

Allergy and migraine: is there a connection?

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Purpose of review

In the last 10 years, otolaryngologists and allergists have become increasingly aware of migraine headaches in their practices. This is partially due to a better understanding of the high incidence of migraine and a realization that the majority of patients presenting as 'sinus headache' are actually suffering from migraine headaches. Considering that the incidence of migraine is approximately 20% in women and 6% in men and that 10–30% of people have allergies (US Department of Health and Human Services. Evidence Report/Technology Assessment No. 54; May 2002. AHRQ Publication No. 02-E024. pp. 1–198), there is obviously a large population of patients who suffer from both conditions. The question then arises that are migraine and allergy comorbid conditions, or is any association between the two a random occurrence?

Recent findings

The present study addresses this association, which has remained controversial for over 100 years. Newer studies focusing on familial trends, shared biochemical pathways and underlying mechanisms are presented.

Relevance

This study will provide a foundation to support future clinical studies.

Keywords

allergy, migraine, sinus headache

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Introduction

In the last decade, physicians treating allergy have been made more aware of migraine headache. With the realization that the majority of patients presenting as 'sinus headache' are actually suffering from migraine and the knowledge that 20% of women and 6% of men suffer from migraine, these patients have always been part of the allergic patient population. The key question to be addressed in this study is that are migraine and allergy comorbid conditions, or is any association between the two a random occurrence?

Sinus headache is a common complaint in general practice. Recent studies [1,2^{••},3[•],4,5] have found that 58–88% of these patients satisfy the International Headache Society (IHS) criteria for migraine headache. Schreiber *et al.* [2^{••}], for example, presented a 2991-patient study of 'sinus headache' patients and found that 80% satisfied the complete criteria for migraine, with an additional 8% having migrainous headache by 1988 IHS criteria (now termed probable migraine). Similarly, Eross *et al.* [3[•]] reported a series of 100 consecutive self-diagnosed 'sinus headache' patients and found that 86% were diagnosed as migraine or probable migraine using IHS criteria. Only 3% were found to have rhinosinusitis-attributable headaches. It is obviously important for otolaryngologists and allergists

to become familiar with the migraine diagnostic criteria and to use them in assessing these patients. The diagnostic criteria for migraine without aura are presented below [migraine with aura (if aura is present): at least two attacks fulfilling criterion 2 is sufficient for diagnosis] [6].

- (1) At least five attacks fulfilling criteria 2–4.
- (2) Headache attacks lasting 4–72 h (untreated or unsuccessfully treated).
- (3) Headache has at least two of the following characteristics:
 - (a) unilateral location,
 - (b) pulsating quality,
 - (c) moderate or severe pain intensity,
 - (d) aggravation by or causing avoidance of routine physical activity (e.g. walking or climbing stairs).
- (4) During headache at least one of the following occur:
 - (a) nausea and/or vomiting,
 - (b) photophobia and phonophobia.
- (5) Not attributed to another disorder.

Even in a specialty setting, migraine is common. Among patients with sinus headache referred to a private otolaryngology practice, up to 75% may have histories satisfying the migraine criterion [5]. Even in a tertiary care rhinology setting, Perry *et al.* [4] found that radiography-normal and

endoscopy-normal headache patients had a 58% incidence of migraine. Jackson and Dial [7] have reported that 49 of 100 patients referred to their otolaryngology office for sinus headache had previously unrecognized migraine. Among them, only 13% had migraine alone, 19% (of the patients with migraine) had allergic rhinitis as well, 11% had sinusitis and 6% had both allergic rhinitis and sinusitis. Obviously, from the series of Jackson and Dial, migraine and allergy are often concomitant. Is this just a random occurrence, or is there an association between the two diseases?

Historical perspective

Despite a recent resurgence, physicians have been suspicious of a migraine/allergy link for over 100 years. Vaughn [8], in 1927, discussed literature dating back to the 1800s (including studies documenting eosinophilia during migraine attacks) and presented 10 case studies of patients with migraine with food triggers who improved with specific food avoidance. He noted that 12 of 33 migraine sufferers in his study (36.4%) had 'definite' allergy triggers. He then noted the common disorder of 'angiospasm' in migraine and anaphylaxis.

Unger and Unger [9] showed that out of 55 patients with migraine headache, 32 had a history of allergy and the family history was positive for allergic disease in well over 50% of the patients, even if they did not have allergies. They noted 'complete relief' from migraine headaches with diets withholding trigger foods (identified by challenges after a withholding period of 2 weeks) such as milk, chocolate or wheat products. They concluded that 'migraine is basically an allergic disease'.

