

Inhalant Allergy Evaluation in ENT Patients

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Abstract

Purpose of Review The purpose of this article is to educate the reader on the current trends in the evaluation of allergic rhinitis, with a focus on inhalant allergy, in otolaryngic patients.

Recent Findings and Summary Recent literature emphasizes the need for a thorough history and physical examination that can lead the practitioner to a clinical diagnosis of allergic rhinitis. Looking at patient cues such as allergic shiners, the allergic salute, polypoid tissue on middle turbinate, tonsillar and adenoid hypertrophy, laryngeal edema, and patients with chronic suppurative otitis media or otitis media with mucopurulent drainage may lead to further diagnostic testing. Diagnostic testing should be determined on an individual basis dependent on their particular geographic location. Negative testing does not rule out allergen sensitivity, and patients should be treated based on their symptoms.

Keywords Allergic rhinitis · Allergic rhinitis diagnoses · Middle turbinate polyp · Skin testing · Asthma

Introduction

The purpose of this article is to educate the reader on the current trends in the evaluation of allergic rhinitis, with a focus on inhalant allergy, in otolaryngology patients. PubMed and

Google Scholar searches were performed using the keywords “evaluation of patients with allergic rhinitis,” “allergic rhinitis trends,” “diagnosis of patients with allergic rhinitis,” “allergic rhinitis guidelines,” and “testing patients with allergic rhinitis”, from 2011 to 2017. Articles were reviewed, and only those relevant to allergic rhinitis and diagnosis were included for review.

Diagnosis

The evaluation of an allergic rhinitis patient begins with taking a thorough history and physical examination. The patient’s history remains the single most important tool in diagnosing allergy [1•]. Patients may self-report a subjective history of “allergies” during an interview, but such complaints always warrant further investigation by the physician and should not be dismissed [2]. Conversely, a patient may present with complaints of recurrent infections of the sinuses, ears, or other head and neck structures; yet, be unaware that allergic disease is the underlying culprit of their symptoms [2].

Classification of allergic symptomatology can assist with more concise diagnosis based on the American Academy of Otolaryngology-Head and Neck Surgery Foundation 2015 Clinical Practice Guidelines definitions based on patterns of exposure and frequency of symptoms. Patterns of exposure can be broken down between seasonal (e.g., pollens) and perennial (e.g., dust mites or occupational allergens), frequency of symptoms can be *intermittent* (<4 days per week or <4 weeks per year), *persistent* (>4 days per week or >4 weeks per year), or *episodic* [3•].

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History

The allergic history can be divided into three components: symptoms, timing, and environment [1•]. The typical and most commonly recognized symptoms of allergic rhinitis include nasal blockage, rhinorrhea, itchy/watery eyes, and sneezing [4]. Less common allergic symptoms include changes in hearing, pain or pressure in the ears, recurrent upper respiratory infections, and postnasal drip [1•]. Allergic rhinitis may also be comorbid with cough, impaired asthma control, and sleep disturbances [4]. While these symptoms are most commonly attributed to allergic rhinitis, they may also be an indicator of asthma, as the two conditions often coexist [4]. A presentation of poorly controlled asthma raises suspicion for allergic rhinitis, as allergic rhinitis can impair asthma control [4].

The timing of allergy includes the age of onset, the seasonal occurrence, and any patterns the symptoms may exhibit. Allergic rhinitis symptoms most commonly first arise in teenagers and young adults. Additionally, it is important to determine if the patient's symptoms occur throughout the year or are only concurrent with certain seasons [1•]. This may provide clues that indicate the underlying cause of symptoms. For example, tree pollen is one of the most common allergens in the spring, grass pollen in the summer, weeds and molds in the fall, while dust mite and indoor molds may be attributable to winter symptoms.

The patient's environment, including their geographic location and any occupational or household exposures, must also be explored in the history [1•]. One should pay attention if their symptoms primarily occur in only one of their environments [4]. Studies have reported that the incidence of atopy, asthma, and allergic rhinitis is increased more than twofold in patients residing in urban locales compared to their rural counterparts. This may be attributed to greater levels of exposure to chemical pollutants in the air, such as biomass fuels [5].

