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Research Submission

CME

The Sinus, Allergy and Migraine Study (SAMS)

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Objective.—The objective of this study is to classify (according to the current International Headache Society's criteria [ICHD-II]) the headache types that those with self-diagnosed sinus headache experience and to determine barriers to correct diagnosis.

Background.—The American Migraine Study II estimates that 28 million Americans suffer from migraine headache. The majority of these patients remain undiagnosed and many are erroneously diagnosed as having sinus headache. Despite this common diagnosis, the concept of sinus headache remains an enigma with a relative paucity of information in the literature.

Methods.—Advertising in the greater Phoenix, U.S. metropolitan area was used to recruit 100 willing and consecutive subjects to participate in this descriptive clinical study (The Sinus, Allergy and Migraine Study [SAMS]). All patients who believed they suffered from sinus headache and were over 18 years of age were enrolled without exclusion. A detailed history and exam was performed in each patient, and patients were given headache diagnoses based on the current International Headache Society's (IHS) criteria.

Results.—Of the 100 subjects with self-diagnosed headache, IHS diagnoses mistaken as sinus headache included migraine with or without aura (52%), chronic migraine associated with medication overuse versus probable medication overuse headache (11%), probable migraine (23%), cluster headache (1%), hemicrania continua (1%), headache secondary to rhinosinusitis (3%), and headaches nonclassifiable (9%). Weather changes (83%), seasonal variation (73%), exposure to allergens (62%), and changes in altitude (38%) were frequent migraine triggers. Seventy-six percent of migraine subjects reported pain in the distribution of the second division of the trigeminal nerve (either unilateral or bilateral), and 62% experienced bilateral forehead and maxillary pain with their headaches. The most common associated features included nasal congestion (56%), eyelid edema (37%), rhinorrhea (25%), conjunctival injection (22%), lacrimation (19%), and ptosis (3%). The headaches nonclassifiable were characterized by a bilateral maxillary pressure of mild to moderate intensity associated with at least one cranial autonomic symptom. Features suggestive of migraine were absent in all 9 of these nonclassifiable cases.

Conclusions.—The majority of those with self-diagnosed sinus headache have migraine or probable migraine. In those patients with migraine, the most common reasons for misdiagnosis include headache triggers, pain location, and associated features ("guilt by provocation, location, and association") commonly attributed to sinus headache. The clinician must be aware of these unique presentations of migraine so that a correct diagnosis can be made and effective treatment instituted. A portion of patients with self-diagnosed sinus headache suffer from a headache type, which is unclassifiable by the current IHS criteria. These headaches are characterized by bilateral maxillary pressure, mild to moderate pain intensity, cranial autonomic symptoms, and the complete absence of migraine features.

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Abbreviations: AAO-HNS American Academy of Otorhinology-Head and Neck Surgery, CAS cranial autonomic symptoms, HIT-6 headache impact test-6, IHS International Headache Society, MCAS migraine with cranial autonomic symptoms, MO medication overuse, MOH medication overuse headache, NIRSH noninfectious rhino-sinus headache, MIDAS migraine disability assessment score, NSAIDs nonsteroidal anti-inflammatory drugs, OTC over the counter

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Migraine affects approximately 28 million Americans, which represents more than 18% of American women and 6% of men.[1] Migraine causes pain, suffering, and disability, which leads to impaired work performance and interference with social activity.[2] Over 80% of patients reported severe or extremely severe pain and moderate to severe functional impairment.[1] The chronic, disabling nature of migraine and the associated loss of productivity has a significant societal and economic impact.[3] These findings on prevalence, disability, and treatment patterns are consistent across a range of studies from the general population.[4,5] Unfortunately, less than 50% of survey participants who meet International Headache Society's (IHS) criteria for migraine have received a medical diagnosis of migraine, and less than 20% received a prescription medication for their migraine.[1,5]

Sinus headache is the most frequent erroneous diagnosis given to patients with migraine.[1,6,7] This diagnostic confusion is based in part on the paucity of nosologic research to define the distinguishing clinical features of the headache associated with rhino-sinus pathology, and the lack of operational diagnostic criteria. The IHS does not recognize sinus headache as a diagnostic entity unless it is associated with underlying acute rhinosinusitis. Even headache associated with an underlying sinus infection is poorly characterized. For these reasons, in addition to the potential for the clinical features of migraine to overlap with the symptoms of sinusitis, physicians may error on the side of caution because the morbidity associated with a missed diagnosis of sinusitis can be substantial.

Recently, there has been an attempt to characterize the headaches of patients suffering with a self-diagnosis or physician diagnosis of sinus headache. In a small study of 37 self-diagnosed sinus headache sufferers, 70% met IHS criteria for migraine with or without aura and an additional 28% met criteria for migrainous headache.[7] Furthermore, 63% recorded a Headache Impact Test (HIT-6) score of greater than 60, indicating severe headache-related disability. In a related study, those with self-diagnosed sinus headache were allowed to treat their "sinus headaches" with 50 mg of oral sumatriptan.[8] Of those who treated their headaches when it was of moderate to severe intensity, 74% experienced headache relief within 2 hours. In the SUMMIT study, 2991 patients with a self-diagnosis or physician diagnosis of sinus headache were evaluated in a multicenter (453 site) study.[9] Employing IHS criteria, 80% had migraine with or without aura; 8% had migrainous headache; 8% had episodic tension headache; and 4% had "other" headaches. While it is clear that the majority of those with undiagnosed migraine have received a diagnosis of sinus headache and continue to suffer substantial headache-related disability, the demographic and clinical characteristics of this group of patients remains unclear. This nosologic study was designed to provide a detailed clinical assessment of patients with a self- or physician diagnosis of sinus headache in an effort to delineate the clinical phenotypes, which may be responsible for the diagnostic confusion, develop operational diagnostic criteria for these migraine subtypes, and determine whether a noninfectious form of sinus headache exists. Ultimately, the ability to clinically distinguish migraine from pain associated with sinus pathology will undoubtedly lead to appropriate treatment, elimination of unnecessary procedures and/or surgeries, and improve the health-related quality of life in a substantial population of patients.

