

Nonallergic Rhinitis in Children

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Nonallergic rhinitis in children is a medical condition that has not been well defined and the true incidence is unknown. Current treatment recommendations are based on data obtained from adult studies. The mechanisms of pediatric nonallergic rhinitis are also unclear. The concept that laryngopharyngeal reflux (LPR) events may play a critical role in the pathogenesis of upper airway disease is presently under investigation. Although LPR is being better delineated and appropriate methods of diagnosis and treatment are being studied, substantial evidence links LPR with several disease states including rhinitis, sinus disease, and middle ear disease. Due to the lack of information concerning the etiology of nonallergic rhinitis in children, LPR should be considered in the differential diagnosis of a child with negative skin tests and chronic rhinitis symptoms. The clinician should especially give attention to this diagnosis when a child presents with recurrent co-morbid conditions such as chronic sinusitis or persistent middle ear disease.

Introduction

In an allergy practice, it is not unusual to see a child with persistent rhinitis symptoms, negative skin tests, and a variable response to therapy. Several studies have looked at this clinical presentation in adults. However, available information concerning pediatric patients with this condition has been extremely sparse. The Agency for Healthcare Research and Quality [1] recently reported that in the past 20 years only 13 nonallergic rhinitis investigational trials have been completed, enrolling a total of 450 patients. Unfortunately, no specific studies of pediatric populations were conducted.

Although current data suggest that non-immunoglobulin (Ig) E-mediated (perennial nonallergic) rhinitis is more common in individuals older than 20 years of age, there is no comprehensive database that provides reliable information regarding the true incidence of pediatric

nonallergic rhinitis patients in clinical practice. The age of onset also remains vague, and no reliable epidemiologic data on this condition in children has been firmly established. In addition, the gender and age distribution of nonallergic rhinitis in children is not well known. Several studies in adult populations have suggested a higher incidence among females [2–4].

Clearly, pediatric nonallergic rhinitis is a significant yet ill-defined disease entity in children, requiring a better understanding of its etiology, appropriate diagnostic testing, and optimal treatment.

This article discusses how a nasopharyngeal reflux disorder called laryngopharyngeal reflux (LPR) contributes to the pathogenesis of nonallergic rhinitis. Hopefully, the review will encourage clinicians to consider this diagnosis when dealing with a difficult-to-treat pediatric patient with nonallergic rhinitis.

Chronic Nonallergic Rhinitis in Children

Pathophysiology

Children suffering from nonallergic rhinitis react with an inflammatory response when exposed to infectious or irritant substances. The response is generally characterized by obstruction and rhinorrhea. This reaction results from a series of complex neuroendocrine pathways interacting at the level of the nasal mucosa, part of an exquisite system designed to enhance retention of offending agents so that defense responses can be initiated. When the presentation of these symptoms cannot be associated with a known allergic trigger, the term *nonallergic rhinitis* is used [5].

Nonallergic rhinitis has been defined as an inflammation of the mucosal surface of the nose, not associated with an IgE-mediated mechanism, generally characterized by nasal congestion, postnasal drip, and rhinorrhea. Less frequently than usually seen in allergic rhinitis, pruritus and sneezing are also present in this disorder. Symptoms tend to be perennial and are often associated with changes in temperature, weather, and humidity, and with strong odors [2]. Researchers have classified nonallergic rhinitis disorders in several different ways, including grouping them by cytological features (eg, NARES—nonallergic rhinitis-eosinophilia syndrome), frequency of occurrence, and causality (eg, vasomotor, inflammatory, metabolic) [5,6].

Because very little is known about the actual pathogenesis of perennial nonallergic rhinitis, it is frequently described as nonspecific nasal hyperreactivity [2]. Some

researchers believe overactive parasympathetic nerve discharge could lead to vasodilatation of submucosal venous sinusoids, resulting in congestion and excess seromucus production [7,8]. Recent work with capsaicin has shown that local neural defects such as altered nociceptor function may also play a role in nonallergic rhinitis [2,9].

Evaluation

Evaluation should always begin by obtaining a thorough medical history. In evaluating chronic nasal symptoms in a nonallergic child, special attention should be focused on issues such as snoring during sleep, daytime somnolence, and recurrent upper airway illnesses.

For an infant, pregnancy and birth history should be reviewed. Delivery trauma to the nasal passages, and birth defects such as cleft palate or craniosynostosis, can contribute to nasal congestion [5]. Perinatal infections, such as those associated with *Chlamydia*, can present as persistent rhinitis.

In the adolescent, inquiries concerning the onset of puberty can be useful because hormonal changes can cause nasal congestion [6]. It is important to determine if the patient is sexually active as well. In some cases, syphilis can present with chronic rhinitis [10].

