Chapter

Non-Allergic Rhinitis

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Abstract

Non-allergic rhinitis is a term used for situations where no allergen can be detected as the cause of rhinitis. In non-allergic rhinitis; Skin test positivity or specific Ig E response cannot be detected. The pathophysiology of nonallergic rhinitis (NAR) is heterogeneous. The most common type is vasomotor rhinitis, also called idiopathic. In addition, there are many types such as hormonal, gustatory, occupational, atrophic, cold air-induced and systemic diseases. Patients; They present with symptoms such as nasal congestion, runny nose, sneezing, and itching in the nose, the symptoms of the patients do not show a seasonal pattern. There are family stories, but they are not as common as allergic rhinitis (AR). An underlying factor such as infection, sinusitis or polyps cannot be detected in patients. It was determined that the patients showed more neurogenic abnormalities in the pathophysiology. These patients have been shown to be hypersensitive to substances with ingredients such as cold air or capsaicin. The diagnosis is made clinically, the onset of the disease is in adolescence. Oral/nasal antihistamines, steroids, leukotriene antagonists are used in the treatment.

Keywords: non-allergic rhinitis, IgE, vasomotor rhinitis, eosinophilic nonallergic rhinitis, rhinitis medicomentosa

1. Introduction

1.1 Non-allergic rhinitis

Non-allergic rhinitis is a term used for situations where no allergen can be detected as the cause of rhinitis. Non-allergic rhinitis occurs in approximately one third of allergic rhinitis. Affects 22 million people (7% of the population) in the USA [1]. In non-allergic rhinitis; Skin test positivity or specific Ig E response cannot be detected. The pathophysiology of nonallergic rhinitis (NAR) is heterogeneous [2]. The most common type is vasomotor rhinitis, also called idiopathic. In addition, there are many types such as hormonal, gustatory, occupational, atrophic, cold air-induced and systemic diseases [3]. Patients; They present with symptoms such as nasal congestion, runny nose, sneezing, and itching in the nose, the symptoms of the patients do not show a seasonal pattern. There are family stories, but they are not as common as allergic rhinitis (AR). An underlying factor such as infection, sinusitis or polyps cannot be detected in patients. It was determined that the patients showed more neurogenic abnormalities in the pathophysiology. These patients have been shown to be hypersensitive to substances with ingredients such as cold air or capsaicin. The diagnosis is made clinically, the onset of the disease is in adolescence [4].

2. Pathophysiology

Non-Allergic rhinitis occurs due to non-IgE mediated mechanisms. Prostaglandins, leukotrienes are found in both the upper and lower airways. These cause mast cell secretion, eosinophils, after exposure to the allergen in rhinitis. Prostaglandins and leukotrienes released from mast cells cause vasodilatation and hypersecretion from the gland, leading to rhinitis symptoms. Although this mechanism is not fully active in non-allergic rhinitis, symptoms occur with a similar effect [5].

3. Vasomotor rhinitis

Vasomotor rhinitis; It constitutes the most important part of rhinitis in the definition of non-allergic rhinitis. Its other name is known as non-allergic rhinopathy. It occurs as a result of impaired vasomotor balance in the nose. There is a loop in the form of sympathetic/parasympathetic innervation in the nose. This cycle is disrupted due to reasons such as exercise, cold, stress, insufficient thyroid functions, pregnancy, excessive or prolonged use of some blood pressure drugs, birth control pills and decongestant drugs. At the beginning of all these reasons, nasal congestion is temporary and reversible. So if the cause is removed, the disease will improve. In addition, if it lasts long enough, this time the blood vessels will lose their elasticity and the event turns into an irreversible situation. Metabolic (Acromegaly, Pregnancy, Hypothyroidism), Autoimmune (Sjogren's syndrome SLE Relapsing polychondritis Churg-Straus),Granulomatous diseases (Sarcoidosis and Wegener's granulomatosis), Other (Cystic fibrosis, Cilia dyskinesia syndromes, Immunodeficiency, Amyloidosis, Chronic fatigue syndrome) are the most common causes of NAR [6].