Occupational exposures can either be a primary cause of allergic rhinitis, in which case they could herald the future development of occupational asthma, or they may exacerbate preexisting allergic rhinitis [4]. Bakers, with exposure to flour or wheat [4] and veterinary technicians or others who work with animals with exposure to pet dander, are the two professions most at risk for development of occupational asthma [4].

Possible household exposures that may trigger allergic rhinitis include pet dander, dust mites, and rodent or insect infestations [4]. House dust mite (HDM) is among the most common allergens implicated in asthma and allergic rhinitis [6–8]. HDM are a pervasive asthma trigger and a significant factor for allergic rhinitis (AR) and allergic asthma (AA). Current literature shows environmental assessment and control of HDM by measuring humidity levels in the home with the use of a hygrometer [9]. Calderon et al. also discusses that

an initial trigger, HDM, begins a cascade of immune responses to effect chronic inflammation leading to the deposition in the respiratory tract [9]. Additionally, specific questions about the floor level of the patient's home, mildew odors, or allergen reservoirs such as carpet and bedding may also be of value in identifying allergens [4].

Smoking history, exposure to secondhand smoke, and presence of wood-burning stoves in the home should also be elicited [4, 5]. Saulyte et al. completed a systematic review drawing a comparison between cigarette smoke and AR. The group studied over 196 studies, mostly cross-sectional studies, that showed a modest link between active and passive smoking and AR. The review also showed an increased risk for allergic disease in passive smoking [10]. More studies are needed due to the heterogeneity of the bulk of the studies and other confounding variables [10]. In a later study, Shargorodsky et al. studies over 4000 adults and positivity for allergens by IgE testing. The authors were unable to validate a correlation between active and passive cigarette smoke and AR. They found a correlation between rhinitis and smoking [11]. Based on these findings, discussing smoking exposure is an important part of the patient history [11]. Other relevant components of the allergic history include past treatment for or diagnosis of allergies and review of all over-the-counter, herbal, and prescription medications [1].

Physical Exam (Insert Fig. 1)

