

Allergic and mixed rhinitis: Epidemiology and natural history

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ABSTRACT

Allergic rhinitis (AR) is a prevalent chronic respiratory problem in the United States associated with significant comorbidities and health care costs. Recent surveys suggest that mixed rhinitis (MR), which refers to patients with nonallergic AR (NAR) and AR, is a specific rhinitis subtype that may represent between 50 and 70% of all AR patients although the true prevalence of these conditions has not been confirmed. It is important to make a clear distinction between these chronic rhinitis (CR) phenotypes as symptom triggers; response to treatment and prevalence of comorbidities such as sinusitis may be significantly different. Incorporating patient centric questionnaires that can reliably characterize AR, MR, and NAR phenotypes will improve our ability to further investigate the natural history/epidemiology, mechanisms, and development of novel therapies for NAR-related CR subtypes.

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Allergic rhinitis (AR) is a prevalent chronic respiratory problem that is estimated to affect up to 60 million people annually in the United States and is associated with significant morbidity resulting in substantial health care costs to society.^{1–4} Most individuals think of “allergy” when they think of chronic upper respiratory symptoms because AR is the chronic rhinitis (CR) subtype that has been most extensively investigated mechanistically and therapeutically and media advertising has been very successful at imprinting the allergic connotations of CR into the minds of the general public. Current prevalence data of AR is primarily generated by the Center for Disease control health surveys that are distributed to thousands of households in the United States that assess a broad spectrum of health problems.⁵ The questions pertaining to rhinitis in these questionnaire surveys are focused on seasonality as a marker for atopy.⁵ Our inability to generate more accurate data regarding the prevalence of CR subtypes is further hampered by the poor clinical char-

acterization of these patients. CR patients usually first present to their primary care physician who typically empirically treats them for AR. Allergists are better equipped to evaluate CR patients because their patient histories tend to be more detailed and their diagnoses are confirmed by either skin testing or specific IgE serological testing to seasonal and perennial aeroallergens. However, allergists in some cases have been slow to grasp the concept of nonallergic rhinitis (NAR) and mixed rhinitis (MR) for a variety of reasons including (1) the lack of a definitive mechanism still to be determined for NAR, (2) the overlap of clinical symptoms between AR and NAR, (3) the poor specificity of questions traditionally used to define AR versus NAR, and (4) failure to interpret specific IgE in the context of the patient's history.⁴ The purpose of this review is to discuss the current understanding of the epidemiology and natural history of both AR and MR as well as progress in the development of patient centric tools that would facilitate more accurate characterization and subsequent disease-specific therapy for these individuals. One would expect that a more refined approach to the evaluation, diagnosis and treatment of patients with CR would lead to significantly decreased complications (asthma, sinusitis, and otitis media) and associated direct and indirect costs to manage this condition.

CASE PRESENTATION

DD is a 30-year-old woman who presents with progressive worsening of nasal congestion and postnasal

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drainage over the past 5 years. She denies these problems as a child, adolescent, or young adult. Her symptoms did seem to get worse after moving from Florida to Ohio. She notes that her symptoms are worse with the change of seasons and around cats and fresh cut grass. Her symptoms are also worsened by strong perfumes, potpourris, and strong cleaning agents. She works as a secretary in a newer office building. She notices her symptoms are worse at work versus home but there is no difference indoors versus outdoors. She has occasional sneezing with watery eyes, ear plugging, and gets frontal and retro-orbital headaches, which coincide with worsening of her upper respiratory symptoms. She is treated by her primary care physician at least three to four times a year for sinus infections. Neither parent has a history of AR but her mother does experience chronic sinus problems. She is a nonsmoker and not surrounded by smoke at home or work. Of note, her boyfriend recently acquired a cat that seems to make her symptoms worse when she spends time at his home. She is otherwise healthy and takes no regular medications. She has tried over-the-counter antihistamines such as loratadine and cetirizine with no relief. Diphenhydramine helped to dry her drainage but makes her sleepy. Skin testing revealed a positive skin-prick test to cats.

