

Sensitization to thimerosal in atopic children

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Thimerosal is an organic mercurial compound widely used as a preservative in vaccines, eyedrops, and contact lens cleaning and storage solutions. 5 infants, 2 female and 3 male, ranging in age from 7 to 28 months and affected by atopic dermatitis (AD) diagnosed according to the Hanifin and Rajka criteria, experienced an exacerbation of their clinical condition 2–10 days after mandatory vaccinations with vaccines containing thimerosal. Cutaneous lesions of nummular eczema appeared on the trunk, limbs and face. All patients were patch tested with serial dilutions of thimerosal in petrolatum. A positive patch test reaction to thimerosal 0.1% pet. was observed in all 5 children. 3 of them also showed a positive reaction at 0.01% and 0.05% pet. Despite their thimerosal-hypersensitivity, all children completed the entire series of mandatory vaccinations, care being taken to use different needles for injection and aspiration of the vaccine. The 2-year follow-up did not reveal other episodes of exacerbation of the AD after vaccination. The present study confirms the high frequency of sensitization to thimerosal in atopic children and suggests that vaccination can cause clinical symptoms in sensitized children. Nevertheless, sensitization to thimerosal does not prevent children from continuing with mandatory vaccinations.

Key words: thimerosal; vaccination; atopic dermatitis; sensitization; children; preservatives; adverse drug reactions; organic mercurials. © Munksgaard, 1999.

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Severe adverse cutaneous reactions due to vaccinations, whether localized or generalized, are rare. However, children with atopic dermatitis (AD) may occasionally develop a worsening of their cutaneous lesions and an increase in itching after vaccinations (1). Since AD typically follows a chronic fluctuating course, these exacerbations, which are also frequently observed after viral and bacterial infections, are usually considered to be related to the transitory weakness of the child and to the immunological deficit due to AD. Reactions to vaccines against measles and flu have been ascribed rarely to egg in atopic children allergic to this food (2).

Thimerosal is an organic mercurial compound (sodium ethylmercurythiolate) widely used as a preservative in vaccines, solutions for intracutaneous skin testing, immunoglobulin preparations, eyedrops, and contact lens cleaning and storage solutions. In Italy, the number of positive reactions to thimerosal in patients undergoing patch testing is high (3–6), but, at present, apart from single case reports (7–10, 13), thimerosal sensitization has been found to be clinically relevant only in patients

with allergic contact conjunctivitis (3, 14–22). Nevertheless, some cases of generalized cutaneous reactions probably due to thimerosal-containing vaccines have been described (1, 9, 23–25).

Since there are few reports on such reactions in children, we present 5 cases of atopic infants who experienced an exacerbation of their clinical condition after mandatory vaccinations, in order to point out the high frequency of such sensitization to thimerosal in atopic children.

Patients and Methods

In 1995, we observed 5 infants, 2 female and 3 male, ranging in age from 7 to 28 months and affected by AD diagnosed according to the Hanifin and Rajka criteria, who experienced an adverse cutaneous reaction after vaccination. The main clinical features of these patients are summarized in Table 1. A family history of atopy was present in all the children; atopic dermatitis had first developed at the age of 2–10 months and was localized on the face and limbs, except for patient no. 1, who had a widespread dermatitis. In all our pa-

Table 1. Patients' main clinical features

Patient no.	Age (months)	Sex	Start of atopic dermatitis	Vaccines used	Injection's route/skin area	Day of exacerbation	External exposure history to mercurials	Details of exacerbation
1	28	female	10 months	DIF-TET-ALL® (Biocine) ACELLUVAX® (Biocine) POLIORAL® (Biocine) ENGERIX-B® (Smith-Kline-Beechan)	intramuscular buttocks	2nd after 3rd vaccination	negative	widespread eczema
2	7	male	2 months	see above	intramuscular buttocks	5th after 1st vaccination	negative	nummular eczema
3	12	female	3 months	see above	intramuscular buttocks	10th after 2nd vaccination	negative	nummular eczema
4	8	male	2 months	see above	intramuscular buttocks	7th after 2nd vaccination	negative	nummular eczema
5	17	male	5 months	see above	intramuscular buttocks	4th after 3rd vaccination	negative	nummular eczema

tients, vaccinations had been performed when the clinical manifestations of AD were in remission and had not required topical corticosteroid for the previous 2 weeks.

Except for patient no. 2, who developed the cutaneous reaction just after the 1st vaccination, all the other patients had previously been vaccinated with thimerosal-containing vaccines without any side-effects. In all cases, parents reported that 2–10 days after vaccination, the children had suddenly presented with numerous itchy eczematous patches over the trunk, limbs and face. In all patients, the reaction had started from the inoculation site of the vaccine containing thimerosal as preservative. In case nos. 2, 4 and 5, the lesions also appeared on previously uninvolved areas and attained a widespread pattern. Enquiry into the individual excipients of vaccines administered in our patients disclosed that they had all been preserved with thimerosal.