METHODS

Following approval by the Mayo Clinic Institutional Review Board, 100 consecutive subjects were recruited from the general population (greater Phoenix, Arizona area) after responding to a newspaper

advertisement. All subjects who believed they suffered from sinus headache and were over 18 years of age were enrolled without exclusion. A detailed headache history (60 minutes) and a complete general and neurological examination (30 minutes) were performed in each subject by a neurologist specializing in headache. The investigators discussed in detail every headache type thought to be experienced by each subject (as many as 8 per subject). Every headache was assigned a headache diagnosis based on the 2004 IHS criteria (ICHD-II).[10] Further details concerning previous medical history, physician consultation, diagnostic investigation, treatment, disability, and headache characteristics were elicited. Brain and sinus imaging were performed at the discretion of the investigator in suspect cases. Data were entered and analyzed using Microsoft Excel programming. Standard deviations were calculated using the n – 1 method.

Therapy Rating Scales.—Each subject was asked to use a 7-point rating scale to represent the efficacy of each of their current medications in relieving pain. The scale ranged from –3 (very dissatisfied) to +3 (very satisfied) with intermediate ratings of dissatisfied (–2), somewhat dissatisfied (–1), neutral (0), somewhat satisfied (+1), and satisfied (+2). The effectiveness of surgeries, allergy desensitization, and "nontraditional" medicine was measured on an eleven-point scale (–5 to +5 including 0). A negative value was used to indicate a procedure or technique that made the subjects' headaches worse, while positive values indicated improvement; positive 5 being the most helpful.

Calculating Cranial Autonomic Symptoms.—Subjects were asked to rate (0 = none, 1 = mild, 2 = moderate, and 3 = severe) the presence of 7 cranial autonomic symptoms (lacrimation, conjunctival injection, eyelid edema, rhinorrhea, nasal congestion, postnasal drip, and reddening of the face or ears) leading up to, during, and after the headache. Time intervals included 1/2–1 day prior to headache, 6–12 hours before headache, 4–6 hours before headache, 2–4 hours before headache, <2 hours before headache, increasing pain prior to peak pain, peak pain, resolving pain, <6 hours after headache resolution, and 6–12 hours after resolution. A maximal cranial autonomic symptom score for any given time period was 21 (7 possible symptoms times 3 [severe]).

Determining Disability.—Both the Migraine Headache Disability Score (MIDAS) and the Headache Impact Test (version 1.1) were used to determine the headache-related disability in each patient. These questionnaires were completed under the supervision of the investigators to assure accuracy.

Definitions.—Medication overuse (MO) was defined by the use of any medication known to cause medication overuse headache (simple analgesics, combination agents, triptans, opioids, etc.) greater than 12 days per month for 2 months or longer.

RESULTS

Demographics of Study Population.—One hundred consecutive subjects with a self-diagnosis of "sinus headache" were enrolled in this study. The average age of these subjects was 51 (S.D. 14.5) years with an age range from 18 to 81 years. Seventy-eight percent were women and 22% were men (3.5:1). All patients came from the greater-Phoenix, U.S. area representing 18 different communities. The vast majority of subjects were Caucasian (90%); Hispanic (6%), African American (2%), Asian (1%), and Middle Eastern (1%) races were also represented. The study population was well educated with 75% of the subjects having a college education or more. The majority (48%) of subjects had an annual income between $30,000 and $70,000.

Overview of Headache Types.—Of the 100 subjects, the types of headaches mistaken as "sinus headache" were migraine [either 1.1, 1.2, or 1.5.1] (52%), chronic migraine [1.5.1] associated with MO versus probable MOH [8.2.7] (11%), probable migraine [1.6] (23%), headache associated with rhinosinusitis [11.5] (3%), episodic cluster headache [3.1.1] (1%), hemicrania continua [4.7] (1%), and headaches nonclassifiable [14.1] (9%) according to the 2004 IHS criteria (Fig. 1).

Migraine Mistaken as "Sinus Headache."—*Demographics.*—Sixty-three percent (n = 63) of the study population mistook migraine headaches as "sinus headache." For purposes of these analyses, these 63 subjects include 11 who suffered from either chronic migraine associated with MO versus probable MOH. Eighty-two percent of these patients were women and 18% were men (4.7:1) ranging in age from 18 to 75 years (mean age of 49.7 years). Ninety-two percent

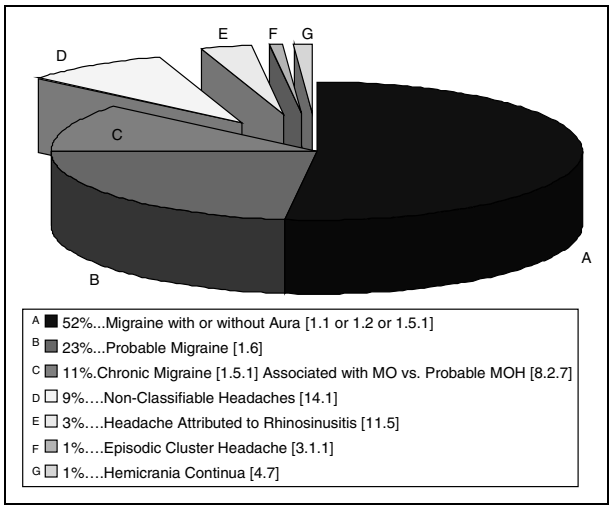

Fig 1.—Overview of actual IHS headache diagnosis that was being mistaken by subjects (n = 100) as "sinus headache."

were Caucasian, 4.8% Hispanic, 1.6% African American, and 1.6% Asian.

