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DIAGNOSIS OF ALLERGY

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ABSTRACT

In modern world allergy is one of the most widespread disease. The word allergy was derived from Greek word 'alol' which mean change and 'ergos' means reactivity. Allergy is an overreaction of the immune system to a substance that is typically harmless to most people. Body's immune system treats the substance, called an allergen, as an invader and reacts inappropriately cause harm to the person. These allergic diseases comprise of asthma, rhinitis, anaphylaxis, drug, food and insect allergy, eczema, urticaria and angioedema. Medical history, family history, environmental history and allergy tests are the key factors in diagnosis of allergic diseases. Medical, family and environmental histories play an important role to identify a temporal association between allergen exposures and allergic symptoms whereas allergy testing focuses on determining which allergen cause a particular reaction, the degree of the reaction and provides recommendations for treatment. Allergic diseases can be suspected or confirmed depending on the consistency and strength of the findings. Positive history, skin-prick tests (SPTs) or specific IgE measurements to commonly prevailing allergens can be used to confirm allergy.

KEYWORDS : Allergy, Allergen, Urticaria, Anaphylaxis, Angioedema

After John Bostock's description of Catarrus aestivus or hay fever in 1819 allergy was recognized in modern era (Bostock, 1828). Pollen grains were identified as potential causative agents for hay fever by Charles Blackley (Blackley, 1873). The term 'allergy' was firstly used by Clemmens Von Pirquet in 1906 to describe the strange, non disease related symptoms that some diphtheria patients developed when treated with a horse serum antitoxin (Von Pirquet, 1906). To describe an immediate hyper reactivity reaction to allergens the term 'atopy' was coined (Coca and Cooke, 1923). Allergy is a state of immune deregulation from T-helper 1 (Th1) and T-helper 2 (Th2) balance and this state leads to overproduction of IgE (Lacour, 1994) which plays a central role in causing allergy (Jujo et al., 1992).

A study carried, over 30 years ago in Delhi reported around 10% allergic rhinitis and 1% asthma in 1964 (Viswanathan, 1964). Thereafter later studies have reported that 15% population develop asthma and 20% to 30% of the suffer from allergic rhinitis (Chhabra et al., 1998; Anonymous, 2000). More than 25% of the population in industrialized countries suffers from different allergies (Valenta, 2002). Studies suggest that worldwide more than 20% individuals suffer with IgE-mediated allergic diseases such as eczema, asthma, rhino conjunctivitis and anaphylaxis (Linhart and Valenta, 2005). Parsad and Kumar, 2013 more recently studied that in India 20% to 30 % of total population suffers from at least one of these allergic diseases (Parsad and Kumar, 2013).

Allergens are mostly proteins or their modified forms e.g. lipoprotein, glycoprotein, or proteins conjugated with drug haptens or chemical (Wagner et al., 2000; Beezhold et al., 2003). Certain carbohydrates can also act like allergens (Aalberse et al., 1981; Jappe et al., 2006). Allergens are classified into four categories on the basis of their route of exposure i.e. inhalants (aeroallergens), ingestants (food), injectants (insect bite, stings etc.) and contactants (cosmetics). Patients are commonly allergic to airborne allergens such as pollen, animal dander, mold, dust mites, urine and saliva. In patient having allergy, the first exposure to an allergen prompts their immune system to produce an antibody called immunoglobulin E (IgE). With each subsequent exposure, their body produces more IgE, IgE attaches itself to two types of cells mast cells and basophils. These cells get activated to release histamine and other chemicals to defend against the allergen invader.