All patients should be asked about any recent sinus surgeries. In addition, head trauma has been associated with cerebral spinal fluid leakage, presenting as clear rhinorrhea [5].

Evaluation regarding the chronicity of the rhinitis is paramount. Intermittent nasal congestion is more closely associated with self-limiting infections such as those due to rhinovirus. Chronic persistent nasal congestion can be representative of more complex disorders such as adenoid hypertrophy or immotile cilia syndrome.

Exploring all possible etiologic factors is crucial in making the correct diagnosis. Inquiry regarding exposure to potential triggers commonly associated with nasal hyperreactivity, such as odors, drafts, cold air, temperature changes, fatigue, stress, and spicy foods, will help the clinician confirm the etiology of the patient's chronic rhinitis. Discussing the patient's physical environment, including exposure to severe air pollution and second-hand cigarette smoke, will also provide valuable information.

Review of past medication use and effectiveness may also aid in confirming the diagnosis. It is important to ask about adherence to medication regimens because patients will often stop taking medication if they feel better, resulting in the eventual return of symptoms and the misperception that the medication is ineffective.

Physical examination

Examination of each nasal passage includes noting the color and consistency of any discharge, the amount of mucosal edema, the presence or absence of turbinate hypertrophy, and the degree of patency. Visualization

of the oropharynx may provide additional information regarding the degree of throat irritation and the severity of postnasal drip. Also, examination of the middle ear should include observation of the color, contour, and mobility of the tympanic membrane. The presence and character of any fluid behind the eardrum should be noted.

Differential diagnosis

The most common trigger of rhinitis in infants and children is the common cold, often caused by rhinovirus or adenovirus. However, rhinitis can also represent a typical prodromal symptom of other common viral illnesses, such as measles or erythema infectiosum [5]. Various conditions may also present as chronic rhinitis in the nonallergic pediatric patient. These include irritant rhinitis from environmental pollutants; obstruction due to foreign bodies in the nose; thyroid disorders; adenoid hypertrophy; rhinosinusitis; nasal polyps; immotile cilia syndrome; midline granulomas; immunodeficiency diseases; cystic fibrosis; and reflux disorders.

Treatment

Pediatric nonallergic rhinitis represents a diagnosis of exclusion. The treatment of this condition is currently based on data from adult studies. Azelastine, a second-generation nasal antihistamine, as well as the aqueous preparations of two nasal steroids (budesonide and fluticasone), have received US Food and Drug Administration (FDA) approval for treatment of chronic nonallergic rhinitis [4] and have proven effective in many cases. Unfortunately, some patients do not improve despite strict adherence to rhinitis therapy.

The potential role of other disorders such as laryngopharyngeal reflux (LPR) in the pathogenesis of nonallergic rhinitis is considered next, including a discussion of treatment options.

Laryngopharyngeal Reflux (LPR)

Background

Reflux disease refers to the backflow of stomach contents into the esophagus. Reflux can be physiologic (infants typically may reflux 50 to 60 times per day) or pathologic [11]. When reflux becomes pathologic, inflammatory changes are initiated by a complex interplay of neurophysiologic mechanisms [12]. The relationship between gastroesophageal reflux (GER) and respiratory tract disorders such as chronic cough and asthma has been well established in both adults and children [12,13].

LPR was first described in the 1970s but has generated much more interest in the medical community within the past 5 years. Previously, patients with "silent" (no heartburn symptoms) reflux and upper airway inflammation were diagnosed with "atypical" reflux [13]. Investigators felt that the inflammation observed in the upper airway structures was a function of vagally mediated pathways

rather than a direct exposure to refluxate. Weiner was the first to place a pharyngeal pH probe and identify gastric contents in the upper airway [14].

Koufman's recent position statement [15], which outlines the current knowledge about LPR, discusses the need for further research into its diagnosis and treatment. Although LPR is a reflux disorder, it primarily affects the upper airway. As a result, most of the investigative work is being conducted within the otolaryngology community. Some experts in the field feel that understanding the impact of extraesophageal reflux events on the pathogenesis of upper airway disease will create a new paradigm for its treatment. Synonyms of this disorder include atypical, extraesophageal, nasopharyngeal, and supraesophageal reflux.

Pathophysiology

LPR differs in mechanism and presentation from traditional reflux. Whereas traditional GER is associated with lower esophageal sphincter dysfunction, LPR is associated with upper esophageal sphincter dysfunction. Patients with LPR do not present in ways that are consistent with traditional GER. For example, many LPR patients reflux more when upright, in contrast to the established supine pattern in GER [11]. In addition, with LPR, throat symptoms predominate and it is seldom associated with reports of heartburn, which is nearly universal in traditional GER [16].

