

Atypical nasal challenges in patients with idiopathic rhinitis: more evidence for the existence of allergy in the absence of atopy?

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Summary

Background The pathophysiology of idiopathic rhinitis is unknown although evidence is accumulating to suggest that many patients may have a localized form of allergic rhinitis in the absence of other atopic symptoms and markers. This study compares detailed nasal challenge results obtained from patients with idiopathic rhinitis to those of atopic and normal controls.

Methods Patients with idiopathic rhinitis ($n = 23$), perennial allergic rhinitis ($n = 8$) and normal controls ($n = 8$) underwent a normal saline challenge to exclude hyper-reactivity and then bilateral nasal allergen challenges. Nasal patency was assessed by anterior active rhinomanometry.

Results All of the patients with atopic rhinitis demonstrated positive bilateral allergen challenges. All normal control subjects had bilateral negative challenges. Two patients in the idiopathic group tested positively to saline and were excluded from further study with 62% of the remainder testing positive to allergens. Of the idiopathic patients testing positive, 85% were sensitive to house dust mite.

Conclusion A significant proportion of patients with idiopathic rhinitis have positive nasal challenges, the vast majority to house dust mite allergen. These findings add to the weight of evidence that suggests 'localized allergy' may exist in the absence of systemic atopic markers.

Keywords allergy; idiopathic rhinitis; non-allergic rhinitis; allergen challenge; rhinomanometry; vasomotor rhinitis

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Introduction

Idiopathic rhinitis (IR) is now the accepted term for the condition previously known as intrinsic rhinitis or non-allergic perennial rhinitis [1, 2]. The pathophysiology of IR is poorly understood but is distinct from true vasomotor rhinitis or autonomic rhinitis which is characterized by having a primary symptom of clear rhinorrhoea without nasal obstruction or sneezing in patients who are usually over 60 years old [2, 3]. Patients with autonomic or vasomotor rhinitis 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 [4–6]. Patients with IR are diagnosed through a process of exclusion and are considered non-allergic because they have no evidence of atopy, indicated by negative skin prick tests and normal IgE levels, despite having perennial symptoms [1, 2].

The concept that IR might be a form of localized allergy is not a new one [7, 8] yet until recently, little hard evidence existed to substantiate this hypothesis. Recent work has shown that IgE is

synthesized in the nasal mucosa [9, 10] and that mucosal cellular changes can occur without a rise in either total or specific serum IgE [11–13]. To accommodate these new findings in immunological ideology, changes in the nomenclature regarding the definitions of 'allergy' and 'atopy' have been produced by the European Academy of Allergy Task force [14]. We propose that some, or all, patients with IR may be suffering from 'IgE mediated non-atopic allergy' [14]. We wished to test this hypothesis by performing detailed nasal allergen challenges on patients with isolated IR and comparing the results to those of patients with perennial 'allergic' rhinitis (PAR) and normal controls (NC).

Methods

Patient selection

Over a four-year period, 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 IR has previously been published in detail [2]. 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 one hour per day for the last three months [1].

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- 2 No personal or first-degree relative history of asthma or other atopic disease.
- 3 Normal total and specific (RAST) serum IgE to aeroallergens.
- 4 Negative skin prick testing to aeroallergens (< 2 mm weal; 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 antineutrophilic 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 computed 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 PAR group, patients had to fulfil criteria 1 and 5–14 and also have a positive skin prick test (> 5 mm weal) and raised specific IgE to perennial aeroallergens.

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

Twenty-three patients with IR fulfilled the inclusion criteria and were recruited into the study. Eight patients were also recruited into each of the PAR and NC groups.

Nasal challenge

Normal saline challenge was performed to exclude patients with hyperactive nasal mucosa. If negative to saline challenge, nasal challenges were performed at weekly intervals (the first being 1 week after the saline challenge) with freshly reconstituted freeze-dried allergen solutions (Allergopharma, Newark, UK) using a metered spray aerosol delivering a dose of 100 µL per nostril (1 + 99 w/v, 0.4% phenol).

