

Review Article

Latex-allergic children

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Introduction

Immediate type allergy to natural rubber latex (NRL) has been recognized as an increasing and clinically important problem in children during the last few years. Clinical reactions may vary from contact urticaria to severe anaphylaxis (1–5). Special interest has been in the risk factors for the development of latex allergy in children during the first five years of life (6).

The allergen

There have been many investigations undertaken to identify the purity and characterize the primary structure of the immunoglobulin E (IgE) binding proteins present in NRL, and NRL products, and to evaluate their clinical significance to NRL allergy in various patient groups. Natural latex is produced by nearly 2000 species of plants, and although attempts have been made to extract latex from different plant species, so far only the rubber tree *Hevea brasiliensis* is commercially valuable as a source material of natural rubber. Whether NRL collected from the rubber trees of Malaysia is different from that collected in Thailand or elsewhere is not known. The preparation of the final products by different firms is certainly different. The rubber content of fresh NRL varies between 25% and 45% depending on season, environmental conditions and the rubber tree clones (7). The total protein content (estimated as nitrogen content) in NRL varies between 1 and 2%. These proteins or peptides

with known amino acid sequences are responsible for the allergenic type I reactions causing NRL clinical allergic symptoms (8).

The major protein determinants have been considered appropriate to standardize various allergens. This seems unrealistic when 20–50% of individually allergic subjects react to 'minor' determinants and may not react to the purified, standardized major determinants (4). Allergy to latex rubber is unusual in that it commonly involves sensitization to multiple constituent proteins (9–12). Also, different groups of patients appear to be sensitized to different groups of latex proteins (13–16). The sensitizing proteins are very specific and have different molecular weights (Table 1).

The changing prevalence of latex allergy

It is not obvious why one or many of these proteins should have become allergenic after many years, or indeed why there has been an epidemic of latex allergy. This has been explained too easily as being due to the increased use of surgical gloves owing to the risk of hepatitis and AIDS and the use of new manufacturing methods. The temporal relationship of latex sensitization agrees poorly with the initiation of universal precautions (17). There would seem to be at least two other reasons for the increase of sensitization, particularly in healthcare workers.

Since 1940 cornstarch has replaced mineral talc as donning powder in surgical gloves (18) because it was considered that silica talc powder was the

cause of peritoneal granulomata. Mineral talc is heavy and only transiently airborne, whilst cornstarch, which remains airborne when used as a glove powder, has also been shown to be a latex carrier (19,20). Latex-contaminated glove powder provokes allergic reactions in sensitized subjects (21) and acts as a 'latex-aeroallergen' in operating theatres (22). Lundberg and coworkers (23) showed with immunochemical investigations that mineral talc has a high capacity to bind firmly to latex allergens in contrast to cornstarch, which captured the latex allergens but the binding was less pronounced and unstable. The silica talc powder in fact acts as an efficient allergen eliminator. The cornstarch powder consists of a mixture of amylose and amylopectose. This mixture is treated chemically to improve its lubricating properties. It was found from the experiments that various lower-molecular-weight latex allergens showed a higher tendency to bind than the high-molecular-weight allergens (24).

The question of how the actual allergen is released from the glove material and also released from the powder has not been studied, although some new work on the role of endotoxin as a cofactor in the pathogenesis of latex allergy (25) may well be important. It may be relevant that Michel and coworker demonstrated that the severity of asthma in mite-sensitive asthmatic patients correlates with the concentration of endotoxin in old house dust (26). Endotoxin effects appear enhanced only in those with persisting allergies to relevant allergens (27).

