

Serological aspects of latex allergy. Some recent developments

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SUMMARY: Since IgE antibodies were shown to be involved in adverse reactions to natural rubber latex, extensive studies of the allergens and antibodies have made latex allergy a model system for IgE serology. Although IgE antibody patterns are individual it is clear that they are influenced by the route and the intensity of the exposure. A range of IgE binding proteins are identified and their role in allergy to natural rubber latex, to latex products, and to more or less related food products are under study. Allergen-specific IgE antibodies can be quantitated in serum, and testing should always be considered in the investigation of suspected latex allergy, in food allergy in children, and in urticaria and anaphylaxis of unknown cause. The clinical efficiency of specific IgE antibody measurement (Pharmacia CAP System™ is high in children and adults, with and without occupational exposure, and in spina bifida patients. Compiled data from 11 published studies show agreement with clinical judgement in 483 / 524 cases (92.2 %).

KEY-WORDS : Latex – IgE antibody – Pharmacia CAP System.

REEVALUATION OF LATEX REACTIONS

Almost 20 years after the reevaluation of adverse reactions to natural rubber latex and the inclusion of immediate type-IgE mediated reactions among the major mechanisms, this area has become one of the most intensively studied in the field of IgE mediated allergy. Recent reviews [16, 14, 26] cover medical, chemical, and immunological aspects of the disease as well as a look into the molecular biology of the plant materials used as source materials for the rubber. These materials are also used for in vivo testing and as reagents in immunoassays for the detection and

quantitation of latex rubber specific antibodies in serum specimens of individuals with suspected allergic reactions caused by rubber products.

EARLY IgE ANTIBODY MEASUREMENTS

Specific IgE antibodies to natural rubber latex and to glove material were detected by radioimmunoassay [12]. Patients with contact urticaria were shown to have IgE antibodies by radioallergosorbent test using an extract from the rubber tree, *Hevea brasiliensis* [27]. Further studies on

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specific IgE against natural rubber latex by means of a histamine release assay as well as by immuno-enzymatic methods suggested that the allergen could be a protein present in the crude natural rubber latex [7].

IgE ANTIBODY PREVALENCE

Children with spina bifida were shown to be at high risk of developing IgE specific for rubber antigens. Furthermore, the presence of rubber-specific IgE was associated with a higher frequency of rubber-associated allergic reactions [23]. Recent studies have reported that the prevalence of latex allergy among health care workers ranges from 2 % to 25 %. The prevalence of anti-latex IgE antibodies in nurses participating in a latex allergy study was 65/741 (8.9 %) [13]. Numerous natural-rubber products are potential risk factors for sensitization also of the general population [14, 21].

IgE BINDING PROTEINS

A number of IgE-reactive proteins have been identified in natural and processed latex products. The proteins represent molecules with very different properties.

An acidic protein (Hev b 5) in the cytoplasm of the laticifer cells of *Hevea brasiliensis* is a potent allergen. This protein has pI = 3.5 and a molecular mass of 16 kD. Its amino acid sequence shows a high degree of homology (47 %) to an acidic protein of kiwifruit [2]. It was also shown to have significant homology to sequences from potato, which is known to cause allergic reactions in some latex-allergic patients. Fifty-six percent of spina bifida patients and 92 % of health care workers with latex allergy were reported to have IgE specific to the protein encoded by cDNA Hev b 5 [24].

Specific IgE antibodies to hevein, a 4.7 kD polypeptide, were detected by enzyme-linked allergosorbent test in 48 of 64 (75 %) sera from health care workers allergic to latex and in three of 11 (27 %) sera from patients with spina bifida and hypersensitivity reactions to latex. Purified hevein completely inhibited IgE binding to the 20 kD protein, prohevein, reported to be a major allergen in latex. Hevein represents the N-terminal domain of prohevein and is responsible for most of the IgE-binding capacity of prohevein [9].

The rubber elongation factor, a 14.6 kD water-insoluble protein (Hev b 1) located on rubber particles is a major latex allergen in hypersensitivity in children with spina bifida. The peptide with amino acids 124-134 in the C-terminal region was

essential for recognition by human IgE antibodies and together with the region with amino acid residues of 31-64 the most allergenic portion of Hev b 1 [8].

