Chapter 7
Allergic Rhinitis and Migraine Headache

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Introduction

Allergic rhinitis (AR) and headache are very widespread and common health conditions with a significant healthcare burden. As an entire spectrum, headache disorders may affect up to 50% of the global population at any given time, whereas chronic migraines affect between 2% and 5% of chronic, daily headache sufferers [1–3]. Similarly, allergic rhinitis has prevalence rates as high as 30% in adults and up to 40% in children, with some variations internationally. The socioeconomic and cost implications of these disorders are considerable, but far more significant are their impact on patient quality of life. In clinical practice, many patients present with "sinus headaches" that are, in fact, found to be headache disorders or migraines [2, 4]. The term sinus headache represents a symptom complex, and does not accurately describe an underlying pathologic process. These patients have often already undergone a multitude of diagnostic workups and treatments, including systemic and topical medications, immunotherapy, and surgical procedures. The diagnostic challenge, in part, is due to the lack of an accurate or standardized clinical definition of "sinus headache." The term is generally applied to the description of pain or pressure emanating from the periorbital, maxillary, or frontal regions. A strictly rhinogenic headache results from pathophysiology that is

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M.E. Mehle (ed.), *Sinus Headache, Migraine, and the Otolaryngologist*,
DOI 10.1007/978-3-319-50376-9_7

centered in the nose with headache or facial pain as a secondary effect [5]. In some cases, autonomic symptoms accompany such complaints, which are also present in migraine.

While headaches can result from sinus inflammatory disorders, including chronic or recurrent bouts of sinusitis, up to 90% of purported sinus headaches actually fulfill the diagnostic criteria for migraine [2, 4, 6–9]. Furthermore, of those patients referred to an otolaryngologist specifically for sinus or nasal inflammatory conditions, up to 75% are ultimately found to have migraines [10, 11]. Contrary to popular belief, sinonasal inflammatory conditions are usually not a direct cause of headache or migraine disorders. Despite the presence of both conditions in many patients, migraine and allergic rhinitis remain separate entities with similar components within their pathophysiological mechanisms.

Pathophysiology of Allergic Rhinitis

The basic concept of allergic rhinitis, a subset of atopic disease, is that an individual's immune system inappropriately reacts to a benign substance, the so-called allergen, and induces an inflammatory response that manifests primarily in the nose. Allergic rhinitis is largely driven via immunoglobulin E (IgE) dependent mechanisms [12]. Once the allergen contacts nasal mucosa, antigen presenting cells (APCs), primarily dendritic cells residing in the mucosal surface, process the allergen and present peptides via major histocompatibility complex class II molecules to CD4 T cells [13]. This interaction induces secretion of chemokines CCL17 and CCL22 from the dendritic cell that along with IL-4 present from basophils, activates the transformation of the naïve T cell into a Th2 cell [12]. Th2 cells secrete cytokines IL-4, IL-5, IL-9, and IL-3 that recruit eosinophils and activate B cells to produce allergen-specific IgE antibodies [12, 13]. IgE itself then activates proliferation of eosinophils, mast cells, and neutrophils, and the allergen/antigen specific IgE subsequently binds to high affinity receptors on mast cells or basophils for later activation [13]. These bound allergen-specific IgE are part of the body's retained memory of the allergy that leads to quicker immunological response with subsequent exposures. The process of mast cell granulation and eosinophil inflammation is postulated to have evolved to just kill parasites, but then extended to react inappropriately to items which the immune system should view as innocuous (i.e., allergens) [12].

Early and Late Reactions

Following exposure to allergens, allergic rhinitis sufferers develop two different reactions according to time sequence. The early reaction occurs within 30 min of exposure and is characterized by sneezing and rhinorrhea [13]. The

pathophysiological mechanism involves degranulation of mast cells once bound IgE links with an allergen peptide (type I hypersensitivity) with release of chemical mediators like histamine, prostaglandins, and leukotrienes [13]. Mast cells are maintained by IL-9 and stem-cell factor [12]. The late reaction occurs approximately six hours after exposure and is characterized by nasal congestion [13]. The main pathophysiologic mechanism involves chemotaxis of eosinophils which is the result of a cascade initiated during the early reaction. Cytokines and chemokines attract eosinophils, mast cells, and T cells to the nasal mucosa causing congestion, cell breakdown, and eventually remodeling of normal nasal tissue [13]. In addition, destruction of the nasal mucosa exposes embedded distal branches of the trigeminal nerve to cytotoxic proteins from eosinophils. In turn, these damaged sensory nerve fibers then secrete neuropeptides including substance P, neurokinin A, and calcitonin gene-related peptide (CGRP), which induce contraction of smooth muscle, mucous secretion from goblet cells, and plasma exudation from capillaries, a process known as neurogenic inflammation [12, 14]. Additionally, inflammatory mediators like bradykinin and histamine activate unmyelinated C fibers [12]. These processes produce the symptoms of nasal congestion, rhinorrhea, nasal itching and sneezing, and overall hypersensitivity to specific allergens as well as stimuli such as cold and dry air, tobacco smoke, and tactile pressure [13].