Pharyngeal reflux events result in micro-aspiration of esophageal contents into the laryngopharynx and tracheobronchial tree [15]. Patients with LPR can also experience significant tissue damage, even with moderate reflux disease. The larynx lacks the protective mechanisms of the esophagus (motility, mucosal barrier, and peristalsis) [16]. Due to these differences, the larynx is a hundred times more sensitive to tissue injury from exposure to activated pepsin [11]. The hypersensitivity of the laryngeal tissue requires aggressive and prolonged treatment for resolution of inflammatory changes [16].

Significant damage occurs with as few as three reflux episodes per week [11]. The pharyngeal epithelium can sustain damage with pH levels up to 5.0 (in traditional GER, the level is 4.0) Subsequent inflammatory changes cause ciliary dysfunction and mucostasis in the posterior pharynx [16]. Recent investigations suggest an enzyme deficiency in patients with LPR. In the normal larynx, vulnerable tissues are protected from reflux damage by the isoenzyme carbonic anhydrase III (CAIII), which catalyzes the hydration of carbon dioxide to produce bicarbonate. Dysfunction of this system results in severe inflammation, up-regulating sensory nerve fibers [16]. Johnston et al. [17] compared laryngeal biopsy samples from patients known to have LPR with normal controls. The tissue was analyzed for pepsin and CAIII. The samples were also matched with the result of previous pH studies. Results showed

a statistically significant ($P < 0.001$) increase in pepsin levels in the LPR group. An association was also shown ($P < 0.001$) between CAIII depletion and pH testing data. The investigators concluded that CAIII depletion predisposes the person to the inflammatory changes observed in LPR patients.

Clinical presentation

In children, cough is the predominant presenting symptom of LPR. These patients are often misdiagnosed as having repetitive croup. Frequent episodes of hoarseness are common. Most patients present with a significant history of chronic rhinitis, sinusitis, or middle ear disease refractory to aggressive therapy. LPR is also associated with asthma and recurrent pneumonia [18•].

Laryngeal examination often reveals edema of the posterior pharynx and diffuse infraglottic edema (pseudosulcus vocalis). The presence of vocal fold and posterior laryngeal edema also helps to confirm the diagnosis. Additional laryngeal pathology can include pharyngeal erythema (a nonspecific finding), hypertrophy of the posterior commissure, thick endolaryngeal mucus, and granulomas.

Diagnosis

Belafsky et al. [19] have developed a diagnostic tool called the Reflux Finding Score, which rates laryngeal findings by degree of severity. Studies in adults have found that a score of 7 or greater predicted LPR with 95% confidence. Although this tool has not been studied in children, its use may be helpful in making the diagnosis, especially in older children who can undergo direct laryngeal visualization. Serial visualizations can further aid in determining interval improvement [19].

Belafsky et al. [20] developed a self-administered nine-item tool termed the Reflux Symptom Index. It has been tested recently for reliability and validity. Studies have demonstrated that a score of 13 or greater predicted LPR with 95% confidence. Patients rate the following clinical symptoms on a severity scale of 0 to 5: hoarseness, throat clearing, excess throat mucus, difficulty swallowing, coughing after lying down, breathing difficulties, annoying cough, sensation of something stuck in the throat, and chest pain. The advantage of this particular tool is that it can easily be used by parents or patients and could assist with the evaluation of children as young as 4 years of age [20].

pH studies can be important in patients who are not responding to treatment. A double-probe is recommended with the upper probe placed 2 cm above the upper esophageal sphincter [15]. This type of study has been found to be more reliable than barium swallow, endoscopies, or single-probe esophageal testing. A precipitous drop in pharyngeal pH temporally associated with an esophageal reflux event is considered to be significant [21].

Treatment

Proton pump inhibitors (PPIs) are now accepted as first-line therapy for LPR and have been found superior to H2 receptor antagonists (H2RAs). A study recently reported by Park et al. [22] presented statistically significant evidence for frequent and prolonged PPI therapy. The study evaluated daily (QD) dosing versus every 12 hours (BID), and showed that 50% of the BID group had good response to therapy as opposed to 28% of the QD group. Among the nonresponders in the QD group, 54% achieved clinical improvement with an additional 60 days of BID dosing. After 4 months of treatment, an additional 22% of patients in all groups achieved symptom relief.

Due to the chronic-intermittent nature of this disorder, patient support is critical to achieve optimal outcomes. Successful results can require 6 months or more of medical treatment [23]. Dietary modifications remain the cornerstone of therapy. These include the avoidance of acidic foods, carbonated beverages, caffeine, chocolate, and highly processed foods. Certain lifestyle modifications such as avoiding food before bed and remaining upright after meals can be extremely helpful. A recent randomized, placebo-controlled trial showed that diet and lifestyle modifications alone improved clinical outcomes [16].