Another insoluble 24 kD protein (Hev b 3), was shown to have a tendency to fragment into several polypeptides of lower molecular weight (from 24 kD to about 5 kD). Aggregation to molecular weights greater than 24 kD may also occur resulting in a range of polypeptides that are allergenic to patients with spina bifida [28].

Several soluble IgE-reactive proteins other than the previously known allergens were recently shown to have high homology with common plant enzymes. They may also act as cross-reacting proteins in various foods [22].

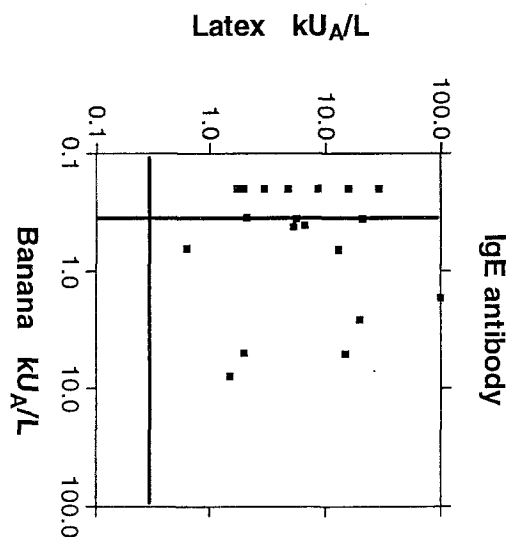


Fig. 1. – Measurements of specific IgE antibody to natural rubber latex (k82) and banana with Pharmacia CAP System in sera from 19 latex allergic patients. Data from Delbourg *et al* [10].

ALLERGEN RELATIONS AND ANTIBODY SPECIFICITY

In addition to those mentioned above a number of reports have been published describing reactions to food items in patients with latex allergy. The distribution of fruit/vegetable specific IgE antibody in latex allergic patients was recently reviewed [6].

The involvement of crossreacting allergens were confirmed or suspected(?) in reactions to banana, avocado, kiwi, potato, sweet pepper, tomato (patatins), papaya/papain, chestnut, melon(?), buckwheat(?), profilin(?), ragweed pollen(?), and blue grass pollen (?). Lack of crossreactivity with latex was claimed for Parthenium, guayule (*P argentatum*), *Ficus elastica*, *Ficus benjamina* (?), birch pollen, mugwort pollen, and timothy pollen.