Self-Reported Diagnoses.—Each subject reported between 1 and 5 headache types that they considered distinct from each other; average of 2.2 headache types was reported per subject. This accounted for a total of 140 headaches. Types of self-diagnosed headaches included "sinus headache" (100%), migraine (38%), tension headache (32%), allergy headache (7.9%), cluster headache (3.2%), and others (35%). There were numerous reasons why patients believed they suffered from "sinus headache" including pain located over the sinuses (98%), pain triggered by changes in the weather (83%), pain associated with rhinorrhea (73%), and the diagnosis suggested by a previous physician (78%). Figure 2 summarizes subject rational for self-diagnosing "sinus headache"; note that this includes the original 100 subjects. The 63 migraine subjects reported a medical history of allergic rhinitis (54%), prior acute rhinosinusitis (76%), and chronic rhinosinusitis (14%).

Actual Headache Diagnoses.—Six different IHS diagnoses were applicable to these 63 subjects: migraine without aura [1.1] (97%), migraine with aura [1.2] (48%), chronic migraine [1.5.1] (27%), probable migraine [1.6] (11%), primary stabbing headache [4.1] (3.2%), and occipital neuralgia [13.8] (1.6%). The average patient had 1.8 different IHS diagnoses ranging from 1 to 4 separate classifiable conditions. Thirty-two percent of this migraine population met criteria for MO. Offending agents included acetaminophen (42%), combination over-the-counter (OTC) headache medications (32%), nonsteroidals (26%), butalbital containing agents (5.3%), opioids (5.3%), and other (5.3%).

Headache Onset and Delay to Diagnosis.—The average age of headache onset was 23.9 years (range 6 to 58 years old). Subjects waited 11.2 years on average (range 0 to 56 years) prior to discussing their headaches with a medical professional and 25.3 years (longest of 62 years) prior to receiving a correct diagnosis.

Headache Characteristics.—In this population (n = 63), the mean frequency of migraine headache days per month was 14.3 (range 2 to 30). The mean headache duration was 40.5 hours with a mean time to peak pain intensity (Tmax) of 105 minutes (range 10 to 480 minutes).

Seventy-three percent of subjects described the quality of their headache pain as "throbbing and/or pounding," 35% as "pressure," and 22% as both "pressure" and "throbbing and/or pounding." The mean pain severity was 6.7 on an ordinal 0–10 scale (range 4 to 10). Several triggers commonly attributed to "sinus headache" were noted by the majority of subjects including weather changes (83%), seasonal variation (73%), exposure to "allergens" (62%), and changes in altitude (38%). Thirty-two percent of the migraine patients reported 2 of these triggers, 29% had 3 triggers, and 24% had 4 such triggers. Forty-nine percent of subjects reported a known allergen as a trigger for their headaches and could identify a specific culprit. These allergens included grass/specific trees (13%), dust (10%), specific food substances (7.7%), cat and dog dander (5.1%), and mold (2.6%).

The vast majority (97%) of subjects reported maximal pain intensity in the face (forehead and/or maxillary portion) in either a bilateral or unilateral distribution. Seventy-six percent experienced maxillary pain (either unilateral or bilateral). Only 14.2% of subjects reported a strictly unilateral pain distribution. Figure 3 summarizes the location of maximal pain intensity.

CAS during headaches were present in 75% of these subjects suffering from migraine. The most frequent CAS were nasal congestion (56%),

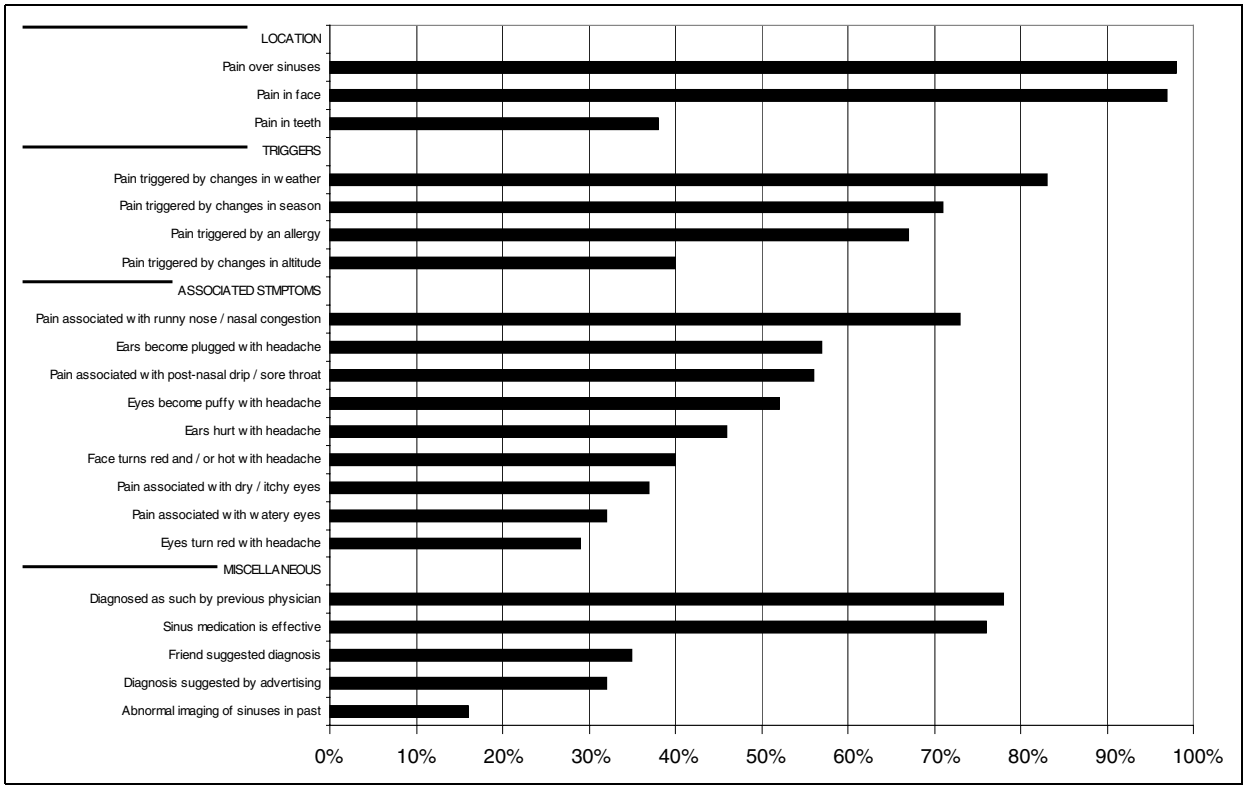

Fig 2.—A summary of the reasons why subjects (n = 100) believed they suffered from "sinus headaches."

