Review article

Immunopathogenesis of allergic rhinitis

Tharwat E. Deraz
*Professor of Pediatrics, Ain Shams University, Cairo*

Rhinitis is defined as inflammation of the nasal membranes[1] and is characterized by a symptom complex that consists of any combination of the following: sneezing, nasal congestion, nasal itching, and rhinorrhea.[2] The eyes, ears, sinuses, and throat can also be involved.

Allergic rhinitis is the most common cause of rhinitis. It is an extremely common condition, affecting approximately 20% of the population. Systemic effects, including fatigue, sleepiness, and malaise, can occur from the inflammatory response. These symptoms often contribute to impaired quality of life.[3,4]

Classification of allergic rhinitis:
The Allergic Rhinitis and its Impact on Asthma (ARIA) group in conjunction with the World Health Organization (WHO), has revised the classification of AR. This classification includes a measurement of the frequency and duration of symptoms. Intermittent AR is defined as experiencing symptoms for < 4 days/week or < 4 consecutive weeks. Persistent AR is termed as symptoms occurring for more than 4 days/week and more than 4 consecutive weeks. Additionally, a severity scale of mild to moderate-severe was included in the revised classification.[5]
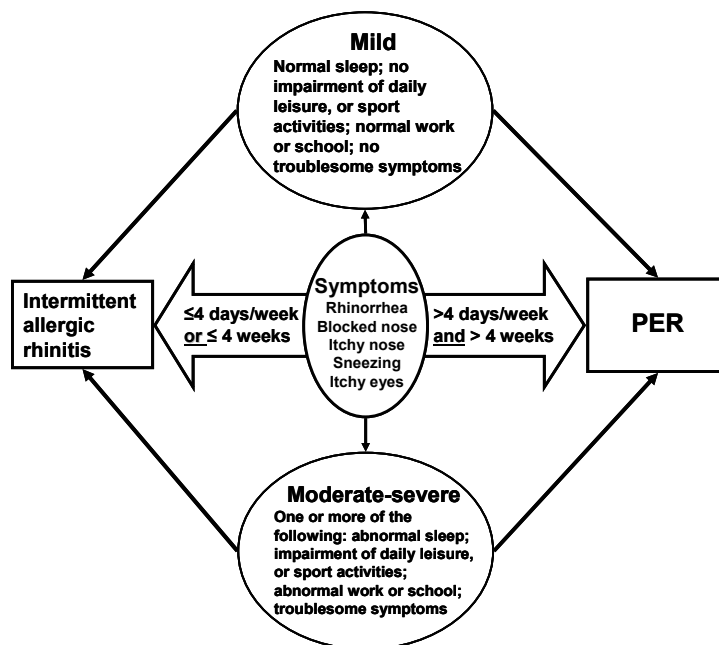
Figure 1. Allergic Rhinitis and its Impact on Asthma (ARIA). Dark lines show that moderate-to-severe symptoms occur most often in persistent allergic rhinitis (PER) with milder symptoms in intermittent allergic rhinitis. Quoted from Bousquet et. al (2001)[6].

Pathophysiology
Allergic rhinitis involves inflammation of the mucous membranes of the nose, eyes, Eustachian tubes, middle ear, sinuses, and pharynx. The nose invariably is involved, and the other organs are affected in certain individuals. Inflammation of the mucous membranes is characterized by a complex interaction of inflammatory mediators but ultimately is triggered by an immunoglobulin E (IgE)–mediated response to an extrinsic protein.[5]

The tendency to develop allergic, or IgE-mediated, reactions to extrinsic allergen has a genetic component. In susceptible individuals, exposure to certain foreign proteins leads to allergic sensitization, which is characterized by the production of specific IgE directed against these proteins. This specific IgE coats the surface of mast cells, which are present in the nasal mucosa. When the specific protein (e.g., a specific pollen grain) is inhaled into the nose, it can bind to the IgE on the

mast cells, leading to immediate and delayed release of a number of mediators.[7-9]