Not all studies were as supportive, however. In 1976, Medina and Diamond [10] studied IgE levels in 89 migraine and 27 muscle contraction headache (MCH) sufferers and found elevated IgE in 5.7% of migraine and 3.7% of MCH patients. They felt that this did not differ significantly from a nonatopic general population. They also questioned 504 patients referred to a headache clinic and found that the prevalence of atopic disorders in migraine patients or their families did not differ significantly from the MCH group. They concluded that their evidence did not support the concept that migraine is an IgE-mediated disease. This study [11], however, included only patients with unilateral headache as being migraine, which may exclude over 40% of migraine sufferers.

Understanding migraine and allergy: common pathways and mediators

Recent interest in migraine and sinus headache has rekindled an interest in the migraine/allergy connection. The neurovascular model of migraine identifies the process as starting in the brain followed by sensitization

of the peripheral neurons of the trigeminal nerve, including those that supply sensation of the meninges. This predominantly peripheral early phase may lead to central sensitization at the level of the trigeminal nucleus caudalis in the brainstem and pain in the distribution of the ophthalmic and/or maxillary divisions of the trigeminal nerve [12]. The migraine attack itself may include secondary parasympathetic nasal symptoms. Cady and Schreiber [13] reported objective endoscopic evidence of nasal congestion and rhinorrhea during a migraine attack, and clinical studies have supported this as well. Similar to allergic rhinitis, migrainous midfacial or nasal pain may be accompanied by the release of a variety of neuropeptides such as substance P, calcitonin gene-related peptide (CGRP), vasoactive intestinal peptide (VIP) and others [12,13]. Allergic rhinitis and migraine thus share similar neural pathways. The question is that is the pathophysiology the same?

Gazerani *et al.* [14] reported serum total IgE and histamine levels in 70 adult patients with migraine without aura. Of these patients with migraine, 60% had a history of allergy. A control group of 45 healthy volunteers was included as well. Both serum IgE and histamine levels were significantly higher in the migraine group than in the controls, and these levels were significantly higher in the allergy/migraine group than in the nonallergic/migraine group. They also found that migraine patients of all kinds had a significantly higher histamine level during a headache than in their pain-free intervals.

In 2001, Kemper *et al.* [15] performed a meta-analysis of the clinical literature regarding migraine and the immune system and found evidence supporting an elevated IgE level in patients with atopic migraine but not in those without type I hypersensitivity. Evidence also supported higher histamine plasma levels in patients with migraine (atopic or otherwise) and increased plasma tumor necrosis factor α (TNF- α) levels. Decreased interictal (between migraine attacks) lymphocyte phagocytic function was reported as well. They concluded that the clinical literature, taken as a whole, does not support a clear-cut immune suppression in migraine sufferers.

In 2006, Bellamy *et al.* [16] studied salivary CGRP and VIP in three groups of patients: those with allergic rhinosinusitis and no history of migraine or 'sinus headache'; those with migraine presenting with 'sinus headache'; and controls with no recent history of symptomatic rhinosinusitis or migraine. They found elevation of VIP and CGRP levels during attacks in the allergic and migraine groups and found that baseline VIP levels were significantly higher between attacks in allergic rhinosinusitis and migraine subjects compared with controls. Baseline CGRP was significantly higher in the migraine group compared with the allergic group, and in both the allergic and

migraine groups compared with the controls. Both VIP and CGRP normalized to baseline levels in patients with migraine treated with sumatriptan and in rhinosinusitis patients treated with pseudoephedrine. They felt that these findings supported a 'physiologically coordinated' regulation of trigeminal and parasympathetic nerve activity in both allergic rhinosinusitis and migraine patients.

Other authors have cited elevated serum prostaglandin D₂ and F₂ [17], IL-1 [18], and tryptase [18] in addition to histamine [19] and TNF- α [15]. A comparison of migraine-related immune changes and allergic rhinitis [20] is presented in Table 1 [15,20,21]. Potential mechanisms for these findings have included common neural pathways or the activation of meningeal mast cells [18]. It is important to remember, however, that mast cell activation may be nonallergic [18]. A secondary release of nitric oxide (triggered by histamine) has been suggested as a pain-causing mechanism in migraine [19].

