

Autoanti-IgE antibodies in patients with allergic and idiopathic rhinitis

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The pathophysiology of idiopathic rhinitis is unknown although evidence is accumulating to suggest that, in a proportion of patients, it may be a more localized form of allergic rhinitis in the absence of other atopic symptoms and markers. Anti-IgE is thought to be a systemic marker of atopy. This study compared serum IgG autoanti-IgE levels in patients with idiopathic rhinitis, perennial allergic rhinitis and normal controls. Serum samples were obtained from 19 patients with idiopathic rhinitis, 17 patients with perennial allergic rhinitis and 10 normal non-rhinitic controls. The presence or absence of IgG1 and IgG4 anti-IgE antibodies was detected using enzyme-linked immunosorbent assays. Eighty-eight percent of the patients with perennial allergic rhinitis had raised levels of autoanti-IgE antibodies in their serum. None of the controls or patients with idiopathic rhinitis showed raised levels ($P < 0.001$). Although patients with idiopathic rhinitis may exhibit clinical and pathological features of allergy, they do not show raised levels of anti-IgE in their serum.

Keywords allergic rhinitis IgE non-allergic rhinitis idiopathic rhinitis vasomotor rhinitis

Idiopathic rhinitis is now the accepted nomenclature for the condition previously referred to as vasomotor rhinitis, intrinsic rhinitis or non-allergic perennial rhinitis.^{1,2} Knowledge of the pathophysiology of the condition is limited, largely because it is a diagnosis of exclusion and previous studies have had flaws in patient selection.¹ The term vasomotor rhinitis has often been used loosely to describe patients with nasal symptoms who had no evidence of atopy with negative skin tests and normal IgE levels or in whom no evidence of other disease could be found. The term vasomotor rhinitis should no longer be used. Patients whose primary symptom is clear rhinorrhoea without nasal obstruction or sneezing, and who are usually over 60 years of age, have an autonomic rhinitis. These patients have often been amalgamated with other non-atopic patients and this may have confused the picture both clinically and pathologically when patients with 'non-allergic' rhinitis have been studied.^{3–5} Patients with

idiopathic rhinitis show evidence of an IgE-mediated inflammatory disease process in the nasal mucosa^{6,7} but without raised serum IgE. It is now known that IgE can be synthesized within the nasal mucosa⁸ and that allergic inflammatory changes can occur without a rise in serum IgE.⁹ This has led workers to suggest that patients with idiopathic rhinitis may show 'local mucosal allergy' in the absence of atopic markers.⁶ It is known that anti-IgE antibodies are present in the serum of patients with a wide spectrum of allergic diseases^{10–13} and their production may be a systemic response to inhibit the inflammatory cascade.^{14–16} Anti-IgE activity is confined to IgG1 and IgG4 subclasses, with IgG4 being responsible for a high percentage of the activity.¹⁷ In this study, we compared the serum levels of IgG1 and IgG4 autoantibodies with IgE in three patient groups: normal controls, patients with idiopathic rhinitis and patients with perennial allergic rhinitis. In our cohort of patients with idiopathic rhinitis, we discovered evidence of allergic-type inflammation at a mucosal level,^{6,7} but we hypothesized that these patients would not show a raised level of systemic autoantibody to IgE, in contrast to patients with allergic disease.

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Patients and methods

PATIENT SELECTION

With ethical committee approval, patients presenting to the Otorhinolaryngology – Head & Neck Surgery Department in Nottingham were screened for possible inclusion in a rhinitis research clinic. The investigative algorithm utilized to establish a diagnosis of isolated idiopathic rhinitis has previously been published in detail.¹ In summary, patients had to fulfil the following criteria:

1. Two from three symptoms of rhinitis (nasal obstruction, rhinorrhoea and irritation/sneezing) for at least 1 h per day for the last 3 months.²
2. No personal or first-degree relative history of asthma or other atopic disease.
3. Normal total and specific serum IgE to aeroallergens.
4. Negative skin-prick testing to aeroallergens (< 2 mm wheal; Allergopharma, Newark, UK).
5. Negative history of a primary symptom of clear rhinorrhoea, responsive to ipratropium bromide.
6. No history of occupational rhinitis.
7. Normal angiotensin-converting enzyme (ACE) and anti-neutrophil cytoplasmic antibody (ANCA) titres.
8. Straight nasal septum.
9. No previous nasal or sinus surgery.
10. No pregnancy or possible drug-induced rhinitis.
11. Normal rigid nasal endoscopy.
12. Normal sinus computerized tomography (CT) appearances.
13. No systemic or local antihistamine for 3 months.
14. No systemic or topical nasal steroid for 3 months.

