IgG subclasses in nonallergic children with chronic chest symptoms

Immunoglobulin and IgG subclass measurements were made on sera from 37 children thought to have asthma whose chronic chest symptoms were unexplained by allergy. There was a higher proportion of low or low-normal levels of IgG subclasses 1, 2, and 4 in these children than in normal children. Those who had low serum IgG values on initial measurement had a higher proportion of low or low-normal levels of IgG1, IgG2, and IgG4; those who had normal IgG values had a higher proportion of low or low-normal levels of IgG2 and IgG4. Thus a normal serum concentration of IgG did not exclude the possibility of an abnormal level of IgG2 or IgG4. Our experience suggests that abnormal levels of IgG subclasses might play an etiologic role in the chronic chest symptoms in some of these children. (J PEDIATR 105:896, 1984)

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CHILDREN WITH HUMORAL IMMUNODEFICIENCY frequently develop chronic respiratory disease.[1,2] Studies of humoral immune function in children with chronic respiratory symptoms associated with asthma, however, have produced conflicting results[3-15] because of confusion in diagnostic terminology and variability in criteria for patient selection. Abnormal levels of one or more serum immunoglobulins have been reported in children with severe, chronic asthma[15] and in children with asthma associated with severe respiratory tract infections[12]; some patients appeared to have depression of serum IgG levels, whereas others were shown to be selectively deficient in serum IgA. Low serum levels of IgG and IgA have been associated with IgG subclass deficiencies.[16-19]

We report the results of measurements of serum immunoglobulins and IgG subclasses in children with chronic intermittent or persistent chest symptoms unexplained by allergy.

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METHODS

Measurements of serum immunoglobulins G, A, M, and E are determined routinely as part of the evaluation of chronic chest symptoms in children referred to the Pediatric Allergy/Immunology Service at the Emory Clinic and the Henrietta Egleston Hospital for Children. IgG subclass determinations were made on serum obtained from children who did not have allergy as part of their illness. Specifically, these children's medical history did not suggest allergy; that is, none had a history of symptoms on exposure to a specific allergen and none had seasonal, environmental, or geographic variation in symptoms. They had normally low serum IgE levels (geometric mean 7.2 U/ml, range 0 to 97 U/ml), peripheral blood eosinophil counts $<700/cm^3$, and negative immediate hypersensitivity skin testing to a standard battery of 32 antigens when performed. Previous diagnoses included severe asthma, asthmatic bronchitis, bronchitis, chronic cough, and recurrent respiratory tract infections. All had a history of chest symptoms associated with respiratory tract infections. All were thought to have asthma because they experienced peripheral airflow obstruction, which was completely reversible. Sweat chloride determinations were normal in all patients. Barium swallow, fluoroscopy, and bronchoscopy also were performed as indicated clinically; no anatomic abnormality was detected in any patient.

Table. IgG subclass measurements in 37 patients

	Immunoglobulin	Low		Low-normal		Total low or low-normal		Z*	P
		n	%	n	%	n	%		
Low IgG group	IgG1	8	57	6	43	14	100	7.86	<0.001
(n = 14)	IgG2	7	50	5	36	12	86	7.14	<0.001
	IgG3	1	7	3	21	4	29	1.33	NS
	IgG4	3	21	3	21	6	43	2.76	<0.01
	IgA	3	21	3	21	6	43	2.76	<0.01
Normal IgG group	IgG1	0	0	3	13	3	13	−0.39	NS
(n = 23)	IgG2	3	13	7	30	10	44	3.66	<0.001
	IgG3	0	0	4	17	4	17	0.13	NS
	IgG4	11	48	2	9	13	57	5.36	<0.001
	IgA	0	0	5	22	5	22	0.79	NS
All patients	IgG1	8	22	9	24	17	46	4.98	<0.001
(n = 37)	IgG2	10	27	12	32	22	60	7.30	<0.001
	IgG3	1	3	7	19	8	22	1.00	NS
	IgG4	14	38	5	14	19	51	5.81	<0.001
	IgA	3	8	8	22	11	30	2.32	<0.05

*Z statistic comparing estimated proportion with expected proportion of 16%.[22]
NS, Not significant.

