
Prevalence of migraine headaches in patients with allergic rhinitis

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Background: Histamine has been implicated in the pathogenesis of migraine headaches. Because allergic rhinitis (AR) is a histamine-driven syndrome and the nasal passage is in close proximity to the central nervous system, we hypothesize that AR may trigger migraine headaches.

Objective: To determine the prevalence of migraine headaches in patients with and without AR.

Methods: Allergic rhinitis was diagnosed based on skin or radioallergosorbent test results, clinical history, and physical examination findings. The diagnosis of migraine headache was made if patients fulfilled the International Headache Society criteria. Surveys were obtained from hospital-based allergy, pediatric, and internal medicine clinics, all serving the same inner-city population.

Results: A total of 294 surveys were completed. Of 76 patients in the AR group, 26 (34%) had headaches meeting the International Headache Society criteria for migraines, and of the 57 patients in the non-AR group, only 2 (4%) had headaches that met the criteria. A Fisher exact test showed $P = 8.2 \times 10^{-6}$. The odds ratio was 14.3, which signifies that the odds of having migraine headaches is 14.3 times higher in the AR group than in the non-AR group.

Conclusions: There is a high prevalence of migraine headaches in patients with AR compared with those without AR. We propose that histamine plays a key role in triggering migraines by means of vasodilation and inflammation in the pathogenesis of migraine headaches.

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INTRODUCTION

Migraine headache is a chronic condition, affecting 6% of men and 18% of women. Attacks can be so severe that migraineurs often cannot perform daily activities and require bedrest. Furthermore, migraines generally last for long periods and can be unrelenting for days.¹ The pathogenesis of this disorder has been studied extensively but has yet to be clearly delineated. One of the mechanisms described involves increased vasodilation leading to stimulation of the trigeminal system, release of vasoactive peptides, and, finally, neurotransmission of pain impulses to second-order neurons. A key substance implicated in the pathogenesis of migraine headaches is nitric oxide (NO), which is known to be a potent vasodilator and a neurotransmitter of nociceptive impulses. Another important mediator is histamine, also a potent vasodilator and a releaser of NO.

Allergic rhinitis (AR), a condition that often leads to “sinus headache,” is an IgE-mediated phenomenon involving activation and degranulation of mast cells and basophils. A key inflammatory mediator released during degranulation is histamine. Given that histamine is a key mediator in AR and a potent releaser of NO and that the nasal mucosa is in close proximity to the central nervous system (CNS) vasculature,

we propose that the local histamine release in AR may trigger migraine headache attacks. Cady et al² showed that many patients with sinus headaches had symptoms that met the International Headache Society (IHS) criteria for migraine headaches. Another study³ showed a higher prevalence of migraine headaches in atopic children than in their nonatopic counterparts. To our knowledge, no studies have investigated the possible association between AR and migraine headaches in the pediatric and adult populations. In this study, we investigate the prevalence of migraine headaches that met the IHS diagnostic criteria in patients with AR vs nonatopic individuals. We also review the literature on the pathogenesis of migraine headaches and AR, propose a mechanism that can explain the association between the 2 disease processes, and discuss its implications in the clinical management of these disorders.

METHODS

The study was approved by the institutional review board at the Long Island College Hospital. Consent was obtained for authorization of investigational participation and disclosure of health information from each person who participated in the study. The prevalence of migraine headaches was evaluated in patients with AR from a hospital-based allergy clinic (Department of Allergy and Immunology, Long Island College Hospital) that mainly serves an inner-city population. Surveys consisting of a series of questions regarding IHS criteria for headaches and typical symptoms of AR were distributed in the waiting room.