For inclusion in the perennial allergic rhinitis group, patients had to fulfil criteria 1 and 5–14 and also a positive skin-prick test (> 5 mm wheal) or raised specific IgE to perennial allergens (house dust mite, feathers, cats, dogs, horses).

For inclusion in the control group, patients had to fulfil criteria 2–14.

Nineteen patients with idiopathic rhinitis, 17 with perennial allergic rhinitis and 10 normal control patients fulfilled the inclusion criteria and were recruited into the study. All patients gave their full informed consent and 10 ml of serum was obtained by antecubital fossa venepuncture.

IGG1 AND IGG4 ANTI-IGE ASSAY

IgG1 and IgG4 anti-IgE antibodies were measured using an enzyme-linked immunosorbent assay (ELISA). The IgE protein used to coat the ELISA microtitre plate wells was isolated from the plasma of an IgE myeloma patient (WT; lambda light chain). The IgE protein was isolated in pure form by precipitation and chromatography to remove contaminants.¹⁸

Serum samples were diluted 1:5 and incubated in IgE-coated (2 µg/ml) microtitre wells (Dynatech Laboratories, Sussex); bound immunoglobulin was detected using mouse monoclonal anti-human IgG1 and IgG4 (Oxoid, Basingstoke). The colour reaction was developed with 100 µl of alkaline phosphatase-conjugated goat anti-mouse IgG (1/500) and p-nitrophenyl phosphate as enzyme substrate (Sigma, Poole). Plates were read on an optical densitometer/plate reader (Dynatech, Sussex) and the mean of duplicate optical density readings was taken following background correction (serum wells with IgE omitted). Values above 0.1 were taken as positive. Four patients known to have raised levels from a pilot study were used as positive controls for one assay only.

DATA ANALYSIS

Data was analysed using Pearson's exact test (STATXACT 4 for Windows) with significance set at the $P = 0.05$ level.

Results

Fifteen patients (88%) with perennial allergic rhinitis showed raised levels of either IgG1 or IgG4 to IgE. Five (29%) had raised IgG1, eight (47%) had raised IgG4 and two (12%) patients had elevated levels of both. No patients from the idiopathic rhinitis or control groups showed elevated levels of either antibody. The data is summarized in Table 1 and detailed in Table 2.

The PAR group significantly differed from the idiopathic rhinitis and control groups when tested independently ($P < 0.001$).

Discussion

We have shown that patients with idiopathic rhinitis, selected using a rigorous algorithm, do not have raised levels of autoanti-IgE antibodies in their systemic circulation. This is in contrast to patients with perennial allergic rhinitis, in which 88% show raised levels of these antibodies. We categorized patients as either 'positive' or 'negative' for the presence of autoantibodies, as it is known that there is a poor correlation between exact titre levels and disease activity.^{12,14}

Previous studies investigating idiopathic rhinitis have been flawed by the inclusion of patients on anti-allergy

Table 1. Results of positive IgG1 and IgG4 anti-IgE enzyme-linked immunosorbent assay (% in brackets)

	<i>n</i>	IgG1	IgG4	IgG1 and IgG4	IgG1 or IgG4
Allergic rhinitis	17	7 (29%)	8 (47%)	2 (12%)	15 (88%)
Idiopathic rhinitis	19	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Control	10	0 (0%)	0 (0%)	0 (0%)	0 (0%)

Table 2. Individual titres for anti-IgG1 and anti-IgG4 (optical readings over 0.1 are in bold type)

