An Updated Insight about Diagnosis of Allergic Rhinitis

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Conflict of interest: None declared.
Funding: No funding sources

Abstract

Allergic rhinitis (AR) is often underdiagnosed or undertreated by physicians. The global prevalence of AR among children and adults is about 25 and 40 %, respectively. Furthermore, it has a negative impact on patients' quality of life (QOL) in form of interference with daily activities, difficulty of breath, sleep problems and school absenteeism. AR is an IgE-mediated disease, triggered by exposure to environmental allergens leading to sensitization and activation of mast cell and basophil with release of several inflammatory mediators (such as histamine, leukotrienes, prostaglandins and platelet-activating factor. The diagnosis of AR is made by taking a detailed history supported by careful clinical examination. Usually, the diagnosis of AR is confirmed by detection of IgE sensitization to certain allergens by in vivo skin tests or in vitro tests, which may be performed in different ways. Molecular allergy diagnosis is based on the detection of IgE specific against single allergen components (molecules) from specific allergen source using native or recombinant allergens. An allergenic component is a single protein molecule that can induce an allergic immune response.

Keywords: Allergic rhinitis, Allergy test, IgE, Molecular diagnosis, Atopy

Tob Regul Sci.™ 2023 ;9(1): 8017-8029
DOI : doi.org/10.18001/TRS.9.1.567

Introduction

Despite being a very prevalent disease, AR is often underdiagnosed or undertreated by physicians. The global prevalence of AR among children and adults is about 25 and 40 %, respectively. Furthermore, AR has a negative effect on patients' quality of life in the form of interference with daily activities, difficulty of breath, sleep problems and school absenteeism. [1].

AR is an IgE-mediated disease, triggered by exposure to environmental allergens. Clinical expression of the disease is a result of a cascade of immunological and biochemical events including

inhalation of allergens, disruption of tight junction of nasal epithelial barrier, engulfment of the allergen by dendritic cells and presentation to T helper 2 lymphocyte (Th2), B lymphocyte class switching and production of immunoglobulin E (IgE). Then IgE binds to high-affinity receptors FcεRl on mast cells and on basophils leading to granule exocytosis and release of preformed or newly created inflammatory mediators (such as histamine, leukotrienes, prostaglandins, platelet-activating factor, etc.). [2].

The diagnosis of AR is made by taking a detailed history supported by careful clinical examination. Allergy testing is also important for confirming that underlying allergy is the cause of rhinitis [3].

I. Clinical history

The clinical history should include symptoms such as nasal discharge, nasal blockage, itching or sneezing, the place and the time of their occurrence, together with any exacerbating or relieving factors. Other symptoms in the chest, ears, throat, eye, gut or skin also must be included. In addition, family history of allergic diseases and history of any previously or currently used medication or any surgical intervention should all be noted [4].

Asking about seasonality of symptoms, indoors/outdoors location, work location and occupational exposure and relationship to potential triggers which can significantly affect the patient's quality of life should also be included in the history [5].

There are several scoring systems for determination of symptoms and disease severity in AR including visual analogue scales (VAS) and quality-of-life (QOL) questionnaires. In addition, total nasal symptoms score (TNSS) is considered one of the commonly used scoring systems. The TNSS is the sum of scores for each of nasal congestion, sneezing, nasal itching, and rhinorrhea at each time point, using a four point scale (0– 3), as illustrated in table (1), where 0 indicates no symptoms, 1 indicates mild symptoms that are easily tolerated, 2 indicates awareness of symptoms which are bothersome but tolerable and 3 is reserved for severe symptoms that are hard to tolerate and interfere with daily activity TNSS was calculated by adding the score of each of the symptoms to a total out of 12 [6].

Score	Symptom
0 = None	No symptoms evident
1 = Mild	Symptoms present but easily tolerated
2 = Moderate	Definite awareness of symptom; bothersome but tolerable
3 = Severe	Symptom hard to tolerate; interferes with daily activity

Table (1): Total Nasal Symptom Scores [6].

