

TITLE: Non-Allergic Rhinitis

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Introduction

Rhinitis in general is defined as two or more nasal symptoms of: nasal congestion, rhinorrhea, sneezing or impairment of smell for more than 1 hr a day. There are different forms of rhinitis, generally divided into three main categories 1) Infectious rhinitis 2) Allergic rhinitis 3) Non-Allergic rhinitis. Allergic rhinitis is defined as immunologic nasal response, primary mediated by immunoglobulin E (IgE).

Non-allergic rhinitis is defined as rhinitis symptoms in the absence of identifiable allergy, structure abnormality or sinus disease. There have been many terms to describe non-allergic rhinitis which include vasomotor rhinitis, vascular rhinitis, perennial, chronic and noninfectious perennial rhinitis, among others.

A quick review of nasal function is warranted. Nasal function includes temperature regulation, olfaction, humidification, filtration and protection. The nasal mucosal lining contains IgA, proteins and enzymes which help protect from infections. Also, nasal cilia propel the matter toward the natural ostia at a frequency of 10-15 beats per minute, which causes a mucous flow at rate of 2.5 to 7.5 ml per minute.

A review of the epidemiology shows that up to 10% of the US population is affected by rhinitis. That is 58 million Americans with allergic rhinitis and another 19 million with non-allergic rhinitis. However, in the population that present to an ENT clinic, 50% of rhinitis patients are diagnosed with allergic rhinitis and the other 50% are diagnosed with non-allergic rhinitis.

Potential problems that arise from non-allergic rhinitis (NAR) are similar to allergic rhinitis, which include development of sinusitis, Eustachian tube dysfunction, chronic otitis media and anosmia. This leads to decreased work productivity and frequent doctor visits. Also, the treatment leads to side effects of drowsiness, epistaxis and nasal dryness.

CAUSES

In this talk, we will discuss the major causes of non-allergic rhinitis. They are broken down into the following:

Occupational, Drug induced, Rhinitis Medicamentosa, NARES, Hormonal, Idiopathic or Vasomotor and Mimicker.

Occupational

Arises from airborne agents at a patient's workplace. These agents do not act through immune mediated systems, but are an irritant to the nasal mucosa and cause hyper responsive reactions. They trigger both the Olfactory nerve and the Trigeminal nerve that senses burning and irritation by airborne chemicals.

There have been over 205 different chemical identified as irritants. They include cigarette smoke, solvents like chlorine, metal salts, latex, glues and wood dust. These patients usually present with a concurrent occupational asthma.

For diagnosis, we use primarily history and nasal provocation with stimuli. About 70% of patients improve with symptoms when triggers are avoided.

Drug Induced Rhinitis

There are a variety of medications that can cause rhinitis when administered either orally or topically. These drugs can be divided into two main groups as pharmacologic or aspirin hypersensitivity.

Here is that include many of the drugs that are common causes rhinitis.

- Cocaine
- Topical nasal decongestants
- phosphodiesterase type-5 inhibitors (PDE-5)--Sildenafil
- Alpha-adrenoceptor antagonists
- Reserpine
- Hydralazine
- Angiotensin-converting enzyme inhibitors
- Beta-blockers
- Methyldopa
- Guanethidine

- Phentolamine
- Oral contraceptives
- Non steroidal anti-inflammatory medications
- Aspirin
- Psychotropic agents
- Thioridazine
- Chlordiazepoxide
- Chlorpromazine
- Amitriptyline
- Perphenazine
- Alprazolam

Many common antihypertensive medication and psychiatric medications cause rhinitis. These are infrequent but predicable side effects. They usually lead to congestion, but PND and watery secretions can be other symptoms.

PDE-5 inhibitors like Sildenafil (Viagra) cause allergic rhinitis by inducing engorgement of the nasal mucosa including the turbinates.

Intolerance to ASA or NSAIDS is unpredictable. However, they predominately cause rhinorrhea. ASA rhinitis may be a part of the ASA triad of hyperplastic rhinosinusitis, nasal polyps and asthma.

Rhinitis Medicamentosa

Rhinitis medicamentosa (RM) is a condition that caused by overuse of topical nasal steroids. Also known as rebound or chemical rhinitis, the incidence is somewhere between 1-9% of non-allergic rhinitis and it is more common in younger adults and pregnant women.

