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Update on the diagnostic considerations for neurogenic nasal and sinus symptoms: A current review suggests adding a possible diagnosis of migraine

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ABSTRACT

Background: Treatment of rhinosinusitis (RS) is one of the leading reasons for prescriptions of antibiotics, although they often fail to provide symptomatic relief. Appropriately diagnosing and treating patients presenting with RS for whom antibiotic therapy has failed or who have normal CT findings is a controversial topic. One explanation is that what these patients are experiencing is misinformation from the trigeminal nerve and autonomic nervous system. Midfacial pain and pressure with rhinorrhea and nasal congestion do not represent an infectious, or even inflammatory, condition within the sinus or nasal cavities, but a mirage that is best treated as a migraine variant.

Observations

Although there is not enough research to definitively prove this alternate etiology, we are reaching a tipping point where the clinical implications, real-world experience, and evolving literature support this possible alternate etiology. Four key factors support a midfacial migraine that mimics RS: 1) Pathophysiology: current pathophysiology literature offers a model of how migraine attacks could replicate clinical presentations of RS; 2) Clinical presentation: patients with infectious RS and midfacial migraine have similar symptomatic presentation, similar demographics, but poorly correlated radiological information; 3) Diagnosis: clinical studies support the proposition that there are alternative diagnostic tools for distinguishing patients with midfacial migraine; and 4) Prognosis: Select RS patients show significant improvement with migraine treatment.

Conclusions: We encourage medical professionals to consider migraine disease as a form of sensory misinformation and as a possible etiology of RS complaints. Clinicians can ask validated questions to determine if possible migraine could be an underlying cause, and there are standard preventative treatments for migraine that could alleviate patient symptoms. Dysfunctional vasomotor activity may be the root of the disturbances, particularly when antibiotic therapy fails and CT findings are discordant with symptoms. Until there is a diagnostic test for migraine, clinicians need to question a patient's self-diagnosis of rhinosinusitis. More research is needed to definitively answer this important question.

1. Introduction

Approximately 30 million adult Americans, or 12% of the US population, are diagnosed with rhinosinusitis (RS) annually [1] and antibiotics are prescribed in 82% of associated office visits [2]. Recent studies demonstrate a persistent failure of oral antibiotics to provide symptomatic relief from rhinosinusitis in many patients [3,4]. This failure of antibiotics is seen with acute rhinosinusitis, where symptoms last < 4 week [3,4], recurrent acute rhinosinusitis, where a person has > 3 acute episodes in a year [5], and chronic rhinosinusitis (CRS), where symptoms last > 12 weeks [6]. The prevailing explanation for the failure of antibiotics is that viral upper respiratory infections and

Abbreviations: RS, rhinosinusitis; CRS, chronic rhinosinusitis; SSN, superior salivatory; PPV, positive predictive value; SNOT-22, Sino-Nasal Outcome Test

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noninfectious conditions (such as, allergic or immunologic inflammation), rather than bacterial agents, cause most cases of RS. A 2016 review of RS etiologies described viral infections, anatomic variants and abnormalities, asthma, biofilms, fungus, osteitis, reflux, vitamin D deficiency, epithelial barrier disturbance, superantigens, microbiome disturbances, ciliary derangement, and immunodeficiency as possibilities, but not neurogenic causes [7].

We urge consideration of an alternative etiology, migraine-generated rhinosinusitis-like symptoms, based on a literature review and clinical observations. Our aim is to encourage clinicians to consider a possible migraine variant in the diagnostic considerations for patients who present with RS. Although the research in this area is substantial, it is often conflicting and based on low quality evidence. However, when compiled as we have around the key concepts of pathophysiology, clinical presentation, assessment and diagnosis, and prognosis, the evidence begins to support both consideration of an alternate diagnosis and a call to action to perform more research in this important area. Additionally, an alternative diagnosis of migraine simply requires a mindset that the symptoms *could* be neurologically based such that the treating physician asks validated questions to identify migraine sufferers [8]. Once identified, there are standard preventative medications for migraine that could help these patients.

2. Pathophysiology

Migraine headaches are distinguished from other headaches by the co-activation of multiple parts of the nervous system, such as the special sensory auditory and visual systems and the autonomic gastrointestinal nervous system [9]. Migraine is a state of multimodal sensory sensitization accompanied by autonomic, and often limbic, hyperactivity. This disorder of sensory processing can affect most of the nervous system, primarily through the complex interconnections between brainstem nuclei (e.g. trigeminal and superior salivatory) and reciprocal connections with the diencephalon and cerebral cortex [10].