II. Clinical Examination

An overall examination of the patient is necessary because rhinitis is usually associated with other co-morbidities. Growth assessment in children is very important, as severe airway problems are usually associated with reduced growth. The presence of facial features such as conjunctivitis, nasal

allergic crease, allergic salute or double creases beneath the eyes (Dennie–Morgan lines) are all suggestive of allergic problem [5].

Nasal examination is needed for patients presented with moderate to severe symptoms or those with uncontrolled symptoms despite optimal treatment. This examination should include observation of the external features followed by internal examination. Observing the position of the nasal septum, as well as the size and color of the inferior turbinates, together with examination of the nasal mucosa and detection of any secretions, polyps, bleeding, tumors, crusts or foreign bodies should be included [2].

The classic appearance of the nasal cavity of AR patients is swollen pale bluish inferior turbinates with profuse clear secretions. However, those features are not specified to AR disease and many times the nose may appear normal. Patients with nasal polyps, bleeding, tumors, crusts and septal lesions should be referred to an ear, nose and throat specialist [4].

Owing to the frequent co-occurrence of asthma and AR, patients with AR should usually be assessed for having asthma. This is done by asking patients about symptoms such as chest wheezes, cough or shortness of breath. An objective measurement with spirometry can also be used in some of those cases. Also, skin examination for concurrent atopic dermatitis should be done [6].

III. Diagnostic tests:

Although history taking and physical examination are needed to establish the clinical diagnosis of AR, further diagnostic tests are necessary to confirm allergen exposure and sensitization as a cause of AR [7].

Usually, the diagnosis of AR is confirmed by detection of IgE sensitization to certain allergens by in vivo skin tests or in vitro tests, which may be performed in different ways [8].

A. In vivo allergy tests:

1. Skin prick test (SPT):

Skin prick testing is safe with high sensitivity and good specificity when performed and interpreted in an appropriate manner. Testing is typically performed using the allergens related to the patient's environment. It is done by placing a drop of an extract of a specific allergen on the skin of the forearms or the back, then pricking the skin through the drop using sharp pointed lancet to introduce the extract of allergen into the epidermis. Histamine and normal saline are used as positive and negative controls, respectively. Within 15–20 minutes, a wheal and flare will be formed, then measured and a wheal size of 3 millimeters greater than the negative control is interpreted as positive, Figure (1) [9,10].

SPTs are difficult to apply in patients with dermographism, severe eczema or with taking antihistamines or other medications as certain antidepressants which may interfere with the interpretation of the results, in vitro testing is highly recommended in these cases. SPTs are also should be cautiously done by experienced practitioners in case of pregnancy, severe asthma, history

of anaphylaxis, and for patients treated with drugs that may increase the risk of extensive allergic reactions such as beta-blockers [11].