With improvement of the patient's clinical status, a tapering dose of PPIs can be considered. Adding an H2RA at that time can be useful as adjunctive therapy [16]. There is evidence to suggest that abrupt withdrawal of PPIs can cause rebound of symptoms; administration of H2RAs at bedtime has been shown to assist the patient in the weaning process [24•]. If an exacerbation of symptoms occurs, prompt return to BID dosing of PPIs is warranted.

Ideally, periodic laryngeal examinations will guide treatment in persistent cases. Surgical intervention involving fundoplication remains controversial because of postsurgical complications. However, when LPR is severe and refractory to medical treatment, surgical intervention should be considered [23].

Review of Literature

Tasker et al. [25••] investigated the role of reflux disease in children suffering from otitis media with effusion. They postulated that contents from the nasopharynx could reach the middle ear when the child was supine, thereby contributing to chronic inflammation. These researchers reasoned that if refluxate reached the middle ear, then there should be a higher concentration of gastric enzymes in the effusion fluid as compared to plasma levels. To test this hypothesis, they analyzed the middle ear fluid of 54 children 2 to 8 years of age, who were undergoing myringotomy for the treatment of otitis media with effusion. The concentrations of pepsin and pepsinogen were found to be 1000 times higher than the serum levels, while the albumin level was equal to

serum levels [25••]. These findings suggested that reflux disorders, in fact, can contribute to chronic middle ear disease. If refluxate is present in the nasopharynx and middle ear fluid, it is logical to expect a direct effect on the nasal passages, thereby leading to chronic rhinitis through the same inflammatory pathways.

Barbero et al. [26] described 22 children between the ages of 15 months and 5 years who were being followed for persistent nasal obstruction and chronic nasal discharge of unknown etiology. All patients had a longstanding history of upper airway symptoms including inflammation of the nasal mucosa, as well as cobblestoning of the posterior pharynx. All of the children underwent pH monitoring to rule out reflux as a cause of their persistent symptoms. Significant reflux was found in 16 of the 22 patients studied. When the reflux was appropriately treated, these patients demonstrated a marked reduction in rhinitis symptoms, further supporting the relationship between reflux and chronic rhinitis.

Contencin et al. [27] performed 24-hour pH monitoring on a group of 31 infants and children suffering from chronic, recurrent rhinitis of unknown origin. Patients with reflux but without nasal symptoms served as controls. Upon analysis, the rhinitis group demonstrated only slightly decreased pH levels over the control group. There was, however, a statistically significant increase in the number of reflux events in the rhinitis group when compared to controls [27].

Nasal congestion in a patient known to have GER may also be a manifestation of LPR in the same patient. Although it is less common for an individual to have concomitant GER and LPR, this condition, in fact, has been reported [11,18•].

Bothwell et al. [28••] recognized that nasal edema is always the first event observed in pediatric sinusitis and felt that treating gastronasal reflux could possibly diminish the severity of chronic sinus disease. He conducted a retrospective study of 30 children 6 to 11 years of age, referred for possible functional endoscopic sinus surgery (FESS) due to chronic nasal and sinus disease. Prior to recommending surgery, patients received a gastrointestinal work-up consisting of a history, physical, and pH study or laryngoscopy. All patients were found to have positive evidence of gastronasal reflux. Patients were treated with a combination of lifestyle and diet modifications as well as PPIs and H2RAs. The amount of clinical improvement was evaluated at 8 months and then again at 2 years after initiation of therapy. Evaluation at 8 months revealed that all patients experienced clinical improvement. At the end of 2 years, only 3 of the 30 children required FESS.

Bothwell et al. [28••] concluded that despite the limitations of a retrospective study without a control group, an 89% reduction rate in the need for surgical intervention made a compelling case for looking at gastronasal reflux as an etiology of chronic sinus disease, often presenting as chronic rhinitis.

Conclusions

At present, pediatric nonallergic rhinitis is not well described in the medical literature. Information concerning the possible mechanisms and appropriate management is available primarily from adult studies.

In the future, as knowledge increases regarding the mechanisms of clinical nonallergic rhinitis, we may be able to better define pediatric nonallergic rhinitis as a specific entity [2,9].

The concept that LPR may play a critical role in the pathogenesis of upper airway disease is now under study. There is substantial evidence linking this disorder with several other disease states that are known to present with rhinitis. LPR may be an important etiologic factor for a significant number of the nonallergic rhinitis cases seen in the pediatric population and should be especially considered in the child with persistent nasal symptoms.

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