Rhinitis: Classification, Types, Pathophysiology

Subjects: Otorhinolaryngology

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Rhinitis describes a pattern of symptoms as a result of nasal inflammation and/or dysfunction of the nasal mucosa. It is an umbrella entity that includes many different subtypes, several of which escape of complete characterization. Rhinitis is considered as a pathologic condition with considerable morbidity and financial burden on health care systems worldwide. Its economic impact is further emphasized by the fact that it represents a risk factor for other conditions such as sinusitis, asthma, learning disabilities, behavioral changes, and psychological impairment. Rhinitis may be associated with many etiologic triggers such as infections, immediate-type allergic responses, inhaled irritants, medications, hormonal disturbances, and neural system dysfunction.

allergic non-allergic occupational gustatory idiopathic atrophic rhinitis

1. Introduction

Rhinitis is an entity that includes many different subtypes and is mainly used to describe a pattern of nasal symptoms such as nasal congestion/obstruction, rhinorrhea, sneezing and pruritus that appear as a result of inflammation and/or dysfunction of the nasal mucosa [1][2][3][4]. There are three distinct rhinitis subgroups that are widely accepted: allergic rhinitis (AR), infectious rhinitis, and non-allergic, non-infectious rhinitis (NAR) [5]. These phenotypes, however, are dynamic and may develop into one another. Therefore, caution against oversimplification should be advised since an overlapping or combined phenotype may exist in several patients [5][6]. For phenotype classification, various criteria may be used, including the severity of disease (mild, moderate/severe), pattern of symptoms (seasonal/perennial or intermittent/persistent), predominant symptom (runners/blockers), possible triggering factor (allergens, infectious agents, etc.) and response to treatment (controlled/uncontrolled) [7][8][9][10]. Recently, another disease categorization has been proposed based on endotype, and grouping rhinitis depending on the specific pathophysiological pathway [1][5].

The prevalence of allergic rhinitis in the United States of America ranges from 9% to 42%, which is translated to approximately 58-million people, when the prevalence of non-allergic rhinitis appears to be 19 million and mixed rhinitis 26-million people [4]. In the UK, the prevalence reaches 26% in adults, with an observed peak in the third and fourth decades of age [11][12]. Rhinitis is considered one of the most common medical conditions, with significant impairment of quality of life. Apart from upper airway symptoms, sleeping and psychological disturbances, decreased work productivity and school performance impairment must be taken under consideration [2][3]. Rhinitis is also associated with a considerable financial burden [1]. All of the above constitute the indirect costs of rhinitis, but there also exist direct costs such as physician office visits, lab tests and medication [1][4].

2. Allergic Rhinitis

Allergic rhinitis is a well-defined endotype according to ARIA. It is defined as an IgE-mediated, type 1 hypersensitivity response to a spectrum of inhaled environmental allergens [5][13][14][15]. Allergic rhinitis is characterized by anterior or posterior rhinorrhea, nasal congestion/blockage, itching of the nose, and sneezing occurring for more than one hour on two or more consecutive days [8]. According to ARIA, allergic rhinitis is categorized based on symptom duration, intermittent and persistent, and severity, mild–moderate and severe. Allergens associated with allergic rhinitis are proteins that come from airborne particles including pollens, dust mites, insect feces, animal dander, and molds [5][13][14][15]. The common comorbidities associated with allergic rhinitis are asthma and conjunctivitis. Its strong correlation with asthma may be explained by the theory of the unified airway, which dictates that the upper and lower airway inflammation share common pathophysiologic mechanisms, coexisting and communicating via the systemic circulation [16][17][18][19]. Clinical expression of the disease is a result of a cascade of immunological and biochemical events. Allergens are inhaled, superimposed to nasal mucous, and diffuse into nasal tissues. Then, antigen-presenting cells (APCs) break antigens into antigenic peptides and migrate to lymph nodes to present the peptides to naïve CD4+ T lymphocytes (T cells) [13].