Suppression of the Allergic Response

Regulatory T cells (Tregs) inhibit cells involved in the allergic inflammatory cascade by directly secreting inhibitory cytokine IL-10 themselves, inducing secretion of IL-10 from nearby cells, or by direct cell-to-cell contact. Some evidence exists that Treg function is impaired in patients with allergic diseases [12]. In fact, the concept of subcutaneous immunotherapy (SCIT) and sublingual immunotherapy treatment (SLIT) is centered on inducing Tregs through high dose allergen extracts [15]. In addition to activating Tregs, immunotherapy also functions by increasing IgG/IgE ratio, inhibiting initial activation of inflammatory cells, and shifting the Th2 to a Th1 response [16]. Other allergy treatment modalities such as antihistamines, decongestants, and steroids only act on a component of the allergic inflammatory cascade and only treat symptoms, not the root cause.

Pathophysiology of Migraine

The brain tissue itself does not contain nociceptive fibers and therefore cannot sense pain. Dural nerves that innervate cranial vessels do however have nociceptive function and are the main players involved in producing symptoms associated with

migraines [17–19]. A plexus of largely unmyelinated C fibers and thinly myelinated Aϑ fibers arising from the ophthalmic division of the trigeminal ganglion surround pial, arachnoid, and dural blood vessels as well as large cerebral and venous sinuses [20, 21]. Activation of these nociceptors by mechanical, electrical, or chemical stimulation has produced migraine-type pain, throbbing headaches with associated nausea, photophobia, and phonophobia [20]. These trigeminal fibers contain substance P and calcitonin gene-related peptide (CGRP) that are released when the trigeminal ganglion is stimulated, leading to increased extracerebral blood flow [22]. In an acute migraine, CGRP is elevated and normalizes with treatment. Studies have demonstrated that stimulation of cranial vessels induces pain [17, 19]. In vitro, triptans have been shown to act on the CGRP promoter and consequently regulate CGRP secretion from neurons; however, triptans can only have this effect once the trigeminovascular system is activated and the appropriate receptors are exposed [23]. These triptan receptors are located within the central nervous system, found at every level of sensory input from trigeminal ganglion through the cervical, thoracic, lumbar, and sacral dorsal root ganglia [24].

Historically, vasodilation of intracranial vessels was thought to be the underlying pathophysiology of migraine; however, recent studies have demonstrated that activation of a specific neuronal pathway induces the symptoms of migraine. Amin et al. [25] found no evidence of extracranial vasodilation in patients undergoing spontaneous migraine. Studies on migraine treatment medications are particularly supportive of the neuronal rather than the vascular theory. Serotonin receptor agonists were initially developed as cranial vasoconstrictors, but pure neural acting 5-HT receptor agonist, lasmiditan, is effective at aborting migraines and causes no vasoconstriction. Newer CGRP drug receptor antagonists (olcegepant, telcagepant) are effective at aborting migraine and also have no vasoconstrictive properties. Additionally, vasodilating substances such as vasoactive intestinal polypeptide (VIP) have been tested for their ability to induce a migraine with no migraine triggered after administration [26]. Migraine pain is caused by specific receptor site activation that starts a chain reaction of neural events rather than vasodilation itself, which is merely a byproduct of the neural cascade. Overall, migraine headache depends on both activation of the trigeminovascular pathway via transmission of pain signals originating in peripheral intracranial nociceptors and on inherent dysfunction of CNS structures involved in modulation of neuronal excitability and pain [20].

Sensitization occurs in migraine sufferers as demonstrated by the symptoms of photophobia and phonophobia. Approximately two thirds of patients experience allodynia, which is pain from non-noxious stimuli. Sensitization likely has a central and peripheral component [27]. The central component likely involves sensitization of thalamic neurons whereas the peripheral component functions via release of local inflammatory markers to activate trigeminal nociceptors [28, 29].