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Inclusion criteria for the study group with AR were as follows: older than 4 years, positive skin test or radioallergen sorbent test reaction to at least 1 common aeroallergen, a positive response to 2 of 6 questions regarding allergic symptoms (nasal congestion, rhinorrhea, sneezing, snoring or mouth breathing, throat drainage, and itchy/watery eyes), and 1 aspect of the physical examination consistent with AR (allergic shiners, nasal crease, pale or boggy turbinates, or mucous discharge in the nasal passage). Patients were excluded if they had other neurologic conditions that may contribute to headaches, such as stroke, cerebral palsy, trigeminal neuralgia, and seizure disorder. Psychiatric conditions were not excluded. The diagnosis of migraine headache was made if patients fulfilled the following IHS criteria: (1) headache attacks last at least 4 to 72 hours at a time; (2) headaches have at least 2 of the following qualities: unilateral location, pulsating quality, moderate-to-severe intensity manifested by inhibition or prohibition of daily activities, and aggravation by walking stairs or similar routine physical activity; (3) during attack, at least 1 of the following symptoms occurs: nausea or vomiting, phonophobia, or photophobia; and (4) at least 5 such headache attacks fulfilling the previous criteria have occurred.

Surveys were also obtained from control nonatopic patients in the internal medicine and pediatric clinics affiliated with the same hospital serving the same population. In this control group, patients were excluded if they had more than 1 positive response to the 6 questions regarding allergy symptoms and if their physical examination showed findings consistent with AR, as mentioned previously herein. They were also excluded if there were concomitant neurologic disorders, as described previously herein.

RESULTS

A total of 294 surveys were completed: 123 from the allergy clinic, 151 from the internal medicine clinic, and 20 from the pediatric clinic. From the allergy clinic, 76 patients fulfilled the inclusion criteria for the AR group and 57 for the control non-AR group. There were no statistically significant differences between the AR and non-AR groups regarding age and sex distribution. In the AR group, 60 patients (79%) were female and 16 (21%) were male; in the non-AR group, 44 patients (77%) were female and 13 (23%) were male ($\chi^2_1 = 0.0588$; $P = .81$). The mean (SD) age of the AR group was 40 (17) years (range, 9–71 years) and of the non-AR group was 45 (21) years (range, 5–81 years). Also, review of the medical history in each group revealed that the groups shared 5 of the 6 most frequently reported chronic medical conditions. In the AR group vs the non-AR group, hypertension was found in 20 vs 22 patients, diabetes mellitus in 9 patients each, osteoarthritis in 16 vs 8 patients, dyslipidemia in 11 vs 5 patients, and depression in 9 vs 3 patients. Only gastroesophageal reflux disease (11 patients in the AR group) and heart disease (4 patients in the non-AR group) were not shared among the groups. These data show that the non-AR

group serves as an adequate control group for comparison with the study AR group.

In the AR group, 26 patients (34%) had headaches that met the IHS criteria for migraines, whereas only 2 patients (4%) in the non-AR group had headaches that met the criteria. A Fisher exact test showed $P = 8.2 \times 10^{-6}$, which is less than .001. Therefore, there is a significant correlation between AR and migraine headaches. Because this is a case-control study, the odds ratio was calculated and found to be 14.3, which signifies that the odds of having migraine headaches is 14.3 times higher in the AR group compared with the non-AR group. The confidence interval of the odds ratio is 3.23 to 63.34, which does not include 1. This strengthens the correlation between AR and migraine headaches. However, the wide confidence interval indicates that the estimation has low precision. This may be due to the relatively small number of patients in the study.

We also found that many patients in the pediatric and internal medicine clinics had symptoms (at least 4 of 6 positive responses) and physical findings (at least 1 of 4) of AR. There were 42 (25%) of 171 patients fulfilling such criteria. Although skin testing had not been performed in these individuals, we used this group as a second AR study group and compared them with the same non-AR group from the pediatric and internal medicine clinics. Results were similar to those of the first comparison. Sixteen (38%) of the 42 patients in the second AR group had migraines compared with only 2 (4%) of 57 in the non-AR group, as mentioned previously. Further analysis continued to show statistical significance by Fisher exact test ($P = 1.12 \times 10^{-5}$, which is $<.001$) and odds ratio (16.9). There was no statistical difference in age and sex distribution between the groups (data not shown). In summary, there was a statistically significantly higher prevalence of migraine headaches in patients with AR compared with those without AR.

