CURRENT PERSPECTIVES IN THE CLASSIFICATION AND CLINICAL DIAGNOSIS OF ALLERGIC RHINITIS.

Corresponding Author: Prof. Clement C. Nwawolo
clementnwawolo@yahoo.com +2348038053390
Otorhinolaryngology Unit,
Department of Surgery,
College of Medicine,
University of Lagos.
PMB 12003, Surulere, Lagos, Nigeria.

Clement C. Nwawolo
Otorhinolaryngology Unit, Department of Surgery,
College of Medicine, University of Lagos.
PMB 12003, Surulere, Lagos, Nigeria.

ABSTRACT

The diagnosis of allergic rhinitis has been a challenge to practitioners as the symptoms of inflammatory diseases of the nose tend to be similar. The inflammatory process can be induced by different factors. However, research efforts have shown allergic rhinitis to be an IgE mediated inflammatory condition in response to an allergen. The disease has been shown to cause considerable burden on patients and the society. Pooled data from systematic reviews and meta-analysis has led to proposed guidelines for the diagnosis and classification of the condition. The increasing prevalence, its link with asthma and effect on sleep/work/school performance led to the establishment of "Allergic Rhinitis and Impact on Asthma" (ARIA) expert panel workshop. This panel has proposed a clearer classification and diagnostic criteria. This is being updated regularly. The guideline shows clearly the clinical diagnostic criteria with the classification based on severity disease. The role of investigative tools is discussed. There is continuous need to disseminate information on the clinical classification and diagnosis of allergic rhinitis to enable appropriate diagnosis, management and comparative studies on the disease profile.

Keywords: Allergic rhinitis, ARIA classification, Clinical diagnosis.

INTRODUCTION

Allergic rhinitis (AR) is an IgE mediated inflammation of the nasal mucosa in response to an allergen. This disease has become a worldwide clinical condition with increasing incidence.[1-3] It is estimated that about 400million of the world population is probably affected by this condition.[4] It was first described as Hay fever in the 19th century by Bostock and later Blackley in relation to exposure to pollen.[5] Later, the term "hay fever" was noted to be a misnomer as it is not a febrile illness.[6,7] However, it is now used to describe the seasonal form of allergic rhinitis. Over the years studies have elucidated the pathophysiology of this condition which has led to changing perspectives in the classification and clinical diagnosis of allergic rhinitis. The changing perspectives are probably responsible for the different diagnostic criteria for the condition which has resulted in the disease being under diagnosed and underestimated.[8] This article is a narrative review of the current views in the classification and clinical diagnosis of allergic rhinitis. The aim is to highlight the current diagnostic criteria that will enable General medical practitioners make accurate diagnosis of allergic rhinitis.

CLASSIFICATION OF AR

Previously, nasal allergy was classified as either seasonal or perennial allergic rhinitis depending on whether it occurs during particular seasons of the year or if it occurs irrespective of seasons of the year. It was thought that the perennial type is caused by indoor allergens and the seasonal type by outdoor allergens

mainly pollens. It was thought that seasonal and perennial allergic rhinitis present as two different clinical entities. Epidemiological studies have shown that this classification system has limitations.[9]It was found that the duration of aeroallergen pollen season is dependent on geographic locations and climatic conditions. In places where the pollen season is year-round, allergic symptoms provoked by exposure to pollen are difficult to distinguish by history from symptoms caused by exposure to allergens that are perennial, like indoor allergens. Also spores from fungal molds have been shown to be both seasonal and perennial allergens. Further studies have shown that in some areas, pollens can induce perennial AR when individuals are exposed to pollens which adhere to indoor furniture even after the pollen season is over. Seasonal AR individuals who are sensitized to multiple allergens may have rhinitis symptoms in all seasons. Furthermore, seasonal exacerbations have been found to occur in perennial AR patients when they are exposed to pollens.[9-11]