Allergic responses depends on immune system, the person with stronger immune system will be healthier. Although laboratory animal allergy remains is an important cause of occupational asthma (Feary and Cullinan, 2016). Different people show different symptoms of allergies, which can be mild (runny nose, sneezing) to severe (anaphylaxis). Symptoms generally depend upon the part of body which came in contact with the allergens e.g., pollens present in air enters in to the respiratory tract via the nose and respiratory symptoms such as cough, itchy and runny nose, and nasal congestion, sneezing, and wheezing appear in patient. Food allergies are mostly related to digestive tract

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Figure 1 : Screening for Contributory Factors

Primary reason for coming to Allergy & Asthma Specialists:

_____

_____

Check your main symptoms- those that prompted your visit here:

Head or Nose	Chest	Skin	Insect Stings
○ Sneezing	○ Cough	○ Eczema	○ Hives
○ Post nasal drainage	○ Shortness of Breath	○ Swelling	○ Shortness of Breath
○ Nose Blocking	○ Hoarseness	○ Hives	○ Itching
○ Runny Nose	○ Wheezing	○ Itching	○ Swelling
○ Sinus Infection	○ Chest Infection		○ Dizziness
○ Sore Throat	○ Voice Loss		○ Fainting
○ Ear Blocking			
○ Headache			
○ Snoring			
○ Nosebleeds			
○ Eye Symptoms			

How many years have you suffered from the chief complaints of :

Head or Nose symptoms _____ Chest symptoms _____

Skin symptoms _____ Insect Sting reactions _____

Please indicate Pattern of symptoms:

	Head/Nose	Chest
Year rounds, no seasonal change	_____	_____
Year rounds, worse seasonally	_____	_____
Seasonally only	_____	_____

If seasonal, list months:_____

Are your symptoms worse at night? O Yes O No

Do you note increased symptoms from any of the following?

Allergens	Irritants	Ingestants	Weather
○ Dead Grass	○ Soap	○ Drugs	○ Cold fronts
○ Mown Grass	○ Perfumes	○ Alcoholic Beverages	○ Windy Days
○ Hay	○ Cleaning agents	○r Foods	○ Damp weather
○ Dead Leaves	○ Detergents	Other (list):	○ Temperature change
○ House Dust	○ Smoke		
○ Cats	○ Paint	_____	
○ Dogs	○ Hair spray	_____	

Please check the ones that best describe your home:

○House (Age____) ○ Apartment ○ City ○ Country

Do you have a basement? ○ Yes ○ No

to be continued...

Type of heating system: ○ Central ○ Floor ○ Electric ○ Other
Type of pillow: ○ Synthetic ○ Down
Type of mattress: ○ Conventional ○ Waterbed
Do you have stuffed animals? ○ Yes ○ No
Do you have carpet in your home? ○ Yes Type_____ ○ No
Are your symptoms worse anywhere in your home? ○ Yes Location: _____ ○ No
Do you have pets at home? ○ Yes What kind: _____ ○ No
Are your pets kept: ○ Inside ○ Outside
Are your symptoms worse at your work place/school? ○ Yes ○ No
Have your symptoms been so severe as to cause you to miss work or school? ○ Yes ○ No
If so, how many days?_____
Has travel affected your symptoms? ○ Yes ○ No
Do you have hobbies that expose you to allergens or irritants? ○ Yes ○ No

If yes, explain briefly: _____

List medicines you use for relief of allergy symptoms (including nose drops and sprays):

_____

_____

List other drugs you take for any reason. (include all over the counter drugs, creams, suppositories, eye drops, etc.):

_____

_____

Can you take Aspirin? ○ Yes ○ No
Are you allergic to any medications? ○Yes ○ No
If yes, please list: _____
What type of reaction occurs? _____
Have you ever taken hypo-sensitization shots (allergy shots) before? ○ Yes ○ No

Have you ever had a sinus x-ray? ○ Yes ○ No If yes, when? _____
Where?_____
Have you ever had a chest x-ray? ○ Yes ○ No If yes, when? _____
Where?_____
Do you smoke? ○ Yes ○ No
If yes, how many packs per day? ____ How long? _____
Have you ever smoked? ○ Yes ○ No
If yes, how many packs per day? ____ How long? _____
Does anyone you live with smoke? ○ Yes ○ No If yes, who? _____
Are you exposed to smoke at work or school? ○ Yes ○ No
Is there a history of any of the following in your family?
○ Asthma ○Eczema ○ Hives ○ Hay fever ○ Nasal polyps

to be continued...