Allergy and migraine associations: statistical evidence

Mortimer [22] assessed the prevalence of headache and migraine in 1077 children (age 3–11) assessed in a health survey. The incidence of headache (migraine or otherwise) was significantly higher in children with a history of asthma, rhinitis or eczema than in those with no history of atopy. Conversely, the incidence of atopic disease was higher in those children diagnosed with migraine.

In 2006, Artto *et al.* [23] studied 1000 migraine family members as part of the Finnish Migraine Gene Project. These families were included if they had at least three first-degree relatives affected by migraine. Although the main goal of this study was to perform genetic marker studies, medical comorbidity was assessed in these families as well. In these 1000 responders, 678 were migraine sufferers. Familial migraine was found to be comorbid with allergy, as well as hypotension and psychiatric disorders.

In 2007, Aamodt *et al.* [24] published a questionnaire-based study in which 51383 patients completed a headache questionnaire as part of a county-wide health study in Norway. Of these patients, 50401 (98.1%) also completed questions about asthma and chronic bronchitis and 47029 (91.5%) completed questions about hay fever questions. They found that both migraine and nonmigrainous headaches were 1.5 times more likely in those with current asthma, asthma-related symptoms, hay fever and chronic bronchitis than those without. The association increased with increasing headache frequency.

Tietjen *et al.* [25] performed a retrospective electronic chart review of 223 consecutive women diagnosed with migraine to analyze comorbidity groups. They found that the incidence of asthma in all groups was fairly high (15–21%) and did not cluster with other morbidity such as hypertension and depression. No attempt was made to assess allergy history in this study.

In 2005, Sen *et al.* [26] used a Web-based questionnaire to compare 108 patients with Meniere's disease with 100 non-Meniere's controls from an ENT clinic. They found that the incidences of both allergy and migraine were significantly higher in the Meniere's group and that the incidence of allergy in the Meniere's + migraine group was significantly higher than that in the group with Meniere's disease alone. The study is somewhat limited by the fact that both allergy and migraine diagnoses were self-reported.

Ku *et al.* [19] conversely studies the incidence of migraine in allergy sufferers. Of 123 rhinitis patient who responded to a headache survey, 76 were found to have allergic rhinitis based on skin or radioallergosorbent testing. In the allergic rhinitis group, 26 (34%) met the IHS criteria for migraine headache compared with only two (4%) in the nonallergic group. They also reported findings in a nonallergy-tested cohort in the internal medicine and pediatric clinics at their institution (for a total of 294 surveys overall) and found that patients with symptoms of allergic

Table 1 Immune mediators in migraine and rhinitis

Immune mediators increased in migraine (either during or between attacks)	Immune mediators decreased in migraine	Inflammatory mediators increased in allergic rhinitis
Serum histamine	Serum monocyte counts	Histamine
Leucocyte spontaneous histamine release	PMN phagocytosis	Cysteinyl leukotrienes
Monocyte chemotaxis	Serum IL-4, IL-2	Prostaglandins
Serum TNF- α	Lymphocyte β -endorphin levels	IL-3
IL-1 β	Monocyte chemotaxis	IL-5
Lymphocyte D5 receptor expression		GM-CSF
CGRP		IL-13
Substance P		Substance P
		Neurokinin A
		Neurokinin K
		TNF- α

CGRP, calcitonin gene-related peptide; GM-CSF, granulocyte/macrophage colony stimulating factor; IL, interleukin; TNF, tumor necrosis factor. Adapted from Kemper *et al.* [15], Gelfand [20] and Sarin *et al.* [21].

rinitis (25% of the group) were significantly more likely to satisfy migraine criteria (38 vs. 4%).

Allergy and migraine: clinical associations

Few studies have focused on the clinical effects of respiratory allergy and migraine. Eross *et al.* [3[•]], in their series of 100 consecutive 'sinus headache' patients (see above), found that many migraine or probable migraine patients reported 'headache triggers' such as weather changes (83%), seasonal variation (73%) and exposure to allergens (62%). Allergens reported as triggers included grass, trees, dust, foods, animal danders and mold.

Far more attention has been paid to food allergy as a migraine trigger. In 1979, Grant [27] presented 60 patients with migraine who were treated with elimination diets (they started with a low-risk diet for 5 days – usually lamb, pears and bottled water – then progressively assessed added foods as migraine triggers). A dramatic reduction of headaches was reported, with 85% becoming headache free. The foods most commonly associated with migraine were wheat, orange, eggs, tea, coffee, chocolate, milk, beef, corn, cane sugar and yeast. Interestingly, 25% of these patients were hypertensive and all became normotensive at the conclusion of the study.