Our argument is that migraine sufferers who present with RS symptoms indicate chronic upregulation of any one or more branches of their trigeminal nerve, primarily the second branch, as well as cranial autonomic hyperactivity, primarily mediated through superior salivatory (SSN) activation, leading to the perception of facial pressure and pain with secondary nasal congestion, rhinorrhea, tearing, and facial swelling. When both the trigeminal and autonomic nervous systems are activated in the brainstem, they create a variety of symptoms that is easily misinterpreted as RS. In other words, migraine is a complex spectrum of nervous system malfunction with a variant that can masquerade as RS [11].

This explanation considers evidence that trigeminal activation generates efferent vasomotor activity. Migraine in other parts of the body is known to have autonomic components, such as nausea. It is also well-recognized that migraine is a common cause of vertigo, indicating activation of the central vestibular system [10,12]. In this pathophysiological model, either chronic neuroinflammatory activity or hormonal fluctuations change the sensory and, secondarily, the autonomic nervous systems. Like vestibular migraine, a “midfacial” migraine requires no trigger, but its spontaneous activity, perhaps still subject to other known migraine triggers, feeds our central nervous system with false information about the nose and sinuses [13]. When the spontaneous activity of the trigeminal nerve and the reflex activation of the superior salivatory nucleus in the brainstem combine to create the symptoms of fluctuating midfacial pressure and pain, nasal congestion, rhinorrhea and more, it creates disturbances mediated by dysfunctional autonomic activation that confuses both patients and clinicians. It is a primary (a head pain caused by the headache disorder itself), not secondary, headache disorder. A neurogenic cause of RS symptoms deserves its own distinction, like vestibular migraine, to allow improved patient care and advanced clinical study [10,12].

3. Clinical presentation

3.1. Similar symptomatic presentation of migraine disease and RS

Rhinosinusitis is multifactorial and heterogeneous syndrome that comprises several phenotypes and numerous endotypes. It is generally diagnosed based on symptomatic presentation of nasal obstruction, facial pain-pressure-fullness, and a cloudy or colored nasal drainage [14]. This is the crux of the problem: this description constitutes a condition, meaning a constellation of symptoms that occur together repeatedly, but is not a diagnosis in the sense that the symptoms do not define an etiology. By this definition, RS is simply a descriptive term and has no specific nosological value. Migraine is defined as moderate to severe head pain, often throbbing, associated with nausea or vomiting and aggravated by exertion or light or sound; it is also commonly associated with a range of cranial autonomic symptoms. Some attacks meet criteria for migraine with little or no head pain at all [15]. The range of autonomic symptoms, as described above, when both the trigeminal and autonomic nervous systems are activated in the brainstem can mimic RS symptoms.

3.2. Similar demographics among patients with migraine and RS

Both migraine and RS are among the most common acute and chronic diseases, affect more women than men, and have peak prevalence between ages 30–60 [16,17]. In a prospective study of 514 adult chronic RS patients, more women were diagnosed with chronic RS without polyposis than men [18]. Women were more likely to complain of facial pain, in contrast to men who complain more commonly of nasal congestion and headache [18]. This observation is likely attributed to the hormonal affect, particularly estrogen, on the female migrainous nervous system [19]. Patients with chronic RS are known to have co-morbidities, such as such as anxiety, depression, fibromyalgia, irritable bowel syndrome, neck and lower back pain, and these are similar to common comorbidities of migraine [20].

These observations highlight two features of migraine biology. First, migraine is a polygenetic disease. Many susceptibility genes have been linked with migraine [21,22]. These genes affect neurotransmission, mitochondrial function, the vascular system and more [10,23–25]. Second, these genes may predispose these patients to related neurological diseases (see above) and so explain the high coexistence of chronic migraine and > 30 other chronic diseases, or comorbidities [26].

3.3. Poor correlation between sinus CT scans and patient symptoms

Since imaging the paranasal sinuses is the most reasonable method to evaluate the conditions within these bony chambers, clinicians rely on this modality to confirm the presence of sinus disease, but most studies conclude that there is little correlation between CT findings and symptoms [6,27,28]. There are two potential radiologic findings among RS patients who also have suspected migraine disease. The first is when these patients are found to have no evidence of sinus disease. Across multiple studies, 35–50% of chronic RS patients have no abnormal sinus findings [29], even with active symptoms [30]. Additionally, a study of acute RS patients reported radiological evidence of minimal paranasal sinus mucosal pathology [31]. Again, these clinical incongruences indicate that RS-like symptoms do not define a specific disease state or etiology.

