

Rostrum

IgE-mediated latex allergy – An exciting and instructive piece of allergy history

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Natural rubber latex represents a potent allergen, which for many years had an important impact on occupational health problems but especially on certain risk groups such as spina bifida. Luckily, these problems decreased when powder-free, latex-poor gloves were introduced. Latest data show that in children with spina bifida, who grew up completely latex-free from birth on, sensitization to NRL as well as clinical relevant allergy significantly decreased. Furthermore, sensitization to aeroallergens also went down and even the prevalence of allergic diseases decreased significantly to rates of the general population. This new data clearly indicates that potent allergens (such as latex) in high-risk groups (such as spina bifida) can induce sensitization spreading, and corresponding avoidance can reverse this development. In conclusion, it can be stated that ‘new’ allergies can suddenly arise, there are allergen-specific risk groups, local IgE-production is also possible in the CNS, allergen avoidance can be made reversible by effective prevention, and finally, certain allergies can luckily become history within a relatively short period of time. Furthermore, these new findings clearly end the debate about whether patients with spina bifida have a disease-inherited risk for allergy to NRL and show that the cause is the meningi and the multiple surgical interventions – and therefore sequelae can be reversed by implementing preventive measures.

Bodo Niggemann

Pediatric Allergology and Pneumology, German Red Cross Clinic Westend, Berlin, Germany

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Bodo Niggemann, MD, Pediatric Allergology and Pneumology, Hedwig-von-Rittberg-Centre, German Red Cross Clinic Westend, Spandauer Damm 130, 14050 Berlin, Germany
Tel: +49 152 0157 5704
Fax: +49 30 3035 5709
E-mail: b.niggemann@drk-kliniken-berlin.de

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Natural rubber latex (NRL) is obtained from *Hevea brasiliensis* – a tree of the family Euphorbiaceae – and treated by vulcanization. In medicine, NRL may be present in gloves, fingerstalls, plasters, tubes, catheters, and masks. In everyday products, NRL is found in balloons, condoms, gloves, mattresses, sports equipment, stretch textiles, and tires. Exposure to NRL may be unobtrusive, e.g., in restaurants when NRL gloves have been used to prepare foods (1).

Abbreviations: CNS, central nervous system; CSF, cerebrospinal fluid; KIGGS, German Health Interview and Examination Survey for Children and Adolescents; NRL, natural rubber latex.

History

The first report of immediate type clinical symptoms to NRL dates back to 1927 with severe generalized urticaria caused by an NRL dental prosthesis (2). Approximately 50 years later, the first case of glove-induced immediate type contact urticaria was reported (3). Since then, IgE-mediated type I allergy to NRL proteins has become a problem for increasing numbers of adults and children (4, 5). The focus on risk groups such as patients with spina bifida started in the 1990s (6).

The wrong track

In the late 1980s, clinical reactions to the use of NRL gloves were thought to be as a result of cornstarch in the glove powder (7–9). It took

some years to realize that cornstarch was only the carrier for NRL on latex products (10). This view was confirmed in prospective studies showing that NRL is the major contributor to latex aeroallergen in operating rooms (11). Possibly, cornstarch acts as a non-antigen-specific adjuvant (12). Furthermore, risk groups for latex allergy were identified (13, 14).

Epidemiology

Numerous studies were performed, which reported prevalence rates of sensitization to NRL in different groups: pediatric and adult general population 0.3% to 0.7% (15–17), blood donors 6.4% (18), health care workers 2.8% to 17.0% (19–23), dentists 10.0–13.7% (24, 25), and atopic children 25% (15). The highest risk group turned out to be patients with spina bifida with prevalence rates ranging from 16.7% (26), 25% (27), 34% (28), 38% (29), 40% (30), 49% (31), and 55.3% (32) to even 64.5% (33).

Allergens

Several allergens have been identified over the past 20 years, named Hev b 1 to Hev b 12 (5, 34). Certain allergens can be attributed to different clinical entities. While spina bifida is associated with Hev b 1, Hev b 3 (35–37), and Hev b 7 (38) in health care workers, problems are associated with Hev b 1 (39), Hev b 6, and in the latex-fruit syndrome with Hev b 2 and Hev b 8 (40, 41).

Hypothesis for the high risk in spina bifida

Patients with spina bifida most probably have the highest propensity of acquiring sensitization and allergy to NRL because of the combination of three factors:

- 1 Operation on the first day of life, offering a window of opportunity because of the TH2-skewed immune system at that early stage.
- 2 Contact by the glove powder resulting in a long-term mucosal depot probably with special emphasis by the meningeal.
- 3 Repeated surgical interventions representing a booster effect for sensitization and enhancing the switch from sensitization to clinical relevant allergy.

