Values and Limitations of Patch Testing and IgE Measurement

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Patch Test (PT):

Is basically a delayed type allergic reaction (Type IV) and is mediated by T-H1, CD8 Cytotoxic T-cells and aided by macrophages.

Clinically P.T. is represented by:

- Contact hypersensitivity dermatitis
- Response to insect bite and venom
- Lepromin test (M. laprae)
- Tuberculin Test

In patch testing the antigen is introduced transepidermal. The antigen could be:

- Protein
- Carbohydrate
- Lipid
- Simple chemical as Nickel or chrome

The simple chemical is of low molecular weight and is known as hapten. Such hapten is not capable of inducing an immune reaction unless it is covalently bound to a protein to form a complete Ag.

Haptens are positively charged and are electron deficient. Such hapten reacts with proteins which are negatively charged with rich electrons leading to covalent bonding to form a complete antigen and such changes occur to the hapten while passing transepidermal during patch testing. The complete antigen appears on receptor or Antigen Presenting Cell (APC), which in response will secrete IL-1, which activates TH-1.

The APC having the complete Ag on its receptor associated with MHC II will present the Ag to activated TH-1 which will secrete IL-2 which is a growth factor to T-cells and macrophages and lead to their proliferation. The activated TH-1, Cytotoxic CD8 positive cells aided by macrophages will lead to a cell mediated type IV allergic reaction to the Antigen presented transepidermally. The Patch Test is read after 48 and 72 hours from applying the patch. The results are interpreted as follows:

- Negative = no reaction as compared to the control P.T.
- ± = erythema which means a questionable reaction
- \+ = erythema + edema or infiltration and no or few papules.
- ++ = erythema + intense edema + many papules and sometimes vesicles.
- +++ = densely aggregated papules and vesicles
- ++++ = irritant reaction with bullae and ulceration

So P.T. is a diagnostic tool for evaluation of patients with suspected allergic contact dermatitis and using standard PT series one can identify relevant contact allergen.

The PT site is usually the back. The PT cannot be done:

- On sites that were treated with topical steroids.
- On excoriated or stripped skin
- If the patient is taking immuno-suppressive drugs including systemic steroid
- Cannot be done if the patient is suffering from medical conditions that will interfere with the result for e.g. Measles, Sarcoidoses, Lymphoma, AIDS and other immunodeficiency diseases.

The result of the PT may depend on the concentration of the patch test material. It was observed that using 0.25% Potassium dichromate for PT gave 9.8% positive result and if the concentration is increased to 0.5% the percentage of positive reaction increased to 19% in patients who suffer from contact dermatitis to K. dichromate which is a well known occupational sensitizer as in cement laborers or those who suffer from leather contact dermatitis .

It can be concluded that with the use of standard PT series one can identify commonly encountered and potentially relevant contact allergens. (1)

The value of PT in drug eruption was only positive in one out of 12 cases. Oral drug provocative test is still necessary to get a definite diagnosis of the drug eruption. (2)

Type IV cell mediated allergic reaction is seen:

- in Allergic Contact Dermatitis
- Graft V.H. reaction
- Rheumatoid arthritis
- Dermatomyositis

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Although allergic contact dermatitis in children was considered rare [3] yet it is now a significant clinical problem. [1,5]

Children suspected to have allergic contact dermatitis might present with a range of problems including atopic dermatitis, hand dermatitis, foot dermatitis, perioral dermatitis and dermatitis of unusual sites.

Patch testing and subsequent avoidance of the allergen may improve the prognosis in children with relevant contact allergen. [6]

Allergic contact dermatitis in children may be due to metal allergy, medicaments, cosmetic, food additives, flavoring agents, shoe chemical and hair dressing chemical.

Patch Testing in children is useful to exclude contact sensitization at certain body sited especially hands, feet and perioral region.

