

Longitudinal Study on Specific IgE Against Natural Rubber Latex, Banana and Kiwi in Patients with Spina Bifida

Verlaufsuntersuchung zu spezifischem IgE gegen Naturlatex, Banane und Kiwi bei Patienten mit Spina bifida

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Key words

- natural rubber latex
- IgE antibodies
- fruit allergy
- Spina bifida
- latex fruit syndrome

Schlüsselwörter

- Naturlatex
- IgE Antikörper
- Fruchallergie
- Spina bifida
- Latex Frucht Syndrom

Bibliography

DOI <http://dx.doi.org/10.1055/s-0031-1273752>
 Published online:
 April 21, 2011
 Klin Padiatr 2011; 223: 352–355
 © Georg Thieme Verlag KG
 Stuttgart · New York
 ISSN 0300-8630

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Abstract

Objective: Up to 2 out of 3 spina bifida (sb) patients with natural rubber latex (NRL) antibodies (ab) have crossreacting IgE-ab against tropical fruit, due to structural homologies between several NRL antigens and allergenic fruit proteins. It is essential to investigate whether the patients were first sensitized against NRL or fruit, to give recommendations for an evidence-based prophylaxis.

Patients and methods: We investigated sera of 96 sb patients for specific IgE ab against NRL, banana and kiwi as examples for crossreacting fruit by FEIA (ImmunoCAP System, Phadia). These tests were repeated up to 3 times (mean after 2 years, maximum after 7 years).

Results: In the first testing only 2 of 50 NRL-IgE negative patients (4%) had ab against banana or kiwi. 4 of the 46 NRL-IgE positive patients (8%) showed ab against banana (2) or kiwi (2), 3 (7%) against both fruit. Symptoms of fruit allergy were presented by 3 patients, all symptomatic patients had high levels of specific fruit-ab. In the follow-up study 2 patients with low sensitization against NRL lost their NRL ab and their fruit ab, another 2 only the fruit ab, whereas 4 NRL-sensitized patients newly developed ab against banana and 1 against kiwi. Only 2 patients developed ab against fruit without being sensitized against NRL. 7 out of 10 patients with banana and kiwi ab were atopic.

Conclusions: In most cases the sensitization against fruit follows the NRL sensitization. There is no need to recommend sb patients without NRL sensitization to primarily avoid tropical fruit.

Zusammenfassung

Problemstellung: Bis zu 2 von 3 Spina-bifida-(Sb-)Patienten mit Antikörpern (Ak) gegen Naturgummi (NRL) haben kreuzreagierende IgE-Ak gegen tropische Früchte. Dies ist durch strukturelle Homologien zwischen einigen NRL-Antigenen und allergenen Fruchtproteinen bedingt. Es ist aber essenziell zu untersuchen, ob die Patienten zuerst gegen NRL oder Früchte sensibilisiert werden, um Empfehlungen für eine evidenzbasierte Prophylaxe geben zu können.

Patienten und Methoden: Wir untersuchten Seren von 96 Sb Patienten mit FEIA (ImmunoCAP System, Phadia) auf spezifische IgE-Ak gegen NRL, Banane und Kiwi als Beispiele für kreuzreagierende Früchte. Diese Tests wurden bis zu 3-mal wiederholt (Abstand im Mittel 2 Jahre, maximal 7 Jahre).

Ergebnisse: In der ersten Testung hatten nur 2 von 50 NRL-IgE-negativen Patienten (4%) Ak gegen Banane oder Kiwi. 4 der 46 Latex-IgE-positiven Patienten (8%) zeigten Ak gegen Banane (2) oder Kiwi (2), 3 (7%) gegen beide Früchte. Symptome der Fruchallergie präsentierten 3 Patienten, alle symptomatischen Patienten hatten hohe Frucht-Ak im Serum. In der Verlaufsuntersuchung verloren 2 Patienten mit niedriger Sensibilisierung gegen NRL ihre NRL- und Frucht-Ak, 2 weitere nur die Frucht-Ak. Dagegen entwickelten 4 NRL-sensibilisierte Patienten neue Ak gegen Banane und einer gegen Kiwi. Nur 2 Patienten entwickelten Frucht-Ak, ohne gegen NRL sensibilisiert zu sein. 7 von 10 Patienten mit Bananen- oder Kiwi-Ak waren Atopiker.

