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Short communication

Anaphylaxis to the 23-valent pneumococcal vaccine in child: a case-control study based on immediate responses in skin tests and specific IgE determination

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Abstract

Injections of the 23-valent pneumococcal vaccine are usually well tolerated. Skin tests (prick and intradermal) and a self-made RAST with pneumococcal vaccine and phenol were performed in a child reporting a severe anaphylactic reaction induced by a 23-valent pneumococcal vaccine, and in ten control children, including one child with a well-tolerated vaccination, and nine non-vaccinated children. Skin tests and RAST with the vaccine were positive in the child reporting anaphylaxis, and negative in nine of the control children. Intradermal test with the vaccine was slightly positive in a non-vaccinated child with negative RAST. Skin tests and RAST with phenol were negative in all the children. These results suggest that immediate responses in skin tests and specific IgE determination have a good diagnostic value in children reporting severe reactions suggestive of IgE-dependent hypersensitivity to pneumococcal vaccine. © 2001 Elsevier Science Ltd. All rights reserved.

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1. Introduction

Infections with *Streptococcus pneumoniae* (*S. Pneumoniae*) are an important cause of morbidity and mortality, both in developed and developing countries, especially in young children, in old subjects above the age of 65 years, and in patients with underlying immunocompromising disorders, with an overall fatality rate for pneumococcal pneumonia, meningitis and bacteraemia of 15–20% [1,2].

With the exception of mild and transient reactions at the injection site, that are quite common, injections of the 23-valent pneumococcal vaccine are usually well

tolerated. Severe reactions are rare, and include Arthus-like reactions in patients receiving booster injections, fever and myalgias, autoimmune-like diseases in predisposed patients, generalised exanthematous pustulosis, and anaphylactic or anaphylactoid reactions that have not been explored [1,3–6].

We studied a child who reported a severe anaphylactic reaction induced by the first injection of a 23-valent pneumococcal vaccine. Skin tests (prick and intradermal) and specific IgE determination were performed with the vaccine and the excipient of the vaccine (phenol). Results were compared with those obtained in ten control children, including one child who had tolerated the pneumococcal vaccination and nine non-vaccinated children. The aim was to confirm or exclude allergy to the vaccine in the patient, to determine the allergens

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responsible for the reaction (pneumococcal antigens or phenol), and to assess the diagnostic value of skin tests and specific IgE determination with the vaccine and phenol.

Skin tests and specific IgE determination were performed after informed consent was obtained from the parents.

2. Subjects and methods

2.1. Subjects

The patient was a 2 year-old non-atopic boy with a short small bowel and hepatic cirrhosis, who was waiting for a liver and small bowel transplantation. The child received parenteral nutrition since the age of 1 year, and reported one bronchiolitis, two staphylococcal septicemias, a transient renal failure, and a red man syndrome induced by Vancomycin®. He developed an anaphylactic reaction (bronchospasm, cutaneous and laryngeal oedema) one minute after the first injection of a 23-valent pneumococcal vaccine (Pneumo 23®, Pasteur-Mérieux, Lyon, France). The symptoms resolved in 1 h with treatment with IV injections of antihistamines and corticosteroids, and with bronchodilator aerosols.

The control children (5 boys and 5 girls, 4 to 10 year-old) included one 3 year-old atopic child with a short small bowel and a well-tolerated Pneumo 23® vaccination at the age of 2 years, and nine non-vaccinated children with hymenoptera venom allergy.

2.2. Skin tests

They were performed 6 months after the reaction (patient), and 1 year after the pneumococcal vaccination (vaccinated control), with the 23-valent pneumococcal vaccine and with the excipient of the vaccine (phenol). Solutions of the required concentrations were prepared by serial dilution of the reagents with 0.9% NaCl.

Prick-tests were performed with the undiluted vaccine on the skin of the inner forearm. Then, 0.02 ml of a 1/1000 dilution of the vaccine were injected intradermally (ID) into the external surface of the arm. ID tests with a 1/100 dilution of the vaccine were performed if there was no response with the 1/1000 dilution. A solution of 0.4% phenol (Dome-Hollister-Stier, Epernon, France) was skin tested with prick and intradermal tests. A wheal ≥ 3 mm (prick) or 5 mm (ID) in mean diameter, present 15–20 mn after application, was defined as an immediate positive response if there was also a negative response to control solution (0.9% NaCl) and a positive response to histamine (prick: 10 mg/ml).

2.3. Specific IgE determinations

Serum specific IgE against the 23-valent pneumococcal vaccine and the phenol solution were determined by a self-made radioallergosorbent test (RAST), according to a modification of the method of Cromwell et al. [7]. Briefly, human serum albumin (HSA, Sigma Chemical Co., St Louis, USA) was first coupled to cyanogen bromide-activated paper disks (Pharmacia, Uppsala, Sweden): disks were added to 50 mg of HSA in 5 ml of 0.2 M sodium bicarbonate (pH 8.5), and mixed for 4 h at room temperature, and 20 h at +4 °C. The disks were then washed four times with phosphate-buffered saline (PBS, pH 7.3), sodium acetate 0.1 M (pH 4), PBS, and sodium bicarbonate (pH 9.5), respectively.