It has been observed and repeatedly shown that in atopic dermatitis. patients skin eczematous lesions can be induced by epicutaneous application of aeroallergens [7,8] and this epicutaenous application is called Atopy Patch Test (APT). [9]

Standardized APT technique is developed and consists of purified allergen preparation in petrolatum applied in 12 mm Finn chamber. [10] There is clear correlation and specificity between result of APT and allergen specific IgE or prick test and the clinical condition depending on type of allergen and the relevance could be up to 87 or 100%.

APT is done on the back on non-lesional skin during remission [9,11] following the same precautions as in PT with conventional contact allergy patch test and APT is read after 48-72 hours. Food allergen makes an important contribution to the pathogenesis of AD in infants.

Food allergens such as wheat and cornflower could produce protein contact dermatitis. [12] Food allergen could be detected very early by APT and consequently could be eliminated from diet and specific IgE to food allergen could be also detected by RAST and Prick Test.[13]

Unwanted side effects of APT occurred in 7.9% of tested patients such as local flare of eczema, contact urticaria, bronchial asthma, systemic reaction, irritation from adhesive plaster.

The strong correlation between APT, RAST and skin prick test suggest a role of allergy specific IgE in the development of eczematous skin lesions after contact with allergens transepidermally.

Langerhan cells in the skin carry IgE receptors of different classes [14,15,16] and this explains IgE associated activation of allergen specific T-cells leading to eczematous lesions in APT. [17,18] The eczema reaction in APT is proposed to be IgE mediated and skin biopsies showed, eosinophils, IgE, CD4+ and CD8+ cells. [19]

APT is not proposed as a screening test in patients with AD. APT may provide an important diagnostic tool to select patients who show special benefit from allergen avoidance measures.

Immunoglobulin E

IgE is one of the 5-clasess of Ig made by B-cells stimulated by IL-4 and IL-13.

The plasma cells produce 90% of Ig. The plasma cell comes from precursor B-cell under effect of IL-5. B-cells can respond independently to Ags, which are large and composed of identical repeated subunits for e.g. Polysaccharides.

Each B-cell clone secretes single monoclonal antibody in response to specific antigen.

IgE is produced as a result of interaction between macrophages or APC, TH-2, B-cells and plasma cells.

TH_2 in response to antigen presented by APC secretes IL-3, IL-4, IL-5, IL-10, IL-13 and TNF-. These cytokines are also produced by activated mast cells.

IgE has a high molecular weight of 200.000. Its concentration in the serum is low (0.02%).

It has a half-life of 2-days.

It does not pass through the placenta

It does not bind complement

It does not bind to monocytes, macrophages, natural killer cell (N.K) and PMN cells.

It does not have agglutination property, antiviral, antibacterial or antitoxin effect.

The immunoglobulins are differentiated by their long chain polypeptide, which is Epsilon in IgE [it is gama in IgG, alfa in IgA, mu (2) in IgM d (delta) in IgD].

Type I allergic reaction occurs when the allergen combines with specific IgE on Mast and basophil receptor leading clinically to

- Urticaria
- Rheinitis
- Conjunctivitis
- Bronchial Asthma
- Anaphylaxis

Serum IgE to a known antigen is measured by Radioallergosorbent test (RAST).

Enzyme Linked Immunosorbent Assay (ELISA) is used to quantify antigen or antibody in patient serum.

The titer of the antibody in patient serum is the highest dilution of patient serum that gives a positive (color reaction).

Increased IgE is a striking common finding in patients with Atopic Dermatitis. [20,21] Total IgE value is 360 Ku/L while maximal value is up to 19700 Ku/L. The clinical relevance of the raised IgE in atopic dermatitis is demonstrated by prick test or Radioallergosorbent Test (RAST). Patients with atopic dermatitis get exacerbation of their dermatitis on exposure to certain aeroallergens as dust mite, pollens or animal dander, while specific IgE is positive as estimated by RAST. Atopic dermatitis improve after avoiding exposure [22] to such specific aeroallergens.

Specific IgE positivity is comparable to skin prick test.