DIAGNOSIS OF CR SUBTYPES

The aforementioned case is a very typical patient presentation to an allergist's office. At first glance there are several aspects of this history that could suggest a diagnosis of AR including symptoms around cats, which correlate with recent exposure and a positive skin-prick test to cats. However, there are several features that are less consistent with an AR history including a later onset of symptoms in life, no family history of allergy, symptoms around odorants, poor response to nonsedating antihistamines, and no seasonality of symptoms. There are several questions that we traditionally ask our CR patients that are nonspecific and therefore not useful for establishing a diagnosis of AR. For example, symptoms in response to fresh cut grass could reflect being outdoors, the pungent smell of grass, mold spores being strewn into the air from the lawn mower, or fumes from the lawn mower. Similarly, seasonal symptoms could be confused with temperature and/or barometric pressure weather changes. The correct diagnosis for this patient would be MR in that she has a clearly defined allergic component based on her symptoms that correlate with sensitization to cats but she also has symptoms in response to irritants such as perfumes, fragrances, and cleaning agents that are not readily explained by a specific IgE-mediated mechanism.

CURRENT DEFINITIONS OF CR SUBTYPES

The current definitions of CR subtypes are relatively underdeveloped. A diagnosis of AR is made if symptoms and triggers correlate with a specific IgE-mediated response whereas a diagnosis of NAR is made if symptoms are induced by irritant triggers in the absence of specific IgE-mediated responses.⁶ The number of skin-prick tests that are used to define AR in clinical trials varies from one to two positive tests. Whether this criterion is sufficient for diagnosis of a pure AR phenotype is questionable. Ongoing analysis of a database developed for determining the relationship between rhinitis and headaches indicates that at least five or more positive skin-prick tests are required before there is a clear separation between AR and MR phenotypes (manuscript in preparation). In contrast, MR is diagnosed if patients manifest specific IgE-mediated responses in conjunction with symptoms induced by both allergic and nonallergic triggers.⁷ Entopic rhinitis, which refers to patients with negative skin-prick testing but evidence of localized specific IgE production in the nose is a new variant of AR that needs to be considered in the differential diagnosis of CR.^{8,9} However, the development of a simple method for measuring specific IgE antibody responses in nasal secretions is necessary for better characterization of this rhinitis phenotype.¹⁰ Although nasal cytology can be very useful for differentiating AR from NAR subtypes, it is not helpful for differentiating between AR and MR because both rhinitis subtypes are inflammatory and usually are characterized by increased eosinophilia.¹¹ Finally, other clinical features such as olfactory threshold responses have not been found to be useful in differentiating CR subtypes.¹²

PREVALENCE AND ECONOMIC IMPACT OF CR SUBTYPES

CR is a very prevalent primary care disorder associated with significant comorbidities such as sinusitis, otitis media, and asthma, which impact both work and school performance. AR is the fifth most common chronic disease in the United States with an estimated prevalence ranging between 5 and 22%, which translates into up to 60 million people. Its economic impact is estimated to cost the health care system \$2.5 billion annually.^{1-3,6,13,14} It is important to emphasize that because these prevalence data are largely based on questions referring to seasonal AR (SAR), the true prevalence of AR (SAR + perennial AR + MR) may be underestimated.

NAR has been estimated to affect 17 million Americans annually.¹⁵⁻¹⁷ Depending on the studies, cross-sectional surveys have found that the diagnosis of AR ranges between 43 and 83% whereas the prevalence of NAR ranges between 17 and 52%.¹⁸ In a 1998 report,

the Joint Task Force on Practice Parameters in Allergy, Asthma and Immunology estimated that 43% of patients presenting with CR have AR, 34% have MR, and 23% have NAR.¹⁷ In addition, large population studies are necessary to determine the true prevalence or incidence of perennial AR, MR, and NAR disorders.

