Curr Allergy Asthma Rep (2014) 14:439
DOI 10.1007/s11882-014-0439-3

Nonallergic Rhinitis

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Published online: 9 April 2014
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Abstract Rhinitis is normally defined by the symptoms of nasal congestion, postnasal drainage, rhinorrhea, and sneezing. It has been associated with various pathologic changes, but can occur in the absence of any inflammation. Thus, the diagnosis is based on the clinical presentation. There are no clear-cut criteria to distinguish when rhinitis becomes chronic, but in its chronic form, it can be complex. Chronic forms of rhinitis that occur in the absence of any detectable specific IgE against relevant aeroallergens in its broadest sense can be called chronic nonallergic rhinitis. This review will concentrate on chronic nonallergic rhinitis in its various forms, discussing the epidemiology, underlying mechanisms, and its therapy.

Keywords Chronic nonallergic rhinitis · Vasomotor rhinitis · Rhinitis · Allergic rhinitis · Chronic rhinosinusitis · Diagnosis · Treatment · Lifestyle modification · Pharmacologic treatment · Decongestants · Surgery · Nasal saline irrigation

Introduction

Rhinitis is defined by its clinical presentation. The four cardinal symptoms are sneezing, rhinorrhea, postnasal drainage, and nasal congestion. It has been traditionally divided into an allergic and nonallergic form. In the allergic form, there is detectable specific IgE against relevant aeroallergens. All forms of rhinitis in which there is no specific IgE against relevant aeroallergens and that exist chronically can be broadly categorized as chronic nonallergic rhinitis. Thus, chronic nonallergic rhinitis is a syndrome with many entities contained within it. This syndrome varies in its underlying mechanisms, and its management can vary, reflecting these underlying mechanisms. The intent of this review is to discuss in detail this syndrome with its ultimate aim being to elucidate its optimal management.

Definition and Terminology

Idiopathic rhinitis is defined by the presence of chronic symptoms of rhinitis (e.g., sneezing, rhinorrhea, nasal congestion, and post-nasal drainage) in the absence of a specific etiology such as immunologic, infectious, pharmacologic, structural, hormonal, vasculitic, metabolic, or atrophic causes. In common parlance, patients with this symptom complex, specifically those who lack detectable IgE to relevant aeroallergens, are said to suffer from chronic nonallergic rhinitis [NAR] [1]. The literature is replete with many synonyms for this term, and there is no well-accepted single terminology to describe this condition. But for the purpose of our discussion, NAR will refer to patients who exhibit chronic symptoms of rhinitis, without known cause, in the absence of clinically significant IgE to aeroallergens. Some investigators have specified that symptoms have to be present for at least 1 year before the diagnosis should be made [2, 3].

Epidemiology

About 10 to 40 percent of the population in industrialized countries has rhinitis based on epidemiologic surveys [4–11]. The true incidence of nonallergic rhinitis is not known, and precise data are difficult to obtain as NAR can coexist with allergic rhinitis and be reported as such. Pure NAR could account from 17 to 52 percent of all cases in adults [6–10,

This article is part of the Topical Collection on *Rhinitis*

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12–15]. The prevalence of NAR in children is less well studied but is less than in adults [17–20].

Approximately 50 percent of patients presenting with rhinitis may have NAR alone or as "mixed nonallergic/allergic rhinitis" based on the Joint Task Force Practice Parameter in Allergy, Asthma and Immunology [13]. In a survey of American allergists, 34 percent of 975 rhinitis patients were identified as having the "mixed" form of rhinitis [9]. These data indicate that NAR alone may affect as many as 17 million Americans and that an additional 22 million may suffer from the "mixed form" of rhinitis [9].

NAR presents later in life than allergic rhinitis, with 70 percent of patients presenting after 20 years of age [8, 20]. In comparison, the onset of allergic rhinitis usually occurs before age 20 (and often in childhood). Women make up the majority of patients with nonallergic rhinitis in most studies, indicating a female predominance. [6, 21].