Aeroallergen	Specific IgE positivity by RAST	Prick test positivity
House dust mite	56%	59%
Grass Pollen	75%	65%
Birch	65%	65%
Cat dander	49%	54%

Serum IgE levels seem to correlate with the degree of Atopic eczema. Children with severe A.D. and high IgE level at risk of sensitization to food and aeroallergens [23] and the role of allergens is very important in immunopathogenesis of A.D. [24]

In AD there is increase in allergen induced IL-13 which leads to early increase in IgE. [25]

Children with very high serum IgE (more than 10000 Ku/L) are at high risk of anaphylactic reaction, bronchial asthma and severe A.D. [26]

Atopic Eczema Dermatitis group (AEDS) covers different subtypes of A.D. Atopic dermatitis is not one single disease but rather an aggregation of several diseases with certain clinical characteristics in common.

The Intrinsic or non-allergic type of AEDS have no allergic rheinitis, no bronchial asthma and show normal IgE and no specific IgE and negative prick test to aeroallergens or foods [27] and this could be due to genetic or environmental differences.

IgE associated AEDS (extrinsic) produce less IFN gamma. Peripheral mononuclear leukocytes from extrinsic and Intrinsic AEDS produce more IL-13 while IL-5 was increased in Intrinsic and not in extrinsic type of AEDS. [28]

Serum level of IgE is increased in patients suffering from:

1- Atopic dermatitis
2- Patients with selective IgA deficiency which is the most common Primary Immune deficiency disease with high incidence of atopic diseases, high IgE and increased eosinophils
3- Parasitic Infection
4- Lymphocyte malignancy
5- Idiopathic
6- Leiner syndrome (low C5, low Ig and high IgE, defective chemotaxis).
7- Netherton's syndrome
8- Hyper IgE syndrome [29,30] (Job's Buckley Syndrome) is a primary immune deficiency disease with defect in leukocyte chemotaxis and is characterized by AD, recurrent staphylococcal abscesses, cold abscesses, otitis media, viral and mycotic infections, recurrent cyst forming pneumonia and elevated serum IgE more the 2000 IU/ml and autosomal recessive and autosomal dominant inheritance were reported.

References:

1- *Wetter DA; Davis MDP; Yiannias JA; et al: Patch Test results from the Mayo Clinic Contact Dermatitis Group, 1998-2000. J Am Acad Dermatol 2005; 53(3): 1-7.*

2- *Puavilai S; Chunharas A; Kamtavee S; et al: Drug eruptions: The value of oral rechallange test and patch test. J Med. Assoc. Thai 2002; 85(2): 263-9.*

3- *Pevny I; Brennenstuhl M; Rasiniskas G: Patch Testing in children (1) collective test results; skin testability in children Contact Dermatitis 1984; 11: 206.*

4- *Barros MA; Baptista A; Correia TM; et al: Patch testing in children. Contact Dermatitis 1991; 25: 156-9.*

5- *Stables GI; Forsyth A; Lever RS: Patch Testing in children. Contact Dermatitis 1996; 34: 341-4.*

6- *Shah M; Lewis FM; Gawkrodger DJ: Patch testing in children and adolescents: Five years experience and follow-up. J Am Acad Dermatol on line 1997; 37(6): 1-6.*

7- *Ring-J; Darsaw U; Abeck D: The atopy patch test as a method of studying aeroallergens as triggering factors of*

atopic eczema. Dermatol Treatment 1996; 1:51-60.

8- Van Voorst Vader PC; Lier JG; Woest TE et al: Patch Tests with house dust mite antigens in atopic dermatitis patients: methodological problems. Acta Derm Venereol 1991; 71: 301-5

9- Ring J; Kunz B; Bieber T; et al: The "atopy patch test" with aeroallergens in atopic eczema (abstract). J Allergy Clin. Immunol 1989; 82: 195.

10- Kerschenlohr K; Darsow U; Burgdorf WH; et al: Lessons from atopy patch testing in atopic dermatitis. Curr. Allergy Asthma. Rep 2004; 4(4): 285-9.

11- Darsow U; Vieluf D; Ring J: Atopy Patch Test with different vehicles and allergen concentrations – an approach to standardization.