The process of activation of CD4+ T lymphocytes includes the interaction of specific surface T-cell receptors with allergen MHC class II complexes on the APCs [13][20]. Dendritic Cells (DCs) and signals from antigen presentation assist the differentiation of naïve T helper cells to Th1 or Th2. Th2 lymphocytes activate the production of specific cytokines which cause the synthesis of IgE antibodies from B-cells. IgE antibodies have the ability to bind to high-affinity receptors on the surface of dendritic cells, on low-affinity receptors on monocytes-macrophages and B-lymphocytes and on high-affinity tetrameric receptors FcεRI on mast cells and on basophils [13][21][22]. The latter interaction induces the cellular allergic reaction and the activation of several signaling cascades. One of these leads to granule exocytosis and release of preformed or newly created inflammatory mediators (such as histamine, leukotrienes, prostaglandins, platelet-activating factor, etc.).

The nasal allergic reaction is distinguished in early and late phases. The symptoms of early phase begin almost immediately after exposure to the responsible allergen, arrive at a peak in a few minutes, and subside within one to several hours [1][5]. Within minutes from the exposure, the interaction between IgE and allergen leads to degranulation of mast cells and release of inflammatory mediators such as leukotrienes, prostaglandins, cytokines, and histamine. These molecules are responsible for symptoms such as sneezing, itching, rhinorrhea, and nasal congestion [1][23]. Histamine binds on the H1 receptors and provokes virtually all of the early phase symptoms. During the late phase, the most dominant symptom is nasal congestion. The release of mediators that has taken place in the early phase leads to infiltration of nasal mucosa by basophils, eosinophils, neutrophils, mast cells and mononuclear cells. The mast cells have been found to play a prominent role not only in the allergic response but also in sustaining the allergic response chronically. This is mainly related to the fact that mediators produced by the degranulation of mast cells and histamine play an important role in the recruitment of Th2 lymphocytes to target organs [23][24]. The cysteinyl leukotrienes are mainly responsible for the activation of eosinophils. Eosinophils are predominant in the late phase response and are associated with the progression of allergic symptoms [23].

Proinflammatory mediators, cationic proteins, eosinophil peroxidase, and cysteinyl leukotrienes are released from eosinophils [1][24].

A thorough medical history and a detailed clinical examination may lead to the suspicion of allergic rhinitis. The diagnostic tests for allergic rhinitis are separated into in vivo, which are percutaneous skin tests (skin prick tests); and in vivo, including the radioallergosorbent test (RAST), multiple antigen simultaneous testing (MAST), fluoroallergosorbent test (FAST), and immunoassay capture test (ImmunoCAP). The most common diagnostic tests for allergic rhinitis are percutaneous skin test (skin prick test) and the allergen-specific immunoglobulin E (IgE) antibody test (RAST), which recently has been replaced with ImmunoCAP tests. Skin prick testing involves introducing controlled amounts of allergen and control substances into the skin. Skin testing provokes both types of responses, early and late; however, the main goal is detecting the immediate allergic response caused by the release of mast cell or basophil IgE-specific mediators, which create the classic wheal-and-flare reaction within fifteen minutes [25]. A positive result is defined as a wheal ≥3 mm diameter [25]. Allergen-specific IgE antibody testing (radioallergosorbent testing [RAST]) is useful in primary care if percutaneous testing is not practical (e.g., problems with reagent storage, expertise, frequency of use, staff training) or if it is contraindicated (e.g., medication such as tricyclic antidepressants, antihistamines) [1][25]. Even if RAST is highly specific, it is costly, time-consuming as to the results and not as sensitive as skin testing. Although the available commercial RAST products are generally reliable, they do not always provide reproducible, accurate data. The ImmunoCAP system is an in vitro test using three-dimensional cellulose solid allergen phase in order to detect specific IgE to allergen components. It has been found that ImmunoCAP tests have similar sensitivity for house dust and lower sensitivity for pollen, dog dander and Candida compared to skin prick tests [26]. The MAST test uses no radioactive agents and allows simultaneous examination of multiple antigens. The MAST system provides similar information as the CAP system [26][27][28]. However, the CAP system seems to have better sensitivity [28]. The FAST is a method that measures specific serum IgE by a chemical-radiating method such as MAST and was first used as an inhibition assay in order to determine cross-reaction activity between aeroallergens [26][29]. In comparison with MAST, FAST requires less time to be analyzed and less serum quantity to be used [26][29].

