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Children with vaccination granulomas and aluminum contact allergy: Evaluation of predispositions, avoidance behavior, and quality of life

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Abstract

Background: Aluminum contact allergy is mostly seen in children with vaccination granulomas, following immunization with aluminum-adsorbed childhood vaccines.

Objectives: To characterize a cohort of children with vaccination granulomas and aluminum allergy concerning early life conditions, exacerbating factors, avoidance behavior, treatments, and potential impact on quality of life.

Methods: A questionnaire study was conducted among 177 children aged 0 to 15 years with vaccination granulomas and aluminum allergy, and a reference group of 61 children aged 3 to 14 years with various types of dermatitis undergoing patch testing.

Results: All children in the granuloma group were reportedly affected by itch. Infection exacerbated the itch in 59%. Other worsening factors were eating tin-foiled/canned food (31%) and use of aluminum-containing sunscreen (46%). Many parents took precautions to avoid aluminum exposure. Children with granulomas were more likely to be nonadherent to the National Vaccination Program than the reference group (27% vs 2%, $P < .001$). Parents in the granuloma group reported a decreased life quality for both parents and children compared with the reference group.

Conclusions: Itching vaccination granulomas and aluminum allergy have a considerable negative impact on affected children and their families, causing avoidance behavior, reduced adherence to vaccination programs, and a negative effect on the overall life quality.

KEYWORDS

Key-words allergic contact dermatitis, aluminum, children, contact allergy, granuloma, patch test, quality of life, questionnaire, vaccine

1 | INTRODUCTION

Aluminum is a common adjuvant in childhood vaccines.¹ Persistent itching subcutaneous nodules after immunization, also known as vaccination granulomas, may occur,²⁻⁴ but until the 1990s, they were

considered to be a rare adverse event. Aluminum contact allergy as a cause of granulomas was established in the 1980s.⁵⁻⁸ The incidence of granulomas in children receiving aluminum-adsorbed childhood vaccines was 0.8% to 0.98%⁹ in Swedish studies including up to 76 000 vaccines.¹⁰ A positive test reaction to aluminum is seen in

77% to 95% of children with granulomas.^{9,11} The granulomas appear from 2 weeks to 13 months after the injections,¹² and are usually present for an average time of 4.6 years.^{10,11} Because of the time gap between vaccinations and the occurrence of the granulomas, they have occasionally been misinterpreted as tumors, leading to unnecessary examinations and fear of malignancy.^{13,14} Both granulomas and aluminum allergy are believed to diminish or vanish with time.^{6,10,15} Although mostly reported in smaller children, contact allergy to aluminum can also be a side effect to allergen-specific immunotherapy (ASIT) in older children and adults.^{3,16-18}

Aluminum is considered a weak allergen and has rarely been reported to cause contact allergy when using skin products containing it or from working in the metal industry.^{19,20} Despite this, there have been parental reports on children with aggravating itch and skin rash when using aluminum-containing sunscreen^{14,21} or when eating various foods rich in aluminum.¹⁴

In recent years there has been an increased focus in Denmark on vaccination granulomas. The number of cases reported to the authorities has risen from 120 in 2014 to 417 in 2018,²² and parents seek medical attention, information, and compensation from governmental insurances. Therefore, more information about potential consequences is needed. In this study, we characterized a cohort of children with vaccination granulomas and confirmed aluminum contact allergy concerning early life conditions, exacerbating factors, treatments, avoidance of future vaccines, and potential impact on quality of life.

2 | METHODS

From January 1, 2010 to September 1, 2018, 283 children 15 years or younger were patch tested at the Department of Dermatology and Allergy, Herlev and Gentofte Hospital, Denmark, due to vaccination granuloma and suspected aluminum contact allergy. Of these, 266 children had a positive patch test reaction to aluminum (94%). Of these children, 245 could be reached and were invited to participate in the questionnaire study. The reference group consisted of 124 children aged 15 years or younger with various types of dermatitis and suspected contact allergy. In total, 30 (24%) of these children had a positive patch test reaction to a contact allergen, mainly nickel or colophonium. Permission to collect personal data was approved by the Danish Data Protection Agency (VD-2018-137, I-Suite 6380), and data from the National Database for Contact Allergy were given by the Regional Clinical Quality Program – National Clinical Registries.