eyelid edema (37%), rhinorrhea (25%), conjunctival injection (22%), lacrimation (19%), and ptosis (3%). Twenty-four percent reported 2 cranial autonomic features, 16% had 3, 7% had 4, and 3% reported 5 concomitant symptoms during attacks. Figure 4 displays the timing and severity of CAS (sum of lacrimation, conjunctival injection, eyelid edema, rhinorrhea, nasal congestion, post-nasal drip, and a red/hot face) in temporal relationship to the onset and resolution of migraine head pain.

Consultation and Diagnostic Evaluation.—The subjects on average had seen over 4 (4.4 [SD 5.5]) previous physicians in consultation (range 0 to 28). Sixty-four percent had been seen in consultation by a family physician, 59% by an otolaryngologist, 25% by an allergist, 25% by an internist, 19% by a neurologist, 3.2% by a pediatrician, and 7.9% by "other" physicians (obstetrics/gynecology, emergency medicine, etc.). Figure 5 depicts the headache diagnoses made for these patients suffering from IHS migraine summarized by subspecialty. Otolaryngologists diagnosed sinus headache most frequently (54%); sinus headache was also the most common diagnosis by allergists (38%), whereas neurologists diagnosed migraine most often (83%).

Thirty-two percent of subjects had at least one neuroimaging test performed (MRI brain [16%], CT brain [14%], and MRI of the cervical spine [1.6%]), and 81% had undergone at least one investigation looking at the sinuses (CT sinuses [41%], sinus X-rays [29%], and endoscopy [11%]). On average, subjects underwent 0.81 sinus X-rays, 0.71 CT sinuses, 0.24 MRI brain, 0.21 endoscopy, 0.14 CT brain, and 0.02 MRI cervical spine.

Headache-Related Disability.—The majority of subjects (51%) experienced severe disability (MIDAS grade IV) as a result of their headaches. Fourteen percent of subjects did not experience any significant disability (MIDAS grade I), 14% experienced mild disability (MIDAS grade II), and 21% experienced moderate disability (MIDAS grade III). MIDAS scores ranged from 0 to 232 (mean 32).

Treatment.—Ninety-five percent of the 63 subjects were taking medications for the treatment of their headaches. Nonsteroidal anti-inflammatory

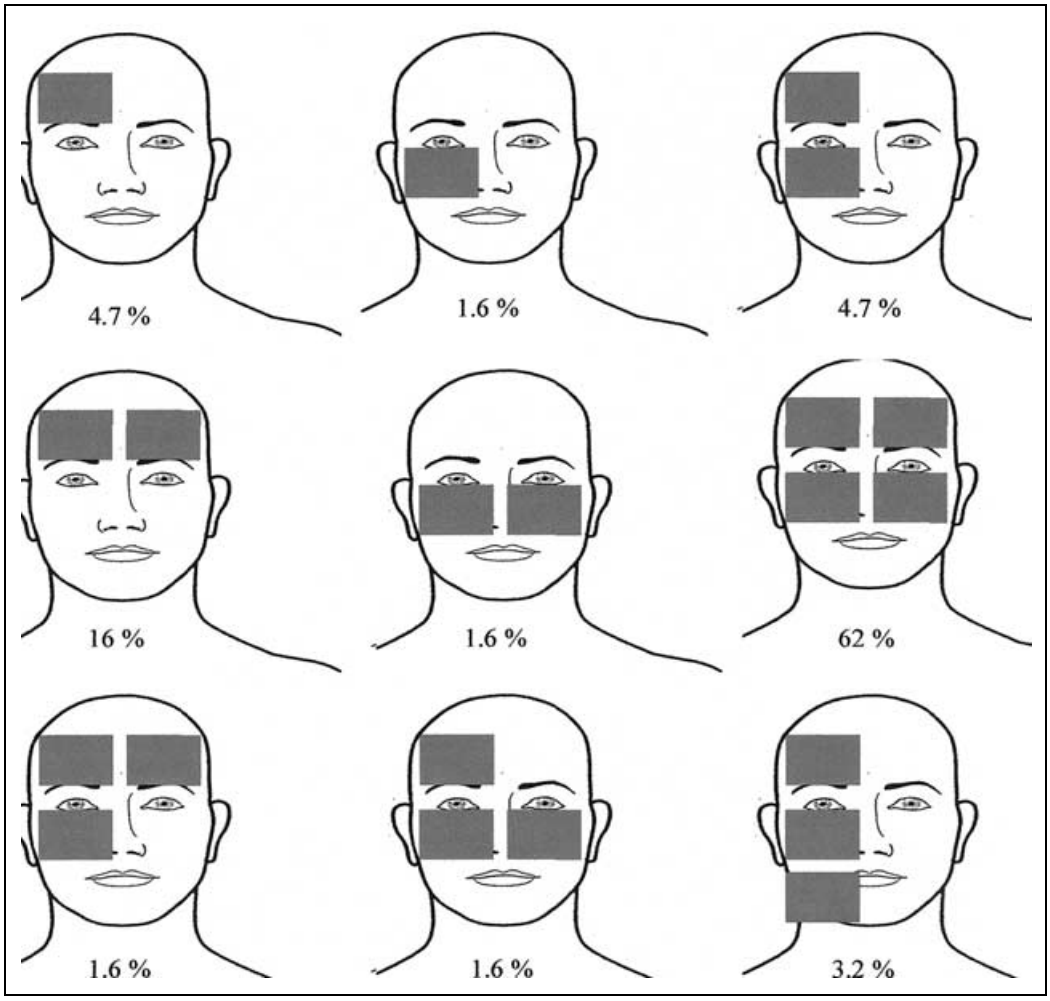

Fig 3.—A summary of the distribution of maximal pain intensity experienced by subjects with migraine. Three percent of the subjects (not depicted above) did not experience any face pain during their attacks.

