bronchitis, rhinitis, sinusitis, or otitis were accepted. Children with a history of pneumonia or any infectious disease within one month before the start of the study were excluded. No significant difference in mean age between groups was observed (Student's *t* test).

Patients and control children were immunised with a pneumococcal vaccine (Pneumovax 23, Merck Sharp and Dohme). Serum samples were taken before and one month after immunisation.

METHODS

IgG subclasses were measured by enzyme linked immunosorbent assay (ELISA) using monoclonal antibodies. The latter were obtained from the Binding Site Limited (Birmingham). The specificity of these monoclonal antibodies was tested as reported by Jefferis and Reimer.²¹ Each serum sample was studied twice and a sample from a normal serum pool was included in every assay plate. A standard curve was constructed for each subclass using a reference preparation supplied by the World Health Organisation (SPSO1). The intra-assay coefficient of variation was 7%, 5%, 4%, and 7% for IgG₁, IgG₂, IgG₃, and IgG₄ respectively. The interassay coefficient of variation was 13%, 12%, 18%, and 15% for IgG₁, IgG₂, IgG₃, and IgG₄ respectively. Our own reference values for IgG subclasses in different age groups are given in table 1. Sera were obtained from 175 healthy children aged 0 to 18 years at the time of visiting the paediatric outpatient department for non-infectious or non-inflammatory diseases or when they were admitted for elective surgery. All control children were selected after they had answered a questionnaire in which the proneness to upper and lower respiratory tract infection was evaluated as mentioned above. If C reactive protein concentration was greater than 10 000 µg/l or α₂ globulin was higher than 0.9

g/l the serum sample was omitted as a control. As immunoglobulin concentrations are not distributed normally, geometric means and normal ranges of the concentrations for each subclass were calculated for each age group from the logarithm of the experimental values.²² Total serum immunoglobulins were measured by nephelometry. Patients were considered deficient for an immunoglobulin class or an IgG subclass if they had values more than 2 SD below the geometric mean for age matched healthy subjects. Total IgE and specific IgE were measured by radioimmunoassay. Ciliary function was examined on bronchial biopsy specimens or nasal swabs in the laboratory of Dr S van der Baan, Amsterdam, The Netherlands.²³ Sweat chloride was measured by the method of Gibson and Cooke.²⁴ Gastro-oesophageal reflux was evaluated by the Tuttle test.²⁵

Subclass specific pneumococcal antibodies were measured by ELISA. Microtitre plates (Nunc, Maxisorp) were coated with 0.1 ml of type 3 pneumococcal polysaccharide (American Type Culture Collection), 10 µg/ml, dissolved in a barbital buffer, diluted 1:100 in distilled water. The plates were incubated for 96 hours at 37°C and kept at 4°C until used. A standard curve for different IgG subclasses was formed with a standard serum (Janssen Biochemico, Belgium). Dilutions 1/100, 1/200, 1/400, 1/800, 1/2000, 1/4000, 1/8000, 1/10 000, and a blank for IgG₁ and dilutions 1/10, 1/20, 1/40, 1/80, 1/200, 1/400, 1/800, 1/1000, and a blank for IgG₂, IgG₃, and IgG₄ were obtained. Serum samples of patients and controls were diluted 1/200, 1/500, and 1/1000 for IgG₁ and 1/40 and 1/80 for IgG₂, IgG₃, and IgG₄ antibodies. After washing, microtitre plates were incubated with serum samples and standard samples 0.1 ml for three hours at 37°C.

Subclass specific pneumococcal antibodies were measured with monoclonal subclass specific antibodies (Janssen). These monoclonal antibodies were conjugated with horseradish peroxidase. The conjugate was diluted 1/2500 for IgG₁, 1/500 for IgG₂ and IgG₃, and 1/250 for IgG₄. After washing, diluted conjugate was added to the microtitre plates and incubated for two hours at room temperature. Microtitre plates were washed five times and 0.1 ml substrate was added. After 30 minutes of incubation at room temperature the reaction was stopped by 0.05 ml of 2 M sulphuric acid. The extinction coefficient was read on an ELISA reader at 492 nm. As well as a standard curve for subclass specific pneumococcal antibodies, a standard curve for the specific IgG subclass tested was also obtained in every plate. For IgG₁ dilutions 1/5000 to 1/320 000 and for IgG₂, IgG₃, and IgG₄ 1/100 to 1/10 000 were used. Extinction coefficients measured for subclass specific antibodies were also read on the simultaneous measured standard curve for the specific IgG subclass. After adjusting for the dilutions used a quantitative value for the specific pneumococcal antibodies could be obtained.