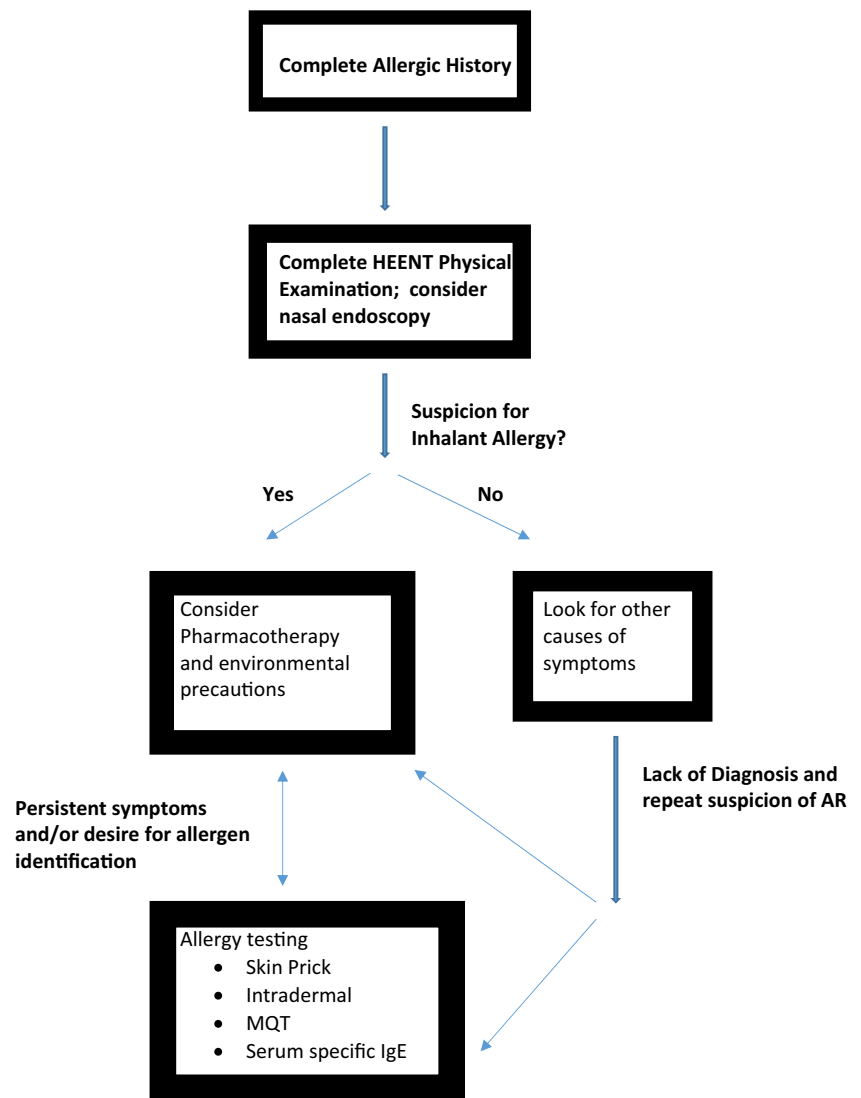
After completion of a thorough history, a physical exam is necessary. There are specific findings on physical exam that are commonly associated with allergic disease. The “allergic salute” is a maneuver performed by patients that eventually creates an indentation on the bridge of the nose known as the “allergic nasal crease.” Presence of urticaria or hives on the body can be associated with allergy. Edema, erythema, or signs of venous congestion surrounding the eye (aka allergic shiners) or erythema of the external auditory canal may also be associated with allergy. Tonsillar and adenoid hypertrophy and laryngeal edema can also be associated with allergy [1]. Additionally, patients with chronic suppurative otitis media, which features chronic otorrhea with mucopurulent exudates, have a higher prevalence of allergic rhinitis [12].

Allergic Rhinitis and Ear Disorders

Allergic Rhinitis and Meniere's Disease

Although the specific mechanisms between Meniere's disease (MD) and AR have not been fully understood and MD is still considered idiopathic [13], an earlier study by Derebery and

Fig. 1 Inhalant allergy workup in ENT patients



Berliner in 2011 opined that patients with AR with a genetic predisposition may have more of a predilection towards MD [13]. They raised the question of whom to test to effectively evaluate AR with MD, including patients with both inhalant allergies as well as food allergies, patients with past or present allergy symptoms, or patients with a strong family history of AR [13]. Weinreich et al. points out that animal studies have shown promise that correlate inner ear allergic activity. The group also elucidated that the risk of adding AR therapy to patients with MD is of low risk and may show some benefit [14]. It is reasonable to conclude that assessment for Meniere's disease in the evaluation for AR may show some benefit [14].

The etiology of MD is multifactorial and diagnosis is difficult, especially in the early stages of the disease [15]. Several past studies show support for the link between AR and MD but a direct causal link has not been well established [15]. Banks et al. provide a literature review that proposes that in

a select group of patients, there may be a final pathway of inflammation leading to MD [15].

Allergic Rhinitis and Chronic Suppurative Otitis Media

Nemati et al. looked at chronic suppurative otitis media (CSOM) in 123 patients with AR in Iran. This study was able to show that patients with chronic otorrhea, mucopurulent exudate, or perforated tympanic membrane (TM) showed a substantially higher rate of AR, 62.5% of affected patients versus 37.5% of controls (verified by skin prick test) [12]. This was clinically significant (CI = 95%; $P = 0.035$). Patients with AR and nonAR have a more than threefold increased risk for developing CSOM compared with their healthy counterparts [12]. Nemati et al. was also able to show that there are differences in patients based on the onset of disease and those who developed CSOM from childhood had a higher incidence of AR [12].