Medical therapy includes intranasal corticosteroids, which are safe in administration to adults and children and are superior to the combination of oral antihistamines and leukotriene receptor antagonists (LTRAs) [1][30]. First-generation antihistamines are no longer recommended due to their side effects, while second generation oral antihistamines have strong H1 receptor selectivity and weak anticholinergic action. Intranasal corticosteroids show efficacy in controlling allergic rhinitis symptoms and are found to be more effective than intranasal antihistamines. The combination of intranasal corticosteroids and intranasal antihistamines has been shown to be even more effective than each agent alone [1][31][32]. Nasal irrigation is widely used in all types of rhinitis with isotonic or hypertonic saline and helps in the removal of mucous and the clearance of inflammatory medication. It remains unclear if hypertonic saline has a better effect compared to isotonic saline [33]. Intranasal cromolyn/nedocromil are used prophylactically in AR because of their inhibitory activity on mast cells degranulation through stabilizing the membrane of mast cells [1][34]. Even though their use is safe, it seems that their action is less effective compared to topical corticosteroids/antihistamines because they have no action in already released inflammatory factors [34]. Omalizumab is an anti-IgE humanized monoclonal antibody which is approved for chronic urticaria and severe

allergic asthma [35]. It has been found that it reduces nasal and ocular symptoms in AR but has not been approved for treatment of AR yet [1][36]. Specifically, a randomized placebo control, double blinded trial was conducted which proved that omalizumab prevents and controls nasal and ocular symptoms in moderate–severe seasonal allergic rhinitis to pollen in Japan [37]. However, it has not been approved for seasonal allergic rhinitis yet [37]. Mepolizumab, reslizumab and benralizumab are humanized mAbs against Il-5 which have an effect on eosinophilic asthma; the effects are even promising in AR, and are still under further investigation [1][38].

Individuals with allergic rhinitis (AR) are positive for the skin prick test and/or serum-specific (s)IgE/RAST. However, some patients with seasonal or perennial rhinitis have negative SPT and RAST and a positive nasal provocation test (NAPT) for specific allergens. This phenotype has been termed local allergic rhinitis (LAR) and is not included in AR or NAR groups [36][38][39]. LAR is characterized by nasal mucosa localized allergic response type 2 [19] with the presence of nasal-specific IgE (NsIgE). The typical profile of patients with LAR includes mostly young women, non-smokers with moderate/severe rhinitis, with persistent/perennial clinical behavior, and with conjunctivitis and asthma [38]. House dust mites are the most common allergic triggers in LAR. Apart from mites, the mold alternaria is an allergen more often found in LAR, while pollen and animal dander appear more often in patients with AR [19] [38]. The diagnosis of LAR begins with clinical history, family history of atopy/asthma, and exclusion of CRS with nasal endoscopy and/or CT scan [38]. If the SPT and sIgE are positive, the diagnosis of AR is made. In case these are negative, the response of the target organ to an allergen challenge must be evaluated [19]. The gold standard in LAR diagnosis is the nasal allergy provocation test (NAPT), and alternatively the detection of sIgE in nasal secretions or a positive basophil activation test (BAT) [19]. It is worth mentioning that there are patients with persistent symptoms of rhinitis who are positive only to seasonal allergens on SPTs. Some of these patients are positive to NAPT to perennial allergens with their rhinitis phenotype characterized as dual allergic rhinitis (DAR), referring to the contemporary local and systemic sensitization in the same individual [38].