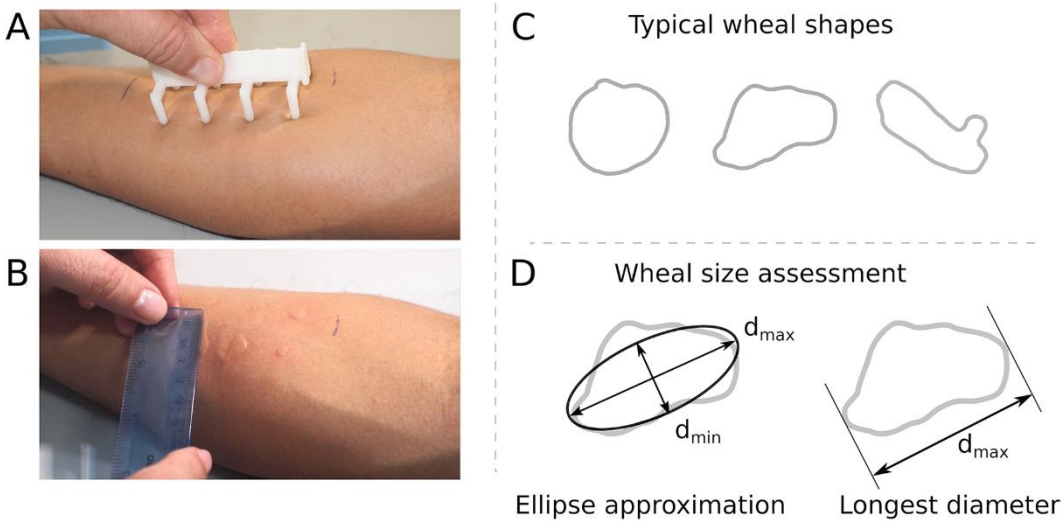

Figure (1): (A) SPTs on the surface of the forearm. (B) Measurement of skin reactions or wheals using a ruler. (C) Different shapes of wheals, (D) The wheal size assessment [11].

2. Intradermal skin test (IDT)

In a patient with a strong clinical history of an IgE-mediated allergy but with negative skin prick tests, IDT may be considered. It has decreased specificity and increased sensitivity compared to SPT. The diluted allergen extract is injected intradermally using a short needle. Histamine is used as a positive control while saline is used as a negative control. The reaction is observed for 15- 20 minutes, formation of a wheal of a minimum 5mm, or any reaction larger than the negative control is considered a positive test. [12].

3. Nasal provocation test (NPT):

Standardized nasal provocation testing has been demonstrated to be a very useful test in the diagnosis of AR. However, its use has been limited to scientific research and has not been widely used as a standard diagnostic test in clinical practice [13].

During NPT, the nasal mucosa of the tested patient is exposed to a suspected allergen and resulting reactions are assessed in a standardized manner. Nasal symptoms including nasal secretions, itching, sneezing and nasal obstruction are observed together with ocular, bronchial, cutaneous, and systemic reactions in addition to using anterior rhinomanometry and acoustic rhinometry in the standard protocol of NPT. The test is contraindicated in cases of acute bacterial or viral rhinosinusitis, AR exacerbation, history of anaphylaxis, and pregnancy [14,15].

B. In vitro allergy testing:

The in vitro diagnosis of IgE-mediated allergy is helpful in the detection of the causative allergens and includes different laboratory procedures for measurement of total and specific IgE in addition to more specific tests, such as basophil activation test (BAT) and mast cell activation test (MAST) [16].

1. Total IgE (tIgE):

Measuring (tIgE) for the purposes of diagnosis and management of allergic diseases is variable. Total IgE assays are usually nonspecific, and their importance is restricted to their ability to identify patients with atopy in general [17].

2. Allergen-specific IgE (sIgE)

In the situation that SPT is difficult to perform, measurement of allergen sensitization in blood can be an alternative method. They can be performed by a singleplexed or multiplexed approaches that provide a measure of the patient's specific IgE level against one allergen only or a set of allergens, respectively. On the other hand, these tests alone cannot provide a definitive diagnosis of allergy due to many false positive results without appropriate clinical history [18].

a. Serum sIgE:

Allergen-specific immunoglobulin E (sIgE) blood assay offers an alternative tool to identify the causative allergen. It is considered comparable to skin prick test for diagnosis of respiratory allergy. There are many advantages for using sIgE blood assay over skin tests, including lack of medication or skin condition interference, no risk of anaphylaxis in addition to providing quantitative or semi-quantitative results. In general, good agreement has been identified between skin test and sIgE blood assay for the most potent aeroallergens including trees, grasses, dust mite, pets' allergens [19].

b. Nasal sIgE

There is an increasing interest in the detection of sIgE in nasal secretions of AR patients. Local production of IgE, in the nasal mucosa, was first detected in 1975 by Huggins et al, and since then many studies have documented measurement of nasal sIgE as a useful noninvasive method for AR diagnosis. In addition, other studies reported that nasal sIgE can predict house dust mite (HDM) driven AR [20].