The interassay coefficient of variation for IgG subclass specific pneumococcal antibodies was 12%, 15%, and 15% for IgG₁, IgG₂, and IgG₄

Table 1 Reference values for IgG subclasses in different age groups. Values are mean (range: mean and 2 SD) in g/l

Age (years)	IgG ₁	IgG ₂	IgG ₃	IgG ₄
0-0.5 (n=13)	2.35 (0.85-6.50)	1.08 (0.13-8.73)	0.18 (0.03-0.93)	0.11 (0.02-0.58)
>0.5-1 (n=10)	4.05 (1.43-11.49)	0.73 (0.22-2.46)	0.35 (0.11-1.10)	0.05 (0.01-0.19)
>1-<3 (n=17)	3.50 (1.54-7.94)	0.88 (0.36-2.17)	0.33 (0.10-1.12)	0.06 (0.02-0.39)
3-<5 (n=21)	5.74 (2.23-14.78)	1.44 (0.51-4.09)	0.38 (0.10-1.43)	0.25 (0.05-0.14)
5-<7 (n=22)	6.44 (2.02-21.67)	1.48 (0.46-4.77)	0.42 (0.13-1.35)	0.34 (0.05-2.12)
7-<10 (n=35)	6.52 (2.73-15.56)	1.51 (0.49-4.66)	0.42 (0.14-1.23)	0.24 (0.03-1.99)
10-<13 (n=23)	5.68 (3.08-9.22)	1.88 (0.69-5.13)	0.44 (0.16-1.20)	0.23 (0.02-2.49)
13-<17 (n=26)	6.24 (3.40-11.11)	3.09 (0.95-9.98)	0.55 (0.27-1.14)	0.20 (0.02-2.52)
≥17 (n=8)	6.01 (3.57-10.11)	4.60 (1.23-17.10)	0.54 (0.23-1.25)	0.20 (0.03-1.10)

Table 2 Mean IgG subclass specific antibody concentrations against pneumococcal polysaccharide type 3 antigen before and after immunisation. Values are mean (2.5-97.5 centiles) in $\mu\text{g/ml}$

	(A) Control group (n=15)		(B) Patient group (n=25)		(C) Patient group (not IgG ₂ deficient) (n=20)		p Values	
							(A) v (B)	(A) v (C)
IgG ₁								
Before	38.5 (14.5-73.5)		23.7 (7.4-63.0)		23.8 (7.6-92.3)		0.008	0.006
After	38.7 (13.0-72.5)	0.8*	34.6 (9.2-109.0)	0.004*	33.7 (9.1-130.0)	0.003*	0.08	0.07
IgG ₂								
Before	51.1 (5.0-260.0)		15.7 (5.0-53.6)		14.8 (5.0-60.0)		0.002	0.003
After	60.5 (7.3-210.0)	0.06*	29.9 (5.0-86.0)	0.003*	26.8 (5.0-76.5)	0.003*	0.01	0.02

*p Values between before and after immunisation for both IgG subclasses.

†p Values between IgG₁ and IgG₂ before immunisation.

respectively. No measurable concentrations of IgG₃ specific pneumococcal antibodies were found.

The significance of differences between groups was determined with the unpaired non-parametric Mann-Whitney U test. Significance of increases in antibody titres after immunisation was evaluated by the paired non-parametric Mann-Whitney U test.

Results

Two of the 25 patients (8%) had a decreased serum concentration for IgG and four (16%) had IgA deficiency. IgG subclass deficiency was found in 17 (68%) of the patients with recurrent bronchitis: two (8%), four (16%), and seven (28%) for IgG₂, IgG₃, and IgG₄ respectively, two (8%) for IgG₂ and IgG₄, one (4%) for IgG₃ and IgG₄, and one for IgG₂, IgG₃, and IgG₄. No immunoglobulin class or subclass deficiency was found in the healthy control group.

The mean and range of serum antibody concentrations against pneumococcal polysaccharide antigen type 3 in the IgG₁ and IgG₂ subclass before and after immunisation in patients with recurrent bronchitis, healthy control children, and patients with normal IgG₂ concentrations with recurrent bronchitis are shown in table 2.