Pathogenesis

Nonallergenic rhinitis is not a single disorder but is composed of a heterogeneous group of diseases. These can be classified broadly into inflammatory and noninflammatory disorders. The inflammatory form has been further subdivided based on histologic findings into eosinophilic, neutrophilic or mixed cellular forms (Tables 1, 2, and 3).

Nonallergic rhinitis with nasal eosinophilia syndrome (NARES) is the most common type of inflammatory NAR. The clear nasal secretions in these patients contain greater than 25 percent eosinophils. Nasal biopsies from these patients commonly show increased eosinophils [22, 23]. Approximately 12 to 25 % of NAR patients have nasal eosinophilia [24–33]. The presence of eosinophilia can indicate responsiveness to glucocorticoids [28–33]. A predominant eosinophilic infiltration can be seen in several other clinical phenotypes including blood eosinophilia nonallergic rhinitis syndrome (BENARS), rhinitis associated with aspirin and nonsteroidal anti-inflammatory drug sensitivity, and chronic eosinophilic fungal rhinosinusitis. The cellular inflammatory infiltrate in NAR patients may have cells other than eosinophils. Nasal cytology in some cases shows a prominent infiltrate of mast cells and neutrophils as well [26, 27]. The predominant neutrophilic infiltrate may occur as well and can be associated with a higher incidence of asthma and more severe symptoms. When mast cells are the predominant cell type, nasal itching is often a characteristic feature [26].

Entopy is defined as local nasal production of IgE and reactivity to allergens without the presence of systemic atopy (the absence of detectable skin or serum-specific IgE anti-aeroallergen) [34–40]. Local nasal production of IgE was demonstrated in two ex vivo studies in which there was production of allergen-specific IgE in nasal explants from patients with rhinitis who had negative skin tests and serum specific IgE tests [39, 40]. Approximately one-half of patients with chronic NAR in these studies reacted to nasal challenge with an allergen, especially dust mite allergen, with symptoms and signs similar to those in patients with typical allergic rhinitis and significantly different from controls without rhinitis [36, 41, 42]. On the other hand, other researchers (using

Table 1 Non-allergic rhinitis with predominant neutrophilic infiltration

Acute and recurrent bacterial rhinosinusitis
Nasal polyps in cystic fibrosis
HIV/AIDS-related infectious rhinosinusitis
Humoral immunodeficiencies of IgA, IgE, and IgG subclasses and common variable hypogammaglobulinemia
Young's syndrome of sinopulmonary disease, azoospermia, and nasal polyps
Kartagener's syndrome of bronchiectasis, chronic sinusitis, nasal polyps, and immotile cilia
Foreign body

Table 2 Nonallergic rhinitis with predominant eosinophilic infiltration

Nonallergic rhinitis with eosinophilia syndrome (NARES)
Blood eosinophil with nonallergic rhinitis syndrome (BENARS)
Chronic eosinophilic sinusitis syndromes
Chronic rhinosinusitis with nasal polyposis and eosinophilia
Asthma , chronic rhinosinusitis with nasal polyps, and NSAID sensitivity
Fungal sinusitis syndromes
Occupational rhinitis with eosinophilia (non-IgE mediated)
Churg-Strauss syndrome with eosinophilic granuloma
Eosinophilic granuloma

Table 3 Nonallergic rhinitis associated with mixed cellular infiltrates or systemic diseases

Common cold syndromes
Granulomatous and vasculitis diseases
Wegener's granulomatosis
Midline granuloma
Sarcoidosis
Granulomatous infections
Tuberculosis
Leprosy
Syphilis
Autoimmune disorders
Relapsing polychondritis
Systemic lupus erythematosus
Sjögren's syndrome
Senile rhinitis

similar techniques) were unable to demonstrate consistent responses to nasal allergen challenge in patients with NAR [43]. Their findings challenge the concept that NAR results from a localized IgE production.