J Allergy Clin Immunol 1995; 95: 677-84.

12- Cristaudo A; Simonato B; Pasini G; et al: Contact Urticaria and protein contact dermatitis from corn in a patient with serum IgE specific for a salt soluble corn protein of low molecular weight.

Contact Dermatitis 2004; 51(2): 84-7.

13- Majamaa H; Moisio P; Halm K; et al: Wheat allergy: diagnostic accuracy of skin prick test and patch tests and specific IgE. Allergy 1999; 54(8); 851-6.

14- Tanaka Y; Anan S; Yoshida H: Immunohistochemical studies in mite antigen induced patch test sites in atopic dermatitis. J Derm Science 1990; 1:361-8.

15- Bieber T; Rieger A; Neuchrist C; et al: Induction of Fce R_2/ CD_{23} on human epidermal Langerhans cells by human recombinant IL-4 and IFN. J Exp. Med. 1989; 170:309-14.

16- Bieber T: Fce R_1 on human Langerhans cells: a receptor in search of new functions. Immunol Today 1994; 15: 52-3.

17- Van Reijsen FC; Bruynzeel Koomen CAFM; Kalthoff FS: Skin derived aeroallergen – Specific T-cell clones of TH_2 phenotype in patients with atopic dermatitis. J Allergy Clin. Immunol 1992; 90: 184-92.

18- Sager N; Feldmann A; Schilling G; et al: House dust mite specific T-cells in the skin of subjects with atopic dermatitis: frequency and lymphokine profile in the allergen patch test. J. Allergy Clin. Immunol 1992; 89: 801-10.

19- Holm L; Maluseviciene G; Scheynius A; et al: Atopy Patch Test with house dust mite allergen – an IgE mediated reaction? Allergy 2004; 59(8): 874-82.

20- Rajka G: Essential aspects of atopic dermatitis. Berlin: Springer 1989.

21- Ruzicka T; Ring J; Przybilla B; editors. Handbook of atopic eczema. Berlin: Springer 1991.

22- Tan B; Weald D; Strick Land I; et al: Double blind controlled trial of effect of house dust-mite allergen avoidance on atopic dermatitis Lancet 1996; 347: 15-18.

23- Laske N; Niggmann B: Does the severity of atopic dermatitis correlate with serum IgE levels? Pediatr – Allergy – Immunol, 2004; 15(1): 86-8.

24- Bardana; E J Jr: Immunoglobulin E (IgE) and non-IgE – mediated reactions in the pathogeneses of atopic eczema / dermatitis syndrome (AEDS) Allergy. 2004; 59 Suppl. 78: 25-9.

25- Contreras JP; Ly NP; Gold DR; et al: Allergen induced cytokine production; atopic disease. IgE and wheeze in children. J Allergy Clin. Immunol 2003, 112(6): 1072-7.

26- Laske N; Bunikowski R; Niggemann B: Extra ordinary high serum IgE levels and consequences for atopic phenotypes. Ann Allergy Asthma Immunol 2003; 91(2): 202-4.

27- Wuthrich B; Schmid Grendelmeier P: The atopic eczema / dermatitis syndrome. Epidermiology, natural course and immunology of IgE associated (extrinsic) and non allergic (intrinsic) AEDS. J. Investig. Allergol Clin Immunol, 2003; 13(1): 1-5.

28- Simon D; Borelli S; Braathen LR; et al: Peripheral blood mononuclear cells from IgE and non IgE associated Atopic eczema / dermatitis syndrome (AEDS) demonstrate increased capacity of generating interleukin-13 but differ in their potential of synthesizing interferon gamma. Allergy 2002; 57(5): 431-5.

29- Grimbacher-B; Hollan SM; Puck JM: Hyper IgE syndrome.

Immunol – Rev 2005; 203: 244-50.

30- Chamlin SL; Mc Caalmont TH; Cunningham BB; et al: Cutaneous Manifestations of hyper IgE syndrome in infants and children. J Pediatr. 2002; 141(4): 571-5.