In 1985, Mansfield *et al.* [28] studied food allergy in 43 adults with recurrent migraine. All patients had unilateral throbbing headaches and nausea, utilizing the migraine diagnostic criteria then in use. Sixteen of these had positive skin testing (using a battery of 83 food allergens). Of these, 11 of 16 had fewer headaches during a 1-month restriction of the allergenic foods, compared with two of 27 skin-test-negative patients who restricted milk, egg, corn and wheat for 1 month. Patients with positive skin test, therefore, had a significantly higher response rate to dietary manipulation. In addition, seven of the patients with positive skin test agreed to a food challenge and in five of seven at least one food provoked a migraine. Placebo challenges (triggering foods and placebo were placed in gelatin capsules) were not found to trigger migraines in this small group of patients. Foods found to trigger migraines in at least one patient included cinnamon, cola, wheat, pea, peanut and corn.

It is important to remember that food intolerance may not involve a true immunogenic mechanism, and by definition may not be an allergy [29]. Mansfield [30] in a review of food allergy and migraine noted that nonallergic mechanisms may be involved as well. Chemicals such as ethanol, sodium nitrate, caffeine, phenylethylamine, tyramine, monosodium glutamate, sodium metabisulfite, theobromine and benzoic acid have been most frequently implicated in this regard. This supported Kohlenberg's 1982 review [31] of the literature regarding tyramine ingestion as a migraine trigger. Despite some contradiction in the

literature, he concluded that there was some validity in the hypothesis that tyramine-containing foods can trigger migraines in some patients. No comment was made regarding any potential mechanisms involved.

Not all literature has supported a food allergy/migraine association. Pradalier *et al.* [32] performed duodenal biopsies in 20 consecutive patients with migraine, 11 with food-induced migraine and nine without. They reported no difference in immunocyte populations between the two groups when assessing plasmacyte populations with anti-IgG, anti-IgM, anti-IgE or anti-IgM immunohistochemistry. They felt that this information did not support the existence of an IgE-mediated allergic mechanism in food-induced migraine.

Allergy/migraine: therapeutic trials

Despite considerable interest in any association between allergy and migraine, few clinical trials have been published regarding allergy therapy (outside of dietary manipulation) in the allergic migraine patient.

In 1990, Mansfield [33] proposed a role for antihistamine therapy in migraine but reviewed the literature showing no benefit from H1 or H2 blockers in preventing migraine headaches, either alone or in combination. Some earlier studies cited in this study suggested that an antihistamine may potentiate pain relief when combined with a narcotic agent like codeine.

In 2002, Carvalho *et al.* [34] reported six children and adolescents with asthma and migraine. They noted that treatment with montelukast 5 mg daily for 24 weeks, in an open-label study, decreased reported asthma attacks and significantly decreased headache frequency compared with the reported pretreatment occurrence.

In summary, the recent medical literature supports a correlation between migraine and atopy. The two diseases share common mediators, common neural pathways and can be linked statistically in patients and their families. Earlier literature, unfortunately, suffers from nonspecific diagnoses of both diseases, prior to broad application of the IHS migraine criteria. The exact nature of the association between these two diseases, however, remains obscure.

Future directions and suggestions

- (1) The real impact of migraine in allergy sufferers will only be known if the patient histories include a headache questionnaire. Considering that over 50% of patients with migraine remain undiagnosed [11] and that the largest portion of the undiagnosed migraine population is self-diagnosed as 'sinus headache', allergists and otolaryngologists need to become familiar with the criteria presented above. Migraine

treatment has been shown to be effective in the 'sinus headache' population [35].

- (2) It is well known that seasonal change and stress can increase migraine headache incidence in patients with migraine [17] and that stressors can include other diseases. Perhaps better control of allergies will lead to fewer headaches in patients who have both diseases. It is also known that migraines can trigger symptoms of nasal stuffiness and rhinorrhea, among other nasal symptoms [2^{••},3[•]]; perhaps better migraine management will lead to fewer symptomatic days in rhinitic patients with migraine. Surprisingly, studies addressing these questions have yet to be published.
- (3) Otolaryngologists and allergists should become comfortable in the diagnosis and treatment of migraine, as well as allergy, to improve patient outcomes in the management of both diseases.

Conclusion

The recent medical literature supports a link between migraine and allergy. The two diseases share common mediators, common neural pathways and can be correlated statistically. Recent diagnostic guidelines are helpful in identifying the migraine sufferers in the allergic patient population. Further study is needed to assess the therapeutic implications of this association.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 298–299).

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