Genetic Basis of Allergic Rhinitis

Predominant genetic mutations in allergic rhinitis sufferers are found in genes encoding the a-chain of the high affinity receptor for IgE (FceRa1), RAD50, located adjacent to the gene for interleukin-13 (IL-13), and signal transducer and activator of transcription 6 (STAT6), which is regulated by IL-4 and IL-13. Genome wide association studies have substantiated that T-helper 2 cytokine genes are involved [12]. Essentially, allergic rhinitis sufferers have increased sensitivity to IgE and a predisposition for a more active Th2 mediated response.

Genetic Basis of Migraine

Numerous genetic mutations have been found in migraine with aura sufferers with most mutations effecting ion channels. A mutation now known as FHMI involving calcium channel gene CACNA1A is responsible for about 50% of migraine sufferers in identified FHM families and mutations in the ATP1A2 gene that codes for Na/K ATPase for about 20%; both mutations result in modulations in glutamate transport [18]. These known mutations suggest the pathophysiology of migraines is a result of ionopathies. Despite the genetic predisposition, environmental factors including stress, exposure to irritants, temperature fluctuations, and other triggers affect severity of the condition [30].

Epidemiology and Disease Burden

Headaches are among the leading causes for outpatient office and emergency room visits annually. Migraine may be episodic or chronic in nature. Most patients presenting to otolaryngologists for sinus headaches suffer from chronic, daily headaches and a subset of these patients suffer from chronic migraines. Headache must be present on more than 15 days per month for at least three months to be quantified as a chronic headache disorder. Approximately 5% of the domestic population suffers from chronic daily headaches, and of these, chronic migraines is by far the most frequent and debilitating. Episodic migraine affects up to 12% of the global population, whereas around 2% of the general population has chronic migraine disorder. Furthermore, the proper diagnosis of chronic migraine is often elusive, as only 20% of patients who fulfill the criteria are actually or ultimately diagnosed [2, 31]. Considering roughly one out of every seven Americans meet the diagnostic criteria for migraines, our low diagnostic rate certainly warrants improvement.

The total annual cost of chronic migraine, which includes diagnostic tests, outpatient or emergency room visits, and treatment interventions, is over three times

that of episodic migraines. Chronic migraine has a total annual cost of approximately $8200 per individual, whereas episodic migraine costs around $2600, with the majority of these direct medical costs attributable to pharmaceutical utilization [32]. Considering these costs for the U.S. population alone coupled with the high prevalence of migraines domestically, the indirect healthcare expenditures are quite staggering.

Similarly, allergic rhinitis is one of the most common health conditions worldwide. In the U.S. alone, over 60 million people carry the diagnosis of allergic rhinitis with at least $5 billion in direct healthcare expenditures [2, 33–35]. Expenditures as a result of allergies on a whole are far greater and approach $15 billion [36]. Allergic rhinitis is the most common chronic health condition domestically in the pediatric population and is expected to continue to rise. Comparatively, hay fever was estimated to affect only 1% of the U.S. population in the 1940s [36]. Allergic rhinitis has a significant impact on quality of life and absenteeism as well. It accounts for several million lost school and work days annually and affects around one in six Americans, with lost productivity approaching $1 billion [2, 36]. The impact has reached a global scale as well and in Europe, projections estimate that 50% of their general population will be affected by allergies within the next 10 years [37].

Surprisingly and despite the significant disease burden of allergic rhinitis, only a small percentage of patients actually seek formal treatment for their condition. A National Medical Expenditure Survey found that only 12.4% of patients with allergic rhinitis visited physician offices for management, whereas the majority of patients used over-the-counter or home remedies [36]. Notwithstanding treatment, approximately 50% of allergic rhinitis sufferers report their symptoms last more than four months per year, and about 20% of patients have symptoms for nine months or longer, which attests to the degree of impairment in quality of life.

Clinical Associations

Given the high prevalence of both migraine and allergic rhinitis, it is not surprising that the conditions are often seen in conjunction. Certainly, inflammatory sinus or nasal disorders can worsen or even precipitate headaches, but there is not necessarily a direct causal relationship. The disorders may share similar symptoms and clinical features, such as nasal congestion, rhinorrhea, periorbital or retro-orbital pressure/pain, facial discomfort or a sense of fullness, dysosmia, and lacrimation. The presence of autonomic symptoms is a primary characteristic of migraines. Barbani et al. [38] found that nearly 46% of patients with migraines had autonomic symptoms, including rhinorrhea, nasal congestion, lacrimation, and conjunctival injection. Another study of 100 patients with chronic migraines demonstrated the most frequent autonomic symptoms as lacrimation in 49%, conjunctival injection in 44%, eyelid edema in 39%, aural fullness in 30%, and nasal congestion in 20% [39]. A host of other data has shown autonomic symptoms as a concomitant clinical