Pollen and latex-associated food allergies

Food reactions in patients with pollen allergic rhinitis and asthma have been studied during the last 20 years, particularly in the Scandinavian countries, because silver birch (*Betula*) pollen allergy is the pollen that causes most seasonal complaints. It is also the pollen that is most commonly associated with IgE-mediated symp-

toms related to fresh fruit and vegetables (28–30). It has been shown (31) that there may be allergenic relationships between taxonomically diverse pollens. There is also much evidence that a family of cytoskelous proteins called profilins, with a molecular weight of 14–18 kDa, are present in several different pollens and plant species (32). Profilins are generally, but not always, thermolabile proteins, which means that patients who may be anaphylactically sensitive to many fresh fruits and vegetables can eat them with impunity when they have been cooked. Profilin is an allergen in many plant species, so that we might assume that profilin might be an allergen in *H. brasiliensis*. It has been found in a group of 19 individuals allergic to latex that only two had antiprofilin IgE antibodies. However, profilin is barely detectable on glove-extract immunoblots. However, profilin is present in banana extract; it is likely to be involved in cross-sensitivity to banana and latex and should be taken into account when interpreting the results of latex IgE antibody assays. It must also be remembered that latex-allergic patients react to a 15-kDa allergen that is not profilin (33–35).

Latex allergy, like pollen allergy, is also associated with a small group of fresh-fruit-allergic responses. The fruits that commonly cause allergic problems are banana, avocado, pear and chestnut; other fruits less commonly associated with latex allergy are kiwi, mango, peach and walnut. The 'latex-fruit syndrome' is very common in the latex-allergic subject because 52% of latex-allergic patients have allergies to various fruits and systemic anaphylaxis occurred in 36% (36). It may be that the patient's reaction to fruit brings to light the latex-allergic symptoms that may have been undiagnosed. The fruits that commonly cause allergic symptoms to the pollen-sensitive patients are not those that are usually related in the latex-allergic subject. Banana allergy is seen in young children, but this has not necessarily occurred with latex

Table 1. Allergen designation by International Union of Immunological Societies (IUIS)

Allergen	Common name	Mol. weight (kDa)	Reactivity (%)
Hev b 1	Rubber elongation factor Associated with spina bifida	14.6 (58)	22
Hev b 2	B-1-3 Glucanase	34–36	?
Hev b 3	Prenyltransferase Associated with spina bifida	24–27	?
Hev b 4	Nficrohefix	100, 110, 115	?
Hev b 5	Acidic protein	16–24 20 (6.01)	62
Hev b 6	Hevein protein	14 (6.03) 5 (6.02)	60
Hev b 7	Patatin homolog	43–46	23

allergy (37). The authors point out it is rare in infants but has been much studied in relation to its cross-allogenicity with latex in adults and older children. In adults we have seen the latex-allergic subject become banana allergic after many years. It can be shown by RAST inhibition that there is a dose-dependent inhibition with increasing concentrations of banana extracts (38,39). An unusual way to become anaphylactic from banana occurred in a latex-allergic patient who was bitten by a monkey that had been eating banana (37). Lysozyme has been shown to be present in detectable amounts in gloves, and this may be one of the cross-reacting allergens that account for the association of NRL and fresh-fruit-allergic responses (36). To study the chemical and immunological properties of latex proteins, it is necessary to clone and express the dozen or more individual latex allergens. The proteins involved in rubber synthesis of *H. brasiliensis* are many (Table 1), but profilin, the pan-allergen of fresh fruit and enzymes such as chitinases, glucanases and lysozymes and papain, may account for the latex–fruit syndrome (Table 2).

Cross-reaction by *F. benjamani* and *H. brasiliensis* and fruit sensitivity

The weeping fig *Ficus benjamani* is used increasingly for indoor decoration. This can cause symptoms of allergic rhinitis and asthma, as well as clinical and immunological cross-reactions with various fresh fruits such as fig, kiwi and papain. It has been reported that there is a cross-reaction between *F. benjamani* and *H. brasiliensis*, demonstrated by reciprocal inhibition of CAP RAST and immunoblot by the two extracts (40,41). Sometimes no cross-reaction can be obtained between *F. benjamani* and *H. brasiliensis* (42). The existence of cross-reactive allergenic structures in plant-derived products such as latex, fruits and enzymes, may explain extensive allergenic reactivity, and it seems likely that plant enzymes such as papain, bromelain and lysozymes are common allergens (43). Because of the ubiquity of *F. benjamani* and because symptoms of rhinitis, conjunctivitis and asthma are usually not related to exposure, it has been suggested that routine skin tests for latex allergy be performed on all patients investigated for respiratory allergy (44). Because the plant is a strong sensitizer, it would seem reasonable to advise the parents of atopic children that such plants must not be in the home.