Blood samples were obtained from these children by venipuncture. Serum was separated and stored in aliquots at −20° C. IgG, IgA, and IgM were measured by rate nephelometry using the Beckman ICS by the clinical laboratory of Henrietta Egleston Hospital; results were compared with normal ranges established for the system.[20] IgE was measured by Pathologists Service Professional Associates, Inc., Atlanta, using a radioimmunoassay and reagents from Kallestad Laboratories, Inc., Chaska, Minnesota. IgG subclasses were determined in the laboratory of Dr. Peter H. Schur, Brigham and Women's Hospital, Boston, by radial immunodiffusion using monospecific antisera.[21] Results were compared with measurements of IgG subclasses determined by Dr. Schur in 281 normal children.[21]

Linear regression was used to estimate the relationship between IgG subclasses and age for the normal children; age was assigned as the midpoint of the age category used by Dr. Schur.[21] Because of the skew of the IgG subclass measurements, the analysis used the logarithm (base 10) of a subclass measurement. The 68% and 95% large sample prediction intervals were determined by standard procedures.[22] Regression lines were determined by the method of least squares.[22]

In our patients low IgG, IgA, and IgM values were designated as those >2 SD below the geometric mean for normal children[20]; low-normal values were considered to be those between 1 and 2 SD below this mean. Low IgG subclass values were designated as those below the 95% prediction interval, and low-normal values as those between the lower 68% and 95% prediction intervals. Comparison of the distribution of immunoglobulins and subclass measurements for the two groups of abnormal children used the Mann-Whitney U test, two tailed. Estimated correlations are Spearman Rank Order Correlations, two tailed.

RESULTS

Immunoglobulin and IgG subclass measurements were made on sera from 37 children (24 boys) aged 6 months to 9.6 years (mean 2.8 years). The results from the 14 children who had low serum IgG levels (low IgG group) were compared with measurements in the remaining 23 children, whose serum IgG levels fell within the normal range (normal IgG group). Twenty-seven of the 37 children were receiving bronchodilators (theophylline or metaproterenol or both). Four children in the low IgG group and five in the normal IgG group were receiving a small dose of corticosteroid (prednisone <1 mg/kg) every other day. Thirteen of the other 28 children had received occasional short courses of high-dose therapy with prednisone in the past; only five had received corticosteroids during the previous month.

In 33 of 37 children one or more IgG subclass measurements were low (22 children) or low-normal (11) (Table). Assuming that results from our patients are distributed normally, 16% would be expected to have low or low-normal IgG levels. However, the study group had an increased percentage of children with low or low-normal levels of IgG1, IgG2, and IgG4 and of IgA values. This

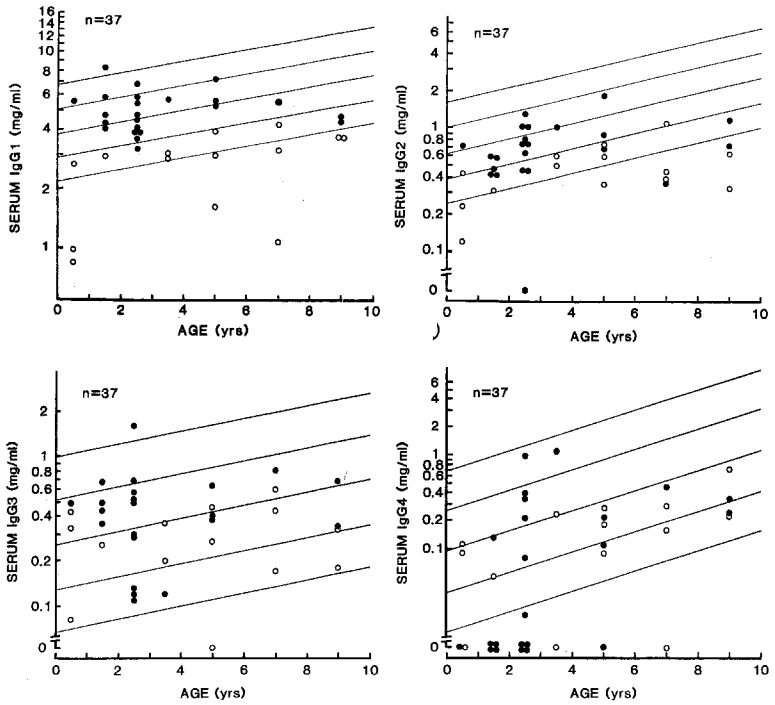

Figure. Serum concentration of each IgG subclass in each of 37 patients (o low IgG group; • normal IgG group), grouped according to the age categories used for normal individuals.[20] Estimated regression lines between IgG subclasses and age and 68% and 95% prediction intervals are indicated.

ranged from 30% of the children who had low or low-normal IgA to 60% who had low or low-normal IgG2. All children in the low IgG group had a low or low-normal IgG1 level; this group also had an abnormally high percentage of children with low or low-normal levels of IgG2 and IgG4 subclasses and of IgA. In the normal IgG group there was an increased number of low-normal levels of IgG (30%) and low or low-normal levels of IgG2 (44%) and IgG4 (57%). Although levels for each subclass increase with age in normal individuals, no such trend was seen in results from the 37 children in the study group (Figure). Also, most patients had an imbalance in subclass levels; that is, few had depression of level of all four subclasses.

