

IgE and IgG4 subclass in atopic families

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Summary

Raised levels of IgG4 were present in twelve (35%) of thirty-four asthmatic children and raised levels of IgE in twenty-three (68%). Eighteen of 104 first degree relatives also had raised levels of IgG4, thirteen had no history of atopic disease and nine failed to give positive skin reactions to *Dermatophagoides pteronyssinus* or to mixed grass pollens. Fifteen relatives had raised IgE, five without symptoms.

No relationship was noted between either raised levels of IgE or IgG4 and infant feeding. Although these immunoglobulin patterns were not consistently associated with symptoms they did tend to be associated in atopic families and it is suggested that the same polygenic factors may govern the IgE and IgG4 levels.

Introduction

Antibodies associated with immediate allergic reactions in man usually belong to the IgE class. However, not all people who have positive skin reactions on prick testing have raised serum levels of IgE (Parish, 1970); nor are specific antibodies of the IgE class always present in subjects who have positive bronchial responses to a particular antigenic challenge (Aas & Johansson, 1971; Stenius *et al.*, 1971). Parish (1970) produced evidence that IgG antibodies were responsible for some immediate allergic reactions and called them 'short-term anaphylactic IgG antibodies'. They have since been shown to be associated with asthma in some atopic subjects with normal levels of IgE (Bryant, Burns & Lazarus, 1973). Evidence has also been produced to suggest that these 'short-term anaphylactic IgG antibodies' may belong to the IgG4 subclass (Stanworth & Smith, 1973).

We have described the clinical features associated with raised serum levels of IgG4 in asthmatic children (Gwynn *et al.*, 1978); and now propose to describe the findings in their first degree relatives

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Patients and methods

Thirty-four asthmatic children from twenty-nine families attending the Central Asthma Clinic in Birmingham were selected because both parents and at least two siblings were available and prepared to take part in the study. All the patients had previously been tested by skin prick to some thirty-five common allergen extracts and had been shown to have positive reactions to at least one of them.

Parents and siblings were similarly tested with extracts of *D. pteronyssinus* and mixed grass pollens and a detailed allergic history was taken. Serum levels of IgE, total IgG and the IgG subclasses were measured. Total IgE was estimated by the double antibody technique (DAT), total IgG and IgG subclasses by a microscale version of a radial immunodiffusion method (Shakib *et al.*, 1975).

Results

Of the thirty-four asthmatic children, twelve (35%) had elevated levels of IgG4 (Tables 1 and 2). This was associated with a poor response to sodium cromoglycate. In patients with raised levels of both IgG4 and IgE eczema was a prominent feature (Table 1), being present in nine out of eleven cases. Sixteen out of the thirty-four children (47%) had raised levels of IgE and normal levels of IgG4 (Table 3). These children responded well to sodium cromoglycate. None had eczema.

Table 1. Patients with elevated levels of IgG4 and IgE

Patient	Age	IgG4 (g/l)	IgE (u/ml)	Associated atopy	Current treatment
J.C.	15	3.88	> 2500	Eczema and hay fever	Aerosol steroid and prednisolone
A.P.	13	0.433	500	Eczema and hay fever	DSCG
S.W.	16	1.32	2150	Eczema and hay fever	Aerosol steroid and prednisolone
C.W.	14	0.374	> 2520	Eczema and hay fever	Aerosol steroid
R.P.	17	0.732	2020	Eczema and hay fever	Aerosol steroid
A.Pu.	15	0.192	760	Hay fever	Aerosol steroid
P.W.	14	0.239	555	—	DSCG
J.Co.	23	0.432	2500	Eczema as a child	Aerosol steroid
R.E.	33	0.197	5000	Eczema as a child	Aerosol steroid
K.L.	35	0.35	1350	Eczema as a child	DSCG
M.R.	21	0.485	400	Eczema as a child	DSCG

Normal range of IgG4 = 0–0.185 g/l.

Normal range of IgE = 0–375 u/ml.

Table 2. Patients with elevated levels of IgG4 only

Patient	Age	IgG4 (g/l)	IgE (u/ml)	Associated atopy	Current treatment
M.C.	16	0.26	282	Hay fever	Aerosol steroid
P.C.	18	0.198	71	Hay fever	Aerosol steroid
K.H.	15	0.352	118	—	No treatment
C.K.	10	0.181	224	Hay fever	Aerosol steroid
P.Q.	15	0.346	100	—	Aerosol steroid

Table 3. Patients with elevated levels of IgE only

Patient	Age	IgG4 (g/l)	IgE (u/ml)	Associated atopy	Current treatment
B.A.	12	0.074	1345	Hay fever	DSCG
K.B.	7	0.125	700	—	DSCG
A.H.	15	0.049	600	—	DSCG
D.H.	16	0.01	6650	—	DSCG
S.K.	15	0.048	650	—	DSCG
S.Ke.	17	0.031	400	—	DSCG
P.K.	13	0.043	539	—	Aerosol steroid
N.K.	8	0.055	543	—	DSCG
J.M.	14	0.025	2290	Hay fever	Aerosol steroid
J.Q.	13	0.012	515	—	DSCG
L.S.	15	0.015	2200	—	DSCG
A.S.	14	0.046	1050	—	DSCG
C.S.	12	0.078	3400	—	DSCG
A.Sh.	9	0.177	1820	—	DSCG
M.E.	12	0.093	1050	Hay fever	DSCG
C.W.	18	0.072	510	Hay fever	Aerosol steroid

Normal range of IgG4 = 0–0.185 g/l.