Patients with recurrent bronchitis, regardless of whether or not there was an IgG₂ deficiency, had lower concentrations of IgG₁ and IgG₂ specific antibody than the controls. Antibody concentrations before immunisation in the group with recurrent bronchitis were significantly higher for IgG₁ than for IgG₂. In the control group antibodies before immunisation were higher in the IgG₂ subclass, although this was not significant.

Both patient groups showed a greater increase in IgG₁ and IgG₂ specific antibodies after immunisation than the controls. A 1.9 ($p < 0.003$) and 1.2 ($p < 0.06$) fold increase in IgG₂ specific type 3 pneumococcal antibodies was seen after immunisation in the patient (group B) and control group respectively. The mean concentration of IgG₂ subclass specific pneumococcal antibodies after immunisation in the patients with recurrent bronchitis remained significantly lower than the mean concentration after immunisation in the control group.

No specific type 3 pneumococcal polysaccharide antibodies were detected in the IgG₃ subclass. In some children a low value of specific pneumococcal antibodies was seen in

the IgG₄ subclass; immunisation did not provoke detectable changes.

Discussion

Before immunisation antibodies against type 3 pneumococcal polysaccharide antigen in control children were mainly of the IgG₂ subclass; this is in contrast to those with recurrent bronchitis who had mainly IgG₁ subclass antibodies. However, antibody concentrations before immunisation in both the IgG₁ and IgG₂ subclass were significantly lower in the group with recurrent bronchitis. In view of the frequent respiratory infections, one would expect a higher antibody concentration in these children. This strongly suggests a primary defect in the humoral immune response in these children.

It is already known that IgG₂ deficient children have a decreased immune response against polysaccharide antigens.¹¹⁻¹⁴ By omitting IgG₂ deficient children, we still find a significant difference, suggesting a decreased humoral immune response against pneumococcal polysaccharide antigen in a potentially larger group of children with recurrent bronchitis and normal serum IgG₂ concentrations.

These findings are in general accordance with the results of Freijd *et al.*⁹ They reported significantly lower concentrations of IgG₁ and IgG₂ specific type 6a pneumococcal antibodies in a group of 15 children with recurrent otitis media compared with control children and healthy adults. In their patient group, specific pneumococcal antibody concentrations were higher in the IgG₁ than in the IgG₂ subclass, but a similar pattern was also seen in their control group. However, in 15 healthy adults specific pneumococcal antibody concentrations were higher in the IgG₂ subclass. Their control group was younger than our control children and were selected from an ear, nose, and throat clinic if they had suffered from one or two episodes of otitis media. It could be argued that their control group contained antibody deficient patients. Our results are in accordance with those of Barrett *et al.*¹⁰ and Schatz and Barrett²⁶ who showed that antibodies against polysaccharide antigens in healthy children over the age of 3 years are mainly of the IgG₂ subclass.

The relatively small increase in pneumococcal antibodies after immunisation in both the control and patient group confirms the findings of Douglas *et al* who reported a poor antibody response after pneumococcal vaccine up to the age of 5 years.²⁷ Paton *et al* reported a 2.1 to 2.9 fold increase in type 3 pneumococcal antibodies

after immunisation in children aged 5 to 15 years.²⁸ Barrett *et al* observed a threefold increase in IgG₂ type 3 specific pneumococcal antibodies after immunisation in adults.¹⁰ These observations suggest an increasing immune reactivity against pneumococcal vaccine with age.

The reason why patients show a greater rise in antibodies after immunisation, compared with controls, is not entirely clear. It might be explained in part by complexing of antibodies with injected antigens, thus reducing the amount of antigen available to stimulate B lymphocytes. This idea is supported by the finding that in the control group, the four children with a low initial concentration of IgG₂ specific pneumococcal antibodies (<10 µg/ml) showed a mean 4.2 fold increase after immunisation.

Ambrosino *et al* found no significant difference in serum concentrations of IgG specific pneumococcal antibodies after immunisation between a group of respiratory infection prone children and controls.¹³ Perhaps differences were not obvious because total IgG was studied instead of IgG subclass specific responses.

No significant differences were observed in antibodies before and after immunisation in subgroups of patients with gastro-oesophageal reflux or high IgE concentrations compared with the whole group. The two IgG deficient patients showed both low antibody concentrations before immunisation (<5 µg/ml); in one there was an excellent and in the other no immune response after immunisation. Two of the four IgA deficient children had a good immune response after immunisation and three of them showed low antibody concentrations before immunisation.