Nonallergic chronic rhino-sinusitis (CRS) can also be characterized by a neutrophilic infiltration in the sinus mucosa. In this condition, most of the cells in the sinus effusion and nasal discharge are neutrophils [44]. Their presence is attributed to IL-8 released from mucosal epithelial cells. Secreted IL-8 enhances transendothelial migration of neutrophils by increasing adhesion molecules on these cells as well as on the vascular endothelium [45]. Necrotic damage to the nasal and tracheobronchial epithelium by pollutants, industrial chemicals, and other inhaled toxicants may release IL-8 and other neutrophil chemokines and cause micro-villous epithelial metaplasia [46]. It has been hypothesized that IL-11 might play a role in the pathogenesis of some cases of NAR based on the observations that children with common colds have elevated IL-11 concentrations in their nasal secretions. And those that do, like patients with NAR, are at risk for the development of asthma [47]. But to our knowledge, there has been no documentation of elevated IL-11 in the nasal secretions of subjects with NAR.

One of the largest single groups of nonallergic rhinitis has a noninflammatory condition that has been referred to by many authors as vasomotor rhinitis (VMR). Employing this terminology, VMR has been considered part of a spectrum of "functional" interoceptive mucosal dysregulation disorders [48]. In VMR, there is increased sensitivity to environmental factors such as climate changes, air pollution, strong odors, etc. These factors trigger symptoms. Bernstein et al. evaluated the neurogenic responses to chemical/olfactory stimuli in patients with NAR using functional magnetic resonance imaging (MRI) [49]. Subjects underwent MRI during exposure to different types of odors. They exhibited increased blood flow in several odor-sensitive regions of the brain in response to both pleasant (vanilla) and unpleasant (hickory smoke) odors. The neurologic responses were associated with the production of symptoms upon exposure to hickory smoke.

Many patients with noninflammatory rhinitis are hyperresponsive to physical and chemical stimuli such as cold air and strong odors [50, 51]. In such patients, abnormalities in neural transmission may underlie the disorder. C-fibers are unmyelinated sensory neurons that innervate the vessels, glands, and epithelium of the nasal mucosa. They release neuropeptides on stimulation by noxious agents. Neuropeptides such as substance P (SP), in particular, and calcitonin gene-related protein (CGRP) are released from C-fibers producing a localized increase in vascular permeability and nasal secretion. Increased C-fiber activity may lead to nasal dysfunction in idiopathic rhinitis [52]. Capsaicin stimulates C-fibers producing burning, rhinorrhea, and nasal congestion through capsaicin receptors (TRP vanilloid; TRPV1) [53]. Repeated nasal provocation with capsaicin can significantly reduce nasal complaints in patients with idiopathic rhinitis [54–56] suggesting either C-fiber desensitization or degeneration or TRPV1 inactivation. Capsaicin treatment has no effect in allergic rhinitis [48]. Cold air challenge can cause hyperosmolarity in the nasal mucosa, thus triggering hypertonic-sensitive capsaicin receptors such as TRPV1. Capsaicin pretreatment can block the nasal secretory response induced by hypertonic saline [57, 58].

Chronic fatigue syndrome (CFS) subjects with nonallergic rhinitis also have an altered response to hypertonic saline nasal administration. In such individuals challenge with hypertonic saline causes pain in a dose-dependent fashion, but they exhibit a flat glandular secretory response to such challenge [51]. This subset of patients also experiences increased sinus tenderness compared to controls and patients with allergic rhinitis [59]. These findings suggest the possibility that trigeminal hyperresponsiveness causing hyperalgesia and allodynia may be present in this group of patients.

