

The relationship of atopic disease and immunoglobulin levels with special reference to selective IgA deficiency

C. COLLINS-WILLIAMS, A. W. CHIU and E. A. VARGA*

*Department of Paediatrics, Division of Paediatric Allergy,
The Hospital for Sick Children, Toronto; and Department of Paediatrics,
University of Toronto, Toronto, Canada*

Summary

We have confirmed that the presence of IgE in selective IgA deficient patients does not give protection against increased susceptibility to infections. Atopic individuals with selective IgA deficiency may have higher levels of IgE than non-atopic individuals. Immunoglobulin levels for G, A or M tend to be lower in atopic individuals than in normal individuals.

Introduction

Ever since the isolation of immunoglobulin E (IgE) by Ishizaka, Ishizaka & Hornbrook (1966), and the finding of raised serum levels of IgE in asthma, hay fever and eczema (Johansson, 1967), attempts have been made to explain the function of this immunoglobulin. The best known action of IgE, that is in allergies, is harmful and of no obvious benefit to the individual or to the survival of the species, except in the immunity provided against intestinal worm disease (Rowe *et al.*, 1968).

Presumptive evidence suggests that the absence of IgE is deleterious (Ammann *et al.*, 1969a, b; Ammann, Roth & Hong, 1970; Cain *et al.*, 1969). The report of Ammann *et al.* (1969a) studied sixteen individuals with ataxia-telangiectasia. Both IgA and IgE levels were measured, and it was found that those individuals who lacked IgE usually had more frequent infections. Bigger *et al.* (1970), reviewing the same individuals and their immediate families, showed that 65% of the families were deficient in IgE and that no correlation could be made between the serum IgE, IgA, IgG or IgM and the clinical histories of infections. These authors suggested that the chance finding of absent IgE was recessively inherited. Schwartz & Buckley (1971) concluded from their study of twenty-six patients with selective IgA deficiency and recurrent infections that the presence of IgE had no protective effect. Good & Choi (1971) were in agreement.

Kaufman & Hobbs (1970) found one or more immunoglobulins to be two standard deviations below the norm in 6.7% of a very selected group of atopic patients.

The purpose of our investigation was to find out whether patients with selective

* Present address: 875 Ouellette Avenue, Windsor, Ontario, Canada.

Correspondence: Dr C. Collins-Williams, Chief, Division of Allergy, The Hospital for Sick Children, 555 University Avenue, Toronto 101, Ontario, Canada.

IgA deficiency are protected from infection by the presence of IgE, and also whether atopic patients have abnormally low serum levels of IgG, IgA and IgM.

Materials and methods

Study 1 (twenty-seven cases of selective IgA deficiency)

Sixteen of the subjects were children whose immunoglobulin levels were under study at The Hospital for Sick Children, Toronto. Members of their families accounted for four more of the subjects (one adult and three children) and the remainder (seven) were children whom a survey (Collins-Williams *et al.*, 1971) revealed as having selective IgA deficiency.

The serum IgA was estimated by radial diffusion in agar using the Hyland Immunoplate Human IgA (Hyland Immunoplate Model 085-030). This method is accurate for IgA levels in the range of 40-400 mg/100 ml. When the IgA levels were below 40 mg/100 ml the IgA was reassayed on the low-level Human IgA immunoplate (Hyland Immunoplate Model 085-110) which is accurate to 4 mg/100 ml.

All the subjects were examined and had serum IgG and IgM levels determined, both IgG and IgM being normal. Serum IgE levels were determined for twenty-two of the subjects by Dr Johansson in Sweden using the radio-immunosorbent method.

Study 2 (188 previously reported cases of asthma)

The results of a study made by Collins-Williams *et al.* (1967) were reviewed for abnormally low levels of IgG, IgA or IgM.

Study 3 (277 private cases of atopy in children)

These were consecutive cases in which quantitative serum immunoglobulins were estimated. The results of immunoglobulin determinations were reviewed for levels of serum IgG, IgA or IgM two standard deviations or more below the normal mean.