The mediators that are immediately released include histamine, tryptase, chymase, kinins, and heparin. The mast cells quickly synthesize other mediators, including leukotrienes and prostaglandin D2.[10-12] These mediators, via various interactions, ultimately lead to the symptoms of allergic rhinitis (nasal congestion, sneezing, itching, redness, tearing, swelling, ear pressure, postnasal drip). Mucous glands are stimulated, leading to increased secretions. Vascular permeability is increased, leading to plasma exudation. Vasodilatation occurs, leading to congestion and pressure. Sensory nerves are stimulated, leading to sneezing and itching. All of these events can occur in minutes; hence, this reaction is called the early, or immediate, phase of the reaction. Over 4-8 hours, these mediators, through a complex interplay of events, lead to the recruitment of other inflammatory cells to the mucosa, such as neutrophils, eosinophils, lymphocytes, and macrophages. This results in continued inflammation, termed the late-phase response. The symptoms of the late-phase response are similar to those of the early phase, but less sneezing and itching and more congestion and mucus production tend to occur. The late phase may persist for hours or days.[13]

When studying the allergic nose, several aspects must be taken into consideration: the genetic background of the patient, various environmental factors (antigens, air pollution, climate), and the peculiar characteristics of the nose itself including its anatomy (total surface area: 150 cm, volume: 15 ml) and histology including the epithelium (ciliated, non ciliated, pseudostratified, columnar, and goblet cells), mucus, immunocompetent cells, lamina propria, basement membrane, blood supply, and nerves and neurotransmitters.[14]

Immunopathogenesis of allergic rhinitis

Allergic rhinitis is an increasing problem for which new and exciting therapies are being developed. These can be understood through an appreciation of the newer concepts of pathogenesis of allergic rhinitis. Allergen induces Th2 lymphocyte proliferation in persons with allergies with the release of their characteristic combination of cytokines including IL-3, IL-4, IL-5, IL-9, IL-10, and IL-13. These substances promote IgE and mast cell production. Mucosal mast cells that produce IL-4, IL-5, IL-6, and tryptase proliferate in the allergic epithelium. Inflammatory mediators and cytokines upregulate endothelial cell adhesion markers such as the vascular cell adhesion molecule-1. Chemoattractants including eotaxin, IL-5, and RANTES lead to the characteristic infiltration by eosinophils, basophils, Th2 lymphocytes, and mast cells in chronic allergic rhinitis.[15]
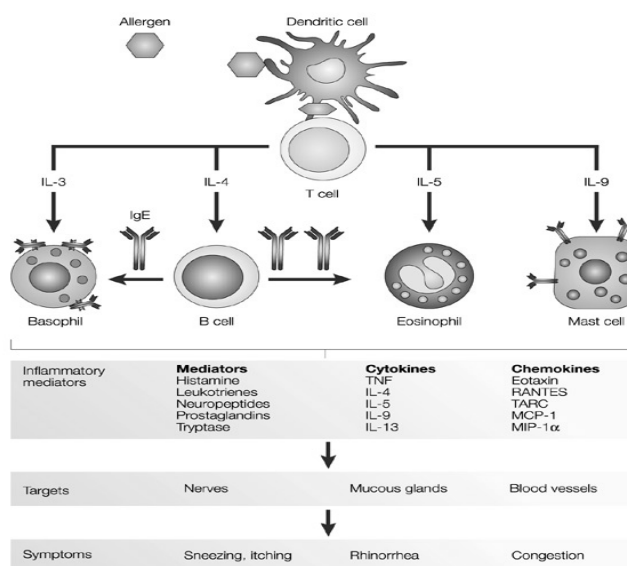
Figure 2. Cell and mediator pathways underlying the pathogenesis of allergic rhinitis. Quoted from Holgate and Broide (2003)[16]

A high degree of cell-to-cell communication is needed to orchestrate this inflammatory immune response. A variety of cytokines and adhesion receptors seem to play an important role in the allergic reaction. Proinflammatory cytokines such as IL-1, IL-8 and TNF-α (tumor necrosis factor-alpha) can be detected in nasal secretions and mucosa. The increased expression of adhesion receptors in mucosal specimens of patients with allergic rhinitis points to their role in regulating the cellular migration and probably represents a key event in allergic inflammation. E-selectin receptor was strongly upregulated by IL-1β, TNF-α and allergen. The induction due to allergen exposure of the mucosa was markedly inhibited by soluble cytokine receptors (sIL-IR, TNF-BP) or by a receptor antagonist (IL-1 ra) and prednisolone. These findings indicate that proinflammatory cytokines may be key factors for the upregulation of adhesion processes in human nasal mucosa and the activation of various cell populations involved in the allergic inflammation. They, therefore, represent a main target for new therapeutic strategies.[15]