If so, which family member? _____

Have you ever been treated in an emergency room? ○ Yes ○ No

If yes, how many times? _____

For what were you treated? _____

List hospitalization in order of most recent:

Cause of Hospitalization	Age
_____	_____
_____	_____
_____	_____

Circle any of following that you might have had:

Stomach ulcer Glaucoma High Blood Pressure Diabetes

Circle any of problems that you might have had with the following:

Blood Bones Head Nervous system Urinary tract

List any medical problems you have not noted above: _____

and symptoms include vomiting, abdominal pain, nausea and diarrhea. Skin allergies include rashes, lesions and blisters (Demoly et al., 1998).

Allergy can affect any organ and organ system. Common types of presentation include rhinitis (nose), conjunctivitis (eyes), urticaria and atopic (allergic) dermatitis (skin), asthma (lungs), and anaphylaxis (multi-organ) (Pucci and Incorvaia, 2008).

DIAGNOSIS OF ALLERGY

The diagnostic algorithm for human allergic disorders begins with appropriate medical history and physical examination.

Absolute Criteria (The Gold Standard)

Reproducible symptoms occurring during double-blind, placebo-controlled, allergen exposure when the route, dose and duration of allergen exposure are consistent with estimated or measured natural or occupational exposure.

The observed symptoms must be the direct result of the release of chemical mediators when the release of the mediators is triggered by the binding of IgE antibodies to the allergen (Bernstein et al., 2008)

Clinical Criteria

A history of signs and symptoms typical of allergic disease at a time and place when allergen exposure is probably occurring.

Demonstration that the patient has IgE antibodies specific for the allergen associated with the occurrence of symptoms (Bernstein et al., 2008).

MEDICAL HISTORY

Medical history is the critical link between allergy test results and allergic disease itself. Patient's history is taken by using a well designed questionnaire (Lieberman and Anderson, 2000). An allergy history is made up of chief complaint, determination of seasonality or diurnal variation of symptoms, identification of triggers, occupational exposure and response to medication, family history, and other pertinent medical history. The following questionnaire is recommended that screens for the contributory factors (Figure 1).

Most importantly, the practitioner needs to start with patient's complaint, rather than what they think they are allergic to. The latter can lead to misdiagnosis, with potential serious adverse consequences. Frequent use of decongestant nasal spray can lead to rebound nasal congestion and rhinitis medicamentosa. Over-the-counter preparations such as aspirin or nonsteroidal anti-inflammatory compounds, vitamins, and alternative remedies and herbal supplements, often not considered medication by the patient, may be causal factors in urticaria. Likewise ocular ß-blockers may lead to cough or worsening of asthma (Fitzgerald, 2009).

Past Medical History

Patient's current symptoms may have relevance to the previous non-allergic illnesses or surgical treatments. For example, a child with a history of prematurity and prolonged oxygen therapy in the neonatal period may develop bronchopulmonary dysplasia that mimics asthma. A physician treating adults with shortness of breath may need to consider a broad differential list of possible diagnoses, from coronary artery disease to a collagen disorder or cancer. However, the more consistent the patient's history and findings are for an allergic issue, the less that alternative explanations will need to be sought.

Prior drug intolerances and allergies need to be documented. A complete list of medications including vitamins and herbal remedies needs to be obtained (Ellington et al., 2002).

Chief Complaint

It is the starting point and include symptoms rather than specific diagnosis. Then focus on the details concerning those complaints. If there are multiple unrelated complaints and symptoms, they must be listed in order of severity or importance to the patient (Bickley, 2007).

History of Present Illness

To obtain history of the present illness open ended questions must be listed firstly, such as, When was your first respiratory complaint? Data should be obtained on the frequency of recurrence, seasonal recurrence, time of day, average duration of symptoms or exacerbations, places, infections, exposures, eating, menstrual period and relationship to specific activities. Allergies can be seasonal, that occur in particular season periodically. Allergic patients often have history associated with symptoms such as suspected cause, age of onset, specific situations, geographical location where symptoms occur and response to prior therapy seems very helpful for correct diagnosis (Walker et al., 1990).