Prevention

Because of cross-reacting antibodies between latex and banana (45), it would be sensible to suggest that children who are known to be at risk of developing latex allergy, or who are already allergic to latex, should omit bananas from their diet (46). A prospective study in atopic multi-operated spina bifida children could confirm or refute this. We know the risk factors for children to develop latex allergy, and it would seem reasonable also to know the chances of the latex-allergic child developing the 'latex–fruit syndrome'. Possibly because of the multiplicity of latex allergens, at present it does not seem possible to predict whether a child will develop anaphylaxis from latex exposure at operation (47).

Prevention of anaphylaxis at operation is possible. Triple-washed powder-free latex gloves contain several thousand times less allergen than standard latex surgical gloves (48). Recently, 140 patients with spina bifida were studied to see how far latex allergy correlated with the number of operations. Patients with 5–7 operations had a least 10 times higher probability of having antilatax IgE antibodies. Prevalence of anti-Hev b 1 IgE antibodies was significantly associated with the number of operations (49). The younger the child is at first operation; the presence of atopic dermatitis; and the number of operations are all factors favoring latex sensitization. However, a history of latex sensitivity given by the parents was often negative (50%), and had to be proved by provocation's tests (50). It follows that any child who is atopic and has had three or more operations should routinely be skin-prick tested for latex allergy, and at the same time asked about any fresh-fruit allergy.

In children with type 1 diabetes, induction of allergic sensitization to latex from insulin vial tops could potentially occur. It was found in 112 diabetic children that 42 (38%) were atopic, and 7 (17%) exhibited specific IgE to latex (although none reported clinical symptoms from latex). This prevalence is similar to atopic children without diabetes, and therefore this sensitization is not related to frequent contact to latex through insulin injections (51,52). However, the possibility exists that rubber medication stoppers and the injection port of intravenous tubing might explain otherwise unexplained anaphylaxis in latex-allergic patients. One group has reported such reactions (53). In some centers it has become the practice to eliminate multi-dose vials and remove latex injection ports from the operating theatre where the patient is known to be

Table 2. Latex allergens without a nomenclature designation

Hevamine
29.550 kDa: A minor latex allergen
Class-I chitinases
32 kDa: Cross-reactive (banana, avocado) and very likely major latex allergens
Class-II chitinases
30 kDa: Cross-reactive and very likely major latex allergens
Mn-superoxide dismutase (MnSOD)
25.8 kDa: The significance is not yet determined, possible cross-reactive allergen between latex and moulds
Enolase (2-phosphoglycerate dehydratase)
46 kDa: Undetermined significance, a putative cross-reactive allergen between latex and moulds
Profilin
14 kDa: A minor/major cross-reactive latex allergen
Latex lysozyme
27 kDa: Undetermined significance, cross-reactivity with homologs from fig and papaya possible
Triosephosphate isomerase
27 kDa: Significance not determined
Proteasome subunit
25.3 kDa: Significance not determined

Adapted from reference (71).

latex-allergic. It should be noted that the presence and bioavailability of antigen in these sources has not been documented. Latex-free syringes are now available commercially.

Pacifier use can cause urticaria of the mouth, in the same way as rubber balloons. This has been associated with nut (walnut) and fresh fruit (kiwi) sensitivity (54). No one seems to have carried out a prospective study on whether pacifiers or rubber teats in non-breast-fed babies gives rise to sensitization. In Canada it has been found that some food samples have borne traces of latex from handling with latex gloves. A change to non-latex alternatives is being considered by some of the large supermarkets.

Confirming latex sensitivity

In all fruit-allergic patients, it would seem reasonable to consider the potential for allergic reactions to latex. This is because latex is an antigenically complex material with structural homology to other plant (fruit) proteins such as havein, hevamine (30-kDa), palatin and a 46-kDa protein homology with palatin. Immunoblot inhibition has demonstrated cross-reactive IgE antibodies to several proteins in latex and banana (54). However, although in fruit-allergic patients there may be 50–100% skin-prick or CAP positive, symptomatic sensitivity is low (10–20%); but, in general, patients with anaphylactic reactions to fruits are more likely to be sensitive to latex (55).