2.1 | Patch test

Children in the granuloma group were patch tested with metallic aluminum (empty Finn Chamber; Epitest, Tuusula, Finland) on Scanpor tape (Norgesplaster; Alpha Pharma, Vennesla, Norway) and aluminum chloride hexahydrate 2% petrolatum (allergEAZE; SmartPractice, Greven, Germany). A plastic chamber from the same producer was used as control. Children in the reference group were tested with a

pediatric test series of 33 allergens from the European Baseline series (Chemotechnique Diagnostics, Vellinge, Sweden or allergEAZE, SmartPractice). No children in the reference group reacted to the aluminum disks used for patch testing. The allergens were applied in Finn Chambers, taped to the upper back for 2 days, and the test site was evaluated on day (D) 2 (the day of removal) and D3 and D4. Only children with a negative or doubtful reaction on D2 to D4 was seen again on D7. Positive reactions were classified as +, ++ or +++, based on scoring according to the ESCD recommendations.²³

2.2 | Questionnaires

We constructed a questionnaire with 66 questions divided into sections. They were sent to the parents by electronic post, asking them to include their child when filling out the questionnaire if possible. Answers were multiple choice, as well as a blank space for comments. The questions covered early life conditions, hereditary factors, allergic and chronic diseases, vaccines, and life quality. Symptoms and characteristics regarding the granuloma and aluminum contact allergy; worsening factors, including various foods and skin products; and other external factors, such as heat, sleep, and infections, were evaluated. We asked about treatment attempts and the effect of these, and if parents deliberately avoided contact to aluminum.

The reference group received a shorter version of the questionnaire, excluding the specific questions related to the vaccination granuloma and aluminum contact allergy. We used the Children's Dermatology Life Quality Index, CDLQI,²⁴ a questionnaire with 10 questions focusing on various aspects of the skin, covering scratching, social behavior, playing, sleeping, and treatment during the last week. Results are a score between 0 and 30, with the higher the score, the more quality of life is impaired (Table S1). We anticipated that some children no longer had symptoms due to a long follow-up time and added four visual analog scale (VASs) covering life quality in general and when the skin symptoms were worst.

Parents of six newly referred children with vaccination granulomas validated the questionnaire, making sure relevant topics were covered and the questions were understandable. The questionnaires were implemented in Research Electronic Data Capture, REDCap,²⁵ and were in Danish.

2.3 | Statistical analysis

Comparisons between groups were mainly made using the chi-square test, except when sample size was $n \leq 5$ in which case the Fisher exact test was used. Odds ratios with 95% confidence intervals were additionally supplied. Data were tested for normal distribution before analysis. The CDLQI and VAS score both had a nonparametrical distribution, and the Mann-Whitney *U* test was thus used to compare the mean scores and determine whether there were any significant differences in the mean score. The CDLQI-score was calculated according to published instructions.²⁴ A *P*-value $< .05$ was considered

TABLE 1 Early life conditions and dispositions

Variable	Granuloma % (n/N of total)	References % (n/N of total)	Odds ratio (95% confidence interval)	P-value
Baseline characteristics				
Sex (male)	47 (83/177)	48 (29/61)	0.97 (0.54-1.75)	.93
Age at test, y (SD)	3.54 (1.79)	9 (3.22)	–	<.001
Follow-up, y (SD)	3.18 (1.39)	2.51 (0.99)	–	.001
Atopic dermatitis (AD) based on MOAHLFA	12 (21/177)	62 (38/61)	0.08 (0.04-0.16)	<.001
Early life conditions and dispositions				
Chronic disease	6 (10/177)	32 (18/61)	0.13 (0.06-0.31)	<.001
Diabetes	–	17 (10/61)	–	–
Asthma	12 (21/177)	22 (13/61)	0.46 (0.21-0.99)	.053
Mother AD	10 (18/177)	18 (11/61)	0.52 (0.29-1.16)	.12
Father AD	3 (5/177)	12 (7/61)	0.22 (0.07-0.74)	.014
Siblings AD	12 (22/177)	15 (9/61)	0.82 (0.36-1.9)	.66
Gestational age			–	.65
Extremely premature	1 (2/175)	–		
Very premature	1 (2/175)	–		
Moderately premature	12 (20/175)	18 (10/56)		
Term	86 (150/175)	82 (46/56)		
Birthweight in gram (SD)	3513 (535)	3533 (648)	–	.60
Nutrition during the first 6 mo of life:			–	.75
Only breastfeeding	45 (79/174)	48 (27/56)		
Primarily breastfeeding, formula supplement	23 (40/174)	27 (15/56)		
Equally breastfeeding and formula	16 (28/174)	11 (6/56)		
Only formula	16 (27/174)	14 (8/56)		
Any vaccines missing	27 (47/177)	<1 (1/61)	21.33 (2.87-158.32)	<.001
Reason for missing vaccines				
Fear of side effects including granulomas	83 (39/47)	100 (1/1)	16.96 (2.28-126.29)	<.001
Infections	2 (1/47)	–		
Forgetfulness	13 (6/47)	–		
Refuse further vaccinations	15 (26/177)	–		

Note: chi-square-test or Fischer exact test applied if $n \leq 5$.

Notes: Independent *t* test used for comparing means, with Mann-Whitney *U* test for skewed data.