drugs (NSAIDs; 33%) were the most common followed by acetaminophen (25%), OTC combination headache analgesics (21%), and OTC combination sinus medications (21%). Triptans were utilized by 9.5%. Based upon indications and contraindications, 92% of subjects were candidates for triptans, but only 12% were utilizing them. Despite their infrequent use, triptans received the highest efficacy rating (average 2.2) followed by narcotics (1.5) and antihistamines (1.4). Figure 6 summarizes the most commonly used medications and their perceived effectiveness.

Of the 63 subjects, 27% (n = 17) received prior/current allergy desensitization. Only 5.9% of these subjects actually had allergy desensitization specifically for headache. The average effectiveness score of allergy desensitization for these subjects was 1.1.

Thirty-five percent (n = 22) of subjects reported prior "sinus surgery" including septoplasty (13%), antrostomy (1.6%), polypectomy (1.6%), etc. Four (18%) of these 22 subjects (6.3% overall) indicated that they underwent their surgery specifically to obtain headache relief.

Alternative therapies utilized included chiropractic manipulation (11%), acupuncture (9.5%), herbal medicine (9.5%), biofeedback (3.2%), nutritional therapy (3.2%), homeopathic medicine (1.6%), and other (6.3%). Subjects ranked the effectiveness of chiropractic medicine the highest (1.9) followed by acupuncture (1.2), herbal medicine (1.2),

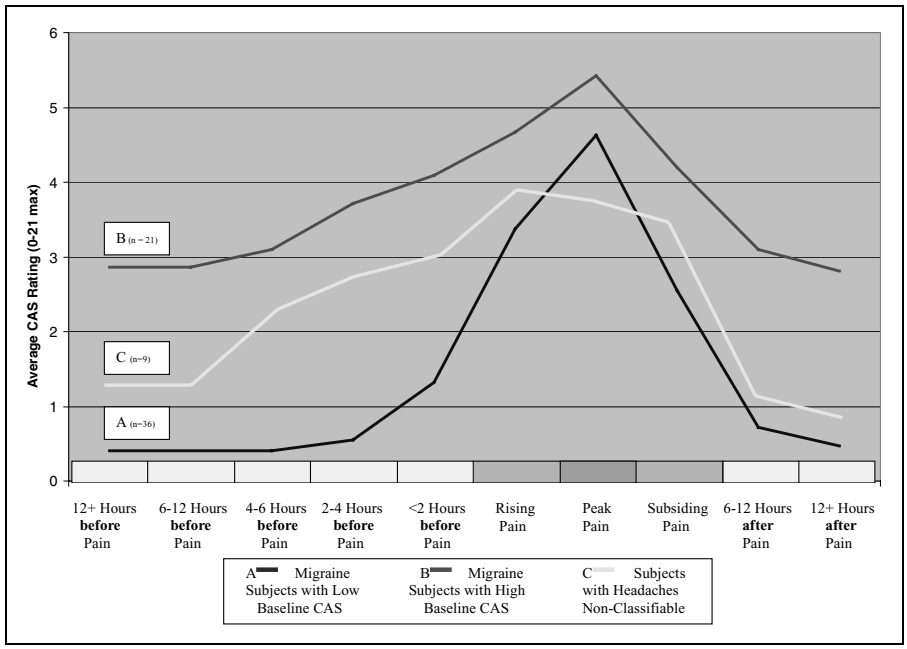

Fig 4.—A summary of the timing and severity of cranial autonomic symptoms in subjects suffering from migraine headaches (n = 57) and headaches nonclassifiable headaches (n = 9). Six migraine subjects (not depicted above) had a "mixed pattern" of CAS.

and biofeedback (1.0). Nutritional alterations, homeopathic medicine, and "other" approaches were ineffective (0.0) but not harmful.

Headaches Associated With Rhinosinusitis.—Three of the total subjects enrolled (3%) had underlying sinus infections as a secondary cause for their headaches. These 3 subjects were women (aged 26, 66, and 79). All 3 subjects had radiographic evidence of infection (air-fluid level in 2 subjects and marked unilateral [and ipsilateral to pain] mucosal thickening in another).