In 2001, the World Health Organization assembled a group of experts to review the current evidence on allergic rhinitis. This became the "Allergic Rhinitis and its Impact on Asthma (ARIA) Workshop Expert Panel". They met to develop guidelines on the classification, diagnosis and treatment of rhinitis. The panel worked on collation of the available knowledge on allergic rhinitis, highlighted the impact of allergic rhinitis on asthma, provided an evidence-based document for revision of the diagnostic methods, provided an evidence-based revision for the treatments available and proposed a stepwise approach to the management of the disease. The acronym "ARIA" comes from "Allergic Rhinitis and its Impact on Asthma". This panel proposed a classification based on frequency of occurrence of symptoms and the disease severity. Thus, it was classified as either "intermittent" or "persistent" instead of "seasonal" and "perennial". The disease severity was classified as either "mild" or "moderate-severe" considering its influence on work/school performance, daily activities and sleep.[12] Subsequently the panel has met in 2008 and 2013 to review this classification and update the guidelines. These reviews are based on analysis of pooled data from new research publication findings.[13, 14]The ARIA recommendations have gradually led to a shift in the management of allergic rhinitis from Opinion – based practice to Evidence – based practice and now to Patient focused care.

ARIA Classification of Allergic Rhinitis

Intermittent symptoms

- <4days per week
- Or <4 weeks

Persistent symptoms

- >4days/week
- OR>4 weeks

Mild

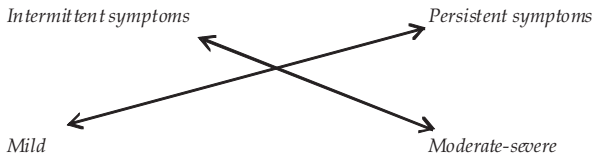
All of the following

- Normal sleep
- No impairment of daily activities, sports and leisure
- No impairment of work or school activities
- No troublesome symptoms

Moderate-severe

One or more of the following

- Abnormal sleep
- Impairment of daily activities, sports and leisure
- Impaired work or school activities.
- Troublesome symptoms



Thus, a patient may have intermittent symptoms that are mild, intermittent symptoms that are moderate – severe or have persistent symptoms that are mild, persistent symptoms that are moderate to severe. This classification is used to determine the stepwise management protocols. Different research efforts have been done using this classification in randomized clinical trials. This has resulted in treatment guidelines provided. The ARIA review of 2008 recommended that asthma should be evaluated in individuals with moderate-severe and persistent symptoms.[13]

Data from more studies are being evaluated and the guidelines are being updated. Also various research groups are also developing and streamlining their guidelines to suit the reality in different environments.[15] These studies are mainly systematic or meta-analytical studies that pool data from published randomized controlled studies. Some have introduced episodic allergic rhinitis and occupational allergic rhinitis[14]. Others have retained the Seasonal allergic

rhinitis (SAR) and the Perennial allergic rhinitis (PAR).[16] These classifications help to guide the development of management protocols.

CLINICAL PHASES OF ALLERGIC RESPONSE.

Acute Or Early Phase.

This occurs within 5-30s, after exposure to a specific allergen in a previously sensitized individual. The main symptoms are sneezing, rhinorrhoea, itching of the nose, nasal blockage and itchy eyes. These are due to the action of vasoactive amines (Histamine) and other mediators released at the early phase.[17]

Late Or Delayed Phase.

This occurs 2-8hrs after exposureto specific allergen in a sensitized individual and continues for more than 24hrs. It is due to infiltration of inflammatory cells and the release of a cascade of mediators. This phase is marked by the continuation of the symptoms of the early phase reaction but more by nasal congestion and secretions. Several factors have been implicated in the continuation of this phase such as the type allergen, the dose of allergen, the cascade of mediators secreted and other factors that regulate the immunologic chain reaction.[17]

DIAGNOSIS OF AR

The diagnosis of Allergic Rhinitis (AR) is based on a typical history of allergic symptoms and diagnostic tests. In 2008, ARIA expert panel proposed the clinical guideline detailed below for the diagnosis of allergic rhinitis with the acronym SOIRE.[13]

ARIA Differential Diagnosis for Symptoms of Allergic Rhinitis: [Bousquet (pocket) 2008]

Symptoms suggestive of Allergic Rhinitis

- 2 or more of the following symptoms for > 1 hour on most days:

- **SOIRE**
  Sneezing
  Obstruction (nasal)
  Itchy nose
  Rhinorrhea
  Eye symptoms – Itchy, watery, redness etc

Confirmation of the diagnosis should be established by a positive skin prick test.