Moreover, several patients exhibit negative SPT and normal levels of serum sIgE, despite a clinical history that suggests AR. This type of AR is called local allergic rhinitis (LAR) and is characterized by the presence of a localized allergic reaction in the nasal mucosa involving the local production of sIgE without a positive skin prick test or an increase in serum sIgE levels. [21].

Nasal IgE can be measured by several non-invasive and invasive methods such as nasal filter disks, cotton swabs, lavage, sinus packs and mucosal brush biopsy or scrapping. Though, a main challenge in sampling of nasal secretion is minimizing sample dilution and patient's discomfort, there is yet no optimal standardized approach on collection, processing, and evaluation of nasal secretion [22].

❖ Invitro immunoassays for sIgE measurement:

According to literature, most specific IgE blood tests are immunoassays including radioallergosorbent assays (RASTs), chemiluminescent assays, dot blot, enzyme-linked immunosorbent assays (ELISAs) or fluorescent enzyme immunoassays (FEIAs) [16].

It is important to illustrate that skin prick tests and specific IgE immunoassays only confirm a specific aeroallergen sensitization; yet the patient's medical history must be used to validate the significance of allergen sensitization and its relationship to symptoms [23].

❖ Classification of invitro immunoassays: [16]

a. Qualitative assay: A qualitative assay is defined by the presence of the analyte over a specific positive threshold level of the assay. However, it does not provide a measurement of IgE concentration. It only demonstrates negative or positive results. Levels may be deemed "borderline" if they are near the system's cutoff point (eg. qualitative ELISA).

b. Semiquantitative assay: A semiquantitative assay generates a series of increasing classes (e.g., from I to VI), thus indicating the response's quantity (eg. immunoblot assay).

c. Quantitative assay: A quantitative assay can measure the IgE antibody concentration based on the interpolation from a calibration curve (eg. ImmunoCAP and quantitative ELISA).

❖ Types of invitro immunoassays:

a. Radioallergosorbent test (RAST):

Radioallergosorbent test (RAST) was first described by Wide and colleagues in 1967 for sIgE detection in serum. This assay is radioisotope-based in which an allergen is covalently attached (allergosorbent) to a paper disc solid phase to bind allergen-specific antibodies from serum. Unbound serum proteins were removed by washing while bound IgE was detected with radioiodinated (I125) polyclonal anti-human IgE and the radioactivity amount is proportional to the serum IgE for the allergen. The main limitations of RAST are the use of the radiolabeled reagents and equipment in addition to being time-consuming as it takes a minimum of two days to obtain results. [24].

b. Fluorescent Enzyme Immunoassay (FEIAs): Figure (2)

In the early 1990s, ImmunoCAP was released. It is considered a “reference standard” for in vitro IgE testing. ImmunoCAP is a fluorescent enzyme immunoassay (FEIAs) in which a cellulose solid phase is used to bind the protein and a fluorometer is used to measure bound IgE levels. The assay's quantitative results are given in kU/L, with 0.35 kU/L serving as the cutoff [25].

ImmunoCAP has been considered a method of choice in measurement of sIgE, due to its very high sensitivity, precise clinical and analytical performances and reasonable consistency in comparison with SPT results. However, this technique has its limitations including high cost, need for automated machines and highly qualified personnel, and solid-phase allergen immobilization are the most important ones [26].

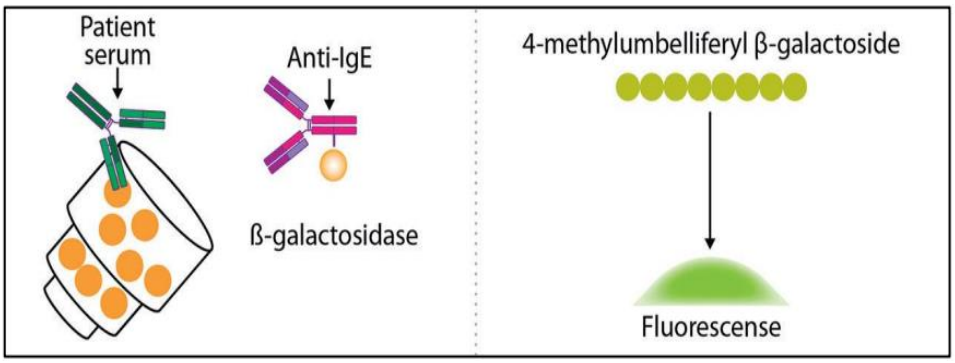

Figure (2): Principle of ImmunoCAP. [27].