Normal range of IgE = 0–375 u/ml.

Of the 104 relatives, eighteen (17%) (ten parents and eight siblings) had raised IgG4 levels. Only five (28%) had symptoms of atopic disease and nine had positive skin reactions to extracts of *D. pteronyssinus* and/or mixed grass pollens (Table 4). Three relatives had raised levels of both IgE and IgG4, all had positive skin reactions and one or more atopic manifestation although eczema was present in only one case. Fifteen relatives (14%) had raised IgE levels and of these ten (66%) had a history of some atopic disease.

Of the eighty children in these atopic families, thirty-one had been breast fed and forty-nine bottle fed. The relationship of infant feeding to the immunoglobulin levels is shown in Table 5.

Infant feeding did not appear to have had any significant effect on these immunoglobulin levels.

Eighteen of the twenty-nine families had a member with raised IgG4 and fifteen of these eighteen families also had members with raised IgE. Twenty-one of the twenty-nine families had a member with raised IgE and, of these, fifteen families had a member with raised IgG4.

Total circulating IgG levels bore no relation to levels of IgG4 except in one child with multiple severe atopic manifestations in whom the IgG4 comprised 21% of the total IgG. In others with raised IgG4 the amount was insufficient to raise the total IgG.

Discussion

We have found that raised levels of IgG4 occur frequently in atopic subjects. Thirty-five per cent of asthmatic children had raised levels of IgG4 and 68% raised IgE levels. Seven (20%) had raised levels of both immunoglobulins. Of their first degree relatives 17% had raised levels of IgG4 and 14% raised levels of IgE.

Table 4. First degree relatives with raised levels of IgG4

Patient	Age	IgG4 (g/l)	IgE (u/ml)	Clinical atopic disease	Positive skin reaction to house dust mite and/or grass pollen
M.S.	P	1.00	490	Hay fever Asthma Eczema	Yes
J.S.	16	0.641	720	Hay fever	Yes
A.E.	21	0.90	412	Hay fever Asthma	Yes
M.E.	P	1.71	60	—	Yes
S.E.	P	1.62	171	—	Yes
M.P.	P	0.48	5	Hay fever	Yes
M.K.	P	0.918	118	—	No
S.K.	P	0.332	126	—	No
S.Ke	P	0.623	150	—	No
M.D.	P	0.612	36	—	No
P.D.	13	0.359	89	Asthma Hay fever	Yes
M.H.	P	0.268	10	—	No
T.Q.	8	0.203	44	—	No
M.Q.	15	0.436	14	—	No
R.H.	13	0.271	103	—	No
B.C.	19	0.186	37	—	Yes
D.K.	14	0.241	41	—	Yes
M.Ki	P	0.632	—	—	No

Normal range of IgG4: 0–0.185 g/l.

Normal range of IgE: 0–375 u/ml.

P = Parent.

Raised IgG4 levels in the asthmatic children were associated with a poor response to sodium cromoglycate, and raised levels of both IgE and IgG4 with the presence of both asthma and eczema (Gwynn *et al.*, 1978). Only two out of twenty individuals with elevated levels of IgG4 responded to disodium cromoglycate. These patients also had elevated levels of IgE, so it may be that IgE was playing the major role in causing their symptoms.

Like serum levels of IgE, an elevated level of IgG4 was not always associated

Table 5. Relationship of infant feeding to immunoglobulin levels

Infant feeding	Raised levels			Normal levels	Total
	IgE and IgG4	IgE only	IgG4 only		
Breast fed	4	9	6	12	31
Bottle fed	5	14	5	25	49
Total	9	23	11	37	80

Differences are not significant.

with clinical disease, 72% of first degree relatives with raised IgG4 and 33% of those with raised IgE had no atopic symptoms.

There seems to be no obvious single inherited factor leading to the production of abnormally high levels of IgG4 rather than IgE. The production of both immunoglobulins may be governed by the same polygenic factors, as both raised levels of IgE and IgG4 tend to appear in the same families. We found only two out of twenty-nine families where IgG4 alone was raised and five families where IgE alone was raised. In two families both husband and wife had raised IgG4 levels with no clinical manifestation of allergic disease.

A significant proportion of allergic reactions may be due to IgG4 as well as IgE, and clinical manifestations are not confined to asthma, but may also be characterized by eczema and hay fever. Further studies of immunoglobulin patterns in allergic families, associated with genetic information, may help to answer some of the unexplained aspects of the pathogenesis of atopic disease.

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