

ORIGINAL ARTICLE

Comparison of reactivity to a metallic disc and 2% aluminium salt in 366 children, and reproducibility over time for 241 young adults with childhood vaccine-related aluminium contact allergy

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Background: An aluminium hydroxide-adsorbed pertussis toxoid vaccine was studied in 76 000 children in the 1990s in Gothenburg, Sweden. Long-lasting itchy subcutaneous nodules at the vaccination site were seen in 745 participants. Of 495 children with itchy nodules who were patch tested for aluminium allergy, 377 were positive. In 2007-2008, 241 of the positive children were retested. Only in one third were earlier positive results reproduced.

Objectives: To further describe patch test reactions to different aluminium compounds in children with vaccine-induced aluminium allergy.

Patients/Methods: Positive patch test results for metallic aluminium (empty Finn Chamber) and aluminium chloride hexahydrate 2% petrolatum (pet.) were analysed in 366 children with vaccine-induced persistent itching nodules tested in 1998-2002. Of those, 241 were tested a second time (2007-2008), and the patch test results of the two aluminium preparations were analysed.

Results: Patch testing with aluminium chloride hexahydrate 2% pet. is a more sensitive way to diagnose aluminium contact allergy than patch testing with metallic aluminium. A general decrease in the strength of reactions to both aluminium preparations in 241 children tested twice was observed.

Conclusions: Aluminium contact allergy can be diagnosed by patch testing without using metallic aluminium.

KEYWORDS

aluminium, contact allergy, follow-up studies, immune tolerance, itchy nodules, patch test, prognosis, reproducibility, vaccination/adverse effects

1 | INTRODUCTION

Aluminium contact dermatitis is very rare, and the clinical importance of aluminium hypersensitivity in primary healthcare or in society is not well known. Aluminium is frequently used in daily life, e.g. in products such as cosmetics, antiperspirants, and sunscreens. Standard vaccination programmes for children worldwide cause aluminium exposure. Aluminium is used in vaccines as an adjuvant to stimulate

the immune system, even though the exact mechanism of action of aluminium as an adjuvant is unknown.^{1,2} Aluminium-adsorbed vaccines can cause long-lasting, intensely itching subcutaneous nodules at the site of injection. Local hair growth, hyperpigmentation, hypopigmentation and eczema in the itchy area have been reported.³⁻⁵ The itching nodules are often related to contact allergy to aluminium, as shown by a positive epicutaneous (patch) test result.^{3,5-9} However, there is no established patch test preparation for diagnosing

aluminium contact allergy. Two decades ago, testing for aluminium contact allergy was rarely performed. An aluminium salt used in a "dental series" and metallic aluminium as an empty Finn Chamber were available in most test clinics.

In the 1990s, in trials of a new pertussis vaccine containing aluminium hydroxide, long-lasting itching nodules at the site of injection were reported in 645 of 76 000 participating children in Gothenburg, Sweden. Of those, 455 were patch tested for aluminium contact allergy in 1998-2002, with positive results in 352 (77%).³ After this report had been published, another 100 children with persistent itching nodules at the vaccination site were identified by our group. Of these, 40 had been patch tested for aluminium allergy and 25 were positive.⁸ Five to 9 years after the initial tests, all children (352 + 25) with demonstrated aluminium allergy were offered a repeat patch test, which was performed in 2007-2008. Of the 241 children tested a second time, in exactly the same way, 186 (77.2%) had negative test results.¹⁰ Type IV delayed hypersensitivity is generally considered to be lifelong, and such a large proportion becoming negative had never been described before.^{11,12} These results were surprising, and showed that very little is known about aluminium contact dermatitis in general, and vaccine-induced contact allergy in particular.

The first aim of the present analysis of data from our previous studies that have not been published before was to examine the outcomes of patch tests with both metallic aluminium and aluminium chloride hexahydrate 2% pet. in detail in 366 children with vaccine-induced persistent itching nodules and contact allergy to aluminium tested in 1998-2002. The second objective of the present study was to examine how the individual outcomes of the patch test results for metallic aluminium and aluminium chloride hexahydrate 2% pet. differ in the group of children tested twice in our studies.