Results

Study 1

Table 1 shows the IgE levels in twenty-two of the twenty-seven subjects listed. Included in this table are the 95% confidence limits set by Berg & Johansson (1969) for the various ages.

Nine of the subjects with selective IgA deficiency have atopy, eight children having asthma and a parent having allergic rhinitis. Two of the nine are free of any disease attributable to selective IgA deficiency. The other seven have frequent respiratory infections. IgE was measured in six of these, two had IgE levels above normal.

Eighteen of the subjects with selective absence of IgA are considered non-atopic, that is, to date they have not manifested any definite atopic symptoms. Among these eighteen, eight were found to be healthy except for the occurrence of psoriasis (one case) and multiple haemangiomas without neurological signs (one case). Eight had frequent respiratory infections. Two patients (10 and 11) have other illnesses possibly associated with IgA deficiency. IgE was measured in sixteen of these, only one had a level above normal.

Of the total of ten healthy patients seven had serum IgE levels measured, of which four were below the 95% confidence limits. Of the seventeen ill patients, fifteen had serum IgE levels measured, of which only three were below the 95% confidence limits.

Table 1. IgE levels in subjects with selective absence of IgA

Patient	Sex	Age (years)	IgE (ng/ml)	95% confidence limits	Clinical details
ATOPIC					
1	M	11	490	(55-703)	Asthma, eczema, bronchiectasis, RURTI
2	M	4	35	(57-244)	Asthma, RURTI
3	M	14	84	(69-1040)	Asthma, urticaria, angioedema, PAR, RURTI
4	F	9	ND		Asthma, RURTI
5	F	7½	3465	(46-860)	Asthma, urticaria, angioedema, RURTI
6	F	6	607	(64-523)	Asthma, eczema, PAR, RURTI
7	M	8	ND		Asthma, hay fever, RURTI
8	M	6	81	(64-523)	Asthma (until 4 years, well now), 'healthy'
9	F	41	ND		Allergies to house dust and grasses, 'healthy'
NON-ATOPIC					
10	F	12	57	(55-703)	Granulomatous colitis, urticaria*
11	M	7	160	(46-861)	Polyarthrits, thalassaemia minor
12	F	8	37	(46-561)	Cataracts, RURTI
13	F	10	61	(53-826)	Recurrent pneumonia, atelectasis
14	F	3	80	(57-244)	RURTI
15	F	11	700	(55-703)	RURTI
16	M	16	10	(69-1040)	Chronic RURTI
17	M	10	120	(53-826)	Croup, RURTI
18	M	14	76	(69-1040)	Ataxia telangiectasia, chest infections
19	F	8	58	(46-861)	Ataxia telangiectasia, RURTI
20	F	7	1800	(46-861)	'Healthy', multiple haemangiomas
21	M	12	ND		'Healthy' except for psoriasis
22	F	14	47	(69-1040)	'Healthy'
23	M	11	315	(55-703)	'Healthy'
24	F	11	31	(55-703)	'Healthy'
25	M	8	13	(46-860)	'Healthy'
26	F	12	45	(55-703)	'Healthy' now, RURTI as a preschooler
27	F	15	ND		'Healthy'

RURTI = recurrent upper respiratory tract infection. PAR = perennial allergic rhinitis. 'Healthy' = with no known disease, even repeated respiratory infections, or with an illness not considered to be related to IgA deficiency (e.g. psoriasis). ND = Not done.

* One isolated, unexplained bout of urticaria.

Study 2

The review of the published data on immunoglobulin levels in 188 asthmatic children, studied as groups because our original data had been discarded, revealed that many of the children had a significantly lowered immunoglobulin level of IgG, IgA or IgM ($P < 0.05$) (Table 2).

Study 3

The 277 patients, 164 boys and 113 girls aged 2 months to 19 years, were all allergic children with one or more of the following diseases: asthma (169 children), atopic dermatitis, hay fever, perennial allergic rhinitis with or without frequent upper respiratory infections, urticaria, allergic conjunctivitis, allergic croup or serous otitis media. Two hundred and forty-five (88%) of the children showed positive skin tests.