3. Non-Allergic Rhinitis (NAR)

Non-allergic rhinitis is a chronic rhinitis without clinical manifestations of endonasal infection and systemic allergic inflammation (negative SPT, negative total blood IgE, and RAST tests) [1][5]. Non-allergic rhinitis represents a heterogenous group of patients which may be classified into at least six subgroups:

(1) Drug-induced rhinitisFurther classification of NAR has been proposed, based on the cellular inflammatory
(2) Hormone-induced rhinitisprofile. NARES (non-allergic rhinitis with eosinophilia) and neutrophilic NAR are the
(3) Senile rhinitis or rhinitis of the elderlymost common types, with NARES defined by more than 20% eosinophils
(4) Gustatory rhinitisin nasal smears without any evidence of allergy or other nasal pathology and is associated
(5) Occupational rhinitiswith other comorbidities such as asthma [5][40]. However, as to whether NARES represents
(6) Idiopathic rhinitisa distinct phenotype or its pathophysiologic mechanisms overlap with various other conditions
(7) Atrophic rhinitisis controversial [5]. Neutrophilic NAR is defined by infiltration of equal to or more than 20% neutrophils on the nasal smear without the presence of other inflammatory organisms such as bacteria or fungi [40]. NAR with mast cells and mixed NAR (with eosinophils and mast cells) are less distinguishable, less common, and more difficult to treat [40].

4. Infectious Rhinitis

Nose and sinuses share common vascular and anatomic pathways, a fact that explains why rhinitis coexists with sinusitis. Acute viral rhinitis is the most common form of upper respiratory infection and is usually due to viral rather than bacterial agents [1][5]. Common causes of viral rhinitis include rhinovirus, coronavirus, adenovirus, influenza virus, parainfluenza virus, respiratory syncytial virus, and enterovirus [5][41]. These viruses provoke damages in tight junctions among epithelial cells, disrupt their membranes, invade the epithelial cells, and dominate host cell metabolic activity, using it for their development and causing host cell destruction and death. Usually, the symptoms of infectious rhinitis are self-limited and there is no need for medical therapy as the initial approach of the disease [41]. Antibiotic administration is not indicated for viral rhinitis, unless there is bacterial superinfection [1][5]. There are antiviral molecules such as interferon alpha (INF-α) that are proved to be effective in acute viral rhinitis by shortening the duration and severity of symptoms [41].

References

1. Papadopoulos, N.G.; Bernstein, J.A.; Demoly, P.; Dykewicz, M.; Fokkens, W.; Hellings, P.W.; Peters, A.T.; Rondon, C.; Togias, A.; Cox, L.S. Phenotypes and endotypes of rhinitis and their impact on management: A PRACTALL report. Allergy 2015, 70, 474–494.
2. Meltzer, E.O.; Blais, M.S.; Naclerio, R.M.; Stoloff, S.W.; Derebery, M.J.; Nelson, H.S. Burden of allergic rhinitis: Allergies in America, Latin America, and Asia –Pacific adult surverys. Allergy Asthma Proc. 2012, 33, 113–141.
3. Ledford, D. Inadequate diagnosis of nonalergic rhinitis: Assessing the damage. Allergy Asthma Proc. 2003, 24, 155–162.
4. Settipane, R.A.; Charnock, D.R. Epidemiology of Rhinitis: Allergic and Nonallergic. Clin. Allergy Immunol. 2007, 19, 23–34.
5. Papadopoulos, N.G.; Guibas, G.V. Rhinits Subtypes, Endotypes, and Definitions. Immunol. Allergy Clin. N. Am. 2016, 36, 215–233.
6. Tran, N.P.; Vickery, J.; Blsid, M.S. Management of rhinitis: Allergic and non-allergic. Allergy Asthma Immunol. Res. 2011, 3, 148–156.
7. Brozec, J.L.; Bousquet, J.; Baena-Cagnani, C.E.; Bonin, S.; Canonica, G.W.; Gasale, T.B. Allergic Rhinitis and its impact on Asthma (ARIA) guidelines: 2010 revision. J. Allergy Clin. Immunol. 2010, 126, 466–476.
8. Bousquet, J.; Bachert, C.; Canonica, G.W.; Casale, T.B.; Cruz, A.A.; Lockey, R.J. Unmet needs in severe chronic upper airway disease (SCUAD). J. Allergy Clin. Immunol. 2009, 124, 428–433.
9. Khanna, P.; Shah, A. Categorization of patients with allergic rhinitis: A comparative profile of “sneezer and runners” and “blockers”. Ann. Allergy Asthma Immunol. 2005, 94, 60–64.

