Thoughts on the Pathophysiology of Nonallergic Rhinitis

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Nonallergic noninfectious rhinitis is a diagnosis by exclusion, meaning that a number of poorly defined nasal conditions that have in common allergy and infection as a cause of the rhinitis have been excluded. The etiology of some subgroups of nonallergic noninfectious rhinitis, like nonallergic rhinitis with eosinophilia (NARES) and drug-induced rhinitis, are quite well defined, but in the majority of the patients, the etiology and pathophysiology are unknown. These patients are classified as idiopathic rhinitis patients. A careful determination of the intensity of the symptoms combined with modern diagnostic tools enables us to discriminate idiopathic rhinitis patients from normal controls. This review discusses the possible pathophysicologic mechanisms of nonallergic noninfectious rhinitis, with emphasis on idiopathic rhinitis.

Introduction

Rhinitis is a very common disorder, affecting 20% to 40% of the western population. Rhinitis can be classified as being allergic, infectious, or nonallergic/noninfectious [1–3]. The exact figures are unknown, but most ENT clinics report a 50-50 division between allergic and nonallergic patients in perennial disease. Rhinitis means inflammation of the nasal mucus membrane. However, markers of inflammation are not examined in daily clinical work. Therefore, the term “rhinitis” is used to indicate a disease of the nasal mucosa, which results in the symptoms of nasal itching, sneezing, rhinorrhea, and nasal blockage [3]. The mucosa of the nose and sinus are contiguous, and thus rhinitis often results in, or includes, (rhino)sinusitis.

Rhinitis Classification

Allergic rhinitis is clinically defined as a symptomatic disorder of the nose induced by an IgE-mediated inflammation after allergen exposure of the membranes lining the nose (Fig. 1). The diagnosis of allergy is based on diagnostic studies like skin-prick tests, or measurement of specific serum IgE.

In the Allergic Rhinitis and Its Impact on Asthma (ARIA) guidelines, the World Health Initiative has subdivided rhinitis into "intermittent" and "persistent" disease, where intermittent is defined as symptoms on less than 4 days a week or less than 4 consecutive weeks a year. Moreover, symptoms are divided into mild, or moderate/severe, which impacts work, school, daily activities, or sleep [3].

The disease is "nonallergic" when allergy has not been proven by proper allergy examination (history, skin-prick testing, measurement of serum-specific IgE antibodies) (Table 1).

Rhinitis is called "noninfectious" when the nasal discharge is clear and watery, and not purulent. Detection of microorganisms (viruses, bacteria, fungi) is not used in clinical work and it can, therefore, not form the basis for the diagnosis. When allergy and infections have been excluded as the cause of rhinitis, a number of poorly defined nasal conditions of partly unknown etiology and pathophysiology remain. The differential diagnosis of nonallergic rhinitis is extensive. The mechanisms are only partly unrevealed.

Nonallergic rhinitis

Occupational nonallergic rhinitis

Occupational rhinitis arises in response to an airborne agent present in the workplace. Many occupational agents are irritants and can cause nonallergic hyper-responsiveness. Most occupational agents that induce nonallergic rhinitis are small molecular weight compounds such as isocyanates, aldehydes, ninhydrin, and pharmaceutical compounds [4,5]. More than 250 different chemical entities have been identified. Although these can act as reactive haptens, nonimmunologic mechanisms are common. Some compounds like chlorine can induce irritant rhinitis in 30% to 50% of exposed workers [6,7].

Drug-induced nonallergic rhinitis

A range of medications is known to cause nasal symptoms. Respirine, hydralazine, guanethidine, phentolomine, methyldopa, ACE inhibitors, β-blockers, chlorpromazine, aspirin, other nonsteroidal anti-inflammatory agents, oral contraceptives, and α-adrenoceptor antagonists such as prazosin have all been associated with nasal symptoms, as have intra-ocular ophthalmic preparations (β-blockers)