The second situation in which RS symptoms and migraine features overlap occurs when affected patients have “positive” findings on sinus CT scans [32]. There are two studies that estimated the frequency of this diagnostic dilemma as high as 80% [32,33]. The question is whether or not these findings represent incidental findings, a true concern when we consider the evidence that abnormal CT findings are known to correlate poorly with symptoms. Furthermore, at least one study reported that among patients presenting with sinus headache who

Table 1
Evidence that rhinosinusitis may be mismanaged.

First author Year	Population (N)	Result	Conclusion
Schreiber 2004 [39]	2991 patients with a history of self-described or physician-diagnosed "sinus" headache.	88% fulfilled the IHS migraine criteria (80%), or migrainous criteria (8%). Symptoms reported by patients included sinus pressure (84%), sinus pain (82%) and nasal congestion (63%).	"…the presence of sinus-area symptoms may be part of the migraine process. Migraine should be included in the differential diagnosis of these patients."
Paulson 2004 [45]	75 patients presenting with facial pain, a normal sinus CT scan, and normal nasal endoscopy were referred to and evaluated by a neurologist.	37% were diagnosed with migraine, 17% with rebound headache, 17% with chronic, and 16% with obstructive sleep apnea	"We recommend neurologic consultation in all patients presenting with facial pain, a normal sinus CT scan, and normal endoscopy findings."
Cady 2005 [40]	An interdisciplinary, ad hoc committee convened to review epidemiological studies of RS and migraine	The studies indicated that most individuals with self-or physician diagnosed sinus headaches have headaches that fulfill the criteria for migraine. Sinus headaches of rhinogenic origin and migraines are frequently confused with one another.	"Sinus features may obscure the diagnosis of migraine, and sole reliance on the IHS diagnostic criteria for migraine may result in a misdiagnosis of migraine with nasal symptoms as sinus headache. Otolaryngologists, allergists, and primary care physicians need to consider a diagnosis of migraine…"
Hessler 2007 [6]	84 adults with CRS	Those receiving medical treatment for CRS showed modest improvement over time: 78% showed improvement in SNOT-20 + 1 scores, although only 39% achieved a clinically meaningful improvement	"These findings highlight the limitations of current medical treatment for CRS and the need for improved diagnostic classification and novel treatment strategies. We found that the degree of improvement was greatest among patients without the presenting symptoms of facial pain or facial pressure."
Ishkanian 2007 [44]	216 patients with self-described or physician-diagnosed "sinus" headache were randomized to treatment with migraine medication (sumatriptan 50 mg) or placebo.	Significantly more patients who received treatment experienced relief of migraine pain and associated symptoms.	"Because the sinuses are also anatomically located in areas of the face where patients commonly experience migraine pain, it is possible that sinus pain and sinus pressure might be misinterpreted. Nasal symptoms (e.g., rhinorrhea, congestion) are distinct features of headaches with autonomic features (e.g., cluster headaches), but the fact that these symptoms are commonly reported by patients with IHS-defined migraine is not well recognized."
Kari 2008 [41]	54 patients with complaints of facial pain, pressure, or headache localized over the area of the sinuses, and a self- or physician- diagnosis of "sinus headache"	Migraine directed therapy significantly reduced headache pain in 92% of patients.	"These findings support that 'sinus headaches' may represent migraines, and response to triptans may aid in diagnosis."
Falagas 2008 [37]	Meta-analysis of 17 randomized clinical trials in patients with acute sinusitis treated with antibiotics (n = 3291)	Cure or improvement of patients was more likely with antibiotic treatment (77%) than placebo (68).	The small difference in treatment effect can be attributed to "the inclusion of a substantial number of patients without disease of bacterial origin, the high rate of spontaneous resolution of symptoms in acute bacterial sinusitis even in some patients not microbiologically cured, the persistence of symptoms caused by factors other than treatment failure, and the confounding effect of the administration of ancillary treatment."
Senbil 2008 [38]	214 children with chronic or recurrent headache in Turkey	116 patients (54.2%) had a history of sinusitis diagnosis, although sinusitis treatment had no effect on headaches in 60.3%. (70/116) of these patients. ~40% fulfilled the IHS-R criteria for migraine and 60% with tension-type headache had been previously misdiagnosed as "sinusitis".	"It may be quite difficult to differentiate the characteristics of sinus headache and other types of headaches, especially in the childhood."
Kaymakci 2013 [43]	103 patients presenting to an ENT clinic with sinus headache but negative endoscopic or computed tomography (CT) scan findings	98 had diagnosis of migraine (62%), tension-type headache or cluster headache. At the end of 3 months following treatment for neurovascular disease, 73% of patients were in complete remission, 15% described a decrease in their headache symptoms and 11% had not responded to treatment.	"Neurovascular event-based headaches, which develop as a result of diseases other than sinonasal pathologies but present with similar symptoms (namely, rhinorrhea, nasal obstruction and tearing) are often evaluated as rhinosinusitis." "We believe that, although the IHS diagnostic criteria were originally developed for neurologists, they should be familiar to all physicians (especially otorhinolaryngologists) who encounter patients complaining of headaches in their routine daily practice. Only by this route will misdiagnosis and inappropriate treatment rates diminish."
Al-Hashel 2013 [42]	130 migraine patients with a past history of sinusitis	106 (81.5%) received a misdiagnosis of sinusitis prior to a migraine diagnosis; mean delay was (7.75 ± 6.29, range 1 to 38 years).	"Symptoms suggestive of sinusitis are frequently seen in migraine patients and may lead to delayed diagnosis and treatment of migraine. General practitioner and otorhinolaryngology specialist should be aware of the diagnostic criteria for migraine and consider it in their differential diagnosis of patients suffering from 'sinusitis.'"
Lal 2015 [33]	Retrospective review of 211 patients seen by a rhinologist for sinus-related headache, pressure, pain or fullness [33]	70.62% met criteria for sinusitis or had rhinologic disease; ~half (48.82%) had primary headache disorder After failing otolaryngic intervention, 36.49% of patients were diagnosed with primary headache disorders upon neurology referral—which confirmed neurogenic factors in 97.7% of cases—and required no further otolaryngic management.	"A headache-neurologist's input is invaluable for sinus headaches refractory to Otolaryngic management, and should be considered prior to offering recurrent antibiotic therapy or revision ESS." "Neurological comorbidities may be culpable in many patients with positive CT and sinusitis."