Schlußfolgerungen: In den meisten Fällen folgt die Fruchtsensibilisierung der NRL-Sensibilisierung. Daher ist es nicht nötig, Sb-Patienten ohne NRL-Sensibilisierung zu empfehlen, primär tropische Früchte zu meiden.

Introduction

Spina bifida patients are a high risk group for developing natural rubber latex (NRL)-sensitization and allergy due to repeated surgery beginning soon after birth [10]. There is reliable data underlining that up to 2 thirds of spina bifida patients with latex antibodies have crossreacting IgE antibodies against tropical fruit [6], mainly banana, kiwi and avocado [1,4,12] and may show allergic symptoms on contact with the crossreacting fruit and/or natural rubber latex products. The so called latex-fruit-syndrome is based on similar IgE epitopes on several NRL antigens like Hev b 6.02 and allergenic fruit proteins [3,7,13,20]. One of the risk factors is a preexisting atopy [15].

The development of crossreacting antibodies has only been published in casuistic reports with controversial results, and no reports exist about larger numbers of patients. The percentage of allergic (symptomatic) patients is low, especially in the group of sensitized spina bifida patients. As it was unknown whether the patients were first sensitized against NRL [9] or fruit [17], evidence based recommendations for prophylaxis similar to those for latex free operations [25] could hardly be given for the latex-fruit-syndrome.

The aim of our retrospective study was to investigate the development of sensitization against NRL and the tropical fruits banana and kiwi over time, especially to address the question whether the sensitization against NRL precedes fruit sensitization or vice versa. We expected information about the prevalence and quality of allergic reactions against fruit.

Patients and methods

Data were taken from the routine tests for NRL- and fruit antibodies, we had done during visits in the outpatient clinic for spina bifida of the Cologne Childrens Hospital. No standardized protocol about test intervals was used. We tested sera of 96 spina bifida patients (44 female, 52 male, 70 of German origin, 14 of Turkish origin, 12 of other origin) for specific IgE antibodies against NRL, banana and kiwi by FEIA (ImmunoCAP System, Phadia, Uppsala, Sweden). Results were classified in CAP-classes from 0 to 6. Values of >0.7 kU/l (CAP class 2) were taken as positive. In all patients these tests were repeated up to 3 times (see ● Table 1) with a maximum interval of 7.2 years (mean 3.4 years). Initially patients were between 0.18 and 25.0 years old (mean 10.2 years).

Allergic symptoms after contact with products containing NRL or ingestion of banana or kiwi were examined by a questionnaire as well as the number of surgeries, which were done under latex free conditions in our hospital since the year 2005. Thus older patients also had undergone surgeries without these precautions.

Atopy was defined as a medical history of asthma, allergic rhinoconjunctivitis or atopic dermatitis and/or a positive CAP-Test on inhalative allergens (SX1).

Informed consent was given by the patients themselves or their parents. Our studies on natural latex allergy on spina bifida patients, especially the follow-up studies were approved by the ethics committee of the Clinics of the City of Cologne.

Statistical analysis was performed using Chi Square tests for qualitative items and Student's t-test for quantitative items using SPSS software.

Results

In the first testing NRL-specific IgE was found in 52 patients (54%): 6 patients (6%) with low values of CAP class 1 (0.35–0.7 kU/l), which were not taken as positive results, 13 patients (14%) with CAP class 2 (0.71–3.5 kU/l), 10 patients (23%) with CAP class 3 (3.51–17.5 kU/l) and 12 patients (13%) with CAP class 4 (17.51–52.5 kU/l), 6 patients (6%) with CAP class 5 (52.51–100 kU/l) and 5 patients (5%) with CAP class 6 (>100 kU/l) levels. 20 of these 46 sensitized patients (48%) (with specific IgE $\geq$ CAP class 2) also showed symptoms of NRL-allergy up to anaphylactic shock in 5 patients, thus 43% of the NRL-sensitized patients were NRL-allergic. Allergic symptoms were found only in patients with at least CAP class 2 antibody levels, all patients with anaphylactic shocks during surgeries had CAP class 6 in NRL-specific IgE.