4. Gustatuar rhinitis

Typically, it starts after consuming hot or spicy food and alcohol. It starts with a food allergy or an unknown mechanism and continues with profuse rhinorrhea. Ipratropium bromide is used in the treatment [7].

5. Occupational rhinitis

Occupationally allergic and non-allergic can occur. There are four types. The first is an uncomfortable rhinitis without inflammation in the nose caused by smell. The second type is rhinitis that is caused by irritant and causes inflammation in the mucosa. The third type is corrosive rhinitis that occurs due to high concentration of chemicals in the nasal mucosa. Ammonia etc. occurs with inhalation of substances. The fourth type is rhinitis, which causes Ig E due to occupational exposure. Latex allergy in healthcare workers depends on this. Nasal saline irrigation solutions, nasal steroids and antihistamines are used in the treatment of this rhinitis [8] (**Table 1**).

6. Hormonal rhinitis

It is divided into two as gestational rhinitis induced by the menstrual cycle. Gestational rhinitis begins in the second trimester of pregnancy and continues until the second week of postpartum. It is related to pregnancy in another form of hormonal rhinitis. This can start in any week of pregnancy. Nasal saline irrigation is used in the treatment. In addition, they can benefit from the tapes used for the

Drugs	Usage areas	Side effects
Antihistaminics	Sneezing, runny nose, itchy nose	Anti-cholinergic side effects such as dryness of mucosal membranes, urinary retention, constipation, tachycardia, decreased visual acuity; Central side effects such as attention deficit and sleep
Steroids (Oral prednisolone, methylprednisolone, nasal mometasone, fluticasone)	Nasal discharge, itching, sneezing (Due to the systemic side effects of oral steroids, nasal steroids are in common use and are used as the first choice in treatment..	Besides growth retardation in children, metabolism disorders in all cases, glaucoma and cataract formation, immunosuppression, suppression of the growth axis, thinning of the skin, behavioral disorders, osteoporosis
Leukotriene antagocytes (Montelukast, zileuton etc.)	It is the gold standard in rhinitis that does not respond to antihistamines and nasal steroids.	Agitation aggression, anxiety, hallucination, depression, insomnia, irritability, restlessness, and suicidal thoughts.
Oral / Nasal decongestants 1. Pseudoephedrine and phenylephrine-oral 2. oxymetazoline, xylo-metazoline and naphazoline (intranasal)	Nasal congestion	When used orally, irritability, insomnia, irritability, headache, tachycardia, hypertension, increased intraocular pressure, urinary difficulty

Table 1.
Drugs used in treatment [15].

nose wings at night. The benefit of intranasal steroids in these patients has not been determined. The use of pseudoephedrine should be avoided during pregnancy, especially in the 1st trimester [9].

7. Rhinitis medicamentosa (drug-induced rhinitis)

It is a severe nasal congestion caused by the continuous use of agents such as oxymetazoline and phenylephrine, which are sympathomimetic agents. They use oral or topical steroids in treatment and sympathomimetic sprays are discontinued. Drugs such as ACE inhibitors, NSAIDs and Aspirin also have similar effects [10].

8. Atrophic rhinitis

Progressive nzal atrophy and Klebsiella ozaenae etc. It occurs due to mucosal colonization with microbial agents. There is a disturbing foul-smelling discharge on the jas. It can also develop after inferior turbinate surgery. Oral antibiotics, salty and oily washing solutions are used for malodorous discharge. Since the disease is very persistent, symptomatic patients should be followed up from time to time [11].