Symptoms usually *not* associated with allergic rhinitis

- Unilateral symptoms
- Nasal obstruction without other symptoms
- Mucopurulent rhinorrhea
- Post nasal drip with thick mucus
- Facial pain
- Recurrent epistaxis
- Anosmia

In 2015, the American Academy of Otorhinolaryngology published a clinical practice guideline to streamline and optimize the diagnosis and care of patients with allergic rhinitis through a review of available evidence from well conducted controlled randomized clinical research works. Levels of evidence were assessed using known parameters and a consensus reached on various action statements.[18]Summary of some of the Guideline Action Statements is as follows:

1. Patient history andphysical examination:

"Clinicians should make the clinical diagnosis of AR when patients present with a history and physical examination consistent with an allergic cause." 1 or more of the following symptoms: nasal congestion, runny nose, itchy nose, or sneezing is needed. There should also be presence of physical signs that are consistent with an allergic cause such as clear rhinorrhea, nasal congestion, pale discoloration of the nasal mucosa, red and watery eyes.

2. Allergy testing

"Clinicians should perform specific IgE (skin or blood) allergy testing for patients with a clinical diagnosis of AR who do not respond to empirical treatment, or when the diagnosis is uncertain, or when knowledge of the specific causative allergen is needed to target therapy."

3. Imaging

"Clinicians should not routinely perform sinonasal imaging in patients presenting with symptoms consistent with a diagnosis of AR."

CLINICAL EVALUATION

Clinical evaluation of patients with allergic rhinitis should be by a thorough history, adequate physical examination and investigations. The history should include the onset, timing, duration, seasonality and severity of symptoms. Associated symptoms, aggravating and alleviating factors should be assessed. Thorough environmental history, family history of atopy and suspected allergens are also important.

Physical examination should include the general appearance to assess the presence allergic shiners, allergic salute and ocular signs. The nose should be examined for presence of septal deviation, polyps, discharge, turbinate hypertrophy andhypo nasality. The ear is examined for middle ear pathology. The chest should be examined for wheezing and rhonchi. The skin is examined for presence of eczema and dermatographism. The findings will assist in diagnosis of straight forward allergic rhinitis, determine other forms of rhinitis that may not be due to allergy and assess the onset of comorbid conditions or complications of allergic rhinitis. The key issues are the presence of inflammation of the nasal mucosa (rhinitis) and the cause of the inflammation (allergy).

INVESTIGATIONS

While many authors have looked at the investigations for nasal allergy as specific and non- specific, others prefer the sub division of screening and diagnostic tests.[19] However, the important issues relate to the ability to confirm diagnosis, determine the offending allergens and confirm the presence of comorbid conditions in order to treat appropriately.

The main investigations include the following main headings:

1. **Allergy Testing**
    a. **Nasal smear**
    b. **Skin testing**
    c. **In vitro testing**
    d. **Nasal provocation**
2. **Radiology**
3. **Lung function tests**
4. **Acoustic rhinometry**

Nasal smear

Studies have shown that the secretions from the nose of patients with nasal allergy contain increased numbers of eosinophils. This forms the basis for the nonspecific but useful test of nasal smear for eosinophils. It is nonspecific because it cannot identify the etiologic specific allergen. The test can be useful as a screening test when there is significant eosinophilia. However, it cannot differentiate allergic rhinitis from non-allergic rhinitis with eosinophilia (NARES).

In countries where specific allergen extracts have not been developed, this may be the main diagnostic tool as studies have shown good correlation between significant eosinophilia with positive skin prick tests in patients with allergic rhinitis.[20-22]

Skin testing

The goal of skin testing is to identify allergens to which patients are symptomatically reactive and to quantify the sensitivity if immunotherapy is planned.[23] Also it may be useful for allergen avoidance and environmental control measures as part of treatment strategies. Skin testing is performed by introducing a specific allergen into the patient's skin. It allows for direct observation of the body's reaction to a specific allergen. The allergen rapidly activates cutaneous mast cells by interacting with IgE antibodies on the surface of those cells. This leads to the release of chemical substances such as histamine from mast cell granules and results in the development of a wheal and flare reaction within 15 to 20 minutes. Skin testing is primarily done by either the skin prick technique or by the intradermal technique.[24]

