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Patients monosensitised to Hev b 8 (Hevea brasiliensis latex profilin) may safely undergo major surgery in a normal (non-latex safe) environment

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Key words

Latex allergy, profilin, component resolved diagnosis, allergens

Summary

Background: *Natural rubber latex allergy is a condition at high risk of anaphylaxis during surgery. However, latex contains several protein allergens and not all of them may show the same clinical relevance.* ***Objective:*** *To investigate the clinical relevance of Hev b 8, the natural rubber latex profilin.* ***Methods:*** *Seven patients without a clinical history of latex allergy but identified as being latex hypersensitive by positive SPT (3/7) and or positive latex-specific IgE during routine pre-surgery allergy investigations were studied. All patients were monosensitized to Hev b 8 (Hevea brasiliensis latex profilin) as shown by the detection of specific IgE to recombinant latex allergen components. Ten subjects with a history of latex allergy (urticaria, asthma, and/or rhinitis), sensitised to latex allergens other than profilin were enrolled as controls. Both patients and controls underwent a latex glove-wearing test; in case of a negative test, patients underwent surgery in a normal surgical setting.* ***Results:*** *All 7 patients scored negative on latex glove wearing test and underwent major surgery (orthopaedic, Caesarean section, pilonidal sinus, vascular, tonsillectomy, uterine revision, and uretral surgery) in a normal (non-latex safe) surgical setting without any consequence. In contrast, 9/10 (90%) controls showed a positive latex glove-wearing test ($p < 0.01$).* ***Conclusion:*** *Latex profilin is either clinically irrelevant or is no longer present in latex products. This study highlights the importance of a component-resolved diagnosis of latex sensitisation as a tool to get a more precise assessment of the risk and to reduce the costs of healthcare.*

Introduction

Although less frequent than some years ago (1), IgE-mediated allergy to latex remains a relevant public health problem (2). During the last decade, a number of allergenic latex proteins have been detected and purified (3), and several of them have been found to behave as major allergens. Natural rubber latex (NRL) allergen proteins show differences both in physico-chemical features; this fact may heavily influence the clinical expression of latex sensitisation as well as the cross-reactivity to plant-derived foods. As a consequence, a component-resolved diagnosis of latex allergy may have great clinical usefulness and prognostic relevance. Profilins are well-know pan-allergens in pollen and plant-derived foods (4-7); their importance as airborne allergens is difficult to establish due to the contemporary sensitisation to major pollen allergens, but they have been shown to behave as relevant food allergens (8). The clinical relevance of latex profilin (Hev b 8) (9-11) sensitisation is still unclear. On one hand, patients monosensitised to Hev b 8 score positive on SPT with latex extract and show circulating latex-specific IgE in-vitro as do all other latex-allergic individuals; these findings alarm both the doctors and the patients very much (particularly if the latter have to undergo surgery) due to a potential risk of severe allergic reactions. On the other hand, sensitisation to Hev b 8 is often found in individuals who are undergoing clinical investigation due to respiratory or food allergy but who frequently do not report any problem following latex exposure (12). Although recent studies found that Hev b 8 is present in minimal (if any) amounts in gloves normally used in healthcare settings (12) the final proof of a harmless exposure of such patients to latex gloves during major surgery is still missing. The present study definitively shows that patients monosensitised to Hev b 8 may undergo exposure to NRL material without any consequence.

Patients and methods

Patients

The study was carried out on subjects referred at the allergy department of the XXX Hospital to undergo pre-surgery evaluations because of suspect NRL allergy. The suspect was based on a reasonably suggestive clinical history, on a prior positive SPT with latex extract, and/or on a prior positive latex-specific IgE assay. Several patients had previously undergone surgery in a latex-free environment due to the fear of adverse intra-operative reactions to latex.

Methods

After giving an informed written consent, all subjects underwent SPT with a commercial latex extract (0.016 mg protein/ml; Lofarma Allergeni SpA, Milano, Italy) and measurement of latex-specific IgE levels (ImmunoCAP; Phadia, Uppsala, Sweden). SPT were performed and read following the EAACI guidelines; wheals showing a mean diameter of 3 mm or more were considered positive. Specific IgE values > 0.35 kU/l were considered positive.
Subjects with doubt clinical histories scoring negative on both in-vivo and in-vitro assays were diagnosed as non-allergic to NRL, whereas those positive on SPT and/or ImmunoCAP with or without a clinical history of latex allergy were further investigated by measuring IgE to NRL recombinant allergen proteins (ImmunoCAP; Phadia). Subjects found to be monosensitised to Hev b 8 (latex profilin) represented the "patients" group, whereas those reacting to latex allergens other than Hev b 8 (irrespective of Hev b 8 reactivity) represented the "positive controls".