9. Non-allergic rhinitis with eosinophilia syndrome (NARES)

Known as non-allergic rhinitis with eosinophilic syndrome (NARES), the disease usually begins in adulthood; It is a type of non-allergic rhinitis characterized by negative skin test and normal IgE levels. Aspirin sensitivity, asthma and nasal polyps may develop in these patients. Eosinophilia is observed in patients. There is

also an increased risk of obstructive sleep apnea syndrome. Another variant is Non-Allergic rhinitis disease with eosinophilia in the blood called BENARES. Although the clinic of the disease is the same as NARES; In this disease, there is eosinophilia in the blood instead of nasal eosinophilia. Intranasal corticosteroids are sufficient in both NARES and BENARES [12].

10. Infectious rhinitis

Infectious rhinitis is a type of rhinitis with acute or chronic runny nose, nasal congestion, frontal headache, smell disorders, post nasal discharge and cough. Most infectious rhinitis in children are viral and resolve with symptomatic treatment. If it is bacterial, antibiotics are used. In addition, nasal solutions, nasal steroids are also effective in treatment [13].

What are the risk factors?

- Exposure to smoke, exhaust fumes, or tobacco smoke
- Being over 20 years old. (Allergic rhinitis occurs before this age, non-allergic rhinitis occurs after the age of 20)
- Continuous use of decongestants: Nasal decongestants, which solve acute nasal congestion, cause congestion when used for a long time and increase congestion with rebaunt effect.
- Gender: Being a woman increases non-allergic rhinitis with hormonal effect.
- Occupation: Exposure to fumes from building materials, solvents or other chemicals
- Chronic diseases: such as hypothyroidism and chronic fatigue syndrome
- Stress. Emotional or physical stress increases susceptibility.

10.1 Complications

1. **Nasal polyposis**: Congestion and fluid increase in the sinuses trigger inflammation. As a result, benign masses form and cause chronic obstruction in the nose.
2. **Chronic Sinusitis:** Congestion and fluid increase in the nasal area disrupt the nasal drainage and cause inflammation.
3. **Middle ear infections**: Congestion and increased fluid in the nasal area can obstruct the eustachian tube, leading to middle ear infections.
4. **Disruption of daily activities:** It can cause disruption of daily activities. It can lead to school failure or business difficulties in school children.

10.2 Diagnosis

In non-allergic rhinitis, the diagnosis is made by exclusion. First of all, allergic rhinitis is ruled out. Sinus problems are then ruled out. So there are no definitive diagnostic criteria. To exclude, respectively.

1. Prick test: It is done to determine whether the symptoms are caused by an allergen. Allergens are applied to the skin and decided as positive or negative depending on the reaction.

2. Blood test: IgE levels are checked to measure immune response.

3. Nasal endoscopy: Pathologies such as nasal polyps and acute sinusitis are ruled out in endoscopy.

4. CT Imaging: Detailed imaging is performed for paranasal sinuses.

11. Treatment

Non-allergic rhinitis treatment is similar to allergic rhinitis. In treatment;

1. **Avoiding causative factors**: Cigarette smoke, perfume, spice or chemical odors should be avoided. Again, some drugs should be avoided. (Antihypertensives, antidepressants, birth control drugs etc.)

2. **Nasal irrigation**: The use of saline nasal solutions provides both opening and moistening of the nose. In addition, oil-containing solutions cause further moistening of the nose and ensure the success of the treatment.

3. **Pharmacotherapy**: First of all, drug therapy should be tried. Treatment can be used with oral or nasal antihistamines, oral or nasal steroids, leukotriene antagonists [14].

- Antihistamines

Antihistamines are molecules that bind competitively to H1 receptors. They help us treat sneezing, runny nose and itchy nose by reducing the sensation of vascular permeability, smooth muscle contraction and itching.