Family History

Family history of an allergic diathesis should be sought. The genetics of allergy are not entirely understood, but each parent with atopy roughly doubles a patient's chance of being atopic; that is, risk of atopy is increased from 25% in the general population to about 75% when both parents are atopic. In one study, 90% of allergic asthmatic children had one or both parents who were atopic (Hansen et al., 1993).

Physical Examination

An allergic patient's history may direct the clinician's examination to a particular area or organ system. Each patient should be approached in a systematic way. Vital signs are a starting point in any examination. Pulse rate and pulsus paradoxicus >10 mmHg are two of the most sensitive indicators of severe airways obstruction. Respiratory rate is important as well, but hyperventilation is more a reflection of minute ventilation (respiratory rate times tidal volume) than respiratory rate alone. Fever is an infrequent manifestation of allergy and points the differential elsewhere (Buttram et al., 2003).

Some findings that may be important include the following-

Eyes

excessive lacrimation, erythema of the bulbar conjunctiva, cobble stoning of the tarsal conjunctiva, dermatitis of the eyelids.

Ears

tympanic membrane dullness, redness, retraction, perforation or lack of mobility.

Skin

Rashes (description and distribution), infection, dermatographism.

Sinuses

Tenderness, purulent drainage from the sinus ostia.

Nose

transverse crease, turbinate edema and pallor or bluish discoloration, nasal septal deviation or perforation, discharge, polyps.

Heart

Gallops, murmurs or rubs.

Chest

Deformity, altered percussion, abnormal sounds by auscultation, chest wall tenderness, egophony, audible wheezing.

Neck

Neck vein distention, adenopathy or tenderness

Abdomen

Tenderness, mass or distention.

Neurologic

Weakness, impaired cognition or thought process, including difficulty in recall

Extremities

Tenderness, signs of a connective tissue disorder, erythema.

Oropharynx

Mouth breathing, dental malocclusion or overbite or postnasal drip, cobblestoning of the oropharyngeal wall, halitosis, hypertrophied tonsils or adenoids.

Other body systems should be included in a comprehensive physical examination and abnormal findings recorded.

ALLERGY TESTING

Skin prick tests and blood tests are equally cost-effective, and health economic evidence shows that both tests were cost-effective compared with no test (Dave et al., 2011).

Allergy Diagnosis

Many physicians have the mistaken impression that allergic diseases are diagnosed by allergy tests. Allergic diseases can be diagnosed only from the patient's history of symptoms and compatible physical findings. If the symptoms are typical of allergic disease and repeatedly associated with allergen exposure, a diagnosis of allergy is highly probable. Two other important factors are the number of times the symptoms have been associated with allergen exposure and whether similar symptoms occur without allergen exposure.

To further clarify the role of allergy tests in allergy diagnosis, it is useful to define a gold standard for diagnosis (Table 1). The patients who are diagnosed with allergic manifestation on the basis of patient's history of symptoms (Figure 1) and compatible physical findings are subjected to allergen testing. Patients are tested for the most prevalent allergens through SPT (Figure 2) (Lieberman and Anderson, 2000).

Physiology of Skin Tests

Skin acts as barrier against external aggressions and has an important physiological role in the homeostasis process , with well-known immunological properties. Skin prick test was found to be most reliable method for allergen sensitivity test in which SPT was accepted as gold standard, in vitro testing has proved less sensitive (Bapna and Mathur,1990). It has been used by allergists for decades as an easily assessed laboratory test for the immunological status of the individual.

First skin testing technique has been developed by Charles H. Blackley in 1865, a Manchester homeopathic physician with allergic rhinitis. He scraped away a quarter-inch area of his skin with a lancet and then applied grass pollen grains. Schloss adopted the so-called scratch test for the diagnosis of food allergy in children (Blackley, 1873) Epicutaneous tests can be divided into scratch tests and prick/puncture tests (Feinberg, 1946). The first method, proposed by Blackley, implied a linear scratch without drawing blood and could either be performed first, then dropped extract on the abraded skin. This technique became progressively obsolete due to patient discomfort, poor reproducibility, possible residual lesions. Therefore, scratch test is mentioned here for historical purposes only (Dreborg, 1989). Sir Thomas Lewis who, in 1924, first applied skin prick tests (SPT) (Lewis and Zotterman, 1927).