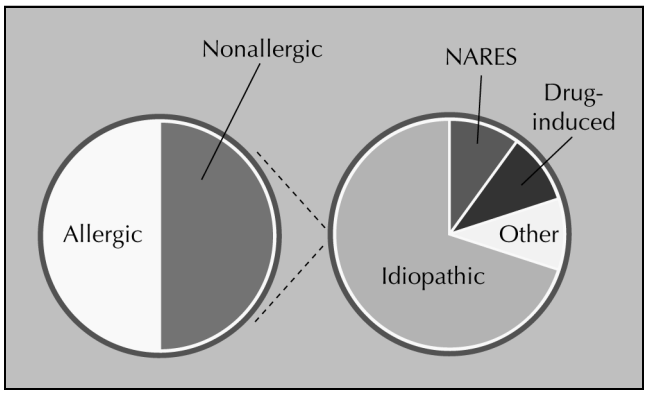

Figure 1. The epidemiology of allergic and nonallergic perennial rhinitis.

Table 1. Known causes of nonallergic rhinitis

Occupational
Drug-induced
aspirin
other medications
Hormonal
Other causes
NARES
Irritants
Food
Emotional
Atrophic

NARES—nonallergic rhinitis with eosinophilia
(*Data from* Bousquet, *et al.* [3].)

[8]. Also, psychotropic agents like thioridazine, chlordiaepoxide, amitriptyline, perphenazine, and alprazolam have been shown to cause nasal symptoms as well [8].

Hormonal nonallergic rhinitis

Changes in the nose are known to occur during the menstrual cycle, puberty, pregnancy, and in specific endocrine disorders such as hypothyroidism and acromegaly [9]. A persistent hormonal rhinitis or rhinosinusitis may develop during pregnancy in otherwise healthy women. Its severity parallels the blood estrogen level. The symptoms will disappear at delivery. Hormonal imbalance may also be responsible for the atrophic nasal changes in postmenopausal women.

NARES

The NARES syndrome was originally described in 1981 by Jacobs *et al.* [10]. They described patients with perennial nasal symptoms of sneezing paroxysms, profuse watery rhinorrhea, and pruritus of the nasopharyngeal mucosa in an "on-again-off-again" symptomatic pattern with a profound eosinophilia in the nasal smear, and no signs of allergy as tested by skin-prick testing, and measurement of total and specific IgE in the nasal secretion. Trigger factors associated by the patients with the acute onset of nasal symptoms were none or unknown in 42%, weather changes in 31%, odors in 15% and noxious or irritating substances in 12%. The same sort of patient group, with perennial symptoms of nasal hyper-reactivity involving sneezing, rhinorrhea, nasal obstruction and pruritus, and frequent hyposmia was later described by others [11,12]. Moneret-Vautrin [11] suggested that NARES is a precursor of aspirin sensitivity. Other groups were not able to find eosinophilia in their population of nonallergic rhinitis patients [13,14]. The differences between these findings can possibly be explained by group selection.

The definition of NARES as a subgroup of nonallergic rhinitis is relevant for therapy. There are some indications that eosinophilia is in important predictor of the effectiveness of local corticosteroid therapy. Patients with eosinophilia seem to be more prone to a positive effect of anti-inflammatory treatment.

Idiopathic rhinitis

If we have excluded all the possible causes named above, a large group of patients persists. For the description of nonallergic noninfectious rhinitis without a known cause, a number of terms have been proposed. Formerly, the disease was called vasomotor rhinitis, but because there is no indication of a disorder in the vasomotor system, this term has been abandoned. Other terms, like NINAR (noninfectious, nonallergic rhinitis) and NANIPER (nonallergic noninfectious perennial rhinitis) are purely descriptive [15••,16•]. Recently, the term idiopathic rhinitis has been proposed [3]. Idiopathic, meaning without known cause, seems to be the best term at this moment to describe this patient group. Before discussing possible pathophysiologic mechanisms in this group, we must provide a workable description.

What is the pathology of idiopathic rhinitis symptoms?

The first question may be whether this group of patients really exists. Occasional sneezing, and rhinorrhea in the morning and upon exposure to cold and/or polluted air, is considered a normal nasal response. Some persons consider even slight nasal symptoms to be abnormal and seek medical advice for that reason. Inquiry about the hours with daily symptoms may help making a distinction between a normal physiologic response and a disease. Also the use of a daily record card of symptoms if appropriate, combined with peak nasal inspiratory flow measurements, will give the physician insight into the severity of the disease. Marked discrepancies between description of the problem at the first visit and data from these daily measurements can often be found.