2 | PATIENTS AND METHODS

In the study of children participating in the vaccine trial described above and published in 2003, 377 children with persistent itching nodules tested positive to aluminium. The testing was performed in February 1998 to October 2002 at the Clinic for Dermatology at Sahlgrenska University Hospital, Gothenburg. This is a further report and analysis of data in which we focus on the relationship between the patch test reactions to aluminium metal and those to aluminium salt. As 11 of the 377 children were patch tested in other dermatology clinics, they are excluded from this analysis.

The patch test for aluminium was applied on the upper part of the back, with 2 different forms of aluminium: metallic aluminium (empty Finn Chamber; SmartPractice, Phoenix, Arizona), and an aluminium salt (aluminium chloride hexahydrate 2% pet.; Chemotechnique Diagnostics, Vellinge, Sweden). The aluminium salt was placed in a plastic chamber from the same producer. For more details of test application and test interpretation, see Reference 3.

In the second part of the study, we analysed the reproducibility of the test reactions to both the metallic aluminium and the salt in 241 children originally tested in 1998-2002 and retested in 2007-2008. The testing was performed in the same way during both test

periods. For exact inclusion criteria, patch testing, and test interpretations, see Reference 10. As described in the previous study, before the test performed in 2007-2008, the parents and children were asked about exposure to aluminium-containing products; see Reference 10 for further information. For a description of the clinical symptoms in the children who participated in the studies in 1998-2002 and 2007-2008, see References 3 and 10.

The patch test studies were approved by the Regional Ethical Review Board of Gothenburg University. All parents, adolescents and young adults received oral and written information about the study, and all parents and/or young adults gave written consent to participate. The present analysis only contains data obtained in the previous patch test studies, and did not require further ethical approval.

All data were analysed with R version 3.0.3 (The R Foundation for Statistical Computing, Vienna, Austria). Correlation between 2 numerical variables was quantified by the use of Spearman's rank correlation coefficient. Wilcoxon's signed rank test was used to test for pairwise differences in numerical variables. The patch test outcomes were recoded in the above-mentioned tests as follows: negative as 0, + as 1, ++ as 2, and +++ as 3. All tests were 2-sided, and and $P < .05$ was considered to be statistically significant.

3 | RESULTS

In the patch tests performed in the 455 children in 1998-2002 and the patch tests performed in the 40 children with itching nodules identified later at the Clinic for Dermatology, Sahlgrenska University Hospital, 366 children reacted positively to aluminium. Of those, 243 reacted positively to both aluminium salt and the metal, and 114 reacted positively to the salt, but not to the metal. Nine reacted only to the metal. The stronger the reaction to aluminium chloride hexahydrate 2% pet., the higher the probability of having a reaction to an empty aluminium Finn Chamber among the 366 children with positive test reactions ($P < .0001$); see Table 1.

Among the 241 children retested in 2007-2008, 14 had positive reactions to both the aluminium salt and the metal, and 40 were positive to the salt, but not to the metal. One reacted exclusively to the metal. When we compared the individual patch tests results of the 241 children tested in 1998-2002 with their test results in 2007-2008, we observed a decrease in the strength of reactions to both metallic aluminium and the aluminium salt. Only 5 individuals were found to have the same results for both aluminium preparations tested. Two individuals showed stronger reactions in the second test, both to the salt; see Table 2. For more detailed information on the distribution of patch test reactions to metallic aluminium and the aluminium salt in the first and the second patch tests, see Figures 1 and 2.