The prick/puncture method of skin testing is one that has been widely accepted as a safe, dependable, convenient and cost-effective procedure (Bernstein et al., 2008; Liccardi et al., 2006). Currently, SPT is one of the most widely-used (Antico et al., 2000) screening (Chinoy et al., 2005) and diagnostic tools in modern allergy practices (Antunes et al., 2009) and is considered the “gold standard” method (Lewith et al., 2001; Chong et al., 2009) against which other testing methods are sometimes compared. Skin testing to detect allergen-specific IgE has been in clinical use for over 100 years (Fatteh et al., 2014).

Intradermal Tests

Intradermal tests are more sensitive than prick or puncture tests, but they are more difficult to perform properly. Intradermal tests are typically performed with 25, 26 or 27-gage needles. After drawing the allergen extract into the syringe, the tip of the needle is inserted into the superficial dermis and approximately 0.02-0.05 mL of extract is injected. If the injection is performed properly, a

Figure 2 : Allergens Used for Allergy Testing

ALLERGEN TESTING

Name: _____ Date: _____

MEDICATION WHICH MAY AFFECT TESTING

Date of Birth: _____ Sex: _____MEDICATION DATE OF LAST DOSE

Location of Test(s): _____

TREES	PRICK	ID	WEEDS	PRICK	ID
Boxelder-Maple			Ragweed Mix		
Sycamore			English Plantain		
Hackberry			Russian Thistle		
Walnut			Lambs Quarter		
Elm			Careless-Pigweed		
Oak Mix			Marshelder-Poverty		
Pecan			Dock,Sorrel		
Willlow			Cocklebur		
Ash			Mugwort		
Beech					
Cottonwood					

MOLDS	PRICK	ID
Birch Mix		
Cedar, Mountain		
Pine Mix		
Alternaria		
Hormodendrum		
Helminthosporium		
Aspergillus Fumigatus		

GRASS	PRICK	ID
Bermuda		

Rye_____	*Rhizopus*_____
Johnson_____	*Aspergillus Niger*_____
Timothy_____	*Fusarium*_____
Bahia_____	*Penicillium Notatum*_____
Kentucky Blue_____	
Redtop_____	
Orchard_____	ENVIRONMENTALS PRICK ID
Meadow Fescue_____	Dust Mite F._____
Sweet Vernal_____	Dust Mite P._____
	Cat 1 (Hair)_____
	Cat 2 (Pelt)_____
	Dog_____

Feathers_____
TREES: GRASSES: WEEDS - 1:20

COCKROACH: DOG - 1:10

DUST MITES F.; DUST MITE P.; - 10000 AU/ML
CAT (HAIR): CAT (PELT) – 10000 BAU/MI

COMMENTS
_____ _____ _____
Control – Positive – Histamine_____
Control – Negative_____
PRICK_____ TIME_____ EMPLOYEE

I.D.s_____ TIME_____ INITIALS_____

SKIN TESTING FOR DETECTION OF ALLERGEN-SPECIFIC IgE

distinct bleb, 2-3 mm in diameter, will be produced. Extracts used for intradermal testing are normally diluted 1000-fold more than extracts used for epicutaneous tests. As with prick or puncture tests, intradermal tests should be placed at least 6 cm apart to prevent interactions leading to false-positive results (Lieberman and Anderson, 2000).