DIAGNOSIS OF AR VERSUS MR

Establishing an accurate diagnosis of CR is challenging because upper respiratory symptoms such as nasal congestion, postnasal drainage, and rhinorrhea are manifested by most CR patients and therefore are not useful for differentiating CR subtypes.^{6,14} A detailed patient history including onset of symptoms, duration, severity, and frequency of symptoms; indoor and outdoor allergic and nonallergic environmental triggers; previous response to over-the-counter and prescription treatments; comorbidities such as recurrent sinusitis, otitis, and asthma; and family history of allergies are all important questions that help to generate an accurate differential diagnosis for CR subtypes.⁶ A previous patient questionnaire was designed to differentiate between AR, MR, and NAR.¹⁹ Using data derived from logistic regression analysis, the probability of diagnosing NAR was 96% in a patient with new-onset symptoms at the age of 35 years with no parental history of allergy, no seasonal symptoms or symptoms around cats, and increased symptoms around perfumes and fragrances.¹⁹ For a similar 45-year-old patient, the probability of having NAR was 98%.¹⁹ However, this questionnaire was not useful for identifying pure phenotypes for AR and MR. To determine if the failure of this questionnaire to predict AR and MR phenotypes was because of the population size, SAR patients recruited to participate in three separate pharmaceutical studies were administered this questionnaire.^{15,20} The results of this analysis revealed that a significant percentage of these patients had nonallergic triggers consistent with a diagnosis of MR rather than pure SAR.^{15,20} These findings have significant ramifications regarding the current criteria used to recruit patients for AR studies. One could speculate that a more precise definition of SAR could lead to recruitment of a purer patient phenotype and more robust treatment outcomes in AR trials.

Recently, an irritant index score was developed to objectively differentiate between CR subtypes.¹⁵ This scale is based on 21 questions pertaining to common nonallergic triggers.¹⁵ The irritant index scale was completed by ~650 subjects as part of a headache rhinitis study. Each patient was instructed to rate the severity of their upper respiratory symptoms in response to each trigger.¹⁵ Preliminary results, using discriminating cut points, have found that 15% of subjects have a pure AR phenotype, 15% have a pure NAR phenotype,

and up to 70% have an MR phenotype.¹⁵ Although the percentage of patients with an MR phenotype is significantly greater than what has been previously reported by other investigators, this is the first analysis to use a quantitative scale to assess the impact of nonallergic triggers on upper respiratory symptoms (manuscript in preparation). Finally, a new subclass of NAR patients without nonallergic triggers was identified.¹⁵ Work is in progress to better determine the clinical relevance of this phenotype. However, based on this analysis, we propose a new classification for CR that include four major phenotypes: (1) AR with a low irritant index score (AR_{lo}), (2) AR with a high irritant index score (AR_{hi} a.k.a. MR), (3) NAR with a high irritant index score (NAR_{hi} a.k.a. vasomotor rhinitis), and (4) NAR with a low irritant index score (NAR_{lo}).

Although physical examination is useful for identifying features of SAR such as nasal creases and pale bluish hue boggy turbinates, in general, there are no physical characteristics that can definitively differentiate between AR and MR.⁶ As previously mentioned, both conditions are associated with nasal inflammation manifesting as nasal eosinophilia and have one or more positive skin test or serum-specific IgE test results to environmental aeroallergens.⁶ Therefore, the primary feature that differentiates these two conditions is that patients with MR exhibit a greater magnitude of nasal symptoms in response to a spectrum of nonallergic triggers.

TREATMENT RESPONSE AS A PHENOTYPIC MARKER FOR CR SUBTYPES

It is important to accurately diagnose AR, MR, and NAR, because the treatments differ considerably.⁶ Primary care physicians tend to be biased toward the diagnosis of AR, because they are more familiar with the disorder. Therefore, treatment is often limited to prescribing second-generation nonsedating antihistamines and/or nasal corticosteroids that often do not adequately control symptoms in patients with vasomotor rhinitis or NAR, thereby resulting in an increased risk for comorbidities such as sinusitis and otitis media.^{6,21} Ryden *et al.* investigated disease perception and social behavior in their patients with CR and reported that prescribed medications were effective in reducing symptoms only 50% of the time and patients with NAR more frequently indicated that medications based on treating underlying allergy had little or no effect at controlling their symptoms.²² Therefore, the current practice for treatment of CR is inefficient and often leaves patients very frustrated and in considerable discomfort. Furthermore, ineffective treatment of CR has resulted in higher health care costs and lost productivity, resulting in a greater economic burden on our health care system.

Treatment for AR and MR should include avoidance measures, pharmacologic therapy, and, if indicated, allergen immunotherapy (AIT).⁶ Avoidance measures should focus on indoor and outdoor aeroallergens but in the case of MR, patients should also be counseled on avoidance of nonallergic triggers such as outdoor air pollution, tobacco smoke, perfumes/fragrances, potpourris, burning wood, ozone generators, incense, cleaning agents, and other strong chemicals and odorants that are commonly present in home or work environments.⁶ Pharmacologic treatment for AR and MR may overlap significantly as first- or second-generation antihistamines, nasal corticosteroids, nasal antihistamines, and leukotriene modifying agents may all be effective.^{6,21} Currently, only intranasal azelastine and intranasal fluticasone are Food and Drug Administration approved for the treatment of NAR.^{23,24} Therefore, patients with MR, because of their nonallergic component, may be somewhat more refractory to treatment and require more combination therapy (*i.e.*, nasal corticosteroid + nasal antihistamine, *etc.*) to control their symptoms.