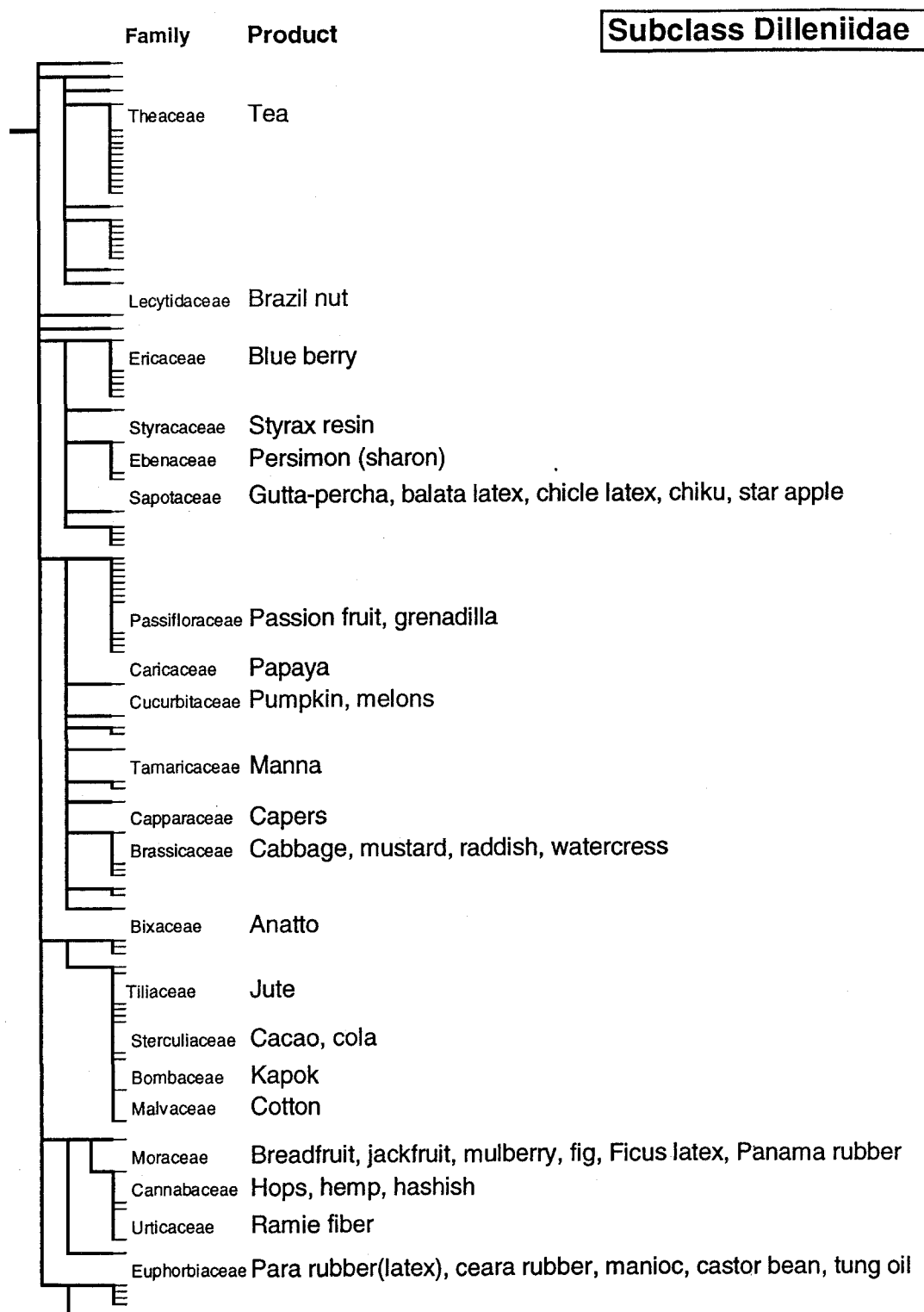


Fig. 2. – Examples of botanical relationships between some natural products commonly used. The subclass Dilleniidae includes 91 of the more than 500 families of the flowering plants.

Inhibition studies used in crossreactivity studies are sometimes difficult to interpret. Fruit specific IgE binding in a serum from a latex sensitive patient may be inhibited by latex; latex specific IgE binding in the same patient is not necessarily inhibited by fruit, and vice versa. Several studies lack proper negative controls showing insignificant inhibition of IgE binding to an independent unrelated allergen for every extract used as inhibitor. Conclusions drawn from such studies need to be confirmed.

Some recent studies indicate that the true situation is extremely complex. Only some of the patients allergic to latex react to food. Ten of 22 (45 %) latex-allergic patients sera recognized altogether 14 allergens in banana by immunoblotting. The most frequently identified banana allergens were 23, 32, 36, 39 and 47 kD proteins [3]. Fourteen of 18 sera (78 %) had IgE antibodies that bound to a total of 17 avocado proteins with apparent molecular weights ranging from 16 to 91 kD [1].

Allergens of banana and avocado carrying epitopes homologous to latex allergens are most probably different proteins with partial sequence homologies, i.e. there is no universal fruit allergen [4]. This is supported by the results of measurements of IgE antibodies to latex and banana in 19 latex allergic patients [10] showing no correlation (fig. 1).

Crossreactivity as a function of botanical relations is essentially unexplored. The subclass Dilleniaceae includes the rubber latex producing genus *Hevea* and many other plants providing products that are eaten or utilized otherwise (fig. 2). Some of these are potential cross-sensitizers because of their close relation to *Hevea*.