Measurement Of Allergen-specific IgE

Basic Methods

In 1964, Millman first time reported allergen-specific antibody (Millman et al., 1964). Allergen associated IgE was discovered and reported by Ishizaka (Ishizaka et al., 1966), Johansson and Bennich (Johansson and Bennich, 1967). In consequence, serum IgE concentration is too low to detect by conventional immunoassay and to enhance the sensitivity of assay, radioallergosorbent test (RAST) was developed by Wide. Due to the safety issues of isotope, it was replaced by fluorescence-tagged assay system (Tsay and Halpern, 1984). Most available assays for allergen-specific IgE antibodies utilize the principle of immunoabsorption illustrated in Figure 3. The allergen of interest is first bound to a solid phase support such as a paper disk, cellulose or sponge plastic microtiter well . The patient's serum is then incubated with the solid phase. If the patient has antibodies specific for the allergen, the antibodies will become bound to the allergen, and the remaining serum proteins, including unbound antibodies, can be washed away from the solid phase (this is immunoabsorption and separation). After washing, a labeled antihuman IgE antibody is incubated with the solid phase to allow binding of the anti-IgE to any IgE bound to the solid phase. After unbound anti-IgE is washed away, the quantity of anti-IgE bound to the solid phase is measured and converted either to units of specific IgE or to a class score. The initial test for IgE antibodies used radiolabeled anti-IgE antibodies and was called the radio allergo sorbent test or RAST. Because of its initial market dominance the term RAST is often used as a generic term to mean any test for allergen-specific IgE antibodies.

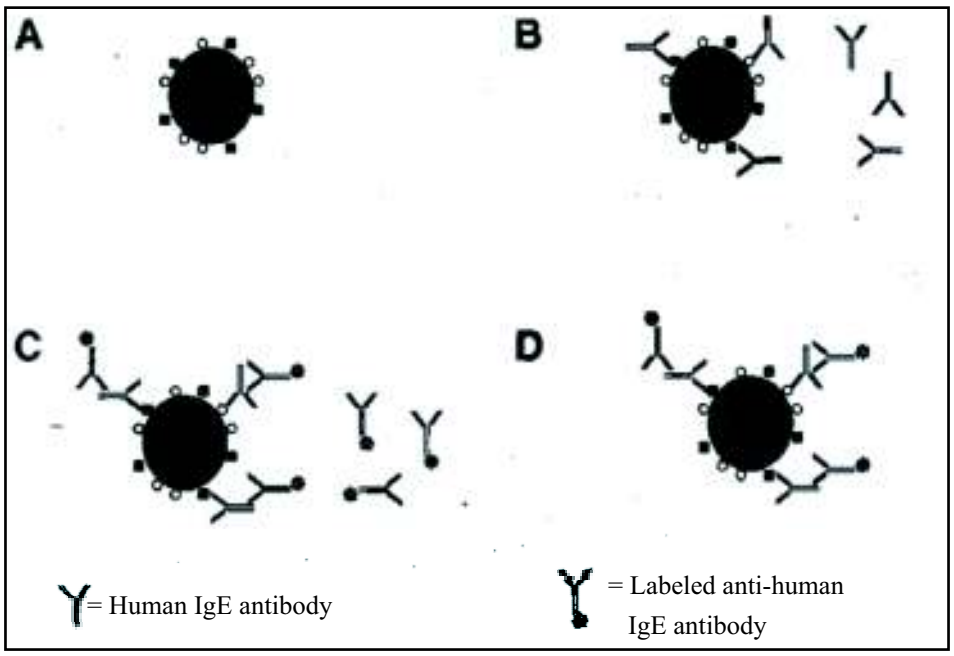

Figure 3 : Schematic Presentation of an Immunosorbent Assay for Allergen-Specific IgE antibody.
A. Allergen Represented by Small Circles and Squares Has Been Bound to Solid Phase.
B. Serum That May Contain IgE Antibodies Specific for the Allergen is Incubated with the Solid Phase. Specific Antibodies Bind to the Allergen, and Non-Bound Antibodies are Removed by Washing.
C. Labeled Antihuman IgE Antibody is Incubated With the Solid Phase, and the Anti-IgE Antibody Binds to the Immobilized IgE. Nonbound Anti-IgE is Washed Away.
D. The Amount of Anti-lgE Antibody on the Solid Phase is Proportional to the Concentration of Allergen-Specific IgE in the Serum Tested.

In recent years, other methods have become more widely available. The major modification in newer assays is the use of enzyme labels in place of radiolabels. Thus, newer assays are most commonly enzyme-linked immunosorbent assays (ELISA), although the term RAST is still commonly used. Both radio labeled and enzyme-labeled assays are capable of detecting specific IgE at concentrations of nanograms per milliliter of serum.

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