feature in migraines [2, 38–42]. While an exhaustive explanation of migraine criteria is beyond the scope of this chapter, it is interesting to note that despite abundant literature highlighting autonomic symptoms in migraines, these features are not included in the current diagnostic criteria. Furthermore and contrary to much mainstream belief, migraines do not typically present with an aura. In fact, migraines without aura are far more common in chronic headache patients. The classic aura is seen in about 20–25% of patients with migraine. The absence of an aura further confounds the clinical picture and may lead to diagnostic errors.

Migraine and allergic rhinitis also share certain seasonal and environmental triggers. The exposure to topical or inhaled chemical and environmental irritants, barometric pressure changes, and seasonal variations may exacerbate symptoms of both migraine and allergic rhinitis. Several studies have shown that migraine and allergic rhinitis are both worse in the spring, summer, and fall months as a result of allergic triggers [43–46]. Due to comorbid allergic rhinitis, migraine patients seek more treatment during the allergy months as their headache intensity and ocular complaints worsen during this time period and almost 15% of migraineurs report seasonal exacerbations [43]. In a Turkish study of 80 AR patients, migraine headaches were detected in 50% of cases, compared to 18.75% in the non-AR, control group. Only 5% of AR patients with migraine had associated auras, and these results were statistically significant [47]. As part of a Norwegian Health Study, over 51,000 patients completed headache respiratory disease questionnaires. Headache disorders were found to be 1.5 times more likely in patients with asthma, allergies, and chronic bronchitis [9, 48].

Although there are some variations, multiple studies have shown that migraines are far more common in the AR population and the broader umbrella of headaches is more frequent in atopic disorders as a whole [2, 10, 47, 49]. Certain foods have also been cited as migraine triggers. Food elimination diets, namely chocolate, milk, and caffeine have shown dramatic reductions in migraines for certain patients [10, 50]. Food allergens have also been postulated as a link to migraine disorders. Mansfield et al. found almost a 70% improvement in migraines following dietary restrictions in a subset of patients with skin test positive food allergies [10, 51]. However, it is well established that non-allergic mechanisms also play a role as certain chemical irritants and preservatives, such as ethanol, sodium nitrate, phenylethylamine, tyramine, benzoic acid, and monosodium glutamate have all been implicated in food-related migraines [10, 51].

Martin, et al. [52, 53], have explored the relationship between atopic disease and migraine. They found that 32.5% of 536 consecutive allergic patients were diagnosed with migraine as well, but the prevalence of migraine was not altered by an increasing degree of allergic sensitization. The study did find some statistically significant frequencies of migraine in smaller subsets of patients upon finely massaging the data, but their clinical relevance is uncertain [52]. In a survey of episodic migraine sufferers, 17% had asthma and were twice as likely as their non-asthmatic cohort to progress on to chronic migraine one year later. In fact, the severity of asthma correlated with a greater likelihood of the progression [53]. One cannot infer causality from these epidemiologic data sets, but these studies are

intriguing. The pathophysiology of these disorders are unique, but some overlap and even potential common pathways are evident in the immune response, inflammatory modulators, and the role of pain receptors on symptoms and clinical features. Certainly, further research into pathophysiologic mechanisms is needed to elucidate the complex interplay between migraine and allergic rhinitis.

Conclusion

Migraine and allergic rhinitis are extremely common conditions with a significant healthcare and socioeconomic burden. Both conditions have a high prevalence and when they coexist in the same individual, the result can be very debilitating with a profound impact on quality of life. Allergic rhinitis is an immune-mediated process primarily involving the peripheral nervous system whereas migraine is a neuronal ionopathy primarily involving the central nervous system. Both processes involve sensitization of trigeminal nociceptors and the neurotransmitters substance P and CGRP, but downstream effects and symptomatology differ. While some pathophysiologic mechanisms and components may overlap, further research is needed to explore the relationship between migraines and allergic rhinitis. Similar characteristics and a high rate of comorbidity between these disorders can make a definitive diagnosis quite challenging; therefore, an astute level of suspicion together with a thorough clinical history and physical exam can help elucidate the diagnosis. An enhanced degree of global clinical awareness of the relationship, similarities, and differences between migraines and allergic rhinitis can help direct therapy, reduce direct and indirect healthcare expenditures, and improve patient morbidity and overall quality of life.

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