Skin-prick tests are the easiest way to establish a diagnosis of latex sensitivity. Patients with a previous history of anaphylaxis to foods or latex can have an anaphylactic response from a skin-prick test with latex (5,56–58). Anaphylactic events associated with latex skin testing can occur without previous history of anaphylaxis. This was seen in a boy aged 6 who had multiple clinical food and inhalant sensitivities. When reviewed he complained of a new food (bananas) now causing the oral allergy syndrome. He was tested for latex by skin-prick test and this produced a mild general reaction. The 'use' test should not be carried out in anyone who has had anaphylaxis, although some investigators consider exposing only one gloved finger for five minutes to be safe. Normally the whole hand is exposed to the latex glove. Fresh-fruit allergy may be missed if commercial extracts are used. It is always important to use the 'prick + prick' technique with fresh fruit (59). This itself, very rarely, can cause anaphylaxis. Inflating balloons is sometimes used or the mucosa of the lips can be exposed if the glove test is negative. Any reaction that occurs is easily controlled with local and oral antihistamines. Nasal latex challenge testing has been shown to be sensitive and specific but this is an unsafe diagnostic method to test latex allergy because anaphylaxis may occur (60).

It can be seen from Tables 1–3 that there are many latex allergens and we do not know, in the extracts that are commercially available, whether when performing a skin-prick test or RAST all or some of the appropriate epitopes are present in the latex solution. Among 907 health care workers, 18 were thought to be rubber-allergic by questionnaire. All 18 were skin-prick test positive with 'prevulcanized' latex. There were 899 history-negative patients of whom 6 were skin-prick test positive; one was subsequently shown to be allergic to rubber by challenge. In this series, skin-prick testing was 100% (18/18) sensitive and 99% (883/889) specific. The predicted value of a positive skin-prick test was 80% (19/24) and the predictive value of a negative test 100% (883/883) (63).

Commercially available extracts of latex vary considerably in their allergen concentration, stability and allergen composition. Skin-prick tests, which can cause anaphylaxis in the latex-allergic, are not quantitative in size but give from the clinical point of view greater sensitivity and specificity than do immunological tests such as RAST or its modifications.

Spina bifida and latex allergy

Routine testing for latex allergy in patients with spina bifida is not recommended. The sensitivity and specificity of the *in vitro* measurement of latex-specific IgE depends on the clinical sensitivity pattern of the population studied. In spina bifida patients, *in vitro* assays are adequately sensitive (64,65). In the Tosi group (65) of 57 RAST-negative patients, there were no untoward reactions even during latex-exposed surgery. In general however, *in vitro* diagnosis has not been as sensitive as skin-prick testing.

Different countries show similarities and differences when considering latex allergy in spina bifida children. Using skin-prick tests and CAP, it was found in 59 Saudi patients aged 1–20 with spina bifida that 25% were allergic to latex. Males were more frequently affected than females, but in some studies females showed more sensitization (66,67). The Saudi Arabian finding that there was no specific correlation between either family or personal history of atopy and sensitization to latex is unusual. It also seems strange that in the Saudi patients there was no significant correlation between the number of surgical procedures and the occurrence of latex sensitization (68). The reason for this may be that none had undergone more than four surgical procedures. It is also noteworthy that none of the latex-allergic in the group under study was food-allergic. However, in their conclusions it is stated that incidence of sensitization to latex in Saudi Arabian children with spina bifida is similar to reports in the world literature. This compares with the findings in atopic children in latex-allergic children in Italy. In 326 atopic children, five children (1.5%) had a positive clinical history to latex exposure. None of the children had spina bifida or had a different

history of using pacifiers in the first 2 years of life. It was not obvious why these children had become latex-allergic, yet in all five latex-symptomatic children, there was an associated fresh-fruit allergy (kiwi, apple and chestnut in four cases; avocado, pineapple, orange, pear and grape in three cases; banana in two; apricot in one case) but only one child with a positive skin-prick test to fruit presented with clinical symptoms after ingestion of kiwi and orange (69).