10. Hellings, P.W.; Fokkens, W.J.; Akdis, C.; Bachert, C.; Cingi, C.; Dietz de Loos, D. Uncontrolled allergic rhinitis and chronic rhinosinusitis: Where do we stand today? Allergy 2013, 68, 1–7.
11. Bauchau, V.; Durham, S.R. Prevalence and rate of diagnosis of allergic rhinitis in Europe. Eur. Respir. J. 2004, 24, 758–764.
12. Eriksson, J.; Ekerljung, L.; Ronmark, E. Update of prevalence of self-reported allergic rhinitis and chronic nasal symptoms among adults in Sweden. Clin. Respir. J. 2012, 6, 159–168.
13. Sin, B.; Togias, A. Pathophysiology of Allergic and Nonallergic Rhinitis. Proc. Am. Thorac. Soc. 2011, 8, 106–114.
14. Bousquet, J.J.; Schünemann, H.J.; Togias, A.; Erhola, M.; Hellings, P.W.; Zuberbier, T.; Agache, I.; Ansotegui, I.J.; Anto, J.M.; Bachert, C.; et al. Next-generation ARIA care pathways fo rhinitis and asthma: A model for multimorbid chronic diseases. Clin. Transl. Allergy 2019, 9, 44.
15. Scadding, G.; Bousquet, J.; Bachert, C.; Fokkens, W.J.; Hellings, P.W.; Prokopakis, E.P.; Pfaar, O.; Price, D. Rhinology future trends: 2017 EUFOREA debate on allergic rhinitis. Rhinology 2019, 57, 49–56.
16. Hellings, P.W.; Prokopakis, E.P. Global airway disease beyond allergy. Curr. Allergy Asthma Rep. 2010, 10, 143–149.
17. Cingi, C.; Gevaert, P.; Mosges, R.; Rondon, C.; Hox, V.; Rudenko, M.; Muluk, N.B.; Scadding, G.; Manole, F.; Hupin, C.; et al. Multi-morbidities of allergic rhinitis in adults: European Academy of Allergy and Clinical Immunology Task Force Report. Clin. Transl. Allergy 2017, 7, 17.
18. Fokkens, W.J.; Lund, V.J.; Hopkins, C.; Hellings, P.W.; Kern, R.; Reitsma, S.; Toppila-Salmi, S.; Bernal-Sprekelsen, M.; Mullol, J.; Alobid, I.; et al. European Position Paper on Rhinosinusitis and Nasal Polyps 2020. Rhinology 2020, 58 (Suppl. S29), 1–464.
19. Vardouniotis, A.; Doulaptsi, M.; Aoi, N.; Karatzanis, A.; Kawauchi, H.; Prokopakis, E. Local Allergic Rhinitis Revisited. Curr. Allergy Asthma Resp. 2020, 20, 22.
20. Bugeon, L.; Dallman, M. Costimulation of T cells. Am. J. Respir. Crit. Care Med. 2000, 162, S164–S168.
21. Liu, Y.J. IPC: Professional type 1 interferon-producing cells and plasmacytoid dendritic cells precursors. Annu. Rev. Immunol. 2005, 23, 275–306.
22. Henry, A.J.; Cook, L.P.; McDonnell, J.M.; Mackay, G.A.; Shi, J.; Sutton, B.J.; Gould, H.J. Partcipation of the N-terminal region of Cε3 in the binding of human IgE to its high-affinity receptor FcεRI. Biochemistry 1997, 36, 15568–15578.
23. Gelfand, E.W. Inflammatory mediators in allergic rhinitis. J. Allergy Clin. Immunol. 2004, 114, 135–138.