DISCUSSION

The pathogenesis of migraines has previously been proposed to occur in 3 key steps. The first step involves dilation of meningeal blood vessels, which activates the sensory trigeminal nerve, with transmission of pain impulses to the caudal brainstem nuclei. This leads to the second key step whereby vasoactive neuropeptides are released, which, in turn, exacerbates and perpetuates the dilation of blood vessels and local inflammation. Of these neuropeptides, the most significant are substance P, neurokinin A, and calcitonin gene-related peptide. The third step involves the transmission of pain impulses to second-order sensory neurons in the trigemino-cervical complex.^{4,5} This theory explains the efficacy of sumatriptan, a selective agonist of D subtype of serotonin, in the treatment of migraine headaches. This drug has a direct vasoconstrictive action, inhibits the neuropeptide-mediated inflammatory response after trigeminal stimulation, and may also inhibit neurotransmission of pain impulses.⁶

In accord with this theory is the important role of NO, which has been implicated in the pathogenesis of migraine headaches. This molecule has several physiologic roles, 2 of

which are thought to be critical in the development of migraine headaches: endothelium-dependent vasodilation and neurotransmission of nociceptive information in the CNS. Both of these effects are key steps in the pathogenesis of migraine described previously herein.

Several studies have demonstrated the role of NO in migraine headaches. Nitroglycerin, a NO donor, was infused in 4 increasing doses, and headache responses were followed prospectively. Patients who previously experienced migraine headaches reported headaches of greater intensity and with more migraine characteristics than their control counterparts.⁷ The immediate headaches lacked the symptoms needed to meet the IHS criteria, but the migraineurs reported delayed headaches that met the IHS criteria.⁸ In another study,⁹ blood velocity was measured in the middle cerebral artery via transcranial Doppler before, during, and after infusion of increasing doses of nitroglycerin into migraineurs, controls, and patients with episodic tension-type headaches. Blood velocity decreased in all 3 groups, but the response was most pronounced in the migraineur group at the higher doses.⁹ These studies supported the role of NO as a trigger of migraine headaches. To investigate its involvement in the subsequent phase of migraine headaches, Lassen et al¹⁰ studied the effect of NG methylarginine hydrochloride, a NO synthase inhibitor, on spontaneous migraine attacks. In a double-blind, placebo-controlled design, patients with migraine attacks were given either this agent or placebo. Ten of 15 patients who received NG methylarginine hydrochloride had relief of symptoms compared with only 2 of 14 patients in the placebo group. Photophobia and phonophobia also improved.¹⁰ Thus, we can conclude from all these studies that NO plays a significant role in the development of migraine headaches.

Histamine has also been implicated in the pathogenesis of migraine headaches. This is consistent with its known effects. First, histamine increases the release of NO and, therefore, could contribute to the effects of NO in the development of migraine headaches. Second, histamine itself causes vasodilation via its H₁- and H₂-receptors. Third, the increase in vascular permeability caused by histamine may contribute to local neurogenic inflammation.¹¹ Together, these actions could trigger and further contribute to the pathogenesis of migraine development described previously herein.

Many studies support this hypothesis. Krabbe and Olesen¹¹ showed that histamine administration induced migraine headaches in migraineurs more often than in controls. During infusion, headache was constant, but it disappeared with discontinuation of infusion. Furthermore, administration of mepyramine, an H₁-blocking agent, almost immediately eliminated the headache. Cimetidine, an H₂-blocker, had less of an inhibitory effect.¹¹ This is consistent with the fact that H₁-receptors play a more dominant role in vasodilatory effects compared with H₂-receptors.¹² In a similar study, Lassen et al¹³ showed that the migraine attacks provoked by histamine infusion could be blocked by pretreatment with pyrilamine maleate but not with placebo. Whole blood from migraineurs was found to have significantly elevated levels of histamine

during headache attacks and remission compared with the control group.¹⁴ Selmaj^{15,16} also showed that histamine release from leukocytes of migraineurs was significantly higher than that of controls. Other researchers¹⁷⁻²⁰ have found similar histamine levels in migraineurs. In the animal model, infusion of histamine caused immediate and consistent dilation of meningeal blood vessels, which was inhibited by pyrilamine maleate, famotidine, and NO synthase inhibitor.²¹ Together, all of these data conclusively show that histamine plays a key role in the development of migraine headaches.