Is latex immunotherapy possible?

Classical immunotherapy has greatly decreased in many countries during the last decade because the risk-to-benefit ratio is not acceptable. The recent discovery that allergen-gene immunization induces a T-helper 1 antiallergen response but no IgE antibodies, and at the same time down-regulates a pre-existing response, suggests that it may be possible to develop a novel and safe form of immunotherapy (70). Already Slater et al. (71) have shown that mice primed with latex allergen Hev b 5 and boosted with pDNA encoding Hev b 5 had a 23% drop in specific IgE 10 days after pDNA injection. Because there are at least 12 different latex allergens that have been characterized in humans, there will be many difficulties to overcome before this form of immunotherapy will be possible.

Immunotherapy may be for the future but much can be done to prevent latex sensitization in the high-risk group of children with spina bifida who require repeated operations (48). Latex-free surgery and anesthesia can be established, and it was found in a recent study that none of 12 patients became sensitized to latex despite up to seven operations in each child (72).

Table 3. Panels of recombinant *H. brasiliensis* allergens for differential diagnosis

'Spina bifida' panel	
Hev b 1, rubber elongation factor	
Hev b 3, small rubber particle protein	
'Latex-fruit syndrome' panel	
Hev b 2, β -1.3-glucanase	
Hev b 5, acidic protein	
Hev b 7, patatin-like protein	
Class I and class II chitinases	
Profilins	
'Latex-only' panel	
Hev b 1, rubber elongation factor	
Hev b 3, small rubber particle protein	
Hev b 4, microhelix component	
Hev b 6, prohevein/hevein	
'Latex-mould' panel	
Mn-superoxide dismutase	
2-Phosphoglycerate dehydratase (enolase)	

Discussion

The molecular biology of latex allergens requires much further study as there are well over a dozen allergens present in NRL. Only recombinant proteins will eventually allow us to use a uniform and standardized mix for diagnostic and therapeutic use. The available extracts are not standardized in that it is not known how many allergens are present in any one commercial extract. Ribonucleic acid (RNA) is not readily available from latex, but until a high-quality RNA is available, full-length allergen-coding genes cannot be used to obtain the basic reagent to produce recombinant latex proteins. Clinically, we know that latex allergy is associated with allergy to various fresh fruits and vegetables and

associated with pollens such as mugwort (*Artemisia*), ragweed (*Ambrosia*), timothy (*Phleum*), and rape (*Brazzica napus*) pollens. It is possible that there is also a cross-reaction between enzymes in the latex and various moulds such as *Aspergillus fumigatus* (73). The presence of common epitopes in the latex-allergic subject helps us to explain many of the associated clinical syndromes seen in latex allergy (Table 3).

The molecular biology of latex allergen is rapidly expanding. Hev b 3 is an allergen that rapidly degrades. This, with Hev b 1, must be present in an allergy extract to diagnose the latex-allergic spina bifida patient but neither of these allergens is enough to diagnose the patient with latex-fruit syndrome. Niggemann and colleagues (66), investigated the course of early sensitization to latex and various lifestyle factors in 398 children in a prospective birth cohort study. It was found that 20 (5%) showed specific serum IgE to latex by the age of 5 years. The only risk factors for developing sensitization or allergy to latex were the number of operations and an atopic predisposition.

We know the risk factors for developing sensitization but it would seem important that babies, when being born, should not routinely be at risk from latex gloves, which have been worn by midwives and obstetricians over the last 30 years. Latex is a potent allergen that the baby meets when being born. Would it be reasonable to remove babies from potential risk by insisting in the future that non-latex gloves are worn by all medical staff present at delivery of the baby? Various recommendations concerning latex testing and avoidance have been made in the USA (74) and Europe (39). The availability of non-latex devices and latex-free areas is so far only available in a few hospitals. One recommendation is that patients with spina bifida are at such high risk of latex allergy that they should avoid latex exposure entirely from birth. Perhaps this recommendation might be extended to all babies at birth.

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