4 | DISCUSSION

Reports of repeated patch testing in children and young adults are rare. The clinical problem of itching nodules and contact allergy to aluminium in vaccinated children in the Gothenburg area have

TABLE 1 Patch test results divided into aluminium metal and the aluminium salt of 366 children reacting positively in the first test in 1998-2002

		Al Salt				Sum	%
		Negative	+	++	+++		
<i>Al Metal</i>	Negative	—	69	40	5	114	31%
	+	9	34	77	32	152	42%
	++	0	7	39	47	93	25%
	+++	0	2	0	5	7	2%
	Sum	9	112	156	89	366	100%
	%	2%	31%	43%	24%	100%	

Al salt, aluminium chloride hexahydrate, 2% petrolatum

TABLE 2 Individual patch test results of 241 children reacting positively in patch tests with the aluminium salt and/or aluminium metal in the first test in 1998-2002 vs individual outcomes in the second patch test in 2007-2008

		Second patch test 2007-2008																								
		Al Salt	Neg				+				++				+++											
		Al Metal	Neg	+	++	+++	Neg	+	++	+++	Neg	+	++	+++	Neg	+	++	+++								
First patch test 1998-2002	Al Salt	Al Metal																								
	Neg	Neg																								
		+	6																							
		++																								
		+++																								
	+	Neg	32				2				1															
		+	16																							
		++	4				2																			
		+++	1																							
	++	Neg	19				5				2															
		+	37				1				12				1											
		++	25								3				1				1							
		+++																								
	+++	Neg	4				1																			
		+	16				4				2				2				2							
		++	24				4				1				3								1			
		+++	2																				1			

Al salt, aluminium chloride hexahydrate, 2% petrolatum

motivated us to study both the test reactions and the clinical symptoms in these children. The main aim of the present analysis was to examine test reactions to aluminium in more detail. In our study, we found that patch testing with aluminium chloride hexahydrate 2% pet. is a more sensitive way of diagnosing aluminium hypersensitization than patch testing with metallic aluminium in terms of an empty Finn Chamber. Similar results have been obtained in other studies.^{13,14} Salik et al¹⁴ reported the testing of 42 children with itching nodules after vaccination, 40 of whom had positive results. Thirty-nine had positive reactions to 2% aluminium chloride hexahydrate pet., and 1 reacted only to an empty Finn Chamber. This was a retrospective study, and it is noteworthy that, among those children with persistent skin reactions, 95% were positive for aluminium, and they were all < 10 years of age when tested. Siemund et al¹³ tested 21 adults, aged 21 to 71 years, with a mean age of 46 years, with 6 different aluminium compounds, including 2% and 10% aluminium chloride hexahydrate pet., and an empty Finn Chamber, and

19 reacted to at least 1 of the aluminium salts, but none reacted to the metallic aluminium disc. They also reported that 10% aluminium chloride hexahydrate pet. gave the highest number of positive reactions to aluminium.

In our study, we used aluminium chloride hexahydrate 2% in 1998-2002, at which time this was the only commercial test available on the market. In our retest study, we repeated the test in exactly the same way, and we considered it unethical to use higher concentrations of aluminium hexahydrate, as a large number of the children had reacted very strongly to the 2% solution in their first test. There were 9 of 241 children in our study with positive test reactions exclusively to the metallic disc. Of those, 7 had doubtful reactions to the aluminium salt, and were therefore classified as being negative to the aluminium salt. Six of the 9 children were tested again, and all were negative. Our conclusion is that metallic aluminium is of very little benefit in patch testing for aluminium contact allergy. We did show that the stronger the reaction to aluminium chloride hexahydrate 2%