Are we able to discriminate idiopathic rhinitis patients from controls?

Various stimuli have been used to try to differentiate idiopathic rhinitis patients from normal controls. A common and characteristic feature of patients with NANIPER is nasal hyper-reactivity to nonspecific stimuli. Hyper-reactivity describes the reactivity of the mucosa, and does not point to any cause of the disease. In addition, patients with

allergic rhinitis usually complain of hyper-reactivity to non-allergic stimuli, obviously as a direct result of allergic inflammation. Until now, the most common diagnostic test for measuring nasal hyper-reactivity was intranasal histamine provocation [17]. Histamine provocations have been proven in allergic rhinitis and asthma to be a good test for hyper-reactivity.

Histamine provocation, however, fails to differentiate between patients with NANIPER and control subjects [18,19•]. Methacholine has been shown able to differentiate idiopathic rhinitis patients with persistent rhinorrhea from controls, but not patients with blockage as the main symptom [17]. Nonallergic rhinitis is also not characterized by increased responsiveness to capsaicin provocation [20].

A group from Baltimore [18,21] was the first to point to cold dry air (CDA) provocation as an effective tool in quantifying the secretory response of hyper-reactivity in persons susceptible to it. Subsequently a group from Rotterdam [19•] proposed a new standardized intranasal CDA provocation method, which is able to make the distinction between idiopathic rhinitis patients and controls. This new, standardized intranasal CDA provocation resulted in increased mucus production and nasal blockage in a dose-dependent manner in patients with NANIPER, but not in control subjects. Sneezing did not occur. The reproducibility, sensitivity, and specificity of this provocation render us with a useful diagnostic tool in idiopathic rhinitis patients.

We can conclude that a careful determination of the intensity of the symptoms when appropriate, combined with modern diagnostic tools enables us to discriminate idiopathic rhinitis patients from normal controls.

Of course, the ability to distinguish a patient group does not make the pathophysiology clearer, nor does it lead to potential treatment of the disease. Although recent studies have tried to focus their patient group as much as possible, and to eliminate all other causes of nonallergic rhinitis, it still has to be anticipated that idiopathic rhinitis is a compilation of different pathophysiologic entities. Using the limited data available at the moment, we might hypothesize which pathophysiologic mechanisms play a role in idiopathic rhinitis. Whether the roles of these mechanisms are major or minor and which important for many or few patients with idiopathic rhinitis, has to be further elucidated.

The pathophysiology of idiopathic rhinitis

Potential deficits in idiopathic rhinitis could be a) the permeability of the mucosa, leading to increase entrance of potential harmful substances, b) non-IgE mediated inflammatory responses, c) hyper-reactivity of the mucosal constituents and/or the neural innervation. These three different aspects are discussed in more detail later in these pages.

Is epithelial permeability increased in idiopathic rhinitis?

Epithelial damage with concomitant increased epithelial permeability might lead to increased accessibility for stimuli to sensory nerve endings, vessels, and glands. Damaged and desquamated epithelium as a reason for airway hyper-responsiveness has always been a popular hypothesis in pulmonology. Contrary to findings in the nasal mucosa [22], damaged epithelium has been found even in mild asthmatic subjects [23]. Mechanisms that might cause this damage, like release of eosinophilic products such as MBP or loss of endopeptidases, are not different from the upper airways and thus not very likely to explain this difference. It is unclear from available data whether the bronchial epithelium is more susceptible to damage, or if most of this damage is iatrogenically induced by the way the bronchial mucosa is obtained. Moreover, studies in the nose [24] have shown that nasal mucosal absorption was decreased instead of increased during allergic rhinitis, and unchanged during the common cold. In fact, it has been suggested that plasma exudation tightens the nasal mucosa [24]. In conclusion, there are not many data pointing to increased epithelia permeability as a cause of nonallergic rhinitis.

What is the role of inflammation in idiopathic rhinitis?