Several researchers have speculated on the possible link between allergy and migraine headaches. Certain foods have been implicated in the precipitation of migraine headaches, and some researchers have argued that proper diet is essential to the treatment of migraines. Some researchers believe that the mechanism by which food precipitates migraine attacks does not involve the type I hypersensitivity IgE-mediated phenomenon, whereas others do. Millichap and Yee²² suggest that certain foods contribute to the pathogenesis of migraine headaches by direct vasoconstriction or vasodilation caused by the release of serotonin and norepinephrine and by stimulation of the neurogenic pathway described previously herein. On the other hand, Mansfield²³ and others^{24,25} suggest that food-provoked migraine is a result of mast cell and basophil degranulation, which leads to increased plasma histamine levels and ultimately the trigger of migraine attacks. However, under these circumstances, other systemic effects of increased histamine would be expected. It is possible that both allergic and nonallergic mechanisms are involved and that certain foods may favor one over the other.

Other allergic disorders have been linked to migraine headaches. Davey et al²⁶ reported an association between migraine headaches and asthma. Mortimer et al³ found that the prevalence of migraine headaches was significantly higher in children with atopic disorders than in those without. The case-control study by Davey et al²⁶ showed that the association between migraine and asthma was stronger in patients without the diagnosis of hay fever, whereas the study by Mortimer et al³ showed a stronger association in patients with rhinitis.³ A study by Wendorff and colleagues²⁷ showed that 40% of children diagnosed as having migraine headaches showed evidence of allergies by skin prick test or IgE levels. Furthermore, treatment of these children decreased the migraine index significantly from 2.45 to 0.33. Several studies²⁸⁻³¹ have reported the importance of recognizing comorbid conditions in the patient with migraine headaches. In these studies, 2 frequently listed conditions are allergy and asthma.

Another interesting finding is the link between asthma and migraine headaches through consecutive generations. Chen and Leviton³² showed that 3.2% of children born to mothers without migraine or asthma or allergies developed asthma. In contrast, more than 6% of children born to mothers with migraines but not asthma or allergies developed asthma.³² Similarly, Gurkan et al³³ found that whereas only 1.8% of nonasthmatic children had a parental history of migraines, 9.3% of asthmatic children did.

Some researchers^{34–36} have argued that migraine headaches have been mistaken for sinus headaches. According to the IHS,³⁷ the diagnostic criteria for acute sinus headaches include purulent nasal discharge, abnormal findings on imaging studies (x-ray, computed tomography, or magnetic resonance imaging) or abnormal transillumination, concurrent symptoms of headache and sinusitis, headaches localized to the area of sinus disease, and disappearance of headaches after treatment of acute sinusitis. The revised IHS classification system relates headache to sinus disease under the classification “headache attributed to rhinosinusitis” and has 4 diagnostic criteria.³⁸ The true prevalence of sinus headaches meeting such criteria is very low. Despite this, sinus headache is a common diagnosis.^{34,35} However, patients with headache referred for sinus evaluation who had no evidence of rhinosinusitis on computed tomography or endoscopic evaluation were diagnosed as having migraine 58% of the time.³⁹ Cady and Schreiber⁴⁰ found that a significant percentage of patients with self-described sinus headaches fulfilled the criteria for migraine headaches and that treatment of these patients with 50 mg of sumatriptan succinate improved their headaches dramatically.