The type and amount of inflammation in allergic rhinitis are regulated by cytokines. Therefore, the production of the Th2-cytokines, IL-4, IL-5, IL-13, of the Th1-cytokines, IFN-γ and IL-12 and of the regulatory cytokine IL-10 that is capable of down regulating their synthesis was investigated. It was found that the production of IL-4, IL-5, and IL-13 was significantly elevated in allergics; the number of IL-12 and IFN-γ-producing cells was significantly elevated as well. IL-10 was also significantly higher in allergics. This investigation of cytokine production during natural allergen exposure demonstrates that the synthesis of both Th2- and Th1-cytokines is increased in allergic rhinitis.[17]

Allergic rhinitis represents a persistent inflammation in terms of activation of eosinophils and constant upregulation of the proinflammatory cytokine IL-1beta in the pollen season and thereafter. Persistent inflammation may furthermore lead to the dysregulation of local cellular immunity by reducing the number and activity of neutrophils on the mucosal surface.[18]

In allergic rhinitis, there is epithelial mast cell accumulation and tissue infiltration by eosinophils. Activation of these cells can be observed by electron microscopy and by elevated levels of tryptase and eosinophil cationic protein in nasal lavage fluid. Seasonal increases in the antigen presenting cell (Langerhans' cell) are also evident. Investigations into the mechanisms involved in cell accumulation and activation reveal upregulation of leukocyte endothelial adhesion molecules and an increase in interleukin-4 (IL-4) in naturally occurring rhinitis, while mRNA for IL-4, IL-5 and granulocyte macrophage colony stimulating factor activity and lavage tumor necrosis factor-alpha (TNF alpha) levels are increased following local allergen challenge. These cytokines may be derived from a variety of sources, including mast cells, eosinophils and T-lymphocytes, and contribute to the underlying inflammatory process in rhinitis.[19]

Allergic rhinitis is a particularly good model for studies of cytokine production in vivo, the occurrence of the cytokines IL-4, IL-5. IL-10 and IFN-gamma as well as the soluble IL-4 receptor in nasal lavage fluid were assayed. It was found that IL-4 levels in patients with seasonal allergic rhinitis were markedly increased in comparison with those in non-atopic patients or in atopic patients before the start of the pollen season. The IL-4/IFN-gamma ratios were significantly higher in atopic than in non atopic patients and it further increased in atopic patients during the season. In addition to IL-4, elevated levels of IL-10 were observed in association with seasonal rhinitis. Following treatment with a topical steroid, there was a statistically significant increase of the levels of soluble IL-4 receptor. These findings indicate that non atopic and atopic individuals react to pollen exposure with distinct cytokine patterns in agreement with the Thl/ Th2 concept.[20,21]

Role of Cysteinyl leukotrienes in allergic rhinitis

Cysteinyl leukotrienes (CysLTs) are a family of inflammatory lipid mediators synthesized from arachidonic acid by a variety of cells, including mast cells, eosinophils, basophils, and macrophages. CysLTs play a multi-functional role as mediators in allergic rhinitis (AR) as follows: CysLTs are released from inflammatory cells that participate in allergic rhinitis, receptors for CysLTs are located in nasal tissue, CysLTs are increased in patients with AR and are released following allergen exposure, administration of CysLTs reproduces the symptoms of AR, CysLTs play an important role in the maturation, as well as tissue recruitment of inflammatory cells and a complex inter-regulation between CysLTs and a variety of other inflammatory mediators exists.[23]