- 1 *D. pteronyssinus*/*D. farinae*
- 2 Cats/dogs
- 3 Grass pollen mix

Following challenge, patients were rested for 15 min and the rhinomanometry repeated. A positive challenge was defined as an increase in unilateral nasal resistance of > 50% of the baseline value.

Rhinomanometry

Prior to testing, all subjects rested in a quiet room for 30 min and caffeine, alcohol and nicotine were prohibited during the period of analysis. Baseline anterior active rhinomanometry was performed using a protocol known to produce a coefficient of variation of < 20% [15]. Rhinomanometry was performed according to the ICSR guidelines [16] using a GM Instruments (Glasgow, UK) NR6 rhinomanometer. For each nostril, inspiratory nasal resistance was calculated over at least 12 inspiratory-expiratory cycles at a fixed pressure of 150 Pascal. The left nostril was always assessed first and the right nostril second.

Data analysis

Data was analysed using the Kruskal–Wallis Test for non-parametric data (SPSS for Windows) with significance set at the $P = 0.0253$ level to allow for a Bonferroni correction.

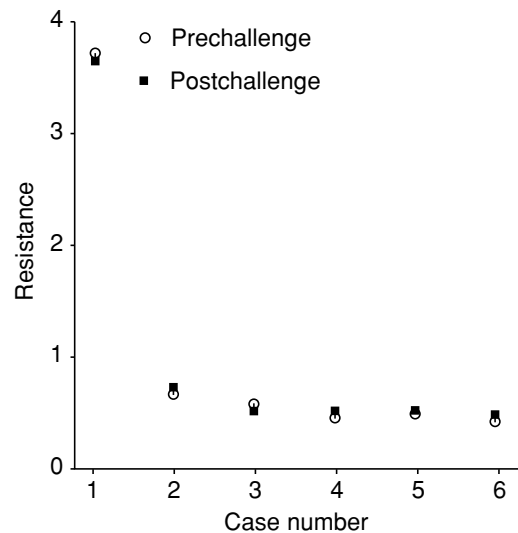


Fig. 1. Normal control patients (unilateral data for most obstructed nostril).

Results

The data are not normally distributed and so, in all groups, median values are presented.

Two patients with IR tested positively to normal saline challenge and were excluded from further analysis.

All eight PAR patients tested negatively to saline but positively in both nostrils to one or more allergen challenges. In the more blocked nostril, median prechallenge resistance in the PAR group was 0.46 with a postchallenge median resistance of 2.05 (median change: 472%).

All eight NC patients tested negatively to saline and all three allergen challenges. Median prechallenge resistance was 0.52 with exactly the same figure postchallenge (0.52). Median change was 107% in the more blocked nostril.

In the IR group, seven patients (33%) exhibited positive bilateral challenges with a further six patients (29%) having positive unilateral challenges. From the 13 (62%) patients with positive allergen challenges in the IR group, 11 individuals were sensitive to house dust mite (85%). Ten were sensitive to house dust mite alone, with one patient sensitive to cats/dogs and one to grass pollen mix. One patient tested positively to both grass pollen and house dust mite. Overall 50% of the IR group tested positively to house dust mite. Median prechallenge resistance was 0.53, rising to 1.09 postchallenge. Median change was 225% for all IR patients. Of those testing positively, resistance rose to a median of 1.25 with a median change of 278%.

Challenge data for all three groups is shown in Figs 1–3.

The IR and PAR groups independently differed significantly from the NC group ($P = 0.007$ and $P = 0.002$). The PAR group also just reached significance against the IR group ($P = 0.0250$).