24. Prokopakis, E.; Vardouniotis, A.; Kawauchi, H.; Scadding, G.; Georgalas, C.; Hellings, P.; Velegrakis, G.; Kalogjera, L. The pathophysiology in hygiene hypothesis. Int. J. Pediatr. Otorhinolaryngol. 2013, 77, 1065–1071.
25. Quillen, D.M.; Feller, D.B. Diagnosing Rhinitis: Allergic vs Nonallergic. Am. Fam. Phys. 2006, 73, 1583–1590.
26. Kwon, S.H.; Cho, Y.S. Comparison of Allergic Skin Prick Test and FAST System in Patients with Allergic Rhinitis. J. Rhinol. 2000, 7, 105–108.
27. Ogino, S.; Kawashima, K.; Nibu, M.; Irifune, M. Comparison of multiple-antigen simultaneous test and CAP systems for diagnosis of nasal allergy. ORL J. Otorhinolaryngol. Relat. Spec. 1995, 57, 210–213.
28. Liang, K.L.; Su, M.C.; Jiang, R.S. Comparison of the Skin Test and ImmunoCAP System in the Evaluation of Mold Allergy. J. Chin. Med. Assoc. 2006, 69, 3–6.
29. Perrick, D.; Stafford, C.T.; Armstrong, E.; DuRant, R.H. Modification of the fluorescent allergosorbent test as an inhibition assay for determination of cross-reactivity among aeroallergens. J. Allergy Clin. Immunol. 1991, 88, 682.
30. Pullerits, T.; Praks, L.; Ristioja, V.; Lotvall, J. Comparison of a nasal glucocorticoid, antileukotriene, and a combination of antileukotriene and antihistamine in the treatment of seasonal allergic rhinitis. J. Allergy Clin. Immunol. 2002, 109, 949–955.
31. Karatzanis, A.; Chatzidakis, A.; Milion, A.; Vlaminck, S.; Kawauchi, H.; Velegrakis, S.; Prokopakis, E. Contemporary Use of Cosrticosteroids in Rhinology. Curr. Allergy Asthma Rep. 2017, 17, 1.
32. Hellings, P.W.; Akdis, C.A.; Bachert, C.; Bousquet, J.; Pugin, B.; Adriaensen, G.; Advani, R.; Agache, I.; Anjo, C.; Anmolsingh, R.; et al. EUFOREA Rhinology Research Forum 2016: Report of the brainstorming sessions on needs and priorities in rhinitis and rhinosinusitis. Rhinology 2017, 55, 202–210.
33. Talbot, A.R.; Herr, T.M.; Parsons, D.S. Mucociliary clearance and buffered hypertonic saline solution. Laryngoscope 1997, 107, 500–503.
34. Greiner, A.N.; Meltzer, E.O. Overview of the treatment of allergic rhinitis and nonallergic rhinopathy. Proc. Am. Thorac. Soc. 2011, 8, 121–131.
35. Vignola, A.M.; Humbert, M.; Bousquet, J.; Boulet, L.P.; Hedgecock, S.; Blogg, M. Efficacy and tolerability of antiimmunoglobulin E therapy with omalizumab in patients with concomitant allergic asthma and persistent allergic rhinitis: SOLAR. Allergy 2004, 59, 709–717.
36. Campo, P.; Salas, M.; Blanca-Lopez, N.; Rondon, C. Local Allergic Rhinitis. Immunol. Allergy Clin. N. Am. 2016, 36, 321–332.

37. Okubo, K.; Ogino, S.; Nagakura, T.; Ishikawa, T. Omalizumab is Effective and Safe in the Treatment of Japanese Cedar Pollen-induced Seasonal Allergic Rhinitis. Allergol. Int. 2006, 55, 379–386.
38. Campo, P.; Eguiluz-Gracia, I.; Bogas, G.; Salas, M.; Seron, C.P.; Perez, N.; Mayorga, C.; Torres, M.J.; Shamji, M.; Rondon, C. Local allergic rhinitis: Implications for management. Clin. Exp. Allergy 2019, 49, 6–16.
39. Krajewska-Wojtys, A.; Jarzab, J.; Gawlik, R.; Bozek, A. Local allergic rhinitis to pollens is underdiagnosed in young patients. Am. J. Rhinol. Allergy 2016, 30, 198–201.
40. Mullol, J.; de Cuvillo, A.; Lockey, R.F. Rhinitis Phenotypes. J. Allergy Clin. Immunol. Pract. 2020, 8, 1492–1503.
41. Cingi, C.; Muluk, N.B. Acute Viral Rhinitis. All Around Nose 2019, 14, 199–202.