CysLTs are synthesized via 5-lipoxygenase metabolism of arachidonic acid by mast cells and basophils during the early-phase response to antigen and by eosinophils and macrophages

during the late phase. The cysLT levels in nasal secretions are elevated after short-term allergen instillation and in allergy season in patients with allergic rhinitis. These lipid mediators act locally and systemically by interacting with receptors, particularly the cysLT1 receptor, on target cells. CysLTs promote allergic inflammation by enhancing immune responses and the production, adhesion, migration, and survival of inflammatory cells such as eosinophils. They also increase the generation of an array of other proinflammatory mediators such as cytokines, which in turn increase the production of and receptors for cysLTs. Clinical trials have demonstrated that leukotriene receptor antagonists (LTRAs) have significant but modest efficacy as single agents but additive efficacy when used with other classes of agents.[24,25]

As our understanding of the basic pathophysiologic features of allergic rhinitis continues to increase, the development of new diagnostic and treatment strategies may allow for more effective modulation of the immune system, the atopic disease process, and the associated morbidity. The production of allergen-specific IgE, activation of mucosal mast cells and the recruitment and activation of effector leukocytes provide potential therapeutic targets, including selective inhibition of cytokines, adhesion molecules and signaling pathways. Blockade of IgE, using monoclonal antibodies and vaccine strategies is a new approach for interrupting the allergic cascade, whereas the use of recombinant mutated allergens, peptides and DNA oligonucleotides will lead to improved efficacy and reduced side effects of immunotherapy for tolerance induction.[16]
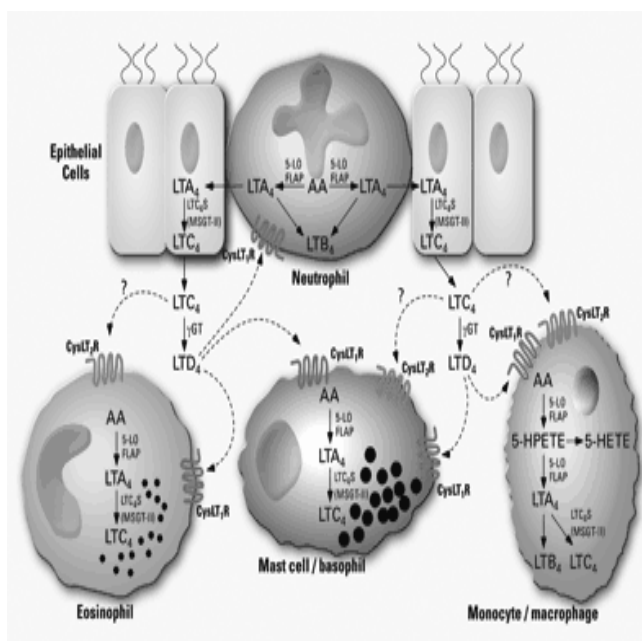
Figure 3. Potential CysLT signaling pathways in inflammatory cells in allergic rhinitis. Adopted from Figueroa et al. (2003).

REFERENCES

1. **Togias AG.** Systemic immunologic and inflammatory aspects of allergic rhinitis. J Allergy Clin Immunol. 2000;106(5):S247-50.

2. **Druce HM.** Allergic and non allergic rhinitis. In: Middleton EM Jr, Reed CE, Ellis EF, Adkinson NF Jr, Yunginger JW, Busse WW, eds. Allergy: Principles and Practice. 5th ed. St. Louis, Mo: Mosby, Year-Book;1998.p.1005-16.

3. **Blaiss MS.** Quality of life in allergic rhinitis. Ann Allergy Asthma Immunol 1999;83(5):449-54.

4. **Thompson AK, Juniper E, Meltzer EO.** Quality of life in patients with allergic rhinitis. Ann Allergy Asthma Immunol 2000;85(5):338-47.

5. **Mullol J, Bachert C, Bousquet J.** Management of persistent allergic rhinitis: evidence-based treatment with levocetirizine. Ther Clin Risk Manag 2005;1(4):265-71.

6. **Bousquet J, Van Cauwenberge P, Khaltaev N; Aria Workshop Group; World Health Organization.** Allergic rhinitis and its impact on asthma. J Allergy Clin Immunol 2001;108(5 Suppl):S147–334.