Under normal circumstances, predominant sympathetic tone results in increased nasal patency. Sympathetic fibers discharge norepinephrine and neuropeptide Y causing vasoconstriction. Parasympathetic nerve fibers release predominantly acetylcholine (Ach) and vasoactive intestinal peptide (VIP), which increase nasal secretion and perhaps to a lesser extent produce vasorelaxation [60], leading to nasal congestion. Stimulation of sensory mechanoreceptors and/or chemosensitive receptors in the nose leads to excitation of the parasympathetic reflex. Mechanistic studies in idiopathic rhinitis have suggested that this balance becomes biased toward the parasympathetic system, i.e., hyporeactivity of the sympathetic system and hyperreactivity of the parasympathetic system, resulting in functional abnormalities of the nasal end organs in these patients [61]. In "skier's rhinitis" exposure to cold air leads to excessive nasal blockage with copious discharge. It results from a hyperactive afferent cholinergic parasympathetic reflex arc and can be blocked by topical anticholinergic medications [62]. In gustatory rhinitis, eating activates oral trigeminal receptors, which recruit parasympathetic cholinergic reflexes and produces glandular secretion. This suggests an increased sensitivity of sensory receptors with an increased parasympathetic reflex arc activity and resultant increased glandular secretion [63].

Abnormal systemic responses to autonomic stimuli in patients with nonallergic rhinitis have also been described. Heart rate variability was found to be higher in patients with idiopathic rhinitis, without nasal eosinophilia, compared with normal control subjects [64]. More generalized dysautonomia involving both the parasympathetic and sympathetic nervous systems has been suggested by other studies [65–67].

Clinical Features

Nasal congestion, facial pressure, rhinorrhea, postnasal drip, and throat clearing are prominent symptoms. Symptoms are usually perennial, but seasonal exacerbations in NAR may result from shifts in temperature, humidity, and barometric pressure [68, 69]. These may be misinterpreted as manifestations of allergic rhinitis when they occur in the spring or fall. As opposed to patients with allergic rhinitis, nasal and palatal itching and ocular symptoms are usually absent [13, 68, 70, 71].

Based on the predominant symptoms, patients often are classified as "runners," who have wet rhinorrhea, or "blockers," who have nasal congestion and blockage to airflow with minimal rhinorrhea [13]. Rhinorrhea patients generally have enhanced cholinergic glandular secretory responses [72] and benefit from anticholinergic drugs. "Blockers" complain of congestion and fullness that may be related to interoceptive and nociceptive mucosal neuron hypersensitivity to innocuous stimuli [13]. Intermittent symptoms may be triggered by cold air exposures, ingestion of certain foods or beverages, irritant chemicals, strong emotions, and changes in menstrual and other hormone levels [73]. Nasal fullness may be subjective and not confirmed by objective measurements of airflow, especially in children [74, 75].

Physical examination in NAR can be entirely normal, but swollen erythematous turbinates can be present. These findings are distinguished from the classically described pale swollen turbinates of AR. Nasal secretions can be clear or mucoid. Nasal crusting, widening of the nares, and a foul odor may indicate atrophic rhinitis.

Diagnosis

There are no pathognomonic symptoms and signs of NAR. However, nasal and palatal pruritus, sneezing as well as itchy watery eyes may distinguish AR from NAR. Symptoms triggered by exposure to environmental tobacco smoke, odorants, cleaning compounds, or changes in air temperature or barometric pressure are more typical of NAR. Allergen-specific skin and serologic tests for relevant allergens are negative or if present do not correlate with symptoms on exposure.

Questionnaires may assist in distinguishing between AR and NAR. Data from these questionnaires indicate that an age of onset after 35 years, symptoms triggered by perfumes and fragrances, and a negative history of seasonality, cat-induced, or familial rhinitis symptoms have a more than 95 % likelihood of indicating the presence of NAR [76]. The Cincinnati Irritant Index Scale developed by Bernstein and colleagues is an effective, validated tool that can assist in the diagnosis. This irritant index questionnaire (IIQ) rates 21 different irritants from 0 (no symptoms) to 10 (severe symptoms) for their ability to cause upper respiratory symptoms and headaches [77]. The irritant triggers assessed are listed in Table 4. A follow-up study by Bernstein et al. [78] further subdivided NAR patients into low burden vs. high burden subjects based on the IIQ score. High-burden NAR patients were more likely to have a physician diagnosis of asthma and a greater number of self-reported rhinitis symptoms and perennial symptoms with seasonal exacerbations than low-burden NAR patients. However, an exaggerated response to irritants does not universally rule out coexistent allergic disease. Both allergic rhinitis (AR) and nonallergic rhinitis (NAR) patients can respond in an exaggerated manner to irritant stimuli. In a prospective study employing cold dry air challenge (CDA) [79], there were no quantitative or qualitative differences in nasal hyperreactivity between AR and NAR patients. The authors concluded that it may not be possible to differentiate NAR subpopulations based only on the response to physical or chemical challenge.

