

False Latex Allergy and Allergy Work-up in a Child Undergoing General Anesthesia

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Abstract

Perioperative immediate hypersensitivity reactions represent rare but not negligible complications during surgery, even in a pediatric environment. Latex is the first cause of hypersensitivity reactions during anesthesia in children. We present the case of a 10 years old asthmatic boy who was labeled as allergic to latex, after an anaphylactic shock occurring right after a general anesthesia. A proper allergy work-up allowed us to rule out such a diagnosis and to precisely advise the anesthesiologist and the surgical team on how to perform a safe intervention on this patient.

Keywords: Latex allergy; Children; Perioperative hypersensitivity reactions; Allergy work-up

Introduction

Immediate hypersensitivity reactions to latex or anesthetics represent rare but not negligible complications during surgery. The reported incidence of Perioperative anaphylaxis varies from 1:3000-1:110000 anesthetic procedures [1]. In most series, allergic reactions represent about 60% of all hypersensitivity reactions observed within the Perioperative period [2,3]. *In vivo* and *in vitro* tests are essential in order to obtain a clear diagnosis and to give the patient and the anesthesiologist indications for future surgeries.

Latex allergy is not common in the pediatric population. The prevalence of latex allergy depends on the evaluated population, ranging from 3% to 64%; on the whole, in the general population, the prevalence ranges between 5% and 10% [4]. Latex is the first cause of hypersensitivity reactions during anesthesia in children, in a French survey [5], and in case of a previous allergic reaction to latex, clinicians may perform skin tests, but also dose IgE levels towards latex allergens: indeed, we are now able to dose specific IgE's directed towards thirteen different latex proteins [6]. Hev b 8, a minor recombinant allergen, may be responsible for positive skin tests to latex extracts and positive specific serum IgE's for latex, but it is generally not associated with clinical symptoms [7].

Case Report

We report the case of 10 years old boy that suffered from a Perioperative hypersensitivity reaction and was then evaluated at our Department, before undergoing surgery for a left inguinal hernia-repair. The patient suffered from allergic asthma, with exacerbations during spring. After performing skin tests, the patient resulted to be sensitized to grass, birch, hazel, olive, peanuts and Rosaceae fruits, without experiencing any clinical sign other than asthma.

He had a first surgery under general anesthesia at the age of 2 years, for a tendon repair on his right hand. He didn't experience any problem during this first surgery. At the age of 6 years, the child had a dental cavity filled under local anesthesia with articaine and was therefore in contact with the dentist's latex gloves without showing any allergic symptom. At the age of 7 years, he underwent surgery for a right inguinal hernia repair, and he presented an anaphylactic shock, treated with epinephrine and rapid vascular loading, 30 minutes after the end of the surgical procedure. His tryptase levels rose 7 times compared to his basal values (4 µg/l), that we dosed to exclude a mastocytosis activation tryptase pattern and to search for an immunologic mechanism able to

justify a hypersensitivity allergic reaction. The possible involved drugs included latex, Neuromuscular Blocking Agents (NMBA), hypnotic agents, and Non-Steroidal Anti-Inflammatory Agents (NSAIDs). The anesthesiologist evaluated specific IgE's for latex, which resulted positive (k82 Immunocap[®]: 46 ku/l). He was therefore advised to avoid latex and, in case of a further surgical procedure, to request a latex-free operating room.

At the age of 10 years, he came to our Department, where a latex-free surgery environment is available, for a left inguinal hernia-repair. Our anesthesiologist performed some *in vitro* tests, including specific IgE's for latex (38 ku/l), and a Cellular Antigen Stimulation Test (CAST) for hypnotic agents, NMBAs and NSAIDs. The CAST resulted positive to atracurium, Propofol, suxametonium, vecuronium, ibuprofen, and indomethacin. He decided then to send the boy to our Unit for further investigations, before surgery.