7. **Ray NF, Baraniuk JN, Thamer M, Rinehart CS, Gergen PJ, Kaliner M.** Direct expenditures for the treatment of allergic rhinoconjunctivitis in 1996, including the contributions of related airway illnesses. J Allergy Clin Immunol 1999;103(3 Pt 1):401-7.

8. **Holgate ST.** The role of the mast cells and basophils in inflammation. Clin Exp Allergy 2000;(30 Suppl 1):28-32.

9. **Skoner DP.** Allergic rhinitis: definition, epidemiology, pathophysiology, detection, and diagnosis. J Allergy Clin Immunol 2001;108(1 Suppl):S2-8.

10. **Haberal I, Corey JP.** The role of leukotrienes in nasal allergy. Otolaryngol Head Neck Surg 2003;129(3):274-9.

11. **Iwasaki M, Saito K, Takemura M, Sekikawa K, Fujii H, Yamada Y.** TNF-alpha contributes to the development of allergic rhinitis in mice. J Allergy Clin Immunol 2003;112(1):134-40.

12. **Cates EC, Gajewska BU, Goncharova S, Alvarez D, Fattouh R, Coyle AJ.** Effect of GM-CSF on immune, inflammatory, and clinical responses to ragweed in a novel mouse model of mucosal sensitization. J Allergy Clin Immunol 2003;111(5):1076-86.

13. **Salib RJ, Kumar S, Wilson SJ, Howarth PH.** Nasal mucosal immunoexpression of the mast cell chemoattractants TGF-beta, eotaxin, and stem cell factor and their receptors in allergic rhinitis. J Allergy Clin Immunol 2004;114(4):799-806.

14. **Hansen I, Klimek L, Mosges R, Hormann K.** Mediators of inflammation in the early and the late phase of allergic rhinitis. Curr Opin Allergy Clin Immunol 2004;4(3):159-63.

15. **Rihoux JP.** Perennial allergic rhinitis and keratoconjunctivitis. Thorax 2000;55 Suppl 2:S22-3.

16. **Holgate ST, Broide D.** New targets for allergic rhinitis - a disease of civilization. Nat Rev Drug Discov 2003;2(11):902-14.

17. **Baraniuk JN.** Pathogenesis of allergic rhinitis. J Allergy Clin Immunol 1997;99(2):S763-72.

18. **Bachert C, Hauser U, Prem B, Rudack C, Ganzer U.** Proinflammatory cytokines in allergic rhinitis. Eur Arch Otorhinolaryngol 2005;252 Suppl 1:S44-9.

19. **Shimizu S, Hattori R, Majima Y, Shimizu T.** Th2 cytokine inhibitor suplatast tosilate inhibits antigen-induced mucus hypersecretion in the nasal epithelium of sensitized rats. Ann Otol Rhinol Laryngol 2009;118(1):67-72.

20. **Howarth PH, Bradding P, Feather I, Wilson S, Church MK, Holgate ST.** Mucosal cytokine expression in allergic rhinitis. Int Arch Allergy Immunol 1995;107(1-3):390-1.

21. **Bachert C, Van Kempen M, Van Cauwenberg P.** Regulation of proinflammatory cytokines in seasonal allergic rhinitis. Int Arch Allergy Immunol 1999;118(2-4):375-9.

22. **Figueroa DJ, Borish L, Baramki D, Philip G, Austin CP, Evans JF.** Expression of cysteinyl leukotriene synthetic and signaling proteins in inflammatory cells in active seasonal allergic rhinitis. Clin Exp Allergy 2003;33(10):1380-8.

23. **Benson M, Strannegard L, Wennergren G, Strannegård O.** Cytokines in nasal fluids from school children with seasonal allergic rhinitis. Pediatr Allergy Immunol 2007;8(3):143-9.

24. **Peters-Golden M, Henderson WR.** The role of leukotrienes in allergic rhinitis. Ann Allergy Asthma Immunol 2005;94(6):609-18.

25. **Peters-Golden M, Gleason MM, Togias A.** Cysteinyl leukotrienes: multi-functional mediators in allergic rhinitis. Clinic Exp Allergy 2006;36(6):689-703.