Although first generation antihistamines are cheap, we know that there is serious central nervous system penetration. For this reason, unfortunately, almost 10–40% of the patients cause severe distraction, sleepiness and concentration impairment. Anti-cholinergic side effects such as dryness in mucosal membranes, urinary retention, constipation, tachycardia, and decreased visual acuity limit the use of these drugs in elderly patients. In addition, the antagonistic effects of these drugs, which require long-term use, related to serotonin receptors, unfortunately, can cause weight gain. Trefenadine and astemizole are the first 2nd generation antihistamines and their central nervous system penetration is less than the old generation; However, they were removed from use in clinical practice due to arrhythmia caused by susceptible patients. Loratadine and cetirizine are generally less sedating new generation drugs. Levocetirizine is an enantiomer of the cetirizine molecule and unfortunately causes sedation at the effective doses. Fexofenadine, terfenadine; deslarotadine are also active metabolites of loratadine; these are sometimes referred to as 3rd generation antihistamines. It is reported that fexofenadine does not cross the blood brain barrier and therefore does not sedate. However, unfortunately, this is not the case in clinical use. Desloratadine is also reported to have more sedation and anti-cholinergic side effects [15].

Recently, anti-inflammatory effects of antihistamines have been mentioned. It is stated that mast cells and basophils stabilize the receptor independently by inhibiting the transmembrane passage of calcium and intracellular cAMP, thus reducing

the release of inflammatory mediators such as histamine, tryptase and prostaglandin. However, many antihistamines are unfortunately unable to stabilize these cells at therapeutic doses. Ketotifen, olopatadine, azelastine, bepotastine and alkaftadine are mostly known as both H1 receptor antagonists and dual-acting antihistamines with mast cell stability. It is stated that some antihistamines inhibit NF-□B and GATA3 transcription via H1 receptor and thus achieve anti-inflammatory effect.

- Corticosteroids

Corticosteroids are the first-line anti-inflammatory drugs we know best for the treatment of many inflammatory diseases. Although corticosteroids have well-known side effects, we see that they are still one of the most important pharmacological agents. In addition to growth retardation in children, side effects such as metabolism disorders, glaucoma and cataract formation, immunosuppression, suppression of the HPA axis, thinning of the skin, behavioral disorders and osteoporosis are the most common ones in all cases. Due to these restrictions arising in systemic use, it is mostly used intranasally in AR. Among the intranasal preparations, they are currently the most used pharmacological products in primary care. Although the anti-inflammatory mechanisms of corticosteroids are not very clear, the most important effects are seen as cytokine and chemokine inhibition. They bind to glucocorticoid receptors (GR) in the cytoplasm, dimerize and pass into the nucleus; they then associate with the glucocorticoid response element (GRE) and consequently increase the transcription of the gene codes of anti-inflammatory proteins such as lipocortin-1, IL-10, IL-1 receptor antagonist and neutral endopeptidase.

Glucocorticoids also cause a considerable reduction in the number of inflammatory cells in nasal lavage fluid. Especially, they cause a significant decrease in eosinophil numbers. This is due to their inhibitory functions on both IL-5 and GM-CSF. Currently, beclamethasone monohydrate, budesonide, flunisolide, triamcinolone acetonide, fluticasone (propionate and furoate), mometasone furoate, and ciclesonide are commercially available nasal topical corticosteroids. There are no significant differences in clinical efficacy between these preparations.

Local burning and stinging sensation, irritation, dryness and sometimes nosebleeds can be encountered as topical side effects with these preparations [15].

- Leukotriene antagocytes

Leukotrienes are inflammatory lipid mediators synthesized from arachidonic acid that can be produced by mast cells, eosinophils, basophils and macrophages. The adventure of arachidonic acid cleavage that started with the posfolipase A2 enzyme from the nuclear membrane continues with leukotriene synthesis. Arachidonic acid is metabolized to LTA4 via the 5-lipoxygenase (5-LO) enzyme. LTC4, LTD4 and LTE4 are then formed through different convertases. We call these leukotrienes "cysteinyl leukotrienes (CsyLTs)". CsyLTs has serious bronchial smooth muscle contraction, mucus production, edema and vascular permeability enhancing effects. LTD4 enhances the P-selectin pathway, increasing leukocyte adhesion and leukocyte aggregation to the inflammation site. It also plays an important role in eosinophil adhesion by increasing β2-integrins. As a result of nasal provocation with LD4 in normal humans, it was observed that nasal mucosal blood flow accelerated and airway resistance increased.