DISCUSSION

It is difficult to compare our study with previous investigations of serum immunoglobulin concentrations in children with respiratory symptoms because of variations in criteria for patient selection and in statistical analysis. Several authors studied children with allergic diseases; others studied asthmatic children and included those with allergy. We specifically excluded children with evidence of allergy.

Low serum IgG values have been noted previously in children with severe chronic asthma. Collins-Williams et al.[3] documented low IgG levels in children with "intractable" asthma and in those not doing well despite vigorous treatment; low levels were not found before age 10 years. Berger et al.[15] also found low levels of IgG in many children who had severe chronic asthma. In their population, differences from normal were apparent by age 3 years. They found that children whose asthma was exacerbated by "infection" had lower IgG levels than did children in whom infection was not a major precipitant. They suggested that decreased IgG levels might reflect an intrinsic immunologic defect in children with severe chronic asthma and noted that steroids might play an additive role in causing decreased levels of IgG in children who had received steroid therapy.

Our study documents low IgG subclasses in a comparable study population. The children investigated are distinguished from the majority of asthmatic children, who usually have normal serum IgG levels, by the chronicity of their symptoms and the lack of allergic factors precipitating asthma. IgG subclass deficiency has been shown previously to be associated with low serum IgG levels[16, 17] and with selective IgA deficiency,[18, 19] both of which were present in increased frequency in our population. IgG subclass deficiency also is related to recurrent pulmonary

infections,[18, 19, 23] and respiratory tract infection–associated symptoms were a prominent feature of the medical history of these patients.

The possible effect of therapy, especially steroid therapy, on immune function in children with severe chronic asthma has been addressed previously.[15] Nine of 37 children in our study group were receiving steroid treatment in small dosage every other day; others had received short courses of high-dose steroid therapy. It is possible that steroids played an additive role in producing low IgG levels in certain children, but the majority of our patients either had never received steroids or had not received them recently; the low IgG values found in these children must be the result of other factors.

It is not clear whether any of the children younger than age 4 years have transient hypogammaglobulinemia of infancy. The diagnosis of transient hypogammaglobulinemia of infancy usually implies that spontaneous recovery will occur by age 2 to 4 years, and these children generally are free from infections. Such children are thought to have normal functional antibody capacity based on assessment of isohemagglutinins and diphtheria and tetanus antibody titers.[24] Although the outcome of individual patients reported here is not yet known, they are distinguished from children with benign transient hypogammaglobulinemia in several ways. Our patients had chronic respiratory symptoms. As a group these children did not demonstrate a trend of rising IgG subclass levels with increasing age. Additionally, IgG subclass imbalances were present in most of our patients; such imbalances were not found in two patients with transient hypogammaglobulinemia studied by Yount.[16] The possibility of a specific subclass deficiency, such as IgG2 deficiency, has not been assessed in other children thought to have transient hypogammaglobulinemia.[24] Measurement of diphtheria and tetanus titers or isohemagglutinins might not detect a deficiency of IgG2 because these antibody responses occur primarily in other subclasses or immunoglobulin classes.[16]

The results of our study raise the possibility that deficiency of IgG subclasses contributes directly to the severity and chronicity of these children's symptoms. Viral illnesses frequently are associated with exacerbations of asthma,[25] and IgG subclass abnormalities might predispose to more frequent or more severe viral illness. Many children in our study group had deficiency of IgG2, which is said to be the primary subclass to respond to polysaccharide antigens.[26, 27] Siber et al.[28] have demonstrated a correlation between IgG2 concentrations and antibody responses to polysaccharide antigens from the encapsulated bacteria *Streptococcus pneumoniae* and *Haemophilus influenzae*. Although bacteria are not thought to be associated with wheezing in asthmatic children,[25] bacterial and viral respiratory infections frequently occur together.[29] Encapsulated bacteria have been associated with chronic respiratory symptoms in children[25] and adults.[30-33] Chronic chest symptoms in children with IgG subclass deficiency might result from an inability to clear encapsulated bacteria present or increased in numbers as the result of inflammation initiated by other factors.

Our experience with these patients suggests that abnormal levels of IgG subclasses might play an etiologic role in the chronic chest symptoms of some of them. We currently are assessing functional antibody capacity in these children. Until more data regarding immune function are obtained, we do not recommend the routine use of immunoglobulin replacement therapy in such patients.

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