QUANTITATIVE ASSAY OF ALLERGEN SPECIFIC IgE ANTIBODIES

Measurement of antibodies to allergen sources as complex as the natural rubber latex requires an efficient immunoassay. Excess of major as well as minor allergens is needed to catch the heterogeneous and individual sets of antibodies represented by specimens from the different allergy risk groups. The high capacity solid phase (ImmunoCAP) of Pharmacia CAP System and UniCAP is designed to carry allergen quantities large enough to satisfy these requirements [17].

As evident from the data reviewed above only allergen preparations representing the complete range of allergens involved in the exposures would be capable of efficient detection of sensitization in all patients. The ImmunoCAP allergen is a non-

ammoniated product derived from latex collected for the purpose in Thailand from *Hevea brasiliensis*. The C-serum or cytosol is isolated by ultracentrifugation. The protein rich solution compares favorably with the FDA reference extract E8 in RAST inhibition (fig. 3) and immunoblotting experiments and binds multiple IgE antibody specificities as shown by the examples presented in figure 4. The molecular weights of the proteins cover the range from <10 kD to >100 kD.

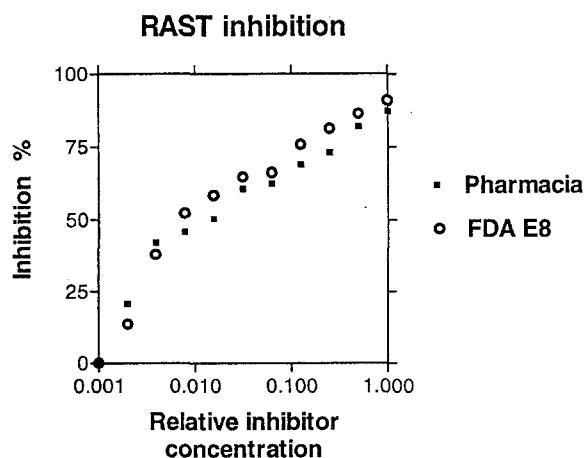


Fig. 3. – Comparison of Pharmacia NRL (natural rubber latex) and FDA preparation E8 by RAST inhibition of a pool of NRL allergic sera (Pharmacia CAP System, latex allergen k82).

CLINICAL PERFORMANCE OF PHARMACIA CAP SYSTEM

The efficiency of diagnostic tests are commonly studied and reported as the sensitivity and specificity in relation to a specialist's clinical diagnosis or in relation to a reference method. Table I summarizes the published documentation of clinical sensitivity and specificity of Pharmacia CAP System. Sensitivity is defined as the proportion (%) of positive tests (≥ 0.35 kU_A/L) in groups of patients with clinical disease. The specificity data are calculated from test results obtained from control groups that are defined as healthy blood donors, healthy controls, or patients without latex reactivity. The data confirm that the system provides a precise and reproducible diagnostic tool with high clinical efficiency. The overall agreement with the clinical judgements in the 11 studies summarized in Table I is 483 / 524 (92.2 %). IgE antibody measurement was also recommended for routine detection of latex allergy in children with food allergy [25, 29] and in urticaria or anaphylaxis without known cause.