What arguments do we have that inflammation plays a role in idiopathic rhinitis? First, we have to exclude all patients with NARES as defined above. This sounds easy but in many studies the difference between NARES and idiopathic rhinitis is not made. We suggest that all patients with eosinophilia in smear or nasal biopsy are taken together in the NARES group. The origin of the eosinophilia is interesting. Biopsy studies comparing different cell populations in nonallergic rhinitis are limited. The only two found in the literature are from Powe [25] and from Blom [26]. Powe describes eosinophilia in his patients comparable to perennial allergic rhinitis [25]. In accordance with this eosinophilia, he found increased numbers of IgE-positive cells. He suggests that NARES is a local IgE-mediated response that does not result in systemic Th2 responses. Although local IgE production was made plausible in the 80s by Platts-Mills and others, the final proof came recently [27]. It has been proven by at least two groups now that local IgE production takes place in the nasal mucosa of allergic patients [28,29]. However, it remains to be proven that the same mechanism also occurs in nonallergic rhinitis patients, and whether this situation is stable over time, or if these patients, as has been shown in small children, develop allergic rhinitis in due time. It is interesting to compare these data on eosinophilia in nonallergic rhinitis with data on smoking. Passive-smoking, nonallergic children share with smoking adults a similar cellular infiltration with the Th2 profile, including eosinophils, increased IgE+ cells, and increased Il-4 [30,31]. Because smoking results in many patients in the same clinical picture of rhinitis with rhinorrhea and nasal obstruction, it might be that the NARES type of nonallergic rhinitis is caused by (passive) smoking or other proinflammatory stimuli inducing an "allergy-like" inflammatory response [30,31].

In the studies by Blom [26,32] with the same sort of in- and exclusion criteria as used by Powe, no signs of inflammation were found. This group was totally comparable to controls. How do we explain this discrepancy? The most likely explanation is the use of corticosteroid therapy. In the Rotterdam study, most patients tried local corticosteroid therapy without success. We hypothesized that patients with eosinophilia are sensitive to local corticosteroid, treatment and thus are excluded from our study population by treatment of general practitioners, which usually treat this group of patients with local corticosteroid nasal spray.

Although many clinicians feel that there is a group of patients sensitive to anti-inflammatory or even antihistamine treatment, data to prove this supposition are limited [33,34]. In a large study from Lundblad *et al.* [33], of 329 patients with nonallergic rhinitis based on clinical grounds, 49% of the patients using a local corticosteroid spray versus 40% of the patients in the placebo group had moderate, marked or complete relief of their symptoms From this study, it could be concluded that 15 patients out of 167 benefited more from local corticosteroid nasal spray than from the vehiculum. The same sort of data have also been shown with an antihistamine [35]. We may conclude that a small number of patients have an inflammatory infiltration of the nasal mucosa. Circumstantial evidence points to anti-inflammatory treatment possibilities in this group. Whether other pharmacologic actions of local corticosteroids or antihistamines may play a role in this group needs further investigation.

The information above describes inflammation existent in the mucosa at the time of symptomatology. A second way to study inflammation is by inducing an inflammatory reaction by exogenous stimuli. The obvious example is allergen provocation in allergic rhinitis. What possible stimuli can be used to induce inflammation in nonallergic rhinitis?

The Baltimore group has done essential studies with Cold Dry Air and hyperosmolal solutions as stimuli [18,21,36]. They have shown in a number of papers that CDA is able to provoke mediator release in patients with CDA sensitivity, which is very much the same as after allergen provocation in allergic rhinitis [21,37]. Mediators like histamine, TAME esterase, kinins, prostaglandins, and leukotrienes have been found to be increased in this group [18,21,36]. Interestingly, antihistamines as well as local corticosteroids did not reduce symptoms in this CDA-sensitive group; although local corticosteroid treatment was able to reduce histamine release [39,40]. From these studies we can conclude that the symptomatology in these nonallergic rhinitis cases is not induced by histamine release, which corresponds with the data showing that histamine provocation fails to differentiate between patients with nonallergic rhinitis, and controls [18,19•].

What Is the Role of Neurogenic Mechanisms?

The neural regulation of the upper airways is complex, and consists of a number of interacting nervous systems. Sensory, parasympathetic and sympathetic nerves regulate epithelial, vascular and glandular processes in the nasal mucosa. The anatomically defined sensory parasympathetic and sympathetic neural systems contain heterogeneous populations of nerve fibers often containing unique combinations of neurotransmitters and neuropeptides [15••,41•]. However, to understand the possible mechanisms of deregulation of the neural control, the anatomical classification is the easiest way to lead our thoughts.