We first run some pulmonary function tests and assessed his asthma control, as indicated in asthmatic patients who need to undergo general anesthesia [8]. He showed a complete control of the disease symptoms. A skin prick test for latex (Stallergenes, Milan-100 IR) was negative. Since he was declared as allergic to latex, we decided to further investigate him and we evaluated specific IgEs for latex (k82, Immunocap[®]) that resulted positive. Considering the disagreement between skin tests and IgE's levels, we decided therefore to evaluate specific IgEs for latex recombinants, which resulted to be positive for the latex profilin Hev b 8 (36.4 ku/l) only. In order to reassure both the family of the patient and the anesthesiologist, we proceeded with a provocation test for latex, which is actually no longer a clinical routine practice. We performed a rubbing test by moistening the forearm of the patient with water and rubbing it with a latex glove for 30 seconds. After 15 and 60 minutes, we evaluated the presence of cutaneous or respiratory reaction [9]. The test resulted negative. We eventually

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completed the work-up with a latex use test: after moistening both hands, the patient wore a latex glove on one hand and a vinyl one on the other for 15 minutes. 15 and 60 minutes after removing them, we searched for cutaneous, respiratory and systemic symptoms, following Turjanmaa method [10]. This test resulted negative as well, and we ruled out the possibility of a latex allergy.

The allergy work-up continued by performing skin tests (prick and Intradermal tests) for those agents used during the procedure related to the reaction. We tested NMBAs (Rocuronium, Cisatracurium), hypnotic agents (Propofol, Midazolam) and opioids (morphine and Fentanyl), using validated concentrations, as shown in Table 1 [11]. All skin tests resulted negative. Before the reaction, the patient received some ibuprofen as well, as post-surgery analgesic medication. We did not perform skin tests for this NSAID, since they seem to have a poor predictive value and a scarce utility in clinical practice [12]. An oral provocation test to ibuprofen resulted positive at the dose of 1 mg. The patient experienced a generalized urticarial and a bronchospasm, 5 minutes after receiving the drug. After the reaction, he had already taken acetaminophen at the dose of 15 mg/kg/dose, without any problem. A further provocation test to piroxicam resulted negative, supplying then a valid alternative to ibuprofen and, at the same time, the possibility to prescribe to the patient, if needed, a non-steroidal anti-inflammatory drug stronger than acetaminophen.

We advised then the anesthesiologist to normally perform his act, and we asked not to use ibuprofen, but acetaminophen, as a post-surgery analgesic medication. All the drugs we tested negative could, on the other hand, be administered to this patient, with the same risk of Perioperative adverse reaction of the general population. We clarified that there was no need to perform the intervention in a latex-free operating room. The patient underwent surgery without any adverse reaction.

Discussion

Hypersensitivity reactions to anesthetics and other agents used during the Perioperative period increased in the recent years in developed countries [13]. They include both allergic and non-allergic hypersensitivity reactions, which are clinically impossible to distinguish [14,15]. After an accurate allergy work-up, it seems that non-allergic reactions represent 30-40% of all Perioperative hypersensitivity reactions [16]. As for NMBAs, they are the most frequent cause of Perioperative anaphylaxis in adults [17], while, in pediatrics, they represent the second cause, following latex-related reactions [5]. Antibiotics are the third main cause of reaction during general anesthesia [18]. Other involved allergens mainly include colloids (such as gelatins, dextran, albumin or hetastarch), morphine, hypnotics and other drugs (such as local anesthetics, aprotinin, dyes and iodinated contrast media) and disinfectants [19,20]. An allergy work-up should be advised in all patients who have experienced a hypersensitivity reaction during anesthesia, in those who have a proven allergy to a drug

that will have to be used during surgery, and in those patients who refer a possible latex allergy or an allergy to those fruits that cross-react with latex. All other patients should not undergo a predictive screening, since there is still no evidence supporting systematic preoperative screening tests in the general population [1,21].

Natural rubber latex is obtained from the milky sap of the rubber tree, *Hevea brasiliensis*. During the manufacturing process, various additives are added (ammonia, potassium dichromate, epoxy resin, fragrance mix, thiuram mix, tetramethylthiuram disulfide, 1, 3-diphenylguanidine), conferring different characteristics to the final product [22]. Latex is part of more than 40,000 products of everyday use, including medical and home tools [4].