Table 2. Immunoglobulin levels in atopic individuals, expressed as the difference (*P*) between the mean values for the patients and the normal means for age

Group	Age (years)	No. of subjects	<i>P</i> (IgA)	<i>P</i> (IgG)	<i>P</i> (IgM)
1 Asthmatic, intractable	2-4	0	—	—	—
	5-9	16	NS*	NS	0.03
	10-15	17	NS	0.02	NS
2 Asthmatic, responding to treatment	2-4	0	—	—	—
	5-9	8	NS	NS	0.001
	10-15	12	NS	NS	NS
3 With allergic respiratory disease other than asthma	2-4	9	0.001	NS	NS
	5-9	28	0.01	NS	0.001
	10-15	12	NS	0.01	0.02
4 Asthmatic, untreated	2-4	20	0.02	NS	NS
	5-9	22	0.001	0.009	0.001
	10-15	6	0.05	NS	NS
5 Asthmatic, treated but doing poorly	2-4	7	NS	NS	NS
	5-9	18	NS	NS	0.002
	10-15	13	NS	0.03	0.01

* NS, not significant. $P > 0.05$.

Twelve patients (4.3%) had serum immunoglobulin levels (IgG, IgA or IgM) two standard deviations below the mean for their age, one child having both low IgA and IgM (Table 3).

Discussion

The data suggest that IgE has no protective effect in IgA deficient patients since patients with no IgA and very low levels of IgE had no increased incidence of repeated infections.

Of the two patients with very high levels of IgE, patient 5 has been a severe asthmatic with frequent infections exacerbating her asthma; patient 20 had multiple haemangiomas with no abnormal neurological findings and no history of atopy. The peripheral eosinophil counts were 10% and 4% respectively. The high levels of IgE which have been associated with chronic uncontrollable infections (Arbesman & Ito, 1971; Buckley, Wray & Belmaker, 1971) might explain the high IgE in patient 5. The possibility of parasitic infections was not investigated in either patient.

Atopic patients are shown to have IgE levels higher than average for their age, with lower than average levels of one or more of the other three immunoglobulins G, A or M. In addition to the above figures, a study (Collins-Williams *et al.*, 1971) of 2170 'healthy' school children from a general population of school children, both

Table 3. Numbers of atopic children in different age groups with immunoglobulin levels 2 SD below the mean (total patients 277)

Age	Patients	Patients with immunoglobulin level 2 SD or more below the normal mean*		
		IgG	IgA	IgM
2-6 months	2	0	0	0
7-12 months	3	1	0	0
13-23 months	14	0	0	0
2-4 years	71	0	3	0
5-9 years	134	0	6†	2
10-15 years	49	0	1†	0
16-19 years‡	4	0	0†	0

* As defined by Collins-Williams *et al.* (1967).

† These figures are true also if the revised means for this age group as reported by Collins-Williams *et al.* (1971) are used.

‡ Normal values assumed to be the same for the 10-15 year group (i.e. adult values).

atopic and 'non-atopic', showed IgA levels to be below the 95% confidence limit in thirty-two (1.47%), which is much lower than the figure for a purely atopic population. In a series of 183 normal patients over 12 months of age reported by Collins-Williams *et al.* (1967) as being a healthy population with no history of recurrent or concurrent infection, allergies, chronic diseases affecting the liver and kidney or collagen diseases, no patient had an immunoglobulin value (IgA, IgG or IgM) two standard deviations below the mean. Our figures, therefore, confirm the finding of Kaufman & Hobbs (1970) that atopic individuals tend to have levels of one or more of the immunoglobulins, other than IgE, below the mean for age.

Acknowledgments

The authors are grateful to Dr S. G. O. Johansson for performing the IgE determinations; to Dr Margaret Wood, biostatistician, The Hospital for Sick Children, Toronto, for helping in the analysis of our data; to the Medical Publications Department, The Hospital for Sick Children, Toronto, for helping in the preparation of the manuscript and to the Medical Research Council (Grant MA-3504).