Sensory nerves

Sensory nerves originating from the ethmoidal and posterior nerves are highly branched neurons innervating the vessels, gland, and epithelium of the mucosa. The most important parts of the sensory nerves are the C-fibers, which are able to react to pain and temperature. The C fibers are unspecialized sensory nerve endings, which reach up between the epithelial cells to the region of the tight junctions. These C-fibers can be stimulated by inflammatory mediators, like histamine, and bradykinin, but also by a number of inhaled irritants like nicotine, cigarette smoke, formaldehyde, and capsaicin [24,42,43]. Depolarization of nerve endings results in release of neuropeptides form neurosecretory swellings (variosities) that are found near glands and vessels. This results in acute stimulation of cells, like endothelial, glandular, and epithelial cells within the nasal mucosa. Substances like substance P and CGRP are able to increase vascular permeability and activate submucosal glands. Some authors describe these events as neurogenic inflammation [43]. Sensory nerve stimulation also leads to impulses in the brainstem and brain, resulting in appreciation of sensations of itch, burning, cough, and stimulation of parasympathetic reflexes. The parasympathetic neural reflexes induce release of acetylcholine, VIP and other peptides that act on their specific receptors.

The actions of neuropeptides and Ach are limited by degration by neutral endopeptidase (NEP) and acetylcholinesterase (Achase) [44••]. What data point to overreaction of sensory C fibers in nonallergic rhinitis?

Capsaicin is the pungent agent in red peppers. When sprayed in the nose, capsaicin induces burning, rhinorrhea, nasal blockage, and lacrimation. Capsaicin is a substance which has only been shown to have activity on C-fibers and some Aδ-fibers [43]. It causes centrally bound actions potentials but also antidromal release of endogenous stored neuropeptides [41•,44••]. Capsaicin stimulates a predominantly central neuronal response, and the induced secretory response is of glandular rather than vascular origin [45]. As we discussed earlier, these neuropeptides lead to neurogenic inflammation. However, provocation with capsaicin has not been able to discriminate between patients with idiopathic rhinitis and control subjects [20], although one study showed a significant difference in patients' hypersecretion as a main symptom [46].

A strong substantiation for the role of C-fibers in idiopathic rhinitis is the effects of treatment with capsaicin.

Repeated provocations with capsaicin leads to a significant reduction in nasal complaints in patients with idiopathic rhinitis [16,47]. However, the mechanism explaining this phenomenon is unclear. Primarily, a depletion of neuropeptides has been suggested. However, the effect of capsaicin treatment lasts for at least 1 year in most patients, making a depletion of neuropeptides an unlikely explanation. Also, no significant differences were found between placebo- and capsaicin-treated groups for leukotriene (LT) C4/D4/E4, prostaglandin D2 (PGD2), and tryptase, and a number of inflammatory cells, reducing the probability of an effect due to reduction of inflammatory mediators [16,32]. The suggestion that idiopathic rhinitis represents a central type of abnormality with increased nasal perceptual acuity which is treated by reducing sensations in the nose, is not implausible [15]. However, increasing evidence showing that objective abnormalities in nasal blockage and rhinorrhea can be found in these patients reduces the chances of this hypothesis [19•,48,49]. The most likely explanation until now is the ablation of C-fibers, although this has not been proven in human models [32].

In conclusion, the finding that capsaicin primarily works via C-fibers and that capsaicin desensitization is an effective treatment in patients with idiopathic rhinitis points to an important role for C-fibers in the pathophysiology of the disease. Direct observations explaining the efficacy and working mechanisms of capsaicin are lacking.

Parasympathetic nerves

For decades, the generally held assumption concerning the etiology of idiopathic rhinitis had been an imbalance of the autonomic nerve supply to the nasal mucosa with excessive parasympathetic or reduced sympathetic activity [50,51]. The fact that recent investigations have focused on the nonadrenergic, noncholinergic system, the peptidergic system, does not diminish the importance of the sympathetic and parasympathetic nervous systems in the pathophysiology of nasal disease. The parasympathetic nerves make up the efferent reflex arc of the nasal reflex.