Glove-wearing test

Both patients and positive controls underwent a latex glove-wearing test. In this test, subjects were asked to wear a latex glove (Sumirubber SDN, Malaysia) on one hand for 15 minutes; the test was considered positive if local itching and erythema/urticaria (with or without angioedema) with or without systemic symptoms (including asthma, and/or urticaria) occurred. The test was immediately stopped if systemic symptoms developed. Five normal subjects underwent a latex glove-wearing test using gloves of the same lot of those used for both patients and positive controls. The latex glove-wearing test was carried out and personally read by a physician (13)

Surgical treatments

Latex-reactive subjects with both negative clinical history and negative latex glove-wearing test underwent their respective surgical treatments in a normal hospital setting (i.e. using latex gloves, catheters, endotracheal tubes, etc).

Those with a positive clinical history and/or a positive latex glove-wearing test underwent surgery in a latex-free environment.

Statistics

Proportions were compared by the chi-square test with Yates' correction. Means were compared by two-tailed Student's t test. Probability values < 5% were considered statistically significant.

Results

Seven patients monosensitized to Hev b 8 (M/F ratio 3/4; mean age 27.1 years, range 14-46 years) (table 1), and 10 positive controls (M/F ratio 3/7; mean age 28.7 years, range 10-38 years) (table 2) were studied. The two groups did not differ significantly in mean latex-specific IgE levels. In contrast, 0/7 (0%) patients vs 9/10 (90%) controls showed a positive latex glove-wearing test ($p < 0.01$). The glove-wearing test was negative in 5/5 normal subjects.

Since no patient had a history of latex allergy, all 7 underwent their respective surgical treatments in a normal hospital setting without any adverse consequence (see below). In contrast, in the light of the positive clinical histories, of specific IgE findings, and of positive latex glove wearing test, all control subjects underwent surgery in a latex-free environment.

Patients case reports

A 17-year-old girl with a long-lasting history of seasonal rhino-conjunctivitis and asthma associated with multiple pollen sensitisation (birch, grass, weeds) and sensitisation to a number of plant derived foods (including tomato, Apiaceae, Rosaceae, potato, kiwi, melon, avocado, and tree nuts) had to undergo orthopaedic surgery due to ankle fracture. SPT with latex extract scored strongly positive (mean wheal diameter 12 mm), although a history of immediate allergic reactions following contact with latex goods was missing. Measurement of serum specific IgE to various recombinant latex allergen proteins showed significant reactivity to profilin (Hev b 8) and only a weak reactivity to Hev b 6 and Hev b 11 (table 1).

A 46-year old pregnant woman with a history of multiple pollen allergy and oral allergy syndrome following the ingestion of a number of raw plant-derived foods was evaluated before delivery. SPT with commercial latex extract scored strongly positive (mean wheal diameter 15 mm) in spite of a negative history of latex allergy. In-vitro tests showed single IgE reactivity to latex profilin. Since the latex glove-wearing test did not induce any appreciable reaction Caesarean section was carried out in a normal surgical setting without any consequence.

A 34-year old man underwent allergy evaluation before pilonidal sinus surgery. He had a history of both birch and grass seasonal rhino-conjunctivitis and of oral allergy syn-

Table 1 - Levels of IgE specific for latex allergen proteins, grass pollen profilin, and birch pollen profilin in 7 cases.

Patient	1	2	3	4	5	6	7
Sex/age	F/17	F/46	M/34	M/38	M/14	F/27	F/14
Glove wearing test	Negative	Negative	Negative	Negative	Negative	Negative	Negative
Latex Extract	2,43	1,15	5,73	1,14	3,22	1,97	1,14
rHev b 1	<0,10	<0,10	<0,10	<0,10	0,14	<0,10	<0,10
rHev b 3	<0,10	<0,10	<0,10	<0,10	<0,10	<0,10	<0,10
rHev b 5	<0,10	<0,10	<0,10	<0,10	<0,10	<0,10	<0,10
rHev b 6.01	0,79	<0,10	<0,10	<0,10	<0,10	<0,10	<0,10
rHev b 6.02	0,77	<0,10	<0,10	<0,10	<0,10	<0,10	<0,10
rHev b 8	4,33	2,29	5,21	0,51	2,51	5,33	0,51
rHev b 9	<0,10	<0,10	<0,10	<0,10	<0,10	<0,10	<0,10
rHev b 11	0,60	<0,10	<0,10	<0,10	0,14	<0,10	<0,10
rPhl p 12	3,71	0,97	2,08	1,22	2,88	17,4	1,22
rBet v 2	3,37	0,92	2,90	13,5	1,60	2,97	13,5

Values are in KU/L

drome following the ingestion of several fresh plant-derived foods. The man did not report a history of latex allergy but showed clear-cut positive SPT with latex extract (mean wheal diameter 10 mm). In-vitro analysis demonstrated monosensitivity to Hev b 8. Since the latex glove-wearing test did not induce any clinical response, the patient underwent surgical intervention in a normal hospital setting.
Four further patients, a 38 year-old man, a 14 year-old boy, a 27 year-old woman, and a 14 year-old girl, all with a history of both grass and birch pollen allergy and of oral allergy syndrome following the ingestion of a number of plant-derived foods were found to have circulating latex-specific IgE (1,14 KU/l, 3,22 KU/l, 1,97 KU/l, and 2,60 KU/l, respectively), in spite of a negative SPT with latex extract. In-vitro analysis showed monosensitivity to Hev b 8 in all four cases. After a latex glove-wearing test was carried out, in all cases with negative results, these patients underwent vascular surgery, tonsillectomy, uterine revision, and uretral surgery, respectively, in a normal setting.