Allergic Rhinitis and Disorders of the Nose

Middle Turbinate Edema or Polyps and Inhalant Allergy

A newer distinction has been associated with the clinical conditions of polypoid change of the middle turbinate versus paranasal sinus polyposis. Polypoid change of the middle turbinate (see Fig. 2) possesses a greater association with allergic rhinitis than does paranasal sinus polyposis, including polyps in the middle meatus [16•]. Diffuse edema of the middle turbinate, in addition to the edema from nasal polyps, is another useful feature to predict the presence of inhalant allergy and carries high positive predictive value [17•]. White et al. performed a study to examine whether an association exists between isolated nasal middle turbinate polyps and inhalant allergy [18•]. Of the 25 patients, they examined with middle turbinate polyps, 16 underwent skin or in vitro allergy testing and all tested positive for inhalant allergy [18•]. The authors concluded that there is strong evidence to support a relationship between isolated nasal middle turbinate polyps and allergy. A recommendation was made for all patients presenting with such polyps to undergo allergy testing [18•]. The authors found this physical exam finding to provide a great clue into a finding of undiagnosed or poorly controlled allergic rhinitis, despite patient's denial or minimizing of allergy symptoms [18•].

Allergic Rhinitis and Respiratory Disease

Allergic Rhinitis and Asthma

Allergic Rhinitis and its Impact on Asthma Guidelines (ARIA, 2008) suggest that 75% of patients with asthma also have concomitant allergic rhinitis [19]. Several older studies point to AR as a precursor to asthma. Tajiri et al. performed a retrospective study of patients with classic asthma and cough variant asthma (CVA). A total of 109 patients with classic asthma and 32 patients with CVA, out of the 190 patients with classic asthma and 83 patients with CVA, had rhinitis during the pollen season [20].

Mojaria et al. discusses the “allergic march” for patients with a predisposition towards allergic rhinitis. The researchers found a two to sevenfold increase in asthma later in life for patients diagnosed with AR in childhood, and the presence of rhinitis increased the likelihood of childhood asthma progressing to adult asthma [21]. The most common finding in the literature was the continued exposure of inhaled antigens. The house dust mite (HDM) was the most common noxious inhalant source. Khan opined that the evidence suggests that patients with asthma have shared rhinitis and share a common physiology sharing a hypersensitivity with a predominance of T-helper type 2 inflammation and eosinophilia [22]. Calderon et al. cited an Italian study that showed that in 300 study patients with diagnosed AR, 46% progressed to

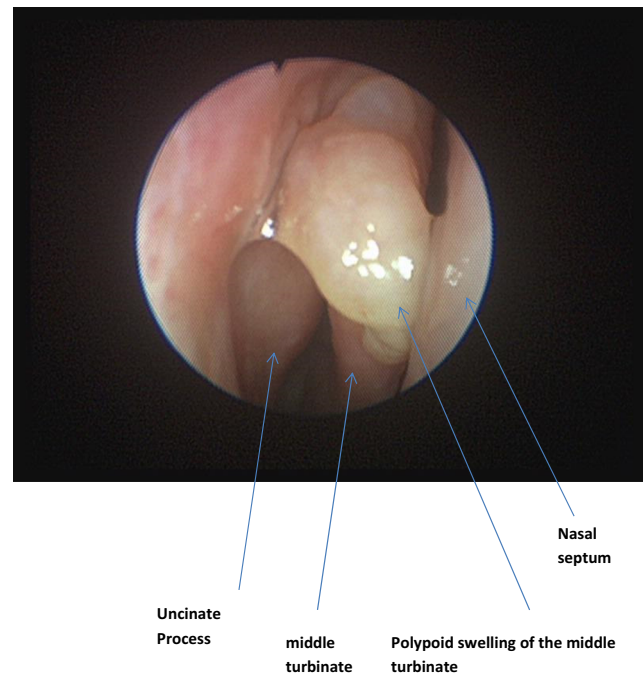


Fig. 2 Right sided nasal endoscopy of patient presenting with isolated nasal congestion. Examination revealing isolated polypoid tissue off the middle turbinate, suggesting possible AR. This patient was later skin prick allergy tested with return of class VI *D. pteronyssinus* and *D. farinae* allergy

develop asthma [9]. Ultimately, practitioners should include ongoing assessment for asthma especially in patients with new-onset adult asthma [21].