Differential Diagnosis

There are numerous causes of nasal symptoms with negative allergy tests (NAR) [80]. These conditions are summarized in Tables 1, 2, and 3.

Some authors have subdivided NAR into categories including NAR with eosinophilia syndrome (NARES), NAR with chronic rhino-sinusitis, NAR with "hidden allergy" with elevated IgE to unknown allergens, blood eosinophilic

Table 4 Irritant triggers of NAR

Ammonia
Antiperspirants, bleach
Cold air
Cooking and frying odors
Cosmetics
Crude oils
Fresh newsprint
Hair sprays
Smog
Cleaning products
Mildew odors
Paints
Perfumes
Pine odor
Soap powders
Solvents and varnish
Weather changes
Tobacco smoke and wood smoke

nonallergic rhinitis syndrome, and NAR associated with hypothyroidism [81]. One of the systemic conditions associated with NAR worth mentioning is systemic mastocytosis. The name nonallergic mastocytosis-associated rhinitis (NAMAR) has been suggested for the entity. Nonallergic persistent nasal complaints in systemic mastocytosis were significantly correlated with elevated nasal tryptase levels as a measure of local mast cell burden. Furthermore, the degree of elevated nasal tryptase correlated with persistent rhinorrhea, sneezing, and itching [82].

Structural anomalies such as those due to septal deviation, septal perforation, cartilage atrophy, and rhinophymoma can contribute to dysfunction of the anterior nasal valve and cause nasal fullness and obstruction or perceived obstruction to airflow. Various other anatomic abnormalities associated with rhinitis symptoms are summarized in Table 5.

Atrophic rhinitis is characterized by nasal crusting, widening of the passages in the nose, a foul smell, and loss of sense of smell. The progressive atrophy leads to the loss of the normal secretory and humidifying functions of the nose. The primary condition is linked to nasal infection with *Klebsiella ozaenae*. It is more common in females and in arid countries. Secondary causes include nasal surgery, radiation, trauma, and granulomatous and infectious diseases. A computed tomography scan commonly shows loss of the nasal turbinates in atrophic rhinitis.

Rhinitis symptoms secondary to hormonal disorders and drugs can closely mimic NAR (Table 6). Hormonal changes in pregnancy can cause mucosal edema, nasal congestion, rhinorrhea, and sneezing in 20 % to 40 % of women [83]. The onset can be at any time during gestation, with the 13th to 21st weeks being most problematic. Symptoms end precipitously with delivery of the baby or placenta. Hypothyroidism may be associated with mucosal vasodilation from the loss of sympathetic vasoconstrictor activity. Autoimmune thyroid disease may be present in 14.7 % of NAR, 10.4 % of AR, and 9.9 % of adults, with a 2:1 female predominance [84]. Medications linked to rhinitis include β-blockers, calcium channel blockers, and other antihypertensives. Nasal congestion can be a side effect of α-adrenoceptor antagonists used for benign prostatic hyperplasia and phosphodiesterase-5 inhibitors for erectile dysfunction. A detailed history of medication use and symptoms is especially pertinent in patients using excessive amounts of topical decongestant nasal sprays [85]. Some observers have found that this condition can be exacerbated by the preservative benzalkonium chloride [86]. Although this entity known as rhinitis medicamentosa is a well-recognized clinical finding, the rebound hypersensitivity associated with this disorder has been difficult to identify in prospective studies. In studies of short duration the co-administration of oxymetazoline with a nasal glucocorticoid increases treatment effectiveness and reduces the likelihood of rhinitis medicamentosa [87, 88].