Leukotrienes can be physiologically antagonized by blocking their synthesis or receptors. Zileuton is a 5-LO synthesis inhibitor and it is a pharmacological product that can block nasal congestion in patients with AR after allergen provocation. For now, only montelukast, which is a Cys LT1 receptor antagonist, has been approved for AR and is a commercial product. Montelukast is observed to improve congestion during the day and at night, nasal discharge, nasal itching and sneezing, difficulty

falling asleep, and sleeping at night. It is thought to reduce the number of peripheral eosinophils and thus create an anti-inflammatory effect. However, despite all these, there are many publications showing that it is much less effective than intranasal corticosteroids in terms of these effects. Although it looks like a safe preparation in general; Some psychiatric side effects such as agitation, aggression, anxiety, hallucination, depression, insomnia, irritability, restlessness and suicidal thoughts are mentioned [15].

- Nasal decongestants

These drugs slow down nasal blood flow by antagonizing α1 and α2 adrenergic receptors in nasal capacitance vessel endothelium. In this way, they reduce nasal mucosal congestion and swelling. Better results can be obtained when combined with an antihistamine. Pseudoephedrine and phenylephrine, which are catecholamines, have oral forms. Although a runny nose can improve symptoms, it has no effect on itching, sneezing and eye symptoms in the nose. The imidazoline derivatives oxymetazoline, xylometazoline and naphazoline are suitable for intranasal use. Although they are fast intranasal decongestants and have fewer side effects, severe rebound congestion effects occur when the drug is discontinued. In some publications, it is mentioned that oxymetazoline inhibits T cells and cytokines such as IL-1β, TNF-α, IL-6 and IL-8. Some local nasal side related to these preparations.

11.1 Monoclonal anti-IgE antibodies

Omaluzimab is a humanized, recombinant, monoclonal antibody that blocks the binding of circulating IgE antibodies to the high affinity receptors in cells such as mast cells and basophil by complexing with the Ce3 region. There are many publications showing that patients with AR provide a very serious clinical benefit by significantly decreasing circulating IgE levels. In addition, it reduces FcR1 expressions on mast cells in both blood and tissue. It improves the nasal symptoms and increases the quality of life. It is an antibody that is well tolerated and has a very low risk of anaphylaxis (0.9/1000 applications). There are studies showing that SIT treatment applied together with omalizumab is more effective in single applications. The most important handicap is that it is currently an expensive treatment model [15].

11.2 Capsaicin treatment, complementary and alternative medicine, surgery

Capsaicin is bound to vanilloid resertors expressed in nasal C-fibers. It has been observed that repeated applications to the skin or intranasally cause desensitization in the peripheral nerve endings. It works well in vasomotor rhinitis in which neurotransmitters play an important role. It has been observed that it reduces symptoms such as nasal congestion, runny nose, and sneezing in AR. However, there are also publications showing that it has no clinical efficacy, especially in patients with house dust mite-sensitive PAR patients.

Nasal irrigation or irrigation with saline is a complementary treatment model in AR. In this form of treatment, it is ensured that the contact of the sinuses and pharynx with allergens and mucus is reduced. At the same time, edema in the nose is reduced. It has been shown that nasal saline application reduces the need for topical corticosteroids in children with AR.

It has been shown that exposure to microbes in children increases the expression of IL-10 and TGF-β inhibitory cytokines as well as the development of Th1-type immune response. There is evidence that beneficial microorganisms do this through toll-like respectors. Especially bifidobacteria and lactobacilli have such effects. There are studies showing that such probiotics can be effective in AR.

There is no sufficient and scientific evidence that acupuncture is effective in AR.