The diagnosis of latex allergy is based on a positive clinical history and positive *in vivo* tests. The first test that should be performed is a simple skin prick test, with a standardized extract. If this is negative, no other investigation is needed. Nevertheless, when the patient history is highly suggestive for latex allergy, despite negative skin tests, an *in vitro* evaluation may be performed, by dosing the levels of specific IgE's for latex. If negative, a latex allergy is completely ruled out. If positive, we may now perform IgE evaluation for specific latex allergens. The identification of latex major allergens and the production of recombinant allergens are, in fact, crucial in these cases in order to understand a latex sensitization and distinguish it from a real allergy. So far, 14 proteins of natural rubber latex have been recognized as latex allergens by the International Union of Immunological Societies (IUIES) and have been included in the Registry Committee of International Nomenclature of allergens (Hev b 1-13) [4,23-26]. Depending on the specific symptoms of the patient (urticaria or angioedema, respiratory symptoms, contact eczema) different provocation procedures may be performed, but their utility in clinical practice is now limited, since the introduction of component-resolved diagnosis has helped better understand the possible mechanisms underlying the reaction and differentiate clinically relevant reactions from not relevant ones [4,27]. Moreover, provocation procedures should be currently discouraged due to possible risk of systemic reactions.

Subjects who are very exposed to latex are those mostly at risk of developing a sensitization and an allergy to this allergen: this group of subjects at risk includes patients who undergo multiple surgical procedures (in particular of the urinary and gastro-enteric tracts), health care workers and children with spina bifida (who need several interventions during their first years of life). They show a higher rate of sensitization to Hev b 1 than the general population [26,28]. Hev b 1, Hev b 2, Hev b 5, Hev b 6, and Hev b 13 are the major latex allergens and need therefore to be included in the extracts used for *in vivo* tests. These allergens are those involved in latex allergy. Hev b 7, Hev b 8, Hev b 9, Hev b 10, Hev b 11, and Hev b 12 may be taken into consideration as possibly responsible for cross-reactivity reactions with other allergens (such as potato and tomato with Hev b 7; banana, celery, birch, grass, pineapple, and bell pepper with Hev b 8; molds with Hev b 9) [4]. Although being of minor clinical relevance, they also must be present in the extracts, in order to assess a possible cross-reactivity [29]. Nevertheless, they are usually not related with clinical symptoms of latex allergy.

CAST may be used to complete the diagnosis of hypersensitivity reactions to drugs, mainly to Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) [30]. Nevertheless, it has still to be considered as a research method, with a specificity of 91%, a positive predictive value of 92%, a sensitivity of 6%, and a negative predictive value of 59%, with regard to NSAIDs. Further studies are needed to better evaluate the potential

	Skin Prick Tests		Intradermal Tests	
	mg/ml	Dilution	mg/ml	Dilution
Rocuronium	10	Undiluted	10	1/200
Cisatracurium	2	Undiluted	2	1/100
Propofol	10	Undiluted	10	10-Jan
Midazolam	5	Undiluted	5	10-Jan
Morphine	10	10-Jan	1	1/1000
Fentanyl	0.05	Undiluted	0.05	10-Jan

Table 1: Concentrations used for skin prick tests and Intradermal tests for the drugs tested in the patient.

utility of the test, but, so far, it doesn't seem useful in clinical practice as a screening test. Nevertheless, in our case the positivity of the test obliged us, for medical-legal reasons, to complete an accurate allergy work-up for each drug resulted positive to the test.

Allergy to latex should be ruled out in those patients who have a history of clinical manifestations after latex exposure, in those who present the risk factors mentioned above, and in those who experience some clinical symptom after eating banana, kiwi, avocado, chestnut or papaya, considering the possibility of cross-reactions between these fruits and latex [4]. Our patient could actually have become sensitized to latex, after his first surgeries, but the first step should have been to perform skin tests, without the risk of threatening him with a false diagnosis of latex allergy. A good knowledge of recombinant allergens is essential in those cases in which skin tests, specific IgE's levels and the patient's clinical history are not completely in agreement. IgE testing for latex hypersensitivity may be positive while the other appropriately Perioperative tests (skin and provocation tests) may be negative. In these cases it is therefore very useful to evaluate and dose "major" and "minor" latex allergens, all of which may be tested for, to better understand if the positivity of the test rely on a real allergy or on a clinically non-relevant sensitization. This is the reason why allergy tests for latex and drugs should always be performed by trained allergists or anesthesiologists, capable of a correct interpretation of the results.

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