The Skin Prick Test

This is performed by placing a drop of the allergen on the skin (usually the forearm). A lancet is then used to prick the top layer of the skin through the drop so that the allergen is introduced under the skin surface. The drop is then wiped away. This process is repeated for each allergen requiring testing. After 15 minutes signs of a reaction may be seen as a wheal. The diameter of the wheal is measured. A negative reaction is when the skin remains normal and a positive reaction is seen when a wheal is seen. This wheal will disappear within 30-60 minutes. The test agents should include histamine which should be positive and saline which should be negative.[25] Skin tests may be slightly uncomfortable, but are usually well tolerated, even by children. If the test comes up positive the wheal may feel itchy for up to 20 minutes. Once the test has been read, a cold compress can be applied or some antihistamine given. Skin prick testing has been shown to be highly sensitive and specific, typically over 80% for both.[26, 27] Skin testing can be used in patients of any age. Infants tend to have small wheals with both positive controls and allergens. Although the prevalence of positive skin tests is known to be lower after the age of 50years, significant positive skin tests can still be detected in the older population.[28]

Skin testing is contraindicated in uncontrolled or severe asthma, presence of skin disease such as eczema, co-existing medical conditions such as severe and unstable cardiovascular disease, and during use of β-blockers and antihistamines. Adverse reactions such as immediate and delayed local swelling,

redness, pain, and itching have been reported with skin testing. However, serious adverse events such as anaphylaxis and death are rare.[29]

In clinical practice, there is variation in the number of skin tests that can be done, the allergen extract concentration used for testing, selection of skin testing devices, interpretation and documentation of results, and quality assurance procedures used.[30]Many authors recommend the use of standardized allergen extracts. In developing countries, most local allergens are not available in standardized allergen extracts. Thus, skin prick testing may not be too useful with relation to allergen avoidance measures or specific immunotherapy.[31]

Intradermal tests

These are other forms of skin testing that are used for identifying IgE-specific allergens. Intradermal skin tests are particularly helpful when the prick test is negative and there is a high clinical suspicion for allergic sensitization to a particular allergen or if increased sensitivity is required. A dilute allergen extract is injected into the dermis, and a superficial wheal formation signifies positivity. The main disadvantage is a higher risk of anaphylaxis.[32]

Nasal provocation test

This is regarded as a nonspecific test. It is a rapid, efficient, and cost effective method to assess allergy. Most allergic individuals will react to common allergens but the allergens should be representative of what the patient may encounter, and should be geographically based. A negative result usually requires no additional testing but a positive result requires further testing of other allergens in the group or family.[33]

Other nonspecific tests include acoustic rhinometry and Lung function tests. Most clinical practice guidelines have no recommendation for or against their use as extensive systematic review and meta-analytical studies have not proven their usefulness in the diagnosis of nasal allergy. They are mainly used to assess bronchial sensitivity.

In vitro testing

The main in vitro test is the radioallergosorbent test (RAST) and it measures allergen specific IgE level in the patient's blood. It is very safe, highly sensitive, best for patients taking beta-blockers, antihistamines, patients with dermatographism, and children that cannot tolerate skin testing. However, it is more expensive and takes a longer time for the results to be available. It was developed in the late 60's for the detection of specific serum IgE antibodies.Initial studies demonstrated a 96% efficiency, sensitivity and specificity. However, the modified RAST is the form now used. It was introduced by Fadal and Nalebuff in 1977 with the advantage of increased test sensitivity without a loss in specificity.[34]

Radiologic Imaging

Clinical practice guidelines do not support radiographic imaging in patients who have met the clinical criteria for the diagnosis of AR. Potential adverse events and cost preclude the benefits of routine imaging. Radiographic testing may have a role in the diagnosis if the clinical presentation points to potential sequelae of AR, such as rhinosinusitis, nasal polyposis, and concerns of suspected neoplasm.[15]

CONCLUSION

Allergic rhinitis is now established as an IgE mediated hypersensitivity reaction of the nasal mucosa to specific allergens. The earlier classification of "seasonal" and "perennial" has been replaced with "intermittent" and "persistent" with clear definitions of timing and duration of symptoms to determine each class. In addition the severity of the symptoms have been clearly defined as either "mild" or "moderate to severe" depending on the effect on the patients perceived tolerance. An important significance of this classification lies in the objectivity which will enable research works to be better compared.

The diagnosis of allergic rhinitis is now better streamlined with clear clinical parameters and confirmatory tests. This enables the ability to differentiate this condition from other common causes of rhinitis and assess the presence of comorbid conditions or presence of complications. In resource poor countries, adherence to the clinical parameters for diagnosis will help practitioners to assess patients with allergic rhinitis more appropriately. The challenge is the inability to perform confirmatory tests.[35] Thus there is need for collaborative studies to determine the prevalent allergens and produce allergen extracts that will be used for confirmatory skin prick tests.

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