To understand the cause of RM, we must first look at some of the basic science behind the nasal mucosa. The mucosa is innervated by sympathetic fiber that release norepinephrine, which stimulate alpha 1 and alpha 2 receptors. This in turns causes vasoconstriction.

The sympathomimetic amines and imidazoline derivatives (phenylephrin and oxymetazoline, respectively) both produce vasoconstriction by endogenous release of norepinephrine.

The problem arises with prolonged use. This leads to reduced production of norepinephrine in the presynapses and decreased sensitivity of the alpha receptors in the postsynapses, which in turn requires higher doses for shorter acting time. This cycle of excess dose use and decrease symptomatic relief will lead to worsening of the original symptoms.

The risk of RM is greatest after 10 days use of medications. Treatment includes gradual stopping of decongestant with introduction of topical corticosteroid. This will lead to a temporary increase in symptoms and patients should be warned beforehand of this and to not restart the original medication. Patients should be off the medication for 3 months before starting any other surgical or medical treatment for the original nasal disease.

NARES

NARES (non-allergic rhinitis with eosinophilia syndrome) is another non-allergic entity that is defined as rhinitis without allergic cause but has 20-25% eosinophils seen on nasal smears. As with the other NAR disease, there is lack of allergy by skin test or IgE antibodies. Prevalence is 13-33% of NAR.

NARES etiology is unknown. However, it is believed to be associated with the ASA triad as NARES patients tend to develop asthma and nasal polyps later in life and they tend to have abnormal prostaglandin metabolism. And yet, eosinophilic counts are elevated in 20% of the nasal smears in the general population and not everyone with eosinophilias have symptom of rhinitis.

Recent studies by Powe et al (2001) show that NARES is a local IgE mediated response that does not result in a systemic response. They found that 50% of non-allergic rhinitis pt that had a negative skin prick test were found to have positive result to nasal allergy challenge. Therefore, skin prick test negative pt with eosinophilia may require allergen challenge nasally before diagnosis of non-allergic rhinitis. This is important to know, because NARES is a subset of non-allergic rhinitis who responds better to nasal corticosteroids than other non-allergic rhinitis groups.

Hormonal Rhinitis

Hormonal rhinitis (HR) is defined as rhinitis during period so known hormonal imbalance. Estrogens are known to affect the autonomic nervous system by increasing a host of factors including parasympathetics, acetyl choline transferase, and acetylcholine content, and also increase inhibition of sympathetic system. Therefore, the most common causes are pregnancy, menstruation, puberty and exogenous estrogen. With pregnancy, HR usually manifests in the second month and will continue throughout pregnancy.

Hypothyroidism is also known to cause hormonal rhinitis. In hypothyroidism, increase TSH release causes edema of the turbinates. Nasal congestion and rhinorrhea are the most common symptoms of RH.

Idiopathic rhinitis

Next we come to Idiopathic rhinitis (IR). This is also known as vasomotor rhinitis and is characterized by nasal blockage and rhinorrhea, with some sneezing and pruritis. Etiology is unclear, with failed attempts to differentiate by hyperactivity to histamine, methacholine, cold air or capsaicin. IR is solely diagnosed by patient complaints and therefore a diagnosis of exclusion.

The exclusion criteria include: having positive skin test, smoking, nasal polyps, pregnancy, medications affecting nasal function, and good response to nasal steroids. Pt who have a good response to nasal steroids tend to have NARES.

IR is not believed to be caused by inflammation. IR patients have no significant increase in mucosal lymphocytes, antigen presenting cells, eosinophils, macrophages, mast cells or IgE positive cells compared to controls. And studies have shown a reduction in immunocompetent cells in the mucosa of IR pt after treatment with nasal steroids did not reduce nasal complaints.

Others

Finally we come to the last group of NAR, the other category. There are a number of conditions that can produce the same signs and symptoms of rhinitis. These include structural conditions like deviated septum, nasal tumors, enlarged adenoids or turbinates, and atrophic rhinitis. One must also look for mimicker like Wegener's, sarcoidosis, and polychondritis.

Diagnosis

To provide an accurate diagnosis, one must always start with **complete history** and **physical exam**.

Here are some pertinent questions to ask with the **history**:

- What are your nasal and sinus symptoms and do they include discharge, congestion, PND, sneezing, itching?
- Do you have environmental allergies, undergone skin testing, or been treated for allergies?
- Are there certain situations, environment in which symptoms are worse like home, work, indoors, outdoors, times of the year or day?
- What is your work, are there exposures to chemicals? Do your symptoms begin with medications or do any medications help your symptoms?
- Do you have asthma, allergy to aspirin, or any sinus polyps?
- Have you undergone any sinus surgeries?