c. Enzyme Linked Immunoassays (ELISA):

ELISA immunoassay is considered an analytical method that can detect antigen antibody reactions through color change by using an enzyme-linked conjugate and enzyme substrate and that serve to identify the presence and concentration of molecules in biological fluids. [28].

ELISA immunoassay exhibits many advantages in sIgE measurement, as it is considered an eco-friendly, simple procedure with high sensitivity and specificity. It can serve as a viable substitute for FEIAs, as they are relatively uncomplicated and cost-effective for measuring specific IgE levels for different allergens. Their utility is particularly valued in situations where ImmunoCAP is unavailable [16].

d. Chemiluminescent assay:

A two-step solid-phase chemiluminescent immunoassay that utilizes solution-phase kinetics in a bead configuration. This is a major advance over older approaches that use allergens attached to solid substrates such as paper discs. Allergens consist of a soluble polymer/copolymer matrix that is progressively labeled with ligands. The introduction of amino acid copolymers increases the number of allergens carried by the matrix [29]. Figure (3)

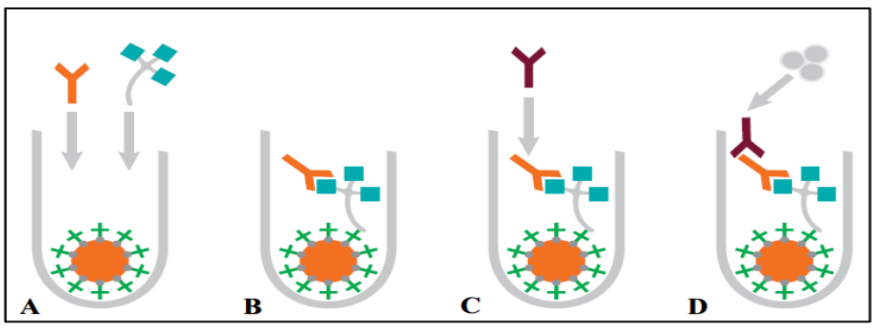

Figure (3): Chemiluminescent assay (A) The first step incubated serum, liquid specific allergen, with an anti-ligand-coated polystyrene bead. (B) Specific allergens bound to serum IgE antibodies and to the bead. (C) During the second cycle, alkaline phosphatase-conjugated monoclonal anti-IgE was added and binds to serum IgE. (D) A chemiluminescent substrate was added, and light was emitted to provide a quantitative IgE result [29].

e. Immunoblot Assay: Figure (4)

The Immunoblot assay, an enzyme-allergo-sorbent test (EAST) system, is considered a semiquantitative assay. It was introduced in clinical practice as a reliable and costly efficient invitro specific IgE test. Several kits have been marketed using immunoblotting for sIgE measurement, such as Polycheck®; Biocheck, Euroline and AllergyScreen® / AlleisaScreen® tests [30].

In this immunoassay, a patient sample is incubated with recombinant or native purified different allergen extracts coating membrane strips in thin parallel lines as line blots. Then the conjugate labeled anti-IgE detection antibody and the substrate are added, all in a blot strip incubation channel on a rocking shaker with washing procedures in-between. Finally, scanning is performed on the dried membrane strip using a computer-linked scanner. The measurement range is given in classes from 0 to 6 according to sIgE concentration with detection limits from 0.35 to 100 kUA/L [23].