IgG subclass measurements are considered important diagnostic tests in children with unexplained recurrent bronchitis. However, measurement of IgG subclass specific polysaccharide antibody concentrations before and after immunisation, compared with controls, is a more sensitive test to detect an antibody deficiency against polysaccharide antigens. Because of the relatively small antibody increase after immunisation with a pneumococcal vaccine, even in healthy children, immunisation with a *H influenzae* type b vaccine may be preferable. Other investigators using this vaccine observed a definite increase in specific antibody concentrations in control children compared with infection prone patients.¹⁷

Although recurrent respiratory symptoms are a common problem in preschool children, most are due to increased non-specific bronchial hyper-reactivity evoked or increased by recurrent viral infections. In these children symptoms can be controlled by antiasthmatic drugs. However, in a small group of patients recurrent bacterial respiratory infections are suspected on a clinical, radiological, and serological basis. Our 25 patients were selected over a three year period from a tertiary paediatric reference centre and an asthma centre with 250 patients from all over Belgium. Although such children are frequently seen in specialised paediatric respiratory clinics, their prevalence in the population is relatively low.

As suspected in some children with IgG subclass deficiency,^{29,30} most of the patients in our study may have retarded development (immaturity) of the humoral immune system and repeat immunisation with polysaccharide antigens will be necessary to confirm a true deficiency. Prophylactic treatment with antibiotics or regular gammaglobulin replacement treatment may decrease respiratory symptoms and prevent serious pulmonary disease. However, controlled clinical trials will be necessary to confirm these possible benefits.

In conclusion, children with recurrent bronchitis show a decreased humoral immune response against pneumococcal type 3 polysaccharide antigen. This finding suggests that a defect in the humoral immune response against polysaccharide antigens is an important cause of recurrent bronchitis in childhood.

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Kawasaki or not Kawasaki

As there is no diagnostic test for Kawasaki disease the diagnosis must be made on clinical findings and the exclusion of other diseases. In my pocket notebook I carry the following list taken from the *New England Journal of Medicine* (1986;315:388):

- (1) Fever lasting at least five days plus four of:
 - (a) bilateral conjunctival injection
 - (b) red throat, or fissured lips, or strawberry tongue
 - (c) peripheral erythema, peripheral oedema, periungual desquamation, or generalised desquamation
 - (d) truncal rash
 - (e) cervical glands
- (2) No other explanation.

In a multicentre study in the United States (Jane C Burns and colleagues, *J Pediatr* 1991;118:680-6) the clinical features were compared of 280 children with Kawasaki disease and 42 who had been referred because of a suspicion of that diagnosis but turned out to have something else. The something else was measles in 12 cases, a presumed but unidentified viral infection in another 12, a drug reaction in six, and group A β haemolytic streptococcal infection in five. Of the other six children one each had juvenile chronic arthritis, a presumed bacterial cervical adenitis, and infection with adenovirus, influenza A virus, Epstein-Barr virus, and *Leptospira interrogans*.

The following findings occurred in a small minority of patients with Kawasaki disease and were significantly more common in the non-Kawasaki disease patients: conjunctival exudate, discrete lesions inside the mouth, exudative pharyngitis, and generalised lymphadenopathy. Several features were found more often in Kawasaki disease to a very high degree of statistical significance ($p \leq 0.001$). They were injected bulbar conjunctivae, red or cracked lips, strawberry tongue, and perineal rash. This, however, is an excellent example of the distinction between statistical significance and clinical usefulness. Red lips, for instance, were found in 94% of cases of Kawasaki disease and 64% of the others. The difference is statistically very significant ($p < 0.001$) but as a single piece of clinical information it is clearly useless for diagnostic purposes. What we need to know about any diagnostic procedure, either laboratory or clinical, is its sensitivity and specificity. The clinical features with a high sensitivity in the diagnosis of Kawasaki disease all seem to have a low specificity when taken as isolated findings. Perhaps certain combinations of features would be more specific but unfortunately these authors have not provided us with that information. Their conclusion is that the clinical criteria for the diagnosis of Kawasaki disease are unreliable. The diagnosis is made by using the specified clinical criteria and excluding other conditions but the decision to treat with immunoglobulin may have to be taken on the basis of an uncertain diagnosis.