Table 5 Differential diagnosis of nonallergic rhinitis secondary to anatomic abnormality

Osteomeatal occlusion secondary to turbinate hypertrophy and deviated nasal septum
Choanal atresia
Tumors (benign and neoplastic)
Adenoidal hypertrophy with recurrent infections
Atrophic rhinitis
Cerebrospinal fluid rhinorrhea

Table 6 Differential diagnosis of NAR secondary to hormonal abnormalities and drugs

Pregnancy
Hypothyroidism
Acromegaly
β-Adrenergic antagonists
α-Adrenergic antagonists (reserpine, α-methyldopa, guanethidine, phentolamine, prazosin)
Phosphodiesterase inhibitors for erectile dysfunction
Rhinitis medicamentosa
Chronic topical α-adrenergic agonist abuse
Cocaine abuse
Chlorpromazine
Protease inhibitors
Angiotensin-converting enzyme inhibitors (ACEIs)

Treatment

The treatment of NAR can be more complex than that of the allergic form of the condition because of the heterogeneous nature of this entity. And the management of this disorder can be challenging [89]. The rational approach is to identify a particular etiology if it all possible by doing a comprehensive workup. Potential triggering medications should be identified and eliminated if possible. Structural abnormalities can be corrected, and related hormonal abnormalities can be treated as well.

Lifestyle and Behavioral Modification Strategies

Non-pharmacologic treatment has a very limited role. Identification and elimination of individual triggers can be helpful sometimes. Avoidance of both active and passive smoking is highly recommended. Individuals with rhinitis triggered by alcohol ingestion should avoid alcohol. Subjects with gustatory rhinorrhea benefit from avoiding triggering foods. Exposure to strong perfumes, colognes, or

chemicals should be avoided as much as possible. During periods of heavy pollution, it is advisable to drive cars with the windows and vents closed. Avoidance of occupational triggers by modifying work place exposure, increasing ventilation, and using filtering masks can be helpful in occupational rhinitis.

Pharmacologic Treatment

Chronic NAR is usually less responsive to pharmacologic therapy than allergic rhinitis [90, 91]. Second generation oral antihistamines are not effective in NAR in nonallergic rhinitis [92, 93]. Older, first generation antihistamines with anticholinergic properties may be of some help with rhinorrhea. But their benefit has not been demonstrated in clinical trials. Topical glucocorticoids and topical antihistamines are useful in treating the total symptom complex of chronic nonallergic rhinitis [9, 94–104]. In addition to these agents, ipratropium bromide has been approved specifically to treat the symptom of rhinorrhea [105]. While topical nasal antihistamines or glucocorticoids alone may be effective in treating mild NAR, combination therapy using both formulations is more effective in allergic rhinitis [106] and theoretically may be helpful in moderate to severe forms of NAR. But such combination therapy has not been studied in nonallergic rhinitis and is not approved for use at this time. Daily use of these agents on a consistent basis is usually more effective than as needed use.

Topical glucocorticoids have been tested in NAR and are approved for use. Some studies have found them more useful when eosinophilia is present [107–109]. The effectiveness of topical steroids has been demonstrated in several studies [96, 97, 99, 110]. Webb et al. [110] performed a combined analysis involving 983 patients with nonallergic rhinitis in three prospective studies. Patients had similar statistically significant improvement with fluticasone propionate in the 200 microgram or 400 μg dose compared with placebo. It performed well in patients with and without nasal eosinophilia. However, in another study fluticasone propionate was not effective in nasal symptoms in nonallergic rhinitis even though it significantly reduced nasal "immune-competent" cells. In a follow-up study fluticasone furoate 110 ug daily for 4 weeks did not statistically significantly improve total nasal symptom scores in subjects sensitive to weather and temperature changes [111]. So the effectiveness of nasal steroids can be variable in nonallergic rhinitis [111], an observation consistent with the heterogeneous nature of the syndrome. In part the response to topical corticosteroids may be dependent on whether or not the effects on irritant stimuli or weather-induced symptoms are being assessed [112].