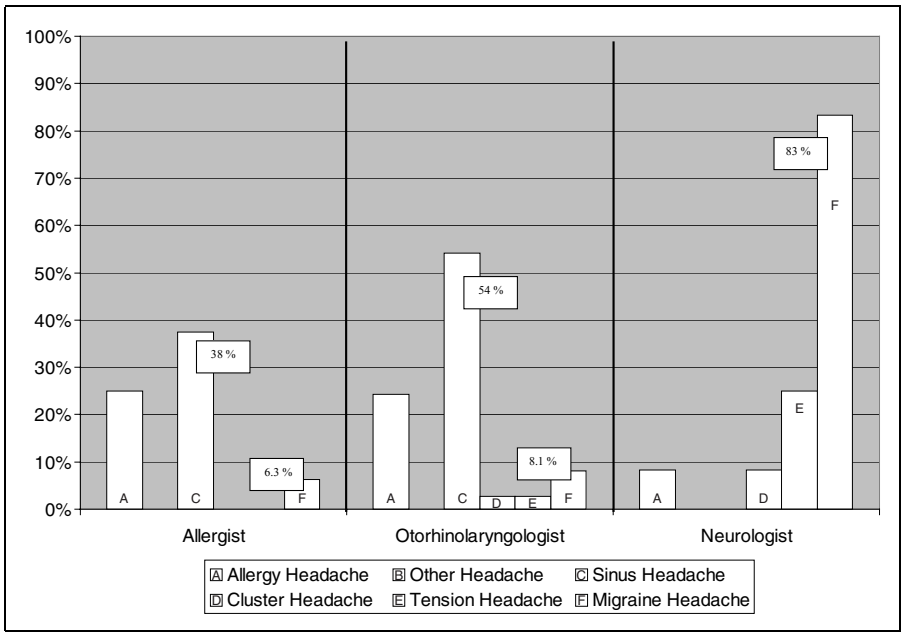

Fig 5.—Headache diagnoses given by various specialties for actual IHS migraine (mistaken as "sinus headache" by subjects).

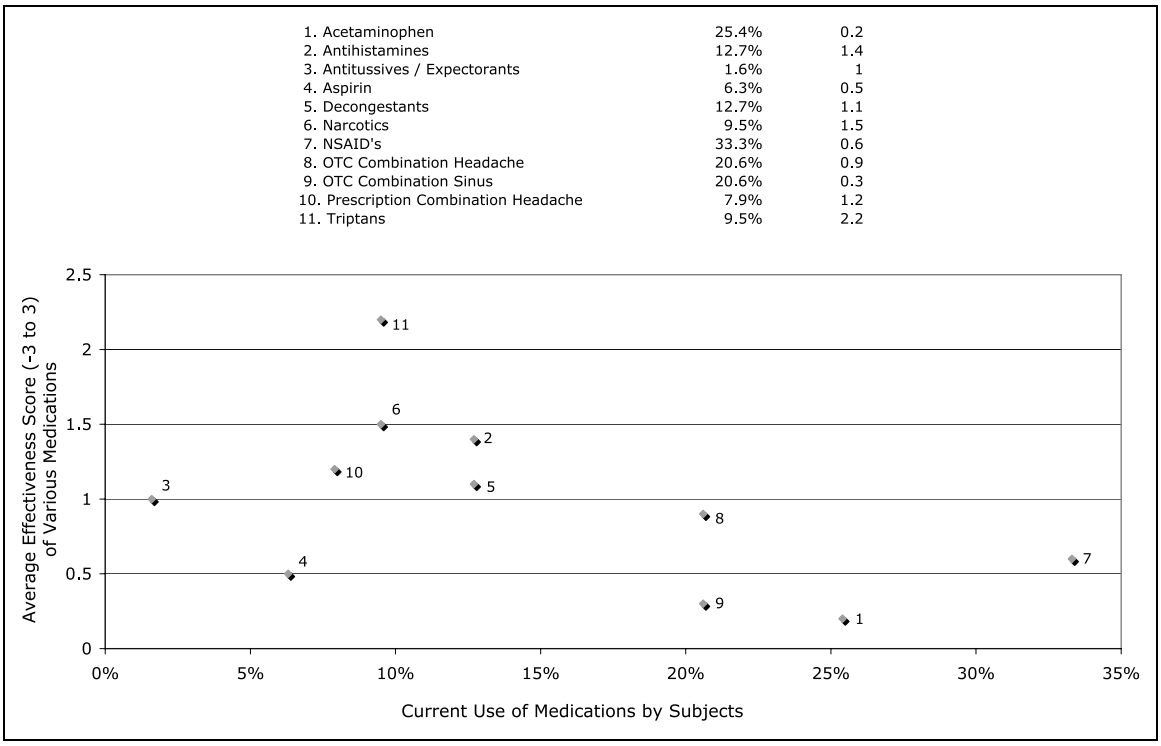

Fig 6.—A summary of the current medications and their effectiveness used by migraineurs (n = 63) who believe they suffer from "sinus headache."

The 26-year-old complained of a bilateral pressure in her forehead with an intensity of 4 out of 10. She had associated thick green nasal discharge but no fever, chills, or night sweats. The 66-year-old complained of a sharp pain (ranging from 2 to 8 out of 10) in her forehead and behind her nose associated with fever, night sweats, and malodorous breath. The 79-year-old woman experienced an uncomfortable pressure (pain of 2–8 out of 10) in the left maxillary region associated with thick discharge but no fever, chills, or night sweats.

Proposed Criteria for Facial Migraine

- A. Fulfills IHS criteria for migraine without aura (1.1) or with aura (1.2)
- B. Maximal pain in two adjacent quadrants of the face, where the quadrants are formed by a vertical line between the eyes and a horizontal line across the bridge of the nose

Proposed Criteria for Migraine with CAS

- A. Fulfills IHS criteria for migraine without aura (1.1) or with aura (1.2)
- B. At least one of the following cranial autonomic symptoms during the headache:
  1. Conjunctival injection
  2. Lacrimation
  3. Nasal congestion
  4. Rhinorrhea
  5. Eyelid edema
  6. Ptosis

Fig 7.—Proposed IHS criteria for both "facial migraine" and "migraine with cranial autonomic symptoms."

Proposed Criteria for Non-Infectious Rhino-Sinus Headache (NIRSH)

- A. At least five attacks fulfilling B-E (if > 15 days / month for longer than 3 month, classified as chronic NIRSH)
- B. Headache lasting 1 hour to 5 days (untreated or unsuccessfully treated)
- C. All of the following:
  1. Pain described as pressure, not pulsating
  2. Mild or moderate severity (may inhibit but does not prohibit activities)
  3. Bilateral maxillary location
  4. No aggravation by walking stairs or similar routine physical activity
- D. All of the following:
  1. No nausea or vomiting
  2. No photophobia or phonophobia
  3. At least one of the following cranial autonomic symptoms (conjunctival injection, lacrimation, nasal congestion, rhinorrhea or eyelid edema)
- E. Not attributed to another disorder including *infectious* rhinosinusitis

Fig 8.—Proposed IHS criteria for "noninfectious rhino-sinus headache."