Discussion

This study has demonstrated that approximately two-thirds of patients with IR, selected using strict diagnostic criteria, had abnormal nasal challenge tests. The predicted findings of the

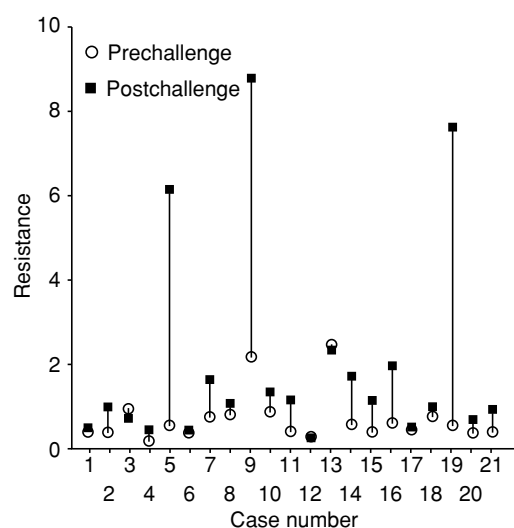


Fig. 2. Idiopathic rhinitis patients (unilateral data for most obstructed nostril).

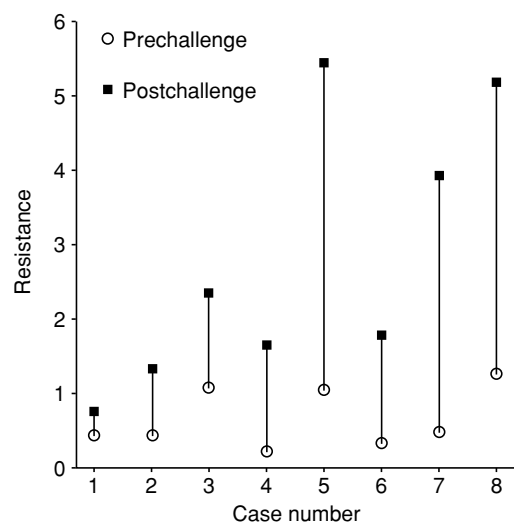


Fig. 3. Allergic rhinitis patients (unilateral data for most obstructed nostril).

PAR and NC groups help endorse the methodology used in this study.

A diagnosis of allergic rhinitis is usually made on the basis of positive skin prick tests or raised levels of specific IgE in the serum [17] yet this only establishes a diagnosis of 'atopy' [14]. The term atopy was first used in 1923 to describe a tendency to develop immediate-type hypersensitivity reactions to common allergens [18]. With the passage of time, the word 'allergy' has become corrupted to be synonymous with atopy but should ideally be used to describe 'a hypersensitive reaction initiated by immunologic mechanisms' [14]. Recently, it has been admitted that there is a clear lack of recognized diagnostic criteria for allergic rhinitis [19, 20] with problems concerning the exact definition of allergy. It is well recognized that there is no ideal clinical test [21, 22]. Recent work has shown a poor correlation between the diagnosis of allergic rhinitis and the results of skin

prick tests and specific IgE alone [23]. Given the original definitions of atopy and allergy, it is logical that nasal provocation tests (in the absence of non-specific nasal hyper-reactivity) should be seen as the gold standard in diagnosing allergy at a clinical level [22, 24].

We have been meticulous in our patient selection for this study. Previous studies of patients with IR have been flawed by the inclusion of patients on steroid/antihistamine medication [25, 26], other types of non-allergic rhinitis (e.g. autonomic rhinitis) and those with other synchronous nasal pathology [2, 27]. Unilateral nasal challenges may also produce misleading results in patients with a deviated nasal septum due to large differences in nasal resistance and unequal distribution of the challenge substance. Although it is time consuming and costly to perform nasal endoscopy, serum serology and CT scanning on patients with rhinitis, we feel it is essential in this type of research in order to exclude other potentially confounding variables. We also excluded patients who tested positive on normal saline challenge [28] as many patients with or without allergy may exhibit non-specific nasal hyper-reactivity [5, 14, 29]. The presence of hyper-reactivity has been used by some authors to try and claim a 'neurological' aetiology for IR [6]. We believe that including such patients could potentially introduce error hence their exclusion from this study.