Topical antihistamines have been shown to be effective in nonallergic rhinitis. Azelastine has been shown to be effective in randomized trials [93, 108] and is the only topical formulation FDA approved for this indication. The various formulations and the recommended doses include azelastine 0.1 %, two sprays to each nostril twice daily (adults), azelastine, one spray twice daily to each nostril (adolescents), and azelastine 0.15 %, one to two sprays in each nostril twice daily. Olopatidine 0.6 % protects from vasomotor challenge in patients with vasomotor rhinitis [113]. The recommended dose of olopatidine 0.6 % is two sprays to each nostril twice daily for adults and adolescents and one spray to each nostril twice daily in children ≤11 years. Both azelastine 0.1 % and olopatidine 0.6 % were shown to be effective and safe in reducing symptom scores in a multicenter randomized study lasting 14 days powered to assess and compare noninferiority of these two agents [114]. Although the mechanism(s) underlying the effectiveness of these topical agents has not been clearly elucidated, it is assumed their anti-inflammatory properties perhaps enhanced by their topical application, which allows for a high local concentration perhaps being responsible. Azelastine possesses both anti-inflammatory and anticholinergic actions. It reduces eosinophil activation and adhesion molecule expression and suppresses inflammatory cytokine generation [102, 103, 115]. It also may inhibit neurogenic excitation from olfactory stimuli as shown in a study by Bernstein et al. in which subjects with NAR were exposed to pleasant and unpleasant odors followed by azelastine administration. Azelastine significantly attenuated exaggerated blood flow to odor-sensitive regions of the brain as assessed by functional brain MRI in this investigation [49].

Combination therapy using a nasal steroid and a topical antihistamine has not been specifically studied in chronic nonallergic rhinitis. Anecdotal experience suggests that such therapy can be useful if the patient is failing to respond to either therapy alone. Combination therapy can be achieved by either using two separate nasal sprays or a combination product such as Dymista (containing azelastine hydrochloride 137 mcg and fluticasone propionate 50 mcg). This combination product has been studied in patients with seasonal allergic rhinitis and has been shown to be superior to single treatment with either agent alone [116]. It is approved for seasonal allergic rhinitis in adults and children ≥12 years.

Rhinorrhea is the predominant manifestation in gustatory rhinitis, cold-induced rhinitis, and rhinitis of the elderly. Ipratropium bromide (0.03 percent), two sprays to each nostril three times daily, is recommended [117, 118]. Placebo-controlled trials have established the effectiveness of ipratropium bromide 0.03 % to control rhinorrhea [105]. It can be used on a regular basis or as needed prior to eating or cold air exposure. This medication is also available at a concentration of 0.06 percent, although this strength is intended for short-term use only (e.g., treatment of rhinorrhea associated with the common cold).

Adjunct Therapies

Oral decongestants, nasal saline sprays and irrigations, and oral antihistamines are often used though studies of their effectiveness in NAR are sparse. Studies of antileukotriene drugs and intranasal chromones in the treatment of NAR are not available.

Oral Decongestants

Pseudoephedrine alone or in combination with antihistamines is available in over-the-counter formulations. It can relieve nasal congestion. Benign prostate hyperplasia and hypertension are relative contraindications to its use. Phenylpropolamine 100 mg daily has been found to be effective in relieving nasal airway resistance among NAR patients and more effective in relieving nasal obstruction, secretion, and sneezing [30].

Phenylephrine is less effective for the treatment of rhinitis symptoms and may not be superior to placebo at the 10 mg dose that is commonly available without prescription [119, 120].

Nasal Decongestants

These agents can be used on a short-term as-needed-only basis to relieve nasal congestion in patients not responding to other agents. The risk of rhinitis medicamentosa increases with prolonged use of nasal decongestants. Management of this complication involves withdrawal of the topical decongestant, treatment of the underlying rhinitis, and the use of topical steroids. Sometimes a short course of an oral corticosteroid (prednisone 30 mg/day for 1 week) is needed to ease the discomfort associated with sudden withdrawal of the topical decongestant. Several studies have found that co-administration of oxymetazoline in association with topical mometasone furoate is safe and more effective compared to either agent alone in seasonal and perennial allergic rhinitis [87, 88, 121–123]. In a study by Rael et al. [88], combination therapy using oxymetazoline and mometasone over 20 days improved nasal congestion in both allergic and nonallergic rhinitis without increasing adverse events.