Interestingly, 5 of the subjects with migraine had experienced at least one episode, which was highly suggestive of a prior acute rhinosinusitis that evolved from a prolonged IHS-defined migraine with cranial autonomic symptoms (MCAS). This was 5% of the total population and 7.9% of the subjects suffering from migraine.

Headaches Nonclassifiable.—*Demographics and IHS Headache Diagnoses*.—Nine percent of the 100 subjects had headaches that were nonclassifiable [14.1] by current IHS criteria. These patients ranged in age from 34 to 69 years with a mean age of 53. Mean age of headache onset was 28.1 years (range 7 to 66). Seven of the 9 (78%) were women and 89% were Caucasian. Thirty-three percent experienced only one headache type, while 44% also experienced IHS migraine [either 1.1 or 1.2] and 44% experienced IHS tension-type headache [2.1]. Forty-four percent reported a family history of headache, often of undetermined type. One of the 9 was overusing medications for headache. Fifty-six percent had a history of allergic rhinitis; 100% reported at least one prior bout of acute rhinosinusitis; none reported a history of chronic rhinosinusitis.

Details of Headaches Nonclassifiable.—Common triggers for these headaches included exposure to suspect allergens (89%) and weather changes (67%). Forty-four percent experienced a seasonal variation in their headaches. The mean headache duration was 26 hours (range 1 hour to 5 days). The mean time to maximum pain intensity was 74 minutes. Pain severity ranged from 2 to 6 (on a 10 point scale) with a mean of 4.2. The mean number of headache days experienced per month was 11 (range 3 to 30). The one patient who experienced daily headache was overusing acute OTC pain medications. All patients treated their headaches with either OTC medications (100%) or prescription medications (11%). These medications included combination OTC headache agents, antihistamines, NSAIDs, decongestants, and aspirin. The mean MIDAS in these individuals was 1.9 (range 0 to 10). Pain was characterized by a bilateral maxillary (and usually forehead) pressure of mild to moderate intensity associated with at least one CAS (see Fig. 4 for timing of autonomic symptoms). Nasal symptoms were most common with nasal congestion occurring in 100% and rhinorrhea in 67%. Thirty-three subjects experienced eyelid edema with their headaches, 22% experienced lacrimation, and 11% experienced conjunctival injection. No patients reported ptosis with their headaches. Fever, chills, night sweats, and thick nasal discharge were absent in all patients. Features suggestive of migraine (pulsatile quality, worsening with activity, nausea/vomiting, photophobia, or phonophobia) were also absent. All 9 patients had normal neurologic/otolaryngology examinations and sinus CT imaging.

COMMENTS

The combined prevalence of migraine, allergy, and sinus disease in the United States is enormous by any measure. The Asthma and Allergy Foundation of America estimates that 50–60 million Americans (1 in every 5 adults and children) suffer from allergies accounting for 3.5 million lost work days, 2.0 million missed school days, and $4.5 billion in medical costs each year.[11] Likewise, the American Academy of Otolaryngology-Head and Neck Surgery (AAO-HNS) estimates that 37 million Americans suffer from at least one episode of acute sinusitis each year.[12] Billions of dollars are spent each year on both OTC and prescription medications aimed at allergies, sinus disease, and "sinus headache."

While it is not surprising, based on prevalence figures, that a history of coexistent allergy and/or sinus pathology will exist in some of those with migraine, the possibility of co-morbidity has not been previously evaluated. In this study, 54% of the patients with IHS-defined migraine reported a medical history of allergic rhinitis, and 76% claimed to have had at least one episode of prior acute sinusitis, numbers higher than expected in the general population. Certainly the relationship between the nose, sinuses, allergies, and headache has been explored in the past, but careful research into this association is scarce. A careful analysis of the clinical characteristics of patients with a self- or physician diagnosis of "sinus headache" using a detailed interview and examination conducted by a team of headache subspecialists is lacking. Previous studies included small numbers of patients, retrospective diary assessments of clinical features, and selection biased toward including patients with migraine.[7-9]

Therefore, consensus regarding the existence of sinus headache in the absence of acute rhinosinusitis is lacking and likely contributes to the diagnostic confusion. Because the majority of the undiagnosed migraineurs in the United States are misdiagnosed as having sinus headache, a careful evaluation of this population of patients is a clinical priority.

In this study, 86% of patients with a self-diagnosis and/or physician diagnosis of "sinus headache" have migraine with or without aura (63%) or probable migraine (23%) as defined by the 2004 International Headache Society Classification Criteria. In this study, probable migraine appears to have been misdiagnosed due to a lack of typical pain features or associated symptoms, whereas distracting symptoms appear to account for the misdiagnosis of patients with migraine. Distracters for migraine, mistaken as sinus headache, include environmental triggers, facial location of pain, and the presence of CAS, a case of "guilt by provocation, location and association." CAS (75% of subjects) and pain located predominantly in the face (97%), were exceedingly common in those with misdiagnosed migraine. Migraine with accompanying facial pain (facial migraine) and MCAS occur with sufficient frequency to warrant the creation of operational diagnostic criteria (Fig. 7). Such criteria should serve to raise awareness of these unique migraine presentations and reduce the prevalence of migraine misdiagnosis.