Postganglionic parasympathetic fibers innervate mainly the seromucous and serous nasal glands. Parasympathetics release classical neurotransmitters like acetylcholine and noradrenaline, but also neuropeptides like VIP. The cholinergic component of parasympathetic reflexes is the predominant stimulus for mucus secretion. Unilateral stimulation of the afferent arc of the nasal reflex (stimulation of sensory fibers) leads to a bilateral neurally mediated response that can be significantly blocked by atropine.

What data do exist that "hyper-reactivity" of the parasympathetic innervation leads to idiopathic rhinitis? Until recently, the only obvious example of parasympathetic hyper-reactivity was the rhinitis of the elderly [52,53•]. The anticholinergic agent ipratropium bromide is a highly effective treatment for hypersecretion in idiopathic rhinitis [52], but does not have any influence on other symptoms like nasal blockage or sneezing [53•,54].

Sympathetic nerves

The sympathetic nerves also make up the efferent reflex arc of the nasal reflex. The sympathetic innervation of the respiratory mucosa is relatively poorly studied. Postganglionic sympathetic fibers innervate mainly the vasculature of the nasal mucosa and release noradrenaline and neuropeptide Y. Both are potent vasoconstrictors. Alpha-adrenergic receptor agonists like xylomethazoline are very effective and prove the relative importance of the sympathetic innervation in the regulation of nasal patency. Are there any indications that sympathetic hypo-reactivity leads to idiopathic rhinitis? Although the magnitude between patients with idiopathic rhinitis and controls were small, some hints have been found recently by the group in Liverpool, UK. Patients with idiopathic rhinitis were found to have an abnormal nasal response compared with controls after isometric exercise [55•], and after axillary pressure [56]. The specificity of these findings compared with other forms of rhinitis, however, must be confirmed.

Glandular Hyper-reactivity

Alterations in the responsiveness of glands to stimuli may be a cause of nonallergic rhinitis. Methacholine stimulates nasal glands at their autonomic (cholinergic) innervation end-plate and can produce a secretary response without involvement of neural reflexes. Methacholine provocation has been performed in patients with nonallergic rhinitis [17]. An increased responsiveness has been demonstrated in idiopathic rhinitis with sneezing and rhinorrhea as its main complaints [17,46], but not in patients who have nasal blockage, or in unselected patients with idiopathic rhinitis [17]. Excessive rhinorrhea has mainly been found in the elderly [57]. Glandular hyper-reactivity seems to be mainly caused by hyperreactivity of the parasympathetic innervation, and can be treated with an anticholinergic agent (ipratropium bromide). Provocation with metacholine is not able to separate responders from nonresponders indicating no direct effect on the glands [58].

Vascular Hyper-reactivity

Testing of vascular hyper-reactivity apart from neuronal stimulation is difficult because many mediators like histamine and bradykinin stimulate blood vessels directly and via the neuronal pathway. The major measurable outcome from the subepithelial capillaries in response to a nonallergic stimulus is plasma exudation. Plasma exudation is not produced by neurogenic stimulation like capsaicin or nicotine and also not produced by methacholine provocation [59]. Moreover, unilateral provocation with bradykinin does not lead to an increase in vascular permeability on the contralateral side [60]. Contrary to the aforementioned study, vascular hyper-reactivity was found to be increased in idiopathic rhinitis [15••].

Conclusions

The etiology of some subgroups of nonallergic noninfectious rhinitis, like NARES, and drug-induced rhinitis, are quite well defined, but in the majority of the patients the etiology and pathophysiology are unknown. These patients are classified as idiopathic rhinitis patients. The limited data available at the moment point to a) inflammatory disorders in a small number of patients; b) an important role for C-fibers in the pathophysiology, although direct observations explaining this mechanism are lacking; c) some indications for parasympathetic hyper-reactivity and/or sympathetic hyporeactivity; and d) indications that glandular hyper-reactivity might play a role in these patients. Further studies are needed to determine whether these mechanisms are separate causes of idiopathic rhinitis, or can be found in combination in the same patient.

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