Notes: Significant *P*-values (<.05) shown in bold.

Abbreviation: AD, atopic dermatitis; MOAHLFA, Male, Occupational dermatitis, Atopic dermatitis, Hand involvement, Leg involvement, Facial involvement, Age<40 years; SD, standard deviation.

statistically significant. Data were analyzed with IBM SPSS Statistics (SPSS, Chicago, Illinois) for Windows (release version 25.0).

3 | RESULTS

The overall response in the granuloma group was 72% (177/245) and 49% (61/124) in the reference group ($P < .001$). Baseline demographic characteristics showed no significant differences when comparing responders with nonresponders in each group, regarding sex, follow-up time, presence of atopic dermatitis (AD), and number of patch test-positive children. In the reference group, nonresponders had a slightly older age than responders (10.5 years vs 9 years, $P = .009$; Table S2).

The reference group had a significantly higher mean age and a higher prevalence of AD and chronic diseases, predominantly type 1 diabetes and asthma compared with the granuloma group ($P < .001$; Table 1). Most children in both groups were born mature with a birth weight appropriate for gestational age. Breastfeeding was the primary source of nutrition during the first 6 months of life in both groups.

3.1 | Avoidance behavior

A highly significant difference regarding future vaccines was found, with 47 (27%) children in the granuloma group already missing vaccines they should have received according to the Danish Childhood

Vaccination Program at the given time, compared with only one in the reference group ($P < .001$). The main reason was fear of side effects including another granuloma (Table 1).

Of the 47 children currently missing vaccines, 26 parents (15% of the total granuloma group) refused to further vaccinate their child. As seen in Figure 1, avoidance behaviors in the granuloma group overlap, and parents avoiding either aluminum-containing sunscreen or foods were also more likely to avoid vaccines, with 27 (15%) avoiding all three.

3.2 | Granuloma: Onset, worsening factors, avoidable behavior, and treatment

The characteristics of children in the granuloma group are summarized in Tables 1 and 2. In total, 61 (35%) children only had one granuloma, 77 (45%) two, and 35 (20%) three or more granulomas. Most children, 137/177 (77%), had a ++ patch test reaction to aluminum. The reactions mainly occurred on D2. A total of 100 (57%) went to their general practitioner at least once, 22 (13%) were seen by a pediatrician, and 61 (35%) by a practicing dermatologist before being referred to Herlev and Gentofte Hospital. Prior to referral, 10 (6%) children had an ultrasound examination, two (1%) had blood tests, and in one child (0.5%) a biopsy was performed.

Establishing the diagnosis of vaccination granuloma took less than 3 months in 99 (56%) children. Forty-one (23%) received the diagnosis 4 to 12 months after the granuloma was noted. In 16 (9%) children it took 1 to 4 years, and finally one child (0.6%) waited between 5 and 10 years for the diagnosis.

In most children, the vaccine associated with the discovery of the (first) granuloma was either the 3rd, 5th, or 12th month vaccination (i.e. the first, second, or third dose of diphtheria, tetanus, pertussis, polio, *Hemophilus influenzae* type b [DiTeKiPol/Hib], and invasive pneumococcal disease), respectively, in 58 (33%), 29 (16%), and

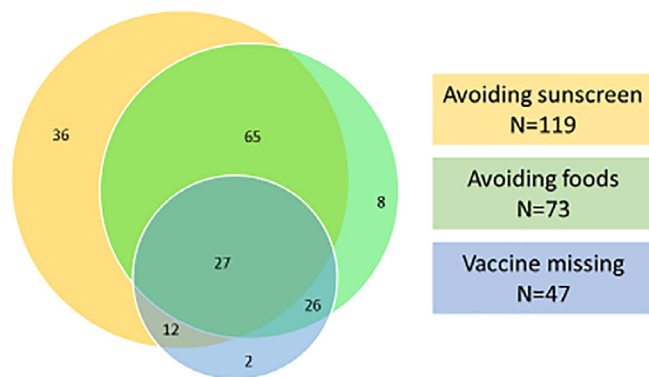


FIGURE 1 Venn-diagram illustrating the avoidable behavior of the granuloma group. Venn diagram showing the number of families stating avoidable behavior, with 65 (37%) avoiding both sunscreen and foods, 12 (7%) avoiding both sunscreen and vaccines, and 26 (15%) avoiding foods and vaccines. A total of 27 (15%) parents show avoidable behavior of all these three mentioned