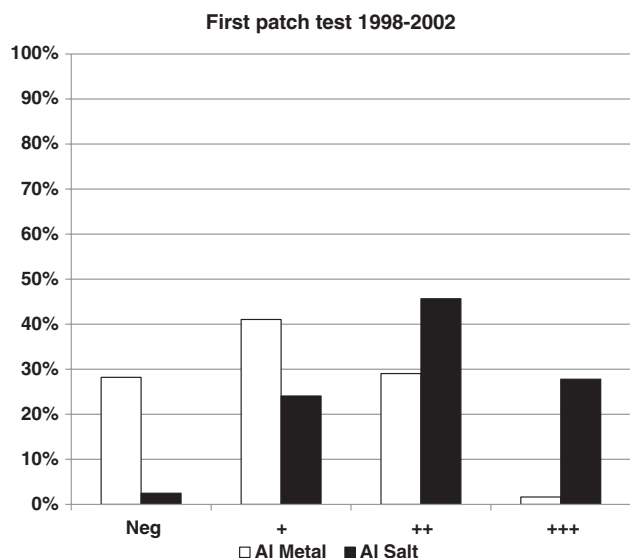


FIGURE 1 The distribution of patch test reactions to aluminium metal and the aluminium salt in the first patch test of 241 individuals in 1998-2002

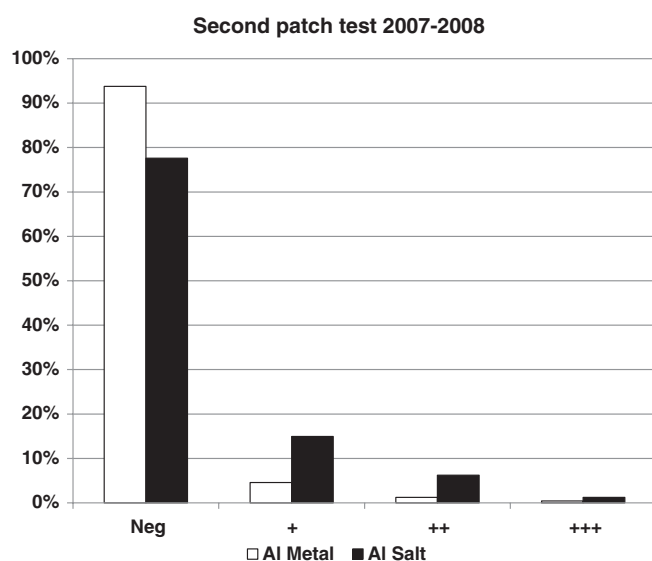


FIGURE 2 The distribution of patch test reactions to aluminium metal and the aluminium salt in the second patch test of 241 individuals in 2007-2008

pet., the higher the probability of showing a reaction to the Finn Chamber ($P < .0001$). In conclusion, we suggest that the standard for aluminium patch testing should be to test without the use of a metallic aluminium disc.

As we have shown before, aluminium allergy induced by aluminium vaccination seems to diminish over time,¹⁰ whereas, traditionally, contact allergy is considered to persist lifelong. Further investigation of our data shows that there were decreases in the frequencies of positive reactions to both metallic aluminium and the aluminium salt between the first patch test and the second patch test in the 241 retested children ($P < .0001$). This indicates that the disappearance of aluminium contact allergy seems to be possible and that our findings are reliable. There is a lack of reports of similar findings with different aluminium compounds in individuals tested twice after

vaccination with aluminium-adsorbed vaccine. However, the most important clinical question is whether a new exposure to aluminium-containing vaccine will give troublesome adverse reactions again.

In the field of immunology, there is great interest in the question of whether delayed hypersensitivity to aluminium can vanish over time. There is only one study in Denmark that re-patch tested aluminium in 4 children with vaccine-induced aluminium allergy. Two of the children were negative in the second patch test.⁸

In our study, we had a high number of losses of reactivity in patch test reactions. In the future, we will analyse adverse events after revaccination with aluminium-adsorbed vaccines or other aluminium exposures in our study population.

In summary, positive patch test reactions to aluminium are not fully reproducible, as shown by us and others. In our study, 77% of the children with earlier positive patch test reactions after vaccination with aluminium-adsorbed vaccine became negative. Such a large loss of contact allergy has not been described in the literature. Avoidance of exposure to the known allergen might have induced tolerance over time. Type IV delayed hypersensitivity in children might have a different prognosis from that in adults. Nevertheless, the question of how to best patch test for aluminium allergy, and the question of whether contact allergy really disappears, remain.

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Conflict of interest

The authors declare no potential conflict of interests.

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