It has been stated that UV-A and UV-B are used, and that the patients are not able to use drugs or get sufficient response in a few small series. In only one study on AR, infrared radiation therapy (FIR) has been tried. It has been stated that the application of the oven affects the thermo-receptors due to the heat it emits and can be effective by increasing the microcirculation.

Surgical intervention may be beneficial for sinusitis, nasal polyps, enlarged turbinates, or nasal septal deviation, if any, that do not respond to medical treatment [15].

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References

[1] Settipane RA, Kaliner MA. Nonallergic Rhinitis. *American Journal of Rhinology & Allergy*. 2013;27(3_suppl):S48-S51. doi:10.2500/ajra.2013.27.3927

[2] Eifan AO, Durham SR. Pathogenesis of rhinitis. *Clin Exp Allergy*. 2016;46(9): 1139-1151. doi:10.1111/cea.12780

[3] Sur DKC, Plesa ML. Chronic Nonallergic Rhinitis. *Am Fam Physician*. 2018;98(3):171-176.

[4] Ellis AK, Keith PK. Nonallergic rhinitis with eosinophilia syndrome and related disorders. *Clin Allergy Immunol*. 2007;19:87-100.

[5] Shahab R, Phillips DE, Jones AS. Prostaglandins, leukotrienes and perennial rhinitis. J Laryngol Otol. 2004 Jul;118(7):500-7. doi: 10.1258/0022215041615155. PMID: 15318955.

[6] Leader P, Geiger Z. Vasomotor Rhinitis. 2020 Aug 16. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2020 Jan–. PMID: 31613484.

[7] Hellings PW, Klimek L, Cingi C, et al. Non-allergic rhinitis: Position paper of the European Academy of Allergy and Clinical Immunology. *Allergy*. 2017;72(11):1657-1665. doi:10.1111/ all.13200

[8] Shao Z, Bernstein JA. Occupational Rhinitis: Classification, Diagnosis, and Therapeutics. *Curr Allergy Asthma Rep*. 2019;19(12):54. Published 2019 Nov 27. doi:10.1007/ s11882-019-0892-0

[9] Wei J, Gerlich J, Genuneit J, et al. Hormonal factors and incident asthma and allergic rhinitis during puberty in girls. *Ann Allergy Asthma Immunol*. 2015;115(1):21-27.e2. doi:10.1016/j. anai.2015.04.019

[10] Zucker SM, Barton BM, McCoul ED. Management of Rhinitis Medicamentosa: A Systematic Review. *Otolaryngol Head Neck Surg*. 2019;160(3):429-438. doi:10.1177/0194599818807891

[11] Balur MB, Koçak HE, Altınay S, Özdamar K, Taşkın Ü, Oktay MF. Is submucosal fat injection effective in atrophic rhinitis? An experimental animal study. *Eur Arch Otorhinolaryngol*. 2017;274(10):3637-3642. doi:10.1007/ s00405-017-4670-0

[12] Becker S, Rasp J, Eder K, Berghaus A, Kramer MF, Gröger M. Non-allergic rhinitis with eosinophilia syndrome is not associated with local production of specific IgE in nasal mucosa. *Eur Arch Otorhinolaryngol*. 2016;273(6):1469-1475. doi:10.1007/s00405-015-3769-4

[13] Marti J, López F, Gascón I, Julve J. Propolis nasal spray effectively improves recovery from infectious acute rhinitis and common cold symptoms in children: a pilot study. *J Biol Regul Homeost Agents*. 2017;31(4):943-950.

[14] Lieberman PL, Smith P. Nonallergic Rhinitis: Treatment. *Immunol Allergy Clin North Am*. 2016;36(2):305-319. doi:10.1016/j.iac.2015.12.007

[15] Daramola OO, Kern RC. An update regarding the treatment of nonallergic rhinitis. *Curr Opin Otolaryngol Head Neck Surg*. 2016;24(1):10-14. doi:10.1097/MOO.0000000000000225