Moreover, the advantage of immunoblotting assay over single allergen test systems is the simple and rapid analysis of a whole range of allergens in a single lab test. In addition, this type of approach is cheaper than single tests and uses less lab materials and less amount of patients' sample [31].

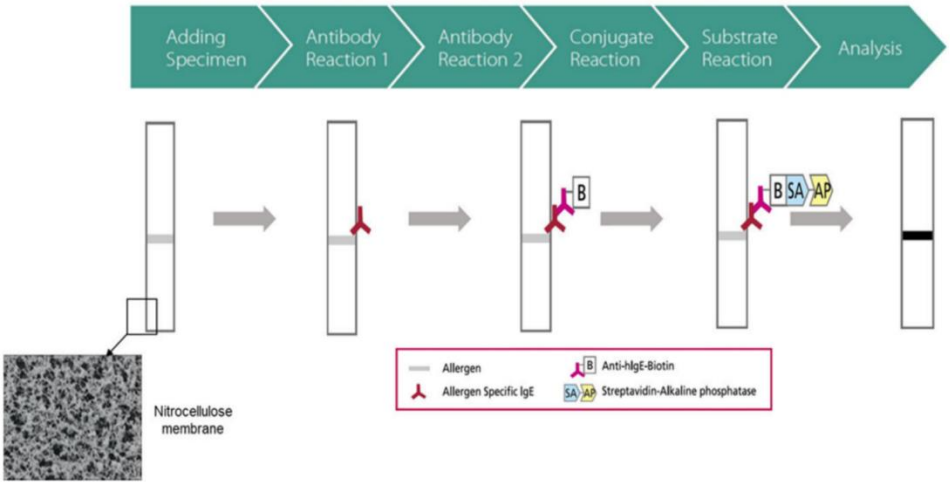

Figure (4): Schematic explanation of the measurement principle of immunoblot assay. [32].

f. Molecular allergy diagnosis or component resolved diagnostics (CRD):

CRD is considered a type of personalized medicine. It enables accurate identification of the allergen molecule to which the patient is allergic. It also provides the opportunity to accurately identify a harmful allergen and discriminate between genuine sensitization or possible cross-reactions. Moreover, it can estimate the expected effectiveness of allergen immunotherapy [33].

Molecular allergy diagnosis is based on the detection of IgE specific against single allergen components (molecules) from a specific allergen source using native or recombinant allergens. An allergenic component is a single protein molecule that can induce an allergic immune response [34].

❖ Types of molecular allergy diagnosis

Currently, several invitro approaches are available for the study of specific IgE against allergen components. This can be performed in two ways by measuring the concentration of IgE specific for single allergen molecules (single-component diagnostics, singlplex) or by simultaneously measuring the concentration of sIgE for many allergenic components in one test (multi-component diagnostics, multiplex) [23].

a. Single-component diagnostics:

Single-component diagnostics is a measurement of the serum concentration of sIgE for only a selected allergen molecule using native or recombinant allergen components and the result gained is always quantitative. These techniques are relatively expensive and require a large volume of serum per allergen. ImmunoCAP, a specific IgE Phadia ™ instruments with full automation, is considered a singleplex assay that can assess the patient's allergic sensitization profile not only for natural extracts but also at molecular level nowadays [35].

b. Multi-component diagnostics: figure (5)

Multi-component diagnostics is based on the determination of specific IgE concentration for many different allergen components in only one test. Microarray technology allows for the simultaneous analysis of thousands of parameters in a single experiment. They can be used to detect either sIgE only for allergen components as in Immuno Solid-phase Allergen Chip (ISAC 74, ISAC 112) test or sIgE for allergen components and the total concentration of IgE in patient's sample as in the Allergy Xplorer (ALEX) Macroarray test [36].