Atopy (positive SX1 test and positive medical history) was found in 38 patients (40%), its prevalence was not significantly higher in NRL-IgE positive than in NRL-IgE negative patients (18 of 46 = 42% vs. 14 of 43 = 32%, Chi Square test n.s.); in 7 patients no SX1 test was performed and medical history was negative.

In the first testing only one of 50 NRL-IgE negative patients (2%) had antibodies against banana and one (2%) against kiwi (● Fig. 1). 2 of the 46 NRL-IgE positive patients (4%) showed IgE antibodies against banana, another 2 against kiwi, 3 (7%) against both fruit. The prevalence of fruit-antibody positive patients was significantly lower in the NRL-negative group compared to NRL-positive patients ($p < 0.01$, Chi Square test).

In the follow-up study very differentiated results could be achieved (● Fig. 1): In the NRL-IgE positive group 4 of 7 fruit-IgE positive patients lost their specific fruit-antibodies (2 of the 4 with low sensitization against NRL lost their NRL-sensitization as well), 3 patients retained their fruit antibodies. In the 39 NRL-IgE positive patients without fruit IgE in the first test 5 patients (13%) developed fruit-IgE antibodies (4 against banana alone and 1 against banana and kiwi).

No patient who had not been sensitized against NRL newly developed IgE-antibodies against fruit.

The 2 fruit-sensitized NRL-negative patients at the initial test both lost their fruit-IgE in the following tests, one of them developed high levels of NRL-IgE after multiple surgery between the tests.

7 out of 10 patients with banana or kiwi antibodies during the course of the study and were atopics.

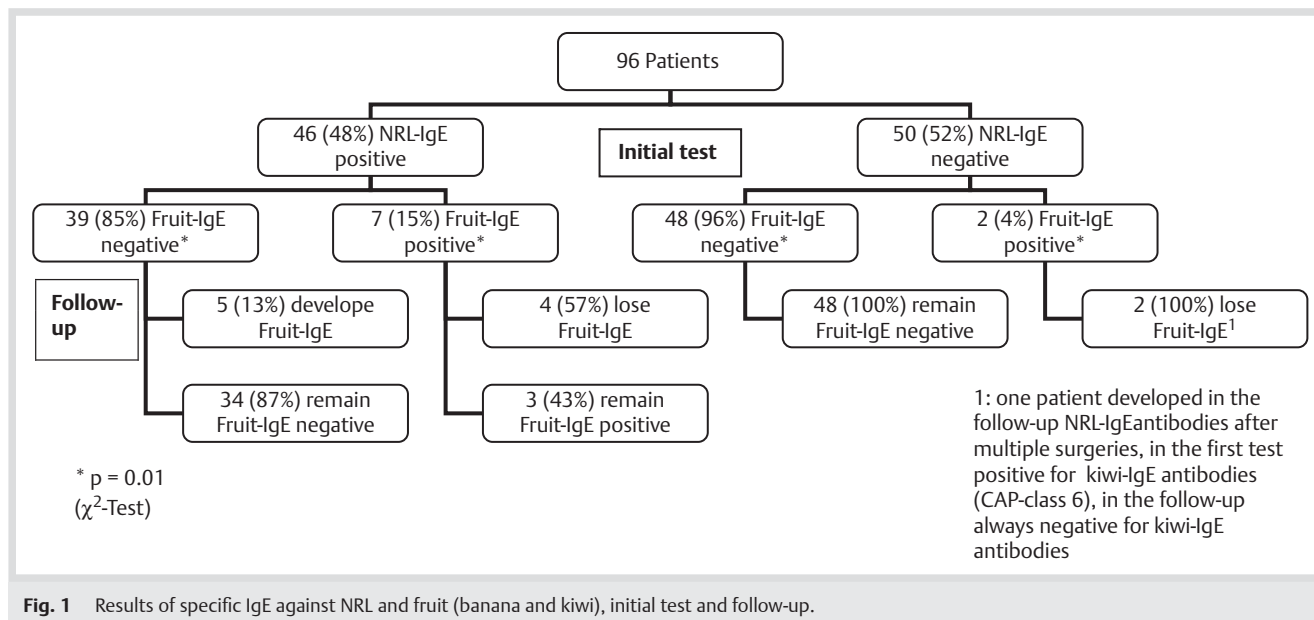
With regard to the aspect of follow-up of NRL-antibodies 2 out of 12, (17%) of fruit- and NRL-IgE positive patients lost fruit and NRL-antibodies during the course of the investigation.