Given the mechanism of migraine pathogenesis described previously herein, the importance of histamine and NO in migraine development, the common association between allergy and migraines, particularly our findings of an increased prevalence of migraine headache in patients with AR, we propose that AR plays an important role as a trigger in the development of migraine headaches. In AR, allergens are deposited on the nasal mucosa. Binding of allergen to specific IgE receptors on mast cells or basophils in the nasal mucosa leads to degranulation and subsequent release of inflammatory mediators. Mediators such as histamine may be performed and exert rapid effects.⁴¹ Histamine may be the critical mediator that triggers the cascade of neurogenic events leading to the migraine headache by means of CNS vasodilation or by stimulation of sensory nerve fibers. This theory is in concert with that described by Meggs⁴² as neurogenic switching, a crossover mechanism between 2 different forms of inflammation, in this case immunologic and neurologic.

Therefore, the allergist must recognize the implications for treatment of patients with AR. There should be heightened awareness of migraine headaches in patients with AR. One should become familiar with the diagnostic criteria of migraine headaches described previously herein and the appropriate evaluation and treatment thereof. Acute migraine attacks may be treated with several pharmacologic agents, such as simple analgesics (aspirin, naproxen, ibuprofen, or acetaminophen), ergot preparations (ergotamine/cafeine or dihydroergotamine), or serotonin agonists (sumatriptan or rizatriptan). Narcotics may be used as well. Treatment for acute migraine attacks must be taken immediately at the onset of symptoms for maximal effect. Prophylactic treatment is indicated for individuals who have frequent attacks, particularly more than once a week, and for those who cannot tolerate treatment for acute attacks. These treatments include but are not limited to anti-inflammatory agents (aspirin and naproxen), tri-

cyclic antidepressants (amitriptyline hydrochloride, nortriptyline hydrochloride, and doxepin hydrochloride), β -receptor antagonists (propranolol hydrochloride, nadolol, atenolol, and metoprolol), anticonvulsants (phenytoin and valproic acid), and calcium channel antagonists (verapamil and nifedipine). However, we do not recommend the use of β -receptor antagonists in allergic individuals solely for migraine, because they may aggravate asthma and allergic reactions. We find it helpful, but do not have supporting clinical data, to obtain neurologic consultation in all patients with migraine or any chronic headache not entirely attributed to nonneurologic conditions. It is likewise suggested that headache specialists consider that chronic headaches may be precipitated by nasal or sinus conditions. Furthermore, patients with symptoms such as sneezing, itchy eyes, itchy nose, and nasal congestion should be referred for an allergy evaluation.⁴³

Some studies have investigated the role of antihistamines in vascular headaches with disappointing results. In a study by Anthony et al,⁴⁴ prophylactic treatment with H₁- or H₂-blockers did not significantly decrease headaches. Similarly, Russel⁴⁵ showed that combination treatment with H₁- and H₂-blockers did not improve symptoms in patients with cluster headaches. We suggest, however, that this is not surprising because antihistamines also have little to no effect on the vascular effects of histamine, specifically, nasal congestion, in AR. Because topical nasal corticosteroids have been shown to significantly reduce nasal congestion, a symptom of vascular instability caused by histamine, we hypothesize that aggressive treatment of rhinitis symptoms with these agents in patients with AR and migraine headaches may be important for the treatment and prevention of migraine headaches. To our knowledge, there have been no studies investigating the efficacy of topical nasal corticosteroids in the treatment of migraine headaches. We are currently investigating this possibility in an open trial.

CONCLUSION

In summary, allergic disease has been associated with migraine headaches. The present study shows a significantly increased prevalence of migraine headaches in individuals with AR compared with those without AR. This is the first investigation to study the prevalence of migraine headaches in adult and pediatric patients with AR diagnosed by specific history, skin test or radioallergosorbent test results, and physical examination findings. Topical nasal corticosteroids may be important in the treatment and prevention of migraines in patients with AR and migraine headaches.

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