The week-long period between challenges was chosen as being the ideal time to allow any mucosal reaction to subside and yet prevent hyporeactive responses which have been shown to exist in some patients once two weeks have passed following allergen exposure [30].

There are numerous techniques available to the rhinologist for the objective assessment of nasal obstruction. These include rhinomanometry, acoustic rhinometry, nasal inspiratory peak flow, rhinostereometry and plethysmography. Each has both advantages and disadvantages and an ideal objective method for nasal challenge does not exist [31]. It is now becoming apparent that unilateral resistance is more important than total measurements in promoting obstructive symptoms [32] hence our choice for using anterior active rhinomanometry for this study. We accept that it has the potential for erroneous measurements [33] and that coefficients of variation in excess of 20% have been obtained during nasal allergen challenge [34]. However, we have been able to reduce our coefficient of variation to <20% using the 'Nottingham Protocol' [15]. The assessment of unilateral obstruction is more precarious as there may be a marked change in resistance measurements taken at different times due to the existence of the nasal cycle [35–37]. It has been estimated that mean coefficients of variation of 21% can occur due to the nasal cycle in patients with rhinitis and a significant proportion will exceed 35% [32]. We therefore repeated baseline measurements for each challenge test and performed the second measurements after 15 min so as to avoid the effects of the nasal cycle. Although other authors have used a 100% change in resistance for the definition of a positive nasal challenge [36], with our improved rhinomanometry protocols [15], we felt that a change of 50% was adequate to avoid a type 1 error. Recent work has shown that patients show large swings in symptom scores with changes in resistance of 50% or more [32] and this is the reason we chose this figure for this study. Only inspiratory flow resistance was recorded as previous studies have shown that no additional information is gained by analysing data during expiration [38].

It is increasingly obvious that patients with nasal allergy to fungi can express symptoms and disease on only one side of the nasal cavity [39]. The theoretical role of 'superantigens' as allergic triggers in the absence of atopy [13, 40] also allows for the possibility of unilateral nasal disease. We will require more longitudinal data over time to ascertain whether these patients with unilaterally positive challenges will go on to develop bilateral and possibly even 'atopic' disease.

It is interesting that such a large proportion of the IR group tested positively on nasal challenge to house dust mite allergens. The main allergen in *D. pteronyssinus* is Der p 1 [41] which has cysteine protease activity that allows it to cleave IgE and interleukin receptors [42, 43] and may allow the allergens to penetrate through normal tissue barriers. This proteolytic activity is known to be variable and we hypothesize that this may allow Der p 1 to act at two different levels of 'allergy'; one involving systemic allergen penetration with all the stigmata of 'atopy' and a second involving a localized tissue inflammatory cascade mediated at a mucosal level. Further work is ongoing to test this hypothesis.

Allergic rhinitis has been identified as an inflammatory disease mediated by Th2-type helper T cells. These cells produce cytokines, including IL-4 and IL-13, which up-regulate IgE synthesis [44]. Mast cells and eosinophils also secrete these cytokines at a mucosal level and may help escalate the inflammatory cascade through the production of IgE within the nasal mucosa itself [9]. Mast cells, eosinophils and IgE-positive cells are increased in number in the nasal mucosa of patients with IR [12] and these findings support the hypothesis that a type-I allergic inflammation may be occurring in some non-atopic patients with rhinitis. Interestingly, in a separate study including many patients studied in this paper, no idiopathic rhinitis patients with positive nasal challenges or mucosal changes [12] demonstrated the presence of systemic markers of atopy (auto-antibodies to IgE) in their plasma [45].

Further work is required to confirm the presence of a Th2 response in the nasal mucosa of patients with IR. If proven, the 'IgE-mediated non-atopic allergy' [14], which occurs in some or all of these patients, may respond to allergen avoidance, antihistamines, topical nasal steroids or allergen desensitization.

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