Imaging

The history and physical examination are the only tools necessary to diagnose a patient with allergic rhinitis, and the routine use of any diagnostic imaging is discouraged. Both plain film radiographs and computed tomography (CT) scans expose patients to unnecessary radiation, and the use of contrast in CT scans carries a risk of anaphylactic reaction [3•]. The only situations in which imaging may be acceptable is evaluating sequelae of allergic rhinitis, such as chronic rhinosinusitis, nasal polyposis, or a suspected neoplasm [3•]. Upon determining which patients may have features of allergic rhinitis via the history and physical examination, it may be appropriate for the clinician to perform allergy testing. This is done if either the patient or physician further wishes to confirm the diagnosis of allergy, identify the exact allergen, or determine the severity of allergy.

Allergy Testing

Current trends in allergy testing suggest that a wide variety of techniques and devices are employed. Guidelines for testing

can also vary between different countries. Before a technique for testing is chosen, it is important to identify which allergens are clinically relevant and should be tested for an individual patient. Note that not all patients with allergic rhinitis must undergo allergy testing. For example, a patient with mild intermittent seasonal AR that is well managed with a simple nasal steroid spray, for example, does not have an indication for allergy testing. Allergy testing should be performed, however, if there is a lack of improvement with pharmacotherapy or if there is a desire by the patient or clinician to further delineate the true allergens. Any patient that may want to pursue allergy immunotherapy must undergo a form of allergy testing to confirm an IgE mediated allergic response.

Allergens

The clinically relevant allergens in each patient are determined by their history and are determined by geographic location, due to the variation in seasonal allergens by region [23•]. The individual species of allergen in each category should be chosen based upon its endemicity to the geographic region of testing. For instance, *Dermatophagoides pteronyssinus*, mugwort, and ragweed are common in the fall in northeast China [24]. In a study done by Lee et al. in Korea, a battery of five to seven antigens was determined to be sufficient to detect a majority of sensitizations in most age groups [25]. House dust mites were the most common sensitization, particularly *Dermatophagoides farinae* [25]. These combined with cockroach, oak, and mugwort were sufficient to detect 90% of sensitized patients [25]. A Turkish study found that a skin prick panel of 12 allergens was sufficient to detect most sensitizations in children and adolescents [26]. The authors found that the most common sensitizations were to dust mites, grasses, weeds, cat, and mold [26].

Ultimately, each class of allergens, including dust mites, weeds, grasses, animal dander, and mold should have representatives included in a panel for allergy testing. Some practices have screening panels as well as complete allergy panels. A battery for testing may comprise anywhere from 6 up to 30 antigens.

Once the allergens appropriate to a patient have been identified, there are a variety of methods that can be employed to determine whether a patient will mount an allergic response to each antigen. Principal among these are skin testing, serum testing, and molecular testing.

Skin Testing

Skin testing is the most widely employed method [7, 8, 27, 28] and is the first-line choice [28] for testing allergic rhinitis patients. The principal benefits of skin testing compared to other modalities are that it generates rapid results, is inexpensive, and produces a visible reaction that can be appreciated by

the examiner as well as the patient [23•]. It also carries a satisfactory level of accuracy in distinguishing between patients who possess allergic rhinitis and those who do not [29]. Skin testing can be divided into epicutaneous (“prick”) tests and intradermal dilutional tests (IDT) [23•].

One benefit of isolated skin prick compared to IDT is that it poses less risk of inciting a systemic response because the allergen is only introduced superficially into the skin [23•]. The optimum location for allergy testing is the dorsal or volar surfaces of the arms [23•]. Multiple-allergen prick device systems can deliver concentrates of multiple antigens at a time and can distribute the pressure from each needle equally across the skin [23•].