underwent sinus surgery ($n = 80$), only 30% had effective symptomatic relief [33]. Other literature reports a high 6-month success rate for patients with confirmed diagnosis of medically refractory CRS who were referred for elective sinus surgery [34], lending credence to the supposition that more research is needed to tease out the differences in how different patients respond to different treatments. Additionally, the placebo effect may also be an important factor, as invasive procedures, specifically injections of medicine, have a remarkably high rate of symptomatic migraine relief versus oral medications [35].

We need to consider two explanations for this poor correlation. One, theoretically any form of inflammation, whether it is a bacterial, viral or fungal infection, an allergic reaction or other immunologic condition, could stimulate the trigeminal afferent nerve receptors and result in a headache, which could include midfacial pain. This offers an explanation for why some patients have diffuse facial pain that does not correlate well with CT findings but have some evidence of sinus mucosal disease. Two, this poor correlation, especially when there is no evidence of sinus mucosal disease, may be related to our argument that this is a spontaneous chronic neurological condition, or a variant of migraine, similar to allodynia or fibromyalgia. While this pathophysiology is currently only speculative, appropriate diagnosis and treatment of the many patients who have chronic sinonasal symptoms in spite of normal CT scans is an unmet challenge.

4. Assessment and diagnosis: Adding migraine to the diagnostic differential of RS

Given the potentially high prevalence of migrainous hyperactivity as the cause of RS symptoms and the clinical impact of choosing between medical or surgical treatment and migraine management, it is important that otolaryngologists and other medical professionals adopt new skills in identifying the etiology of a patient's RS presentation. And more broadly, no medical professionals will recognize migraine as the cause of RS symptoms unless they look for it. Until there is a diagnostic test for migraine, clinicians need to question a patient's self-diagnosis of rhinosinusitis. Patients can be very passionate about what they feel. But the clinician needs to resist being focused only on the sinus complaints. It is useful to explore other symptoms and the patient's past personal and family history. The primary diagnostic clue is that patients who experience neurogenic RS symptoms are more likely to have a history of current or past migraine headaches. Therefore, when interviewing a patient with symptoms of rhinosinusitis, patients should complete the validated three-question questionnaire ID Migraine© [8], which asks the following three questions:

"Has a headache limited your activities for a day or more in the last three months?

Are you nauseated or sick to your stomach when you have a headache?

Does light bother you when you have a headache?"

Clinicians should consider a possible migraine diagnosis if a patient has two or more positive answers [8]. A positive response to two of these 3 questions has a positive predictive value (PPV) of migraine of 93%; a positive response to all 3 questions conveys a PPV of 98% for a diagnosis of migraine.