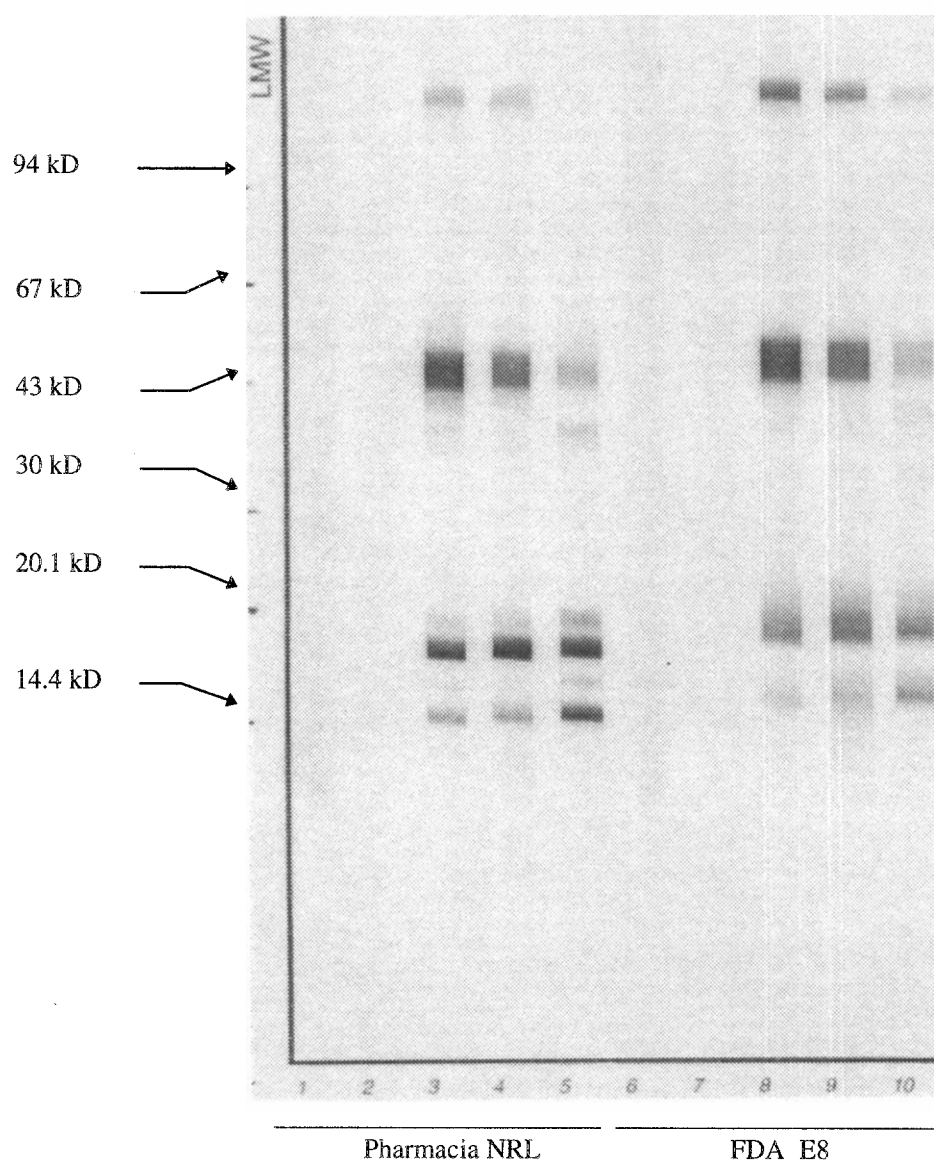


Fig. 4. - Example of immunoblotting patterns of Pharmacia NRL (lane 1-5) and FDA E8 (lane 6-10). Two negative controls (lane 1, 2, 6, 7) and three sera with NRL specific IgE antibodies were included in the experiment. One serum is a pool (lane 4, 9) (Unpublished data, Hans Perborn 1996).

Table . - Clinical performance of Latex specific IgE antibody assay (Pharmacia CAP System)

Author (Ref N°)	Patients/Controls	n	Sensitivity %	Specificity %
Blanco [5]	Adult LA	25	92	-
Ahlroth [1]	18 LA/14 nonallerg. contr.	32	89	100
Latasá [15]	Adult LA	7	876	-
Mäkinen-Kiljunen [20]	61 LA/30 nonallerg. contr.	91	77	100
Sorva [25]	Atopic children LA	11	100	-
Alenius [3]	Adult LA	22	82	-
Lundberg [18]	Adult LA	22	82	-
Michael [19]	Spina bif. 37 SPT +/44 SPT-	81	97	80
Ylitalo [30]	Children LA	30	97	-
Chen [9]	76 LA (11 Spina bif.)/10 nonallerg. contr.	86	99	100
De Swert [11]	Spina bif., 17 LA/57 nonLA	74	89	93

LA = Clinical latex allergy.

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