Intradermal dilutional testing (IDT) injects the allergenic concentrate below the epidermis and can identify clinically relevant allergens that may go undetected by skin prick testing [23•, 30]. While this technique confers a higher sensitivity, it may also place the patient at greater risk for an adverse reaction [23•].

There is controversy as to the significance of a positive IDT that is drawn following a negative skin prick test [13]. The value of such results is at the discretion of the clinician, based on their knowledge of the patient and their clinically relevant allergy [23•]. The IDT method of serial dilution, where dilute levels of allergen are injected into the skin, and the concentrations are increased fivefold until the patient’s skin produces a wheal of 7 mm or greater in diameter followed by a confirmatory wheal which is 2 mm greater, is also used by some offices [23•]. Despite the advantages of IDT, it has not been identified as a superior method over skin prick [23•]. In fact, it has been determined that IDT is less likely to detect clinically significant allergens compared to skin prick or serum IgE testing [30].

Modified quantitative testing (MQT), first identified in 2003, is a blended technique where skin prick testing is first used to estimate the range of skin reactivity followed by the use of an isolated intradermal test to determine an approximate endpoint.

Location of Skin Testing

With skin prick tests, an important consideration is the location on the patient’s skin on which the test will be performed. The upper back is the most sensitive area of the skin to skin testing and will produce the greatest response with respect to wheal size [31]. In older children and adults, however, the volar surfaces of the forearm are preferred because they allow the patient to appreciate the results of the test [31].

In Vitro Testing

Serum IgE testing, a type of in vitro testing, exposes samples of patient serum to assays containing a range of allergens, then

determines which of the allergens a patient's IgE has bound to by using an anti-IgE molecule labeled with a reactive enzyme [32]. The predecessor to testing with enzyme-linked immunoassays is the radioallergosorbent test (RAST), which employs a radioactive anti-IgE antibody instead of an enzyme-tagged one [32]. RAST has been replaced by enzyme-based testing due to its use of radioactivity [32].

The advantages of serum IgE assays include their lower coefficients of variation and the possibility of IgE levels to be used to track response to treatment [32]. Similarly, to IDT, a patient's sensitivity to an allergen can also be quantified [32]. They also are not confounded by any medications the patient may be taking (antihistamines, β -blockers) and pose no risk of adverse reactions [32]. However, the test is hindered by the lack of standardization of the commercially available allergen assays and the fact that negative testing may not rule outpatient sensitivity to an allergen, especially the findings of a delayed response [32].

Molecular-based allergy (MA) diagnostics is another method of in vitro testing, and uses natural or recombinant allergen molecules, as opposed to extracts [32, 33]. This is not routinely used in clinical practice. By applying a sample of a patient's blood to an assay containing several allergenic extracts, a patient's sensitivity to multiple allergens can be determined and quantified at once [33]. MA diagnostic testing can distinguish between genuine allergy and cross-reactivity [33]. One area in which this is particularly beneficial is in the diagnosis of food allergy. To elaborate, a patient with a peanut allergy may be sensitized against Ara h 2, a genuine allergic marker that portends a systemic reaction [33]. Or, they may be sensitized against Ara h 8, which would indicate cross-reactivity between food allergens and the *Fagales* tree pollen, and only produce a mild oral response [33]. The distinguishing element between the two molecules is their resistance to heat [33]. Ara h 8 is a heat-labile compound and would not tolerate the acidity of the stomach [33]. Conversely, Ara h 2 is heat-stable, which is what enables it to cause a systemic reaction [33]. This illustrates the ability of MA diagnostic testing to qualify and predict the *severity* of response a patient may mount against an allergen, beyond simply establishing the presence of an allergy. These principles are consistently testable across a variety of foods, including egg, wheat, and shellfish, as well as inhalant allergens such as molds, mites, and cockroaches [33]. However, while promising, such modes of therapy are not feasible in standard clinical practice, given that identifying specific molecules in polysensitive patients creates a vast number of permutations for an allergy profile, and also requires each molecule to be individually tested [33]. Thus, the superiority of MA diagnostic testing lies in its accuracy, but the expense and level of specificity required currently render it impractical for routine use.