CAS occur with a variety of primary headache disorders such as cluster headache, chronic paroxysmal hemicrania, SUNCT syndrome, and migraine. The prevailing hypothesis is that first-division trigeminal pain leads to the expression of facial autonomic symptoms through the trigeminal-autonomic reflex, which activates cranial parasympathetic efferents. While 57% of patients in this study experienced CAS that temporally emerged and peaked with their migraine headache, 33% of patients clearly had chronic and persistent CAS which, when exacerbated, were associated with the onset of headache. This relationship raises the possibility that recurrent mucosal edema and inflammation in patients with seasonal allergic rhinitis could potentially trigger migraine in susceptible individuals and may in part explain the seasonal variation of headache described by over 70% of the migraine subjects in this study. This observation requires further study and confirmation because the therapeutic implication is that interventions (both acute and preventative) such as antihistamines, decongestants, nasal steroids, and desensitization therapy, may play a role in migraine prevention for certain patients.

Endoscopic evidence of nasal mucosal swelling has been shown to occur during a migraine attack and resolve after administration of sumatriptan.[13] Obstruction of the sinus ostia by mucosal edema may result in a loss of mucus clearance, decreased oxygen, and increased carbon dioxide tension.[14] This creates the ideal circumstances for normal sinus flora to proliferate resulting in an acute sinus infection. Indeed, this is speculated to be the mechanism by which patients with uncontrolled allergic rhinitis have frequent sinus infections. Therefore, it is of interest that 5 patients in this study described an episode of acute rhinosinusitis that occurred during the resolution of a prolonged but otherwise typical migraine attack that was characteristically associated with nasal congestion. Whether some patients with migraine and accompanying nasal congestion are at risk for recurrent acute bouts of sinusitis is another area worthy of exploration.

This study underscores the consequences of misdiagnosis—inadequate and inappropriate medical and surgical treatment, marked headache-related disability, inappropriate diagnostic investigations, and substantial health care costs. Migraineurs in this study were evaluated for headache by an average of more than four physicians without receiving a correct diagnosis. Potentially unnecessary diagnostic sinus investigations were performed in the majority (81%) of subjects contributing to the explosion in health care costs. Inadequate headache relief with NSAIDs or acetaminophen resulted in severe headache-related disability in 58% of subjects. Retrospective estimates revealed a staggering absence or reduced productivity at work, school, or home in patients who suffered from undiagnosed migraine for an average of 25 years.

Surprisingly, 9% of the subjects in this study suffered from headaches that could not be classified according to the ICHD-II. These headaches were characterized by pain, which was bilateral, located in the maxillary region, and associated with at least one CAS. The most common CAS were nasal congestion and rhinorrhea. Importantly, these headaches lacked all

of the pain and associated features of migraine and were distinguishable from tension headache based on their maxillary location and associated facial autonomic symptoms. We propose the term noninfectious rhino-sinus headache (NIRSH) to describe this unique primary headache disorder and suggest diagnostic criteria (Fig. 8).

As the name suggests, NIRSH is unrelated to an underlying infection or anatomic abnormality (eg, contact point, choncha bullosa). Unlike headaches associated with acute rhinosinusitis, subjects with NIRSH have normal sinus imaging and no clinical features suggestive of infection. The 3 cases of headache secondary to rhinosinusitis in this study had at least one clinical characteristic (thick nasal discharge, fever, chills, sweats, or abnormally malodorous breath) of an underlying sinus infection and abnormal sinus imaging (air-fluid level or marked asymmetric mucosal thickening). While the mechanism underlying this particular headache disorder is uncertain, mucosal edema and inflammation of the nasal turbinates or sinus ostia is one potential explanation.[15] It is of interest that the clinical features experienced by patients with experimentally induced sinus pain—bilateral location (91%), nasal obstruction (89%), duration of hours to several days, and improvement with either antihistamines or decongestants—are very similar to those symptoms experienced by the patients in this study with NIRSH.[16]

Two of the 3 subjects (with an underlying rhinosinusitis) experienced daily headaches, which temporally correlated with a diagnosis of chronic rhinosinusitis and both experienced headache relief with corrective surgery. Since the IHS only recognizes acute (not chronic) rhinosinusitis as a cause for headache, these cases do not conform to any primary or secondary headache disorder in the current IHS classification. In contrast, the AAO-HNS recognizes headaches as a frequent consequence of chronic rhinosinusitis.[17] Previous studies have demonstrated that up to 48% patients with chronic rhinosinusitis suffered from a dull headache often described as fullness or pressure.[18,19] In addition, one report suggested that up to 94% of patients with chronic sinusitis experienced headache resolution within 2 months after treatment of the chronic sinus infection.[20] Because the International Headache Community does not recognize an association between chronic rhinosinusitis and chronic headache, the results of this and other studies suggest that a careful evaluation of the relationship between the two is warranted.

The limitations of this study include (1) a study sample that was skewed toward an older, well-educated Caucasian population, (2) the lack of an independent assessment by experts in otolaryngology and allergy/immunology, and (3) not all patients underwent nasal endoscopy and imaging of the nose and sinuses. The strength of this study is the interview-based evaluation of each patient by experienced headache specialists. Revised International Headache Society Criteria were used to apply diagnoses in each case. Unlike previous studies, this study evaluated a large population of consecutive self-diagnosed "sinus headache" sufferers without exclusion. The medical records for each patient were evaluated by an independent neurologist and headache specialist who was blinded to the diagnosis.

Migraine, allergic/vasomotor rhinitis, and rhinosinus-related disease are each major public health problems in the United States. The relationship between these disorders is clearly a fertile area for research, and clarification of the pathogenic mechanisms should facilitate the development of enhanced therapeutic strategies. This study identified the potential for significant comorbidity between these disorders, and identified the major reasons, which account for why migraine is frequently misdiagnosed as sinus headache. A potentially new primary headache disorder has been defined and operational diagnostic criteria are proposed for facial migraine, MCAS, and NIRSH. These criteria should be field-tested to determine their sensitivity and specificity. They should facilitate accurate diagnosis of migraine phenotypes, which have thus far created significant diagnostic confusion, and ultimately decrease the burden of illness and limit the cost of inappropriate diagnostic evaluations and treatment of this group of patients.

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