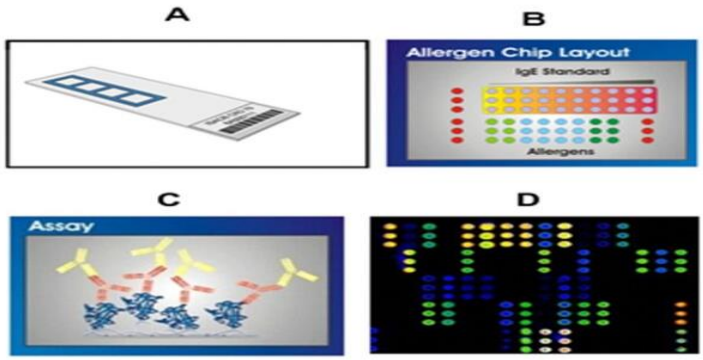

Figure (5): ISAC system. A, chip with 4 reaction chambers. B, purified allergens spotted on the microarray. C, detection of IgE – allergen complex by a fluorescent dye conjugated to anti human IgE antibodies, allergenic proteins immobilized to the chip are in blue, Human IgE are in red and anti- are in yellow. D, fluorescence intensity is measured by a microarray scanner. [37].

❖ Limitation of molecular allergy diagnosis:

Although having a great impact on precise allergy diagnosis, Molecular diagnosis has many drawbacks including the high cost, the need of a strong computer system and highly trained

personnel, in addition to the availability of such tests in only major hospitals, all these obstacles make it difficult to generalize the use of such new techniques in allergy diagnosis [36].

3. Cellular assays:

a. Basophil activation test (BAT):

BAT is a functional assay that measures the degree of degranulation following stimulation with allergen or controls and it correlates directly with histamine release. It is a flow-cytometric based assay which measures the expression of activation markers on the surface of blood basophils; CD63 and CD203c. It plays a significant role in allergy diagnosis, particularly with negative or equivocal results obtained from other in vivo and vitro tests. Moreover, because BAT is a laboratory test, it spares patients from being exposed to the allergen under investigation, improving patient and family comfort and safety throughout the diagnostic procedure [38,39].

Despite the BAT's many advantages, a few remaining weaknesses prevent it from being used more widely. It should ideally be carried out within 4 hours of collection and around 15% of tested patients may be non-responders. In addition, it is challenging to standardize the BAT [40].

b. Mast Cell Activation test (MAT):

MAT is a new approach based on flowcytometry in which patient serum is added to a mast cell line and then incubated with allergen invitro, after that mast cell activation and degranulation can be assessed. It can be a promising diagnostic approach over BAT as it uses serum or plasma samples that can be frozen or stored [41].

To conclude, AR diagnosis mainly relies on the clinical history and physical examination of patient, together with in vivo skin tests and nasal provocation test, in addition to in vitro allergen specific IgE such as ELISA, chemiluminescent assays, FEIAs, Immunoblotting assays and CRD. Moreover, BAT and MAST are considered alternative methods which will confirm the correlation between clinical history and assumed allergens in diagnosis of AR. Figure (6)

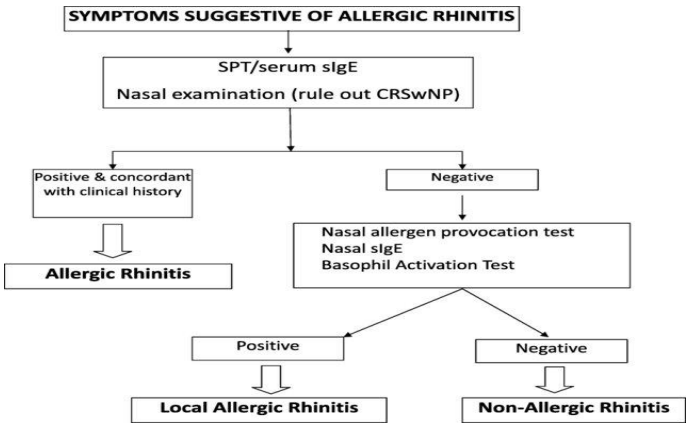

Figure (6): Diagnostic algorithm of AR, CRSwNP: chronic rhinosinusitis with nasal polyps [42].

No Conflict of interest.

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