Additional Lab Testing

Nasal Testing

The nasal allergen provocation test uses multiple aeroallergens to detect polysensitization in patients [34]. Patient responses can be quantified by measuring nasal levels of tryptase and eosinophil cationic protein [34]. This has been determined to be a sensitive and less time-consuming diagnostic test to screen for local allergic rhinitis [34]. Another testing modality is nasal cytology. Sampling patients' nasal secretions and examining them under light microscopy allows for detection of inflammatory cells, the most prevalent of which are neutrophils and eosinophils [35]. Eosinophils are an important marker of inflammation, and as such are the target of many anti-inflammatory drugs [36]. Nasal cytology results are graded based upon the number of inflammatory cells per field, and the results can be used to guide staging and treatment in allergic rhinitis patients [35–37]. The methods are not commonly used in the clinical setting.

Nitric Oxide

A patient's levels of nitric oxide may be another metric by which to measure an allergic response. Exhaled nitric oxide is believed to be directly correlated with levels of eosinophilic inflammation in the airway, and may, therefore, be a valid feature to estimate the severity of allergic rhinitis [4, 38, 39•]. Kalpaklioglu et al. measured the levels of fractional exhaled nitric oxide (FeNO) in patients with allergic rhinitis and compared them against patients with nonallergic rhinitis [38]. The authors found that patients with allergic rhinitis had higher FeNO levels than did those with nonallergic rhinitis, and patients with allergic rhinitis and asthma had significantly higher FeNO levels than did those with nonallergic rhinitis [38]. It was concluded that elevated FeNO levels may be used as a potential clinical tool to monitor asthma and allergic and nonallergic rhinitis [38]. Levels of nasal nitric oxide have been studied in children as well, and it has been determined that children with allergic rhinitis exhibit higher levels of nasal nitric oxide than do healthy patients, and that these levels correlate positively with increased severity [6].

Vitamin D Deficiency and Allergic Rhinitis

Allergic rhinitis and vitamin D deficiency is becoming a notable trend and may assist in identifying patients with allergic rhinitis and asthma. In 2015, Bener et al. examined 1833 Qatari children with severe vitamin D deficiency and found there was a higher incidence with 23.4% of children with wheezing, 18.5% with AR, and 17% with asthma, whereas only 10% of healthy children were at risk [40]. This study correlates higher risk for asthma, AR, and wheezing. It may

be prudent to check a vitamin D level in patients who present with symptoms of AR, asthma, or wheeze especially in the absence of a positive ssIgE or skin prick testing [40].

Tian et al., in the most recent study, compared several studies that have inferred a link between vitamin D levels, AR, and asthma. Tian elucidated that children with higher levels of vitamin D3 had lower incidence of AR and allergic exacerbations [41]. Conversely, several studies showed that those with lower vitamin D levels were a risk factor for prevalence, exacerbations, and severity of their disease [41]. The data does not provide information on the pathogenesis of vitamin D, and further studies are warranted to further understand the link. Several studies in the paper reveal conflicting results and treatment of the deficiency and its benefit is now known [41].

Conclusion

Recent literature reiterates the importance of diagnosing inhalant allergic rhinitis via a thorough history and a complete physical examination. Careful attention to patient findings within the ear, nose, and throat can lead to an increased suspicion of the diagnosis of AR. The history and physical examination can direct the practitioner to determine more individualized testing including SPT, IDT, MQT, or in vitro testing. Screening and testing panels should be limited to allergens that are relevant to one's geographic region. Additional modalities such as nasal allergen provocation test and FeNO measurements of eosinophilic inflammation are more commonly used for research and benchwork studies at this time.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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