The disks used for pneumococcal specific IgE determination were added to 2.5 ml of a solution of Pneumo 23® in PBS, containing 1 mg/ml of capsular pneumococcal antigens, and mixed for 4 h at room temperature, and 20 h at +4 °C. The same treatment was applied to the disks used for phenol specific IgE determination, after addition of 2.5 ml of the phenol solution. The disks were then washed twice with 0.1 M Tris-HCl (pH 8) (Merck, Darmstadt, Germany) and five times with PBS, and were stored at +4 °C in 1% PBS Tween 20 (Prolabo, Fontenay-sous-Bois, France).

For specific IgE determination, the disks were incubated with 50 µl of serum during 3 h at room temperature in polystyrene tubes. The disks were then washed three times with PBS Tween, incubated with 50 µl of ¹²⁵I-anti-IgE (Pharmacia, Uppsala, Sweden) for 18 h, and washed again three times with PBS. The tubes were counted for 60 s in a LKB-Wallac automatic γ -counter (Evry, France). Results were classified as positive if ≥ 0.35 PRU/ml were detected.

3. Results

The results of skin tests and specific IgE determinations in the patient and control children are shown in Table 1. Skin tests and RAST with the 23-valent pneumococcal vaccine were positive in the child reporting anaphylaxis, and negative in nine of the control children. ID was slightly positive in a non-vaccinated child with negative RAST. Skin tests and RAST with phenol were negative in all the children studied.

4. Discussion

The most worldwide available pneumococcal vaccines are Pneumo 23® (Pasteur-Mérieux) and Pneumovax 23® (MSD). These two vaccines contain 25 µg of each of 23 purified capsular polysaccharide antigens diluted in a solution of 2.5 p. 1000 phenol as a preser-

Table 1
Results of skin tests and specific IgE determination (RAST) with the 23-valent pneumococcal vaccine and phenol in the patient with anaphylaxis and in the control children

Tests	Patient	Vaccinated control	One non-vaccinated control	Eight other non-vaccinated controls
<i>Pricks (wheal/flare: mm)</i>				
Histamine	7/23	8/25	7/25	6/25 (mean)
Saline	0	2	0	0
0.4% phenol	0	0	0	0
Pure vaccine	5/8	2	0	0
<i>ID (wheal/flare: mm)</i>				
0.4% phenol	0	0	0	0
Vaccine 1/1000	(+)	0	0	0
Vaccine 1/100	10/20	0	7/11	0
<i>RAST (PRU/ml)</i>				
0.4% phenol	0	0	0	0
Vaccine	0.47	0	0	0

vative. With the exception of mild and transient reactions at the site of injection, that are quite common, injections of these 23-valent pneumococcal vaccines are usually well tolerated. Anaphylactic and anaphylactoid reactions are very rare, and have not been explored [1,4].

We have performed skin tests (pricks and ID) and RAST with the vaccine and the phenol excipient of the vaccine in a child reporting a severe anaphylactic reaction induced by the first injection of Pneumo 23[®]. The results were compared with those obtained in ten control children, including one child who had tolerated the vaccination with Pneumo 23[®], and nine non-vaccinated children.

Our results show that the phenol preservative is not responsible for the reaction reported by the patient. Skin tests and RAST, performed with a commercial solution of 0.4% phenol, that was more concentrated than the solution used for the preservation of the vaccine, were negative in all the children studied, including the child reporting anaphylaxis. In medical use, phenol is used for its disinfectant, devitalising, analgesic and sclerosing properties. To our knowledge, there are no reports on IgE-dependent reactions to phenol, and most reactions to phenol and phenol derivatives are irritative and toxic [8,9], or result from delayed-type hypersensitivity [8,10].

Our results suggest that the pneumococcal antigens included in the 23-valent vaccine are responsible for the anaphylactic reaction reported by the patient. RAST with the vaccine was positive in this child, and were negative in the control children, including a child who had tolerated the vaccination with Pneumo[®]. Moreover, skin tests with the vaccine were strongly positive in the patient, and were negative in nine control children, including the child who had tolerated the vaccination with Pneumo[®]. However, skin tests with the 23-valent pneumococcal vaccine were slightly positive in one

non-vaccinated control. The origin of the IgE-dependent sensitisation to pneumococcal antigens, leading to anaphylaxis, and to positive skin tests in the non-vaccinated control child is unknown. Bacteria and fungi, such as *Haemophilus influenzae* [11], *Staphylococcus aureus* [12–14], *Candida albicans* [15], *Pityrosporum ovale* [16], and *Trichophyton rubrum* [17] may induce the production of specific IgE, especially in patients with atopic dermatitis and/or asthma. As far as the pneumococcus is in concern, specific IgE to *Streptococcus pneumoniae* have been demonstrated in the sera of numerous patients with bronchial asthma [18]. More recently, Ortigas et al. have shown that pneumococcal antigens induced CD40-ligand and IL-4 expression in human blood mononuclear cells in vitro [19]. Thus, carriage or occult infection with *S. pneumoniae* may have induced an IgE-dependent sensitisation to pneumococcal antigens, responsible for the anaphylactic reaction in the patient, and for positive skin tests to the pneumococcal vaccine in one non-vaccinated control child.

5. Conclusion

Our results suggest that anaphylactic reactions to the 23-valent pneumococcal vaccine result from IgE specific for the pneumococcal antigens, and are not due to the phenol preservative of the vaccine. They also suggest that immediate responses in skin tests and specific IgE determination have a good diagnostic value in children reporting severe reactions suggestive of IgE-dependent hypersensitivity to the 23-valent pneumococcal vaccine.

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