References

- AMMANN, A.J., CAIN, W.A., ISHIZAKA, K., HONG, R. & GOOD, R.A. (1969a) Immunoglobulin E deficiency in ataxia-telangiectasia. *New England Journal of Medicine*, **281**, 469.
- AMMANN, A.J., GOOD, R.A., BIER, D. & FUDENBERG, H.H. (1969b) Long-term plasma infusions in a patient with ataxia-telangiectasia and deficient IgA and IgE. *Pediatrics*, **44**, 672.
- AMMANN, A.J., ROTH, J. & HONG, R. (1970) Recurrent sinopulmonary infections, mental retardation, and combined IgA and IgE deficiency. *Journal of Pediatrics*, **77**, 802.
- ARBESMAN, C.E. & ITO, K. (1971) A new method for measuring IgE. Presented at the American Academy of Allergy, Chicago, Illinois, 22-24 February.
- BERG, T. & JOHANSSON, S.G.O. (1969) Immunoglobulin levels during childhood, with special regard to IgE. *Acta Paediatrica Scandinavica*, **58**, 513.
- BIGGAR, D., LAPOINTE, M., ISHIZAKA, K., MEUWISSEN, H.J. & GOOD, R.A. (1970) IgE in ataxia-telangiectasia and family members. *Lancet*, **ii**, 1089.

- BUCKLEY, R.H., WRAY, B.B. & BELMAKER, E.Z. (1971) Extreme hyperimmunoglobulinemia E and undue susceptibility to infection. Presented at the American Academy of Allergy, Chicago, Illinois, 22-24 February.
- CAIN, W.A., AMMANN, A.J., HONG, R., ISHIZAKA, K. & GOOD, R.A. (1969) IgE deficiency associated with chronic sinopulmonary infection. (Abstract). *Journal of Clinical Investigation*, **48**, 12A.
- COLLINS-WILLIAMS, C., KOKUBU, L., LAMENZA, C., NIZAMI, R., CHIU, T.A.W., LEWIS-MCKINLEY, C., COMERFORD, T.A. & VARGA, E.A. (1971) Incidence of isolated deficiency of immunoglobulin IgA in the serum of Canadian children. (To be published).
- COLLINS-WILLIAMS, C., TKACHYK, S.J., TOFT, B., GENEROSA, L. & MOSCARELLO, M. (1967) Quantitative immunoglobulin levels (IgG, IgA and IgM) in children with intractable asthma. *Annals of Allergy*, **25**, 177.
- COLLINS-WILLIAMS, C., TOFT, B., GENEROSA, L. & MOSCARELLO, M. (1967) Quantitative immunoglobulin levels (IgG, IgA and IgM) in children determined by the Hyland Immunoplate technique. *Canadian Medical Association Journal*, **96**, 1510.
- GOOD, R.A. & CHOI, Y.S. (1971) Relation of IgA and IgE to bodily defenses. *New England Journal of Medicine*, **284**, 552.
- ISHIZAKA, K., ISHIZAKA, T. & HORN BROOK, M.M. (1966) Physicochemical properties of reaginic antibody. V. Correlation of reaginic activity with γ -E-globulin antibody. *Journal of Immunology*, **97**, 840.
- JOHANSSON, S.G.O. (1967) Raised levels of a new immunoglobulin class (IgND) in asthma. *Lancet*, **ii**, 951.
- KAUFMAN, H.S. & HOBBS, J.R. (1970) Immunoglobulin deficiencies in an atopic population. *Lancet*, **ii**, 1061.
- ROWE, D.S., MCGREGOR, I.A., SMITH, S.J., HALL, P. & WILLIAM, K. (1968) Plasma immunoglobulin concentrations in a West African (Gambian) community and in a group of healthy British adults. *Clinical and Experimental Immunology*, **3**, 63.
- SCHWARTZ, D.P. & BUCKLEY, R.H. (1971) Serum IgE concentrations and skin reactivity to anti-IgE antibody in IgA-deficient patients. *New England Journal of Medicine*, **284**, 513.

This document is a scanned copy of a printed document. No warranty is given about the accuracy of the copy. Users should refer to the original published version of the material.