Alternatively, when interviewing a patient, there are 4 specific questions that may identify a migraine sufferer. 1.) Determine if the patient had a history of migraine headaches at any time in his or her life. Since about 50% of migraine sufferers have never been diagnosed with migraine, it is useful to ask a more general question about a history of any recurring headaches of varying intensity associated with nausea or light sensitivity or an experience with visual symptoms typically associated with aura. 2.) Ask about a childhood history of motion intolerance, or more practically a history of nausea when reading a book in the back seat of a moving car. Approximately 50% of migraine sufferers have a childhood history of carsickness [36]. 3.) Check for comorbid conditions, such as anxiety or depression, fibromyalgia or irritable bowel syndrome, as 80% of migraine suffers have a coexisting chronic disease [26]. 4.) Ask about a history of migraine among family members. 70% of migraine sufferers have a history of this polygenetic disease [10].

5. Prognosis: Significant improvement in RS symptoms with migraine management

In recent years, several clinical studies (Table 1) have documented patients with rhinosinusitis symptoms who respond poorly to traditional therapy [6,37,38], and who meet the criteria for migraine disease and were likely misdiagnosed [38–43]. When RS patients who may have migraine disease are treated for this condition, their sinus symptomatology improves significantly [41–46]. Of patients who were initially diagnosed with RS, 50–82% improved with migraine medications [41,42,45]. However, the treatment can be complex and require months to control Sino-Nasal Outcome Test (SNOT-22) symptoms [40].

Since there is no methodology to prove when RS symptoms are caused by abnormal neural activity, we argue that there is sufficient preliminary data in the existing literature to encourage otolaryngologists to understand more about the pathophysiology, diagnosis and management of migraine disease, particularly when patients have normal or conflicting endoscopic and radiographic evidence or do not respond to traditional RS therapies. While a neurogenic cause of rhinosinusitis-like symptoms is a challenging diagnosis to prove, this literature supports the need to identify those RS patients who might have an underlying neurogenic cause for their symptoms.

The inherent ambiguity, or nonspecific nature, of the symptom complex we call "rhinosinusitis" indicates a need for careful consideration of a greater number of etiologies that can present in this way. Based on clinical and pathophysiological studies of migraine, there is ample evidence that this disorder is a readily verifiable cause of the multifactorial and heterogeneous syndrome we have previously labeled "RS". We acknowledge that the body of literature involves studies of small patient populations and may not include placebo controls; thus, the current clinical evidence has weaknesses (and more research is needed), but the evidence points to a pattern that strongly suggests an alternative explanation and management of patients with the hallmark RS symptoms of facial pain/pressure, nasal congestion and rhinorrhea. This alternative point of view has tremendous public health implications. We highlight the need for improved basic science and clinical studies of how the nervous system that alerts us to a problem with our nasal and sinus system may be malfunctioning and misleading us. For now, and for the sake of patients, we encourage increased awareness among clinicians, both otolaryngologists and neurologists, that migraine belongs on the differential diagnosis for patients presenting with chronic RS to include a possible diagnosis of migraine.

6. Conclusions

There are a number of recent clinical guidelines [1,47–49] and interdisciplinary consensus groups [7,40,50–52] that, in some cases, acknowledge that altered sensations caused by migraine disease do affect the symptomatic presentation of RS, but have all failed either to find consensus about how to define this condition or to offer an effective guideline that includes a neurogenic etiology for the treatment of RS symptoms. Since patients with complaints of facial pressure and pain usually present to the otolaryngologist, it is not surprising that neurologists are less familiar with the importance of this diagnosis. Otolaryngologists are the natural champions of the expanding definition of what migraine disease is and how it should be managed.

It is incumbent upon the otolaryngology scientific community to include a neurogenic etiology for RS symptoms in their differential diagnosis and to learn to treat this disease. The challenge is to open our minds to the possibility that many patients complaining of rhinosinusitis symptoms are suffering from a nervous system that is

spontaneously producing long spells of sinus pressure, nasal congestion, and postnasal drip. Not considering this diagnosis has serious implications for our patients. They may be subjected to inappropriate treatments with antibiotics, steroids and surgery, as well as delays in diagnosis, which can make the treatment for chronic migraines more refractory. The medical scientific community needs rigorous clinical and basic science research to prove or disprove this concept.

Disclosure of potential conflicts of interest

FG is on the speaker's panel of Amgen, and is the president of the Association of Migraine Disorders (volunteer position).

RC has associations with Medtronic, Olympus, and NeilMed.

MM is on the advisory board of OptiNose and Olympus and on the speaker's bureau of Meda, Stallergenes, ALK, and Novartis.

CG is an associate editor for Headache (journal of the AHS, American Headache Society); served on the Alder Migraine Expert Council; speaker's bureaus: Amgen, Avanir, Depomed, Promius.

BM consults with X1 Alder, Consulting Promius, and has a stock (minor) in Pfizer.

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