Number	Category	IgG1	IgG4	Number	Category	IgG1	IgG4	Number	Category	IgG1	IgG4	Number	Category	IgG1	IgG4
1	IR	0.042	0.054	14	PAR	0.029	0.078	27	IR	0.016	0.017	40	PAR	0.032	0.195
2	IR	0.027	0.036	15	IR	0.033	0.015	28	IR	0.010	0.018	41	NC	0.008	0.009
3	IR	0.095	0.065	16	PAR	0.021	0.130	29	PAR	0.284	0.395	42	PAR	0.068	0.506
4	IR	0.060	0.043	17	PAR	0.111	0.033	30	IR	0.037	0.029	43	NC	0.085	0.027
5	IR	0.031	0.067	18	IR	0.021	0.015	31	IR	0.009	0.032	44	PAR	0.761	-
6	PAR	0.291	1.709	19	NC	0.017	0.048	32	NC	0.028	0.013	45	PAR	-	0.116
7	IR	0.042	0.041	20	PAR	1.015	0.007	33	PAR	0.217	0.084	46	NC	0.006	0.021
8	IR	0.023	0.032	21	NC	0.030	0.046	34	PAR	0.002	0.128				
9	IR	0.079	0.075	22	PAR	0.744	-	35	NC	0.031	0.017				
10	IR	0.017	0.061	23	PAR	-	0.222	36	NC	0.004	0.008				
11	PAR	0.017	0.501	24	NC	0.012	0.085	37	IR	0.033	0.096				
12	IR	0.008	0.051	25	NC	0.016	0.016	38	IR	0.020	0.018				
13	IR	0.033	0.092	26	PAR	0.019	0.015	39	PAR	0.027	0.167				

medication with other types of non-allergic rhinitis (e.g. autonomic rhinitis) and those with other synchronous nasal disease.^{1,3-5} We feel it is essential to perform nasal endoscopy and serum serology on all research patients with rhinitis in order to exclude other potentially confounding variables. Previously, it has been claimed that up to 35% of patients with non-allergic rhinitis have raised levels of IgG1 and IgG4 anti-IgE.¹¹ However, the selection algorithm used in this previous work was different to that in the present study and it is possible that patients with other forms of rhinitis or other systemic diseases entered the non-allergic group. Our finding that our normal control patients tested negatively (in contrast to the 10% who had raised levels in our previous study)¹¹ adds support to the selection criteria we used in this work.

The concept of blocking antibodies in allergic reactions was first introduced in 1935,¹⁹ but it was only when detailed assays became available that naturally occurring anti-IgE was identified.²⁰ IgG autoanti-IgE antibodies are now known to be present in the serum of patients with atopic disorders such as asthma and urticaria^{10,12,21} and also in helminth infections.¹⁸ Although their exact role is uncertain,^{14,16,22} it is known that high levels of these antibodies at birth protect children from the development of atopic disease.²³ IgG1 and IgG4 anti-IgE can prevent the binding of IgE to its high affinity receptor by competitive inhibition¹¹ and, thus, it is possible that they have a protective role in reducing the allergic inflammatory cascade in the systemic circulation.²² More recently, anti-IgE antibodies have been used therapeutically against atopic disease,^{24,25} but their exact efficacy remains to be determined.²⁶

The diagnosis of allergic rhinitis is made on the basis of positive skin-prick tests or raised levels of specific IgE in the serum,²⁷ yet this only establishes a diagnosis of 'atopy'. The term atopy was first used in 1923 to describe a tendency to develop immediate-type hypersensitivity reactions to allergens.²⁸ Since then, the word 'allergy' has become synonymous with atopy, but should ideally be only used to describe 'changed or altered reactivity' at a tissue level involving Th2 helper cells.²⁹

Th2 helper cells produce interleukin 4 (IL-4) and IL-13, which upregulate IgE synthesis.²⁹ Mast cells and eosinophils also produce these cytokines within the nasal mucosa and may help to promote the inflammatory cascade by producing IgE within the nasal mucosa itself.⁸ In our laboratories, nasal mast cells, eosinophils and IgE-positive cells are now known to be increased in number in a similar cohort of patients with idiopathic rhinitis.⁶ In a detailed study, we have also showed that approximately two-thirds of patients with idiopathic rhinitis, chosen with an identical selection algorithm to that utilized in the current study, had abnormal nasal challenge tests.⁷ Interestingly, the vast majority of these patients tested positively to house dust mite allergens. The findings from these two papers add to the evidence suggesting that a type-I

allergic inflammation may be occurring in the nasal mucosa in the absence of positive skin-prick tests or raised serum IgE.

The data from this present study suggests that this localized mucosal inflammation does not trigger a systemic IgG response against IgE in patients with idiopathic rhinitis, but the exact reasons for this are not clear.

Further work needs to be performed to ascertain why the inflammatory cascade remains confined within the nasal mucosa and to establish the exact role of allergens (and especially the house dust mite) in the pathophysiology of idiopathic rhinitis.

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