The role of the central nervous system

The case of a 6-year-old boy with intraventricular hemorrhage and a clinically relevant latex

allergy (urticaria on contact), who underwent 15 surgical interventions related to ventricular shunt systems may illustrate the special conditions of primary sensitization via the meningeal. He showed 80% eosinophils in the cerebrospinal fluid (CSF) compared to 25% in the peripheral blood; furthermore, he had a total IgE of 961 kU/l, a latex-specific IgE of 95.1 kU/l as well as positive screening tests for aeroallergens and nutritional allergens in serum, while in the CSF total IgE was 87.4 kU/l and latex-specific IgE was 73.0 kU/l with no specific sensitization to other allergens (42). The fact that a large proportion (84%) of the total IgE in the CSF was directed against latex and no other specific IgE could be found in the CSF can only be interpreted as a local production of latex-specific IgE in the CSF – by the immune system of the meningeal mucosa. This may elucidate the exceptional role of the central nervous system (CNS) for the development of allergy to NRL in patients with spina bifida. CSF eosinophilia has been reported before, but no specific IgE was measured in CSF (43).

Risk factors in patients with spina bifida

There is a clear dose-response relationship between the number of surgical interventions and the concentration of specific IgE to NRL in serum (6). Having more than seven surgical interventions significantly increases the risk of sensitization to NRL and more than nine operations the risk for clinical relevant allergy to NRL (14, 32). Patients with spina bifida who have a ventricular shunt are at particularly high risk because they undergo a significantly higher number of operations than patients without a ventricular shunt (44). However, although latex-specific IgE is higher in shunt patients and they are more often provocation positive, the ventricular shunt does not seem to be an independent risk factor (45).

Other risk groups

Other diseases, which require surgical interventions early in life include gastrointestinal malformations (e.g., laparoschisis) and urologic malformations (e.g., urethral valves, obstruction of the ureteropelvic junction). These children also had a higher risk for sensitization and allergy to NRL – but not to the extent of children with spina bifida (46). This may be explained by the fact that these children usually do not need so many re-operations compared to those with spina bifida and that the mucosal

contact with latex glove powder on the meninges may be more allergenic compared to the abdominal mucosa.

Latex-Fruit Syndrome – what's chicken, what's egg?

Many foods show cross-reactivity and cross-allergy to NRL, such as avocado, chestnut, banana, kiwi, and papaya (47). Less-common cross-reactive foods include lychee (48). Longitudinal data from the Multicentre Allergy Study indicate that a primary sensitization beginning with foods or mattresses turning into allergy to NRL is unlikely (49). The other way round is much more probable. It could also be shown that pollen sensitization is followed by latex sensitization (41).

Preventive measures

Measures to reduce the content of NRL proteins in gloves included leaching, radiation, enzymatic cleavage, and chlorination (50, 51). Alternative materials, such as neoprene, have the disadvantage of a reduced tactility for the surgeon and too high costs. Rather unrealistic were suggestions to perform surgical intervention only on Monday mornings, when there are no latex particles in the air and air conditioning system or to wash hands with gloves before touching the patient. Other potential latex sources such as rubber stoppers or rubber wheels do not seem to be a major risk factor. However, the fundamental step was the introduction of powder-free and latex-poor NRL glove, which marked the start of an era of reduction of sensitization and allergy to latex (52).

At the turning point

The turning point came when high-risk groups for latex allergy were operated NRL free from the first day of life, beginning in general around 1994. Using powder-free gloves led to a dramatic reduction of airborne latex allergen (53). In the year 2000, it could be shown that latex-specific IgE decreased from 1994 to 1999 longitudinally as well as cross-sectionally in children with spina bifida (54). Similar results were reported by other authors (55). Latex sensitization in children with shunted hydrocephalus decrease from the 5-year interval 1995 to 2000 (56). For occupational asthma, it could be demonstrated that prevalence rates declined with the increased use of powder-free and low-latex gloves (57).

The breakthrough

Latest data finally show that in children with spina bifida, who grew up completely latex free from birth on, sensitization to NRL was 5% in comparison with 55% for a former non-latex-free group and clinical relevant allergy decreased from 37% to 1% ($p < 0.001$) (58). Furthermore, it is very remarkable that the sensitization to aeroallergens was also lower (43.7% vs. 23%, $p = 0.002$) and even the prevalence of allergic diseases (such as asthma and hay fever) decreased significantly to rates of the general population (34.9% vs. 15%, $p < 0.001$), as demonstrated in comparison with the recent huge epidemiologic study (KIGGS) in children (58). This new data clearly indicates that potent allergens (such as latex) in high-risk groups (such as spina bifida) can induce sensitization spreading, and corresponding avoidance can reverse this development.

Conclusions

In conclusion, it can be stated:

- 1 “New” allergies can suddenly arise
- 2 Sometimes one gets on the wrong track
- 3 There are allergen-specific risk groups (not genetically determined)
- 4 Latex allergy has taught us a lot about mechanisms of sensitization
- 5 Local IgE-production is also possible in the CNS, probably at the meninges
- 6 Allergen avoidance can be very effective in terms of primary prevention
- 7 Secondary sensitizations or sensitization spreading can be made reversible by effective prevention
- 8 Finally, certain allergies can luckily become history within a relatively short period of time.

Furthermore, these new findings clearly end the debate about whether patients with spina bifida have a disease-inherited risk for allergy to NRL (59–61) and show that the cause is the meninges and the multiple surgical interventions – and therefore sequelae can be reversed by implementing preventive measures (58).

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