With the **physical exam**, one should do a nasal endoscopy. Boggy, edematous mucosa suggest noninfections, while inflammation and purulent discharge from middle meatus suggests infection.

Treatment

The key to treatment is patient education. Teach patient to avoid triggers, have them change their environment, change their medication. If these are not feasible, then medical therapy is the next course of action.

Immunologic therapy has no benefit to non-allergic rhinitis and therefore it is important to distinguish the disease before considering immunotherapy. Nasal lavage has been shown to have minor decongestion benefits and improves mucociliary function.

Topical nasal steroids have been used widely for use with NAR. Fluticasone, budesonide and beclomethasone are the only ones approved by FDA for use in NAR. However, efficacy is inconsistent and use must be for a minimum of 6 wks. With the exception of NARES, topical steroids do not provide the same relief as they do with allergic rhinitis.

Antihistamines have given us inconsistent results. Histamine release is the main pathophysiology for allergic rhinitis and therefore, not a good consideration for NAR. Azelastin intranasal have been proven efficacious for all forms of NAR, including Idiopathic rhinitis. It is an H1 receptor antagonist that also inhibits synthesis of leukotrienes, kinins, cytokines and free radicals. The exact mechanism behind its relief is unknown.

Anticholinergic drugs also have their place in treatment. Ipratropium bromide has been shown to be effective with rhinorrhea symptoms. The strength used is 0.03% with 2 sprays TID initially. The dose is slowly lowered to one spray BID as maintenance.

Mast cell stabilizers such as cromolyn have been shown to have no benefit with non-allergic rhinitis. There have been no studies that have looked at leukotriene modifiers in the treatment of non-allergic rhinitis.

Capsaicin has been shown to be of benefit to idiopathic rhinitis. This is the main chemical with in hot peppers. This substance is known to activate C-fiber in the nose which is responsible for pain. With repeated application of capsaicin, a desensitization and degeneration of c-fibers occur. A five dose treatment of high dosages at 1 hr intervals has been shown to work as well as five high dose treatments over 2 wks. Up to 75% of patients will show long lasting relief. There are lower dose capsaicin formulation nasal sprays that are available OTC at pharmacies that can be used in higher frequencies.

Surgery is used only for failed medical treatment. Although nasal polyps and septal deviation do not cause NAR, they can cause problems with medications reaching its desired goal and therefore should be corrected.

Silver nitrate has been studied as therapy. Given topically, it has been shown to down regulate stimuli of the mucosa. Clinical trials show improvement over placebo and anosmia was

shown to be rare side effect. A 20% solution was applied by cotton tip for 1 minute once a wk for 5 wks.

Vidian Neurectomy has been demonstrated as treatment modality. Since 1961, it has been used successfully to relieve rhinorrhea. Initially done transantral, it has been moved to transnasally by endoscopy. Efficacy is up to 88%.

Turbinate reduction has also been beneficial. In a randomized control trial of 382 pt, with 6 yr follow up, a sub-mucus resection with lateral displacement has been found to be better in term of efficacy to turbinectomy, laser, cryotherapy, or electrocautery.

Recently, Ikeda et al (2006) has shown benefit to a combined vidian neurectomy with inferior turbinate resection for treatment of chronic rhinitis.

Follow up

Follow up is key for patient with non-allergic rhinitis. In a recent study by Rondon et al (2009), non-allergic rhinitis pt shown previously to have no sensitization to rest were found to sensitized to allergens on follow up. As many as 24% of the pt were found to develop sensitization. This suggest that sensitization may appear later in the coarse of rhinitis disease. Other studies have shown differences in allergy test dosages that may impact diagnosis.

Conclusion

In conclusion, non-allergic rhinitis is mainly a diagnosis of exclusion of IgE causes. NAR is seen in up to 50% of ENT pt with rhinitis. H+P is important step in diagnosis as are allergy testing.

Treatment includes avoidance, medication changes, and monitor of hormones. Topical steroids and Topical H-1 receptor antagonist Azelastine are FDA approved for NAR. Anticholinergic medications and capsaisin have been proven beneficial for treatment, while mast cell stabilizers and leukotriene modifiers have not.

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