There are many unanswered questions regarding treatment response differences between AR and MR. For example, do MR patients respond as favorably to topical therapy or AIT compared with AR patients?²⁵ Are there similar cost benefits such as reduced comorbidities, medication requirements, and improved quality of life for AR and MR patients treated with AIT? In a recent historical pre- and posttreatment study designed to investigate the therapeutic benefit of AIT in AR compared with MR patients, it was found that both groups achieved therapeutic benefits from this treatment (submitted for publication). However, the AR group was able to reduce the number of medications to a significantly greater extent than the MR group after 3 years of treatment. Interestingly, the MR group was observed to have significantly fewer number of sinus infections over the course of AIT. Whether this was caused by taking more medication, an immunomodulatory effect of AIT on the AR component of MR, or both was not possible to determine. To further investigate whether treatment response is a useful phenotypic marker for differentiating AR and MR subtypes, it will first be necessary to develop better consensus definitions for AR, MR, and NAR subtypes. This approach will also permit designing *in vitro* and clinical studies for investigating the underlying mechanism(s) for NAR.

APPROACH TO MANAGEMENT OF CASE PRESENTATION

For the aforementioned case presentation, this patient likely has MR based on her history and skin test results. Management should focus on trying to reduce

exposure to cats in the home and initiation of treatment with a nasal corticosteroid, nasal antihistamine, or combination of these two agents as a first step approach. Other adjunctive therapies could include nasal irrigation with saline, topical or oral anticholinergic agents to control postnasal drainage, oral decongestants, and, potentially, leukotriene modifying agents with the intent of using the fewest number of medications to maximize therapeutic outcomes at the lowest cost. AIT may be the best long-term approach to treatment but it is still not entirely clear whether patients with MR achieve the same therapeutic outcomes as observed for patients with pure AR.

CONCLUSIONS

AR and MR are overlapping conditions that until recently have been classified as AR. It is becoming clearer that these conditions may behave differently with respect to clinical presentation, comorbidities, and response to treatment. There is ample evidence in the medical literature that shows a synergistic interaction between specific IgE-mediated responses and air pollutants such as diesel exhaust particulate and ozone.^{26–29} Further investigation is required to determine whether MR represents a continuum from AR that develops over time as a result of an enhanced immunologic response secondary to continued exposure to chemicals and/or particulate matter in the home or work environment or merely represents the development of NAR independently of the patient's atopic status. Regardless, it is important for the clinician not to trivialize the distinction between these two CR conditions because it is clear that the clinical management of MR can be more challenging, leading to increased morbidity and health care costs and decreased quality of life.

REFERENCES

1. Meltzer EO, Blaiss MS, Derebery MJ, et al. Burden of allergic rhinitis: Results from the Pediatric Allergies in America survey. *J Allergy Clin Immunol* 124(suppl):S43–S70, 2009.
2. Settipane RA. Demographics and epidemiology of allergic and nonallergic rhinitis. *Allergy Asthma Proc* 22:185–189, 2001.
3. Meltzer EO, Nathan R, Derebery J, et al. Sleep, quality of life, and productivity impact of nasal symptoms in the United States: Findings from the Burden of Rhinitis in America survey. *Allergy Asthma Proc* 30:244–254, 2009.
4. Meltzer EO, Nathan R, Derebery J, et al. Physician perceptions of the treatment and management of allergic and nonallergic rhinitis. *Allergy Asthma Proc* 30:75–83, 2009.
5. Centers for Disease Control and Prevention. International study of asthma and allergies in childhood. Available online at www.cdc.gov/asthma/survey/isaac.html; last accessed May 21, 2010.
6. Wallace DV, Dykewicz MS, Bernstein DI, et al. The diagnosis and management of rhinitis: An updated practice parameter. *J Allergy Clin Immunol* 122(suppl):S1–S84, 2008.
7. Bernstein JA, and Rezvani M. Mixed rhinitis: A new subclass of chronic rhinitis? In *Current Reviews of Rhinitis*, 2006, 2nd ed.