Only 1 patient in the fruit-IgE positive group (this patient showed high levels of specific IgE against kiwi-CAP class 3 to 6 at repeated tests) and 6 out of 84 patients (7%) in the fruit-IgE negative group developed new NRL-antibodies.

Symptoms of fruit allergy were presented by 3 patients (1 reacting to banana, 1 to kiwi and 1 to both fruit), all symptomatic

Table 1 Interval between measurements of specific IgE (years).

Interval (years)	First – second (last) test
minimum	0.12
maximum	7.2
mean	2.3 (3.4)



patients had high levels of specific NRL-IgE (at least CAP class 4, 2 of them with allergic reactions on NRL as well) and were atopics (SX1 test positive).

The level of fruit-IgE ranged from CAP class 2 to 3 (1 with banana antibodies, 1 with kiwi antibodies, 1 with antibodies against both fruit). Symptoms after fruit intake were urticaria after eating banana (2 patients, one of them to kiwi as well), or oral burning after eating kiwi in 1 patient. Anaphylactic reactions, which had been reported after NRL-contacts, did not occur.

There were significantly more atopics in the fruit IgE-positive patients than in negative patients (63% vs. 31%, $p=0.01$, Chi Square test).

The number of surgeries differed significantly ($p<0.05$, Chi Square test) between NRL-IgE positive and negative patients (mean 7.7 vs. 4.1 surgeries) but not between fruit-IgE positive and negative patients (mean 6.6 vs. 6.2 surgeries).

Discussion

For a variety of fruit, mainly of tropical origin, cross-reactions with NRL are described (often cross-reactions with banana, kiwi, avocado, chestnut and papaya; seldom cross-reactions with tomato, peach, lychee, nectarine, passion fruit, pineapple, strawberry, pistacchio, mango, cherry, melon, fig, potato, acerola [21], zucchini, and turnip, as recently published [18]). The spectrum of crossreacting fruit is constantly increasing. Crossreactions were also found for some grass allergens, for instance wheat germ agglutinine [2] or *Ficus benjamins*. By identification and sequencing of latex allergens the structural homologies to fruit allergens could be understood, for instance the hevein domain in avocado endochitinase explains the avocado allergy of NRL allergic patients [8] or the cross-reactivity between acerola and NRL [5]. In a recent publication the NRL allergen Hev b11 was more frequently found in NRL allergic patients with kiwi fruit allergy than without specific kiwi IgE [7]. Unfortunately due to the retrospective study design there are no more sera available to test our patients reactivity on single NRL allergens. This would enable us to distinguish patients with sensitizations against allergen specific major allergens from those with cross-sensitization, which is clinically irrelevant in most cases.

We performed such a study with a slightly other cohort of spina bifida patients on sensitization on single NRL allergens and found, that Hev b 8 and Hev b11 are only minor allergens [22, 24]. This is of clinical importance, as it seems, that patients monosensitized to Hev b 8 can safely undergo surgery without precautions of NRL avoidance [19].