Positive controls (table 2)

A history of urticaria, rhinitis, and/or asthma upon contact or inhalation of latex was present in 8, 7, and 5 cases, respectively. Three of them had a history of latex-fruit allergy syndrome (offending foods avocado [n=2], chestnut [n=2], peach, banana and kiwi m[n=1]). All these patients scored positive on SPT with latex extract. No patient showed IgE reactivity to Hev b 8; 9 patients reacted to Hev b 6, 3 to Hev b 5 (1 monosensitive), 3 to Hev b 11, and 1 to Hev b 1.

Discussion

All our Hev b 8-monosensitized patients underwent general surgery in a normal (not latex-free or latex-safe) setting without any problem. As shown by component-resolved diagnosis in-vitro, all of them, but one that showed a weak additional reactivity to Hev b 5 and Hev b 6, were sensitised uniquely to latex profilin as a consequence of primary pollen sensitisation. Although the number of patients included in this study is limited due to the difficulty in recruiting patients that are monosensitized to latex profilin and have to undergo surgery, our observations suggest that single sensitisation to Hev b 8 is unlikely to result in allergic reaction upon exposure to latex and does not represent an indication to a latex safe medical/surgical practice. Whether this is the consequence of the lack of profilin allergen in latex devices (12,14) or of a clinical irrelevance of the allergen per-se (8) has to be established.

Table 2 - Levels of IgE specific for latex allergen proteins in 10 positive controls

Control	1	2	3	4	5	6	7	8	9	10
Sex/age	F/33	F/33	F/16	M/33	F/37	M/16	F/38	F/33	M/10	F/38
Glove wearing test	Positive	Positive	Positive	Positive	Negative	Positive	Positive	Positive	Positive	Positive
Latex Extract	44.4	1,97	1.95	0.5	5.8	0.8	25.8	3.7	32	1.03
rHev b 1	<0,10	<0,10	<0,10	<0,10	<0,10	<0,10	<0,10	0,14	1,5	<0,10
rHev b 3	<0,10	<0,10	<0,10	<0,10	<0,10	<0,10	<0,10	<0,10	<0,10	<0,10
rHev b 5	8,9	<0,10	2,2	<0,10	<0,10	<0,10	18,1	<0,10	4,4	0,10
rHev b 6.01	16,7	0,91	<0,10	0,9	6,9	0,7	9,4	3,9	49,5	1,2
rHev b 6.02	8.8	0.94	<0,10	1.0	7.2	1.0	8.8	5.3	48.5	1,5
rHev b 8	<0,10	<0,10	<0,10	<0,10	<0,10	<0,10	<0,10	<0,10	<0,10	<0,10
rHev b 9	<0,10	<0,10	<0,10	<0,10	<0,10	<0,10	<0,10	<0,10	<0,10	<0,10
rHev b 11	0.2	0.27	<0,10	<0,10	2.1	<0,10	1.6	<0,10	0.3	<0,10
rPhl p 1		25.0				34,1				1,96
rPh p 12		1,0				0,1				0,1
rBet v 1	22,1						12,5			
rBet v 2	0,1						0,1			

Values are in KU/L

Until recently, clinical decisions regarding latex-hypersensitive subjects to be submitted to surgical treatments had to be based on the measurement of total IgE and of latex-specific IgE levels and on questionnaires (15, 16). However, our study suggests that latex-specific IgE levels cannot be adopted as a reliable means to discriminate between patients at high or low risk of adverse reaction upon contact with latex, as shown by the latex glove-wearing test. Even this latter procedure, although useful in detecting patients likely to react upon latex contact, does not seem totally reliable, as it scored negative in 1 control subjects with a history of latex allergy and specific IgE levels for rHev b 6. In effect the usefulness of the "use test" has been questioned in view of the widely varying allergen contents of gloves from different manufacturers and from different lots (17).

On the other hand, one patient showing sensitization to profilin and a weak additional reactivity to Hev b 5 and Hev b 6 showed a negative provocation test and underwent surgery in a normal setting without any consequence, suggesting that such additional IgE reactivity was clinically irrelevant although this needs to be established by a proper follow-up program. It is also possible that the recent improvements in manufacturing processes resulting in an overall reduction of latex allergens levels in surgical gloves may have played a role in the negative latex glove wearing test as well as in the absence of any intra-surgery allergic reactions in this patient (18).

In conclusion our study provide evidences that component-resolved diagnosis is a more sensitive marker than latex specific IgE for the outcome intra-operatory anaphylaxis in patients sensitised to latex who undergo surgery. It may also help clinicians to take decisions that may eventually reduce the costs of healthcare (e.g. avoiding unnecessary latex-free procedures) without any increase in risks.

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