- Kaliner M (Ed). Philadelphia, PA: Current Medicine, Inc., 69–78, 2006.
8. Powe DG, and Jones NS. Local mucosal immunoglobulin E production: Does allergy exist in non-allergic rhinitis? *Clin Exp Allergy* 36:1367–1372, 2006.
 9. Khan DA. Allergic rhinitis with negative skin tests: Does it exist? *Allergy Asthma Proc* 30:465–469, 2009.
 10. Bernstein IL, Li JJ, Bernstein DI, et al. Allergy diagnostic testing: An updated practice parameter. *Ann Allergy Asthma Immunol* 100(suppl 3):S1–S148, 2008.
 11. Romero JN, and Scadding G. Eosinophilia in nasal secretions compared to skin prick test and nasal challenge test in the diagnosis of nasal allergy. *Rhinology* 30:169–175, 1992.
 12. Rezvani M, Brandt D, Bernstein JA, et al. Investigation of olfactory threshold responses in chronic rhinitis subtypes. *Ann Allergy Asthma Immunol* 99:571–572, 2007.
 13. Ciprandi G, et al. Seasonal and perennial allergic rhinitis: Is this classification adherent to real life? *Allergy* 60:882–887, 2005.
 14. Skoner DP. Allergic rhinitis: Definition, epidemiology, pathophysiology, detection, and diagnosis. *J Allergy Clin Immunol* 108(suppl):S2–S8, 2001.
 15. Bernstein JA. Characteristics of non-allergic rhinitis. *World Allergy J* 2:102–105, 2009.
 16. Ciprandi G. Treatment of nonallergic perennial rhinitis. *Allergy* 59(Suppl 76):16–22, 2004.
 17. Settipane RA, and Lieberman P. Update on nonallergic rhinitis. *Ann Allergy Asthma Immunol* 86:494–507, 2001.
 18. Settipane RA. Epidemiology of vasomotor rhinitis. *World Allergy J* 2:115–118, 2009.
 19. Brandt D and Bernstein JA. Questionnaire evaluation and risk factor identification for nonallergic vasomotor rhinitis. *Ann Allergy Asthma Immunol* 96:526–532, 2006.
 20. Bernstein JA, Brandt D, Rather P, and Wheeler W. Assessment of a rhinitis questionnaire in a seasonal allergic rhinitis population. *Ann Allergy Asthma Immunol* 100:512–513, 2008.
 21. Rosenwasser LJ. Treatment of allergic rhinitis. *Am J Med* 113(suppl 9A):17S–24S, 2002.
 22. Ryden O, Andersson B, and Andersson M. Disease perception and social behaviour in persistent rhinitis: A comparison between patients with allergic and nonallergic rhinitis. *Allergy* 59:461–464, 2004.
 23. Lieberman P. The role of antihistamines in the treatment of vasomotor rhinitis. *World Allergy J* 2:156–161, 2009.
 24. Meltzer EO. The treatment of vasomotor rhinitis with intranasal corticosteroids. *World Allergy J* 2:166–179, 2009.
 25. Jacobs R, Lieberman P, Kent E, et al. Weather/temperature-sensitive vasomotor rhinitis may be refractory to intranasal corticosteroid treatment. *Allergy Asthma Proc* 30:120–127, 2009.
 26. Bernstein JA, Alexis N, Barnes C, et al. Health effects of air pollution. *J Allergy Clin Immunol* 114:1116–1123, 2004.
 27. Diaz-Sanchez D, Proietti L, and Polosa R. Diesel fumes and the rising prevalence of atopy: An urban legend? *Curr Allergy Asthma Rep* 3:146–152, 2003.
 28. Diaz-Sanchez D, Tsein A, Fleming J, and Saxon A. Combined diesel exhaust particulate and ragweed allergen challenge markedly enhances human in vivo nasal ragweed-specific IgE and skews cytokine production to a T helper cell 2-type pattern. *J Immunol* 158:2406–2413, 1997.
 29. Peden DB, Setzer RW Jr, and Devlin RB. Ozone exposure has both a priming effect on allergen-induced responses and an intrinsic inflammatory action in the nasal airways of perennially allergic asthmatics. *Am J Respir Crit Care Med* 151:1336–1345, 1995. □