The patients were therefore patch tested with a children's standard series (Hermal-Trolab), according to the recommendations of the International Contact Dermatitis Research Group (ICDRG), and with serial dilutions of thimerosal in petrolatum (pet.) using Curatest (Lohman) patches; patient nos. 2, 3, 4 and 5 were patch tested with thimerosal 0.01%, 0.05% and 0.1% pet., but patient no. 1 only with thimerosal 0.1% pet. Patch tests were applied for 2 days on disease-free skin on the upper back with readings performed at 2 and 3 days. As controls, we applied the same concentration of thimerosal on the upper back of 5 children affected by AD, matched for sex and age.

Results

The results are reported in Table 2. A positive patch test reaction (+++; +++) to thimerosal 0.1% pet. was observed in all 5 children; 3 of them also showed a positive reaction at 0.01% and 0.05% dilutions. Patient nos. 1 and 2 experienced an exacerbation of their eczema after patch test application, and for this reason, we did not make patient no. 1 undergo other tests. Since patient no. 2 also showed a contact dermatitis on the left shoulder, exactly on the site of the press-buttons of his cotton "body", he was also positive on patch testing with nickel sulfate 2.5% pet. None of the 5 control children showed any positive reactions.

We completed the investigation of our 5 children by performing differential blood count, immunoglobulin-assay (IgG, IgM IgA, IgE), C3, C4,

Table 2. Results of patch tests with serial dilutions of thimerosal in petrolatum*

Patient no.	Thimerosal 0.01% D2/D3	Thimerosal 0.05% D2/D3	Thimerosal 0.1% D2/D3
1	NT	NT	-/+ +
2	-/+ +	-/+ +	-/+ +
3	+/+ +	+/+ +	+/+ +
4	-	-	+/+ +
5	-/+ +	+/+ +	+/+ +

* +: Weak positive reaction; erythema, infiltration and possibly papules.

++: Strong (vesicular) positive reaction; erythema, infiltration, papules and vesicles.

+++ : Extreme positive reaction; bullous reaction.

RAST and prick tests. IgE immunoglobulins and eosinophil counts were higher than the normal values in patient nos. 1 and 4 (IgE 223, eosinophils 4798; IgE 512, eosinophils 4490). RAST revealed specific IgE against bee and wasp venom and milk in patient no. 1 and against egg, milk and wheat in patient no. 4. Prick tests with the major inhalant and food allergens showed a significant positivity to egg only in 1 patient (case no. 3).

A 2-year follow-up did not reveal other episodes of exacerbation of AD after vaccinations; in fact, despite their thimerosal hypersensitivity, all children completed the entire series of compulsory vaccinations, care being taken to use different needles for injection and aspiration of the vaccine, to prevent further relapses from being caused by thimerosal-contaminated needles.

Discussion

Until a few years ago, many considered allergic contact dermatitis rare in childhood, and there were few studies on patch testing in children under the age of 2. However, recent studies have shown that contact allergy, documented by patch testing, may also be present in early infancy, in both non-atopic and atopic children, though not always with clinical relevance (6, 26–29, 31–33).

Positive patch test reactions to thimerosal are frequent, frequency rates varying from 1% (30) to 37% (4), depending on the country (10, 34–36); this world-wide sensitization to thimerosal, including infants and children (6, 10, 31, 37), may be explained as an iatrogenic consequence of mandatory parenteral vaccinations (9–12), or exposure to antiseptics containing this substance, which are commonly used in Italy (6). In addition, hyposensitization therapy with thimerosal-containing antigenic extracts has been abolished, because of the abnormal reactions that appeared after their administration (4).

Iatrogenic sensitization to thimerosal-containing vaccines and its clinical relevance are a “major bone of contention in the literature” (19). In general, the intra- and epicutaneous routes of administration are a much higher risk for sensitization than the subcutaneous and intramuscular routes (24). It has been proposed that thimerosal-contaminated outer surfaces of needles may also increase the risk of sensitization (9).

In some studies performed on children in different countries to investigate the most common childhood allergens, thimerosal has not been tested because its positivity is frequently without any clinical relevance. When thimerosal is included in the standard series, it represents one of the allergens producing the largest number of positive reac-

tions in children, especially in infancy, even more than nickel (6). In a recent series of 670 children patch tested with the European standard series over a 7-year period, positive results were observed in 42% of cases. 77% of sensitized patients were atopic (6).

All 5 children reported here were affected by atopic dermatitis, presented patch test positivity to thimerosal and worsened after vaccination. 2 different hypotheses could be proposed to explain this exacerbation:

(i) it could be considered a mere casual association; (ii) it could be caused by administration of the mandatory parenteral vaccination; in this case, there would be a causal relationship between thimerosal sensitization and the cutaneous reaction. This could be confirmed by the temporal relation between the vaccination and the onset of the cutaneous reaction and by the spread of eczema out from the inoculation site. The presence of nickel allergy in 1 of our 5 children shows how even such young children may become sensitized. Atopic dermatitis worsening after thimerosal exposure has previously been reported by Barbaud et al. (1).

Finally, our study also confirms that sensitization to thimerosal does not prevent children from completing the entire series of mandatory vaccinations. We have informed pediatricians that mandatory vaccinations may bring about a worsening of atopic dermatitis. We have also stressed the importance of using different needles for injection and aspiration of the vaccine. As a result, they no longer refer children with such reactions to our department.

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