There is an association between latex-fruit syndrome and certain HLA class II alleles (DQB1*0201, HLA-DR functional group E) in Spanish patients [15], while in a cohort with mainly German patients an association between the sensitization to hevein, which has a homology to avocado endochitinase, and HLA DR4 and DQ8 was found [23].

According to the literature cross-reacting antibodies are detectable in up to 2 thirds of all spina bifida patients sensitized against NRL [6]. Our data show, that 85% of the NRL sensitized patients are negative for antibodies against banana and kiwi at the beginning and 87% of them remain without antibodies against both fruit.

We did not test avocado in our follow-up study, as this fruit is not common in infant nutrition in Germany. Therefore we did not assume that a sensitization by food intake would happen.

In our study, 9 of 96 patients had banana and/or kiwi antibodies in the first tests. If differentiated according to NRL-sensitization, 15% of the NRL-sensitized patients are also fruit-sensitized, a smaller value than reported in the literature. For instance, Mäkinen-Kiljunen et al. found banana antibodies in 81% of NRL positive patients [16], Brehler et al. reported banana antibodies in 33% and kiwi antibodies in 16% [6] and Blanco et al. found banana antibodies in 28% and kiwi antibodies [4] in 20% compared to 19% banana antibodies positive patients and 13% kiwi antibody-positive patients in our study. On the other hand 4 out of 46 (9%) NRL-positive patients developed new fruit antibodies in our follow-up study. Starting from the first testing there were always significantly more patients with fruit antibodies in the NRL-positive group than in the group without NRL-antibodies.

The development of sensitization is subject to discussion. In the literature there are no studies dealing with the time course of latex fruit-syndrome in larger cohorts, only some case reports describing a symptomatic fruit allergy (banana) before symptoms

of NRL allergy were noted [17] as well as NRL-allergic symptoms preceding a banana allergy [9].

Our own study is the first dealing with long-term follow-up of latex and banana/kiwi antibodies in spina bifida patients. There is good evidence that in spina bifida patients NRL sensitization usually precedes fruit sensitization. A remarkable case was the atopic patient who developed NRL-antibodies (CAP class 5) after multiple surgeries while losing kiwi IgE completely, which had been up to CAP class 6 before.

The publication of Isola and coworkers [14] about fruit allergy in non-atopic NRL-allergic patients, though not being designed as a follow-up study, confirms our findings, that in most cases symptomatic NRL-allergy was reported before the symptoms of fruit allergy.

We could show, that only in patients with NRL-sensitization a new sensitization against banana or kiwi occurred. In addition, less patients with NRL-antibodies lost their fruit antibodies than in those without NRL-antibodies (43% vs. 100%). The simultaneous loss of antibodies against fruit and NRL in 5 of 6 patients losing their fruit antibodies in the course of the investigation gives good evidence for crossreactive IgE epitopes in NRL and banana/kiwi. The same phenomenon can be assumed in 4 patients, who developed banana- and NRL-IgE, or in 3 patients with kiwi- and NRL-IgE simultaneously during the study. For this group of patients studies on sensitization against single NRL-allergens would be of high interest.

The loss of NRL-IgE antibodies may be due to our strict prophylaxis, whose results were previously described [11].

Factors influencing the fruit sensitization can hardly be found by analysing our data. Having done no inhibition experiments we cannot decide whether the fruit antibodies are due to cross-reactivity or co-sensitization [20].

Based on our data, which show a very small risk for a NRL-IgE negative patient to develop a fruit allergy and vice versa we do not recommend a strict avoidance of tropical fruit to our spina bifida patients, unless they have either allergic symptoms after ingestion of a fruit with specific antibodies against this fruit (CAP class 2 or higher, as all patients with allergic symptoms had such high levels of specific IgE). Nevertheless patients and parents have to be carefully instructed about allergic symptoms.

Conclusions

For spina bifida patients the relevance of cross-reacting antibodies appears to be less important, as allergic symptoms are rarely reported. In most cases the sensitization against fruit follows the latex sensitization. There is no need to recommend to spina bifida patients to avoid tropical fruit primarily.

Conflict of interest: The authors have no conflict of interest to disclose.

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