Nasal Saline Irrigation

Daily nasal lavage or the use of nasal saline sprays may be helpful to relieve postnasal drainage. Prospective studies have demonstrated that both nasal lavage [125] and nasal irrigation can be helpful in NAR [125]. The Cochrane database reviewed eight randomized controlled trials [124] of this treatment. Saline was evaluated in comparison with no treatment, placebo, as an adjunct to other treatments, or compared to other treatments. Saline alone was not beneficial in the treatment of chronic rhinosinusitis. However, it can be effective as an adjunct treatment for chronic rhinosinusitis symptoms. Over-the-counter devices, including bulb syringes and bottle sprayers, are effective, provided the system delivers an adequate volume of solution (>200 ml per side) into the nose. Intranasal saline sprays have been found to be effective in relieving postnasal drip, sneezing, and congestion in NAR patients [9, 126]. They are less effective but more convenient than nasal lavage for some patients [127].

Other Therapies

Topical Capsaicin

Capsaicin has been found to be safe and effective in several studies [128–130]. Sinus Buster, a proprietary homeopathic preparation of *Capsicum annum* and eucalyptol, improved nasal congestion, cutaneous sinus region pain and pressure sensations, and headache. In a randomized trial of 52 patients, Sinus Buster was used twice daily for 2 weeks. Average time to first relief was 52.6 s, and the effect lasted for 60 min. There were no apparent adverse events [131].

Silver Nitrate

Topically applied silver nitrate can improve rhinorrhea, sneezing, and congestion. It was found to be effective in a trial comparing silver nitrate, flunisolide, and placebo in patients with NAR [132]. Other prospective studies also found silver nitrate to be effective in improving nasal symptoms in nonallergic rhinitis [133, 134].

Acupuncture

Two small pilot studies have evaluated the role of acupuncture in NAR [135, 136]. In the earlier study, acupuncture produced an improvement in nasal airways resistance after treatment in a small number of patients. On a follow-up study, a total of 24 patients with a confirmed diagnosis of vasomotor rhinitis were randomly allocated to either acupuncture or sham laser acupuncture. The main outcome measure was the alteration of the nasal sickness score. Treatment showed a significant effect of acupuncture compared to a sham treatment in the nasal symptom score.

Role of Surgery

Surgical measures to treat nonallergic rhinitis have been described but not widely used because of lack of efficacy and risk of complications. Surgery can be considered after medical measures fail to control refractory symptoms. Turbinectomy has been used to control prominent nasal congestion. The risk of complications is less with laser turbinectomy, and there is preservation of ciliary anatomy [137]. Other surgical measures

such as vidian nerve resection, electrocoagulation of the anterior ethmoidal nerve, and sphenopalatine ganglion block [138, 139] have been tried without much success [16].

Conclusions

Chronic nonallergic rhinitis is a syndrome comprised of many different entities. These entities differ in terms of their underlying mechanisms, to some extent their clinical presentations, and their response to treatment. A knowledge of these entities is necessary for optimal management of this disorder. Many treatments for allergic rhinitis such as antihistamines and antileukotrienes are often ineffective in chronic nonallergic rhinitis. In addition, the drug of choice, intranasal steroids, is less consistently effective in the treatment of allergic rhinitis in nonallergic rhinitis. Nonetheless, with a knowledge of the mechanisms underlying different forms of chronic nonallergic rhinitis, successful treatment programs can usually be designed [134].

Compliance with Ethics Guidelines

Conflict of Interest Phil Lieberman has served as a consultant for and received honoraria from MEDA.

Debendra Pattanaik declares that he has no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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