TABLE 2 Characteristics related to the granuloma

Variable	Number of children, % (n/N of total)
Granuloma still present	72 (128/177)
Itch	100 (177/177)
Patch test reaction	
+	20 (36/177)
++	77 (137/177)
+++	3 (4/177)
Number of granulomas	
1	35 (61/173)
≥ 2	65 (112/173)
Elapsed time from debut to diagnosis	
1-6 months	71 (125/177)
7-12 months	8 (15/177)
13 months to 2 years	6 (11/177)
3-4 years	3 (5/177)
5-10 years	0.5 (1/177)
Do not remember	11 (20/177)
Examinations and procedures before diagnosis	
Ultrasound	6 (10/176)
Blood test	1 (2/176)
Biopsy	0.5 (1/176)
Vaccine in the Danish Vaccination Program associated with the discovery of the (first) granuloma	
3 months	33 (58/177)
5 months	16 (29/177)
12 months	26 (46/177)
15 months	10 (17/177)
4 years	0.5 (1/177)
5 years	1 (2/177)
Do not remember	14 (24/177)
Exacerbating foods	
Canned food	31 (55/175)
Dried fruit (raisins, figs)	28 (49/175)
Fresh fruit/vegetables	15 (27/175)
Exacerbating skin products	
Sunscreen with aluminum	46 (81/177)
Lotion	14 (25/177)
Aluminum-free sunscreen	9 (16/177)
Other exacerbating factors	
Infections	59 (104/175)
Heat/sweat	45 (80/175)
Bedtime	34 (60/175)
Avoiding behavior	
Use aluminum-free sunscreen	67 (119/177)
Avoid tinfoil/canned food	41 (73/177)
Avoid aluminum -containing food	35 (62/177)

46 (26%) children. Seventeen (10%) stated that the 15th month vaccine (measles, mumps, and rubella vaccine not containing aluminum) was associated with development of the granuloma. Only two children (1%) developed the granuloma after the 5-year DiTeKiPol booster vaccine.

Parents reported worsening factors in 139 (79%) cases, mostly infections ($n = 102$, 58%) and heat/sweats during playtime ($n = 80$, 45%) and during bedtime ($n = 60$, 34%). Skin products were reported to exacerbate itch, especially aluminum-containing sunscreen ($n = 80$, 45%) and regular moisturizers ($n = 25$, 14%). Various food items were also reported to exacerbate itch, mostly tin-foiled or canned food ($n = 55$, 31%) and dried fruit, especially raisins and figs ($n = 49$, 28%).

Worsening factors led to changes in behavior in 141 (80%) families. The most common was avoiding the use of aluminum-containing sunscreens ($n = 119$, 67%). Sixty-six (37%) even stated that they chose to avoid the use of aluminum-containing sunscreen, although reportedly never having had a reaction to this type of product. Avoiding tin-foiled and canned food ($n = 73$, 40%) and aluminum-containing foods in general ($n = 62$, 35%) was also common.

Treatment of symptoms had been tried by 108/177 (61%) in various ways, shown in Figure 2. The main treatment offered by dermatologists in Denmark is topical corticosteroids, tried by 82 with a good effect in only 18 (22%). Injected corticosteroids and surgical removal were not reported by any responders.

In 49 (28%) cases, the granuloma had disappeared at the time of this questionnaire study. In these children, the duration of the granulomas was less than 2 years in 11 (23%), 3 to 4 years in 28 (60%), and for more than 5 years in eight (17%). The tendency of avoidance behavior and reported worsening factors did not differ statistically between the two groups of children with present vs vanished granulomas.

3.3 | Quality of life

The mean CDLQI score (Table 3) was 3.10 for the granuloma group but higher for the reference group with a score of 3.86, though no significant difference was found ($P = .92$). Only one of the subquestions

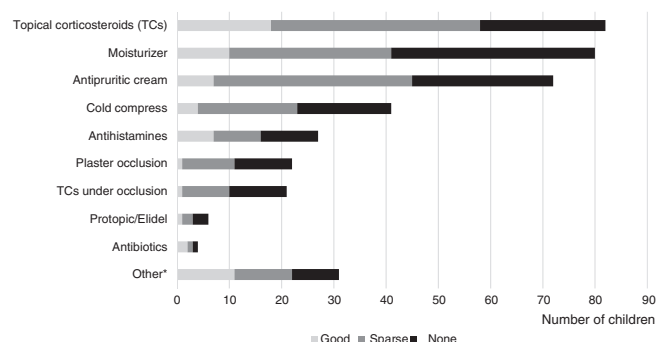


FIGURE 2 Attempted treatments. Attempted treatments of the granulomas and self-evaluated effect hereof. Other*: massage, drinking FIJI water or SILICIUM water, reflexology, sleeping with tight pajamas. Surgical removal of the granuloma was also an option in the questionnaire, but not chosen by any of the participants

in the CDLQI had a significantly different P -value of .001. This was the question "Over the last week, how much of a problem has the treatment for your skin been?," with the reference group having a higher score (mean 0.52 vs 0.26 for the granuloma group). In all four VASs (Table 3), the granuloma group had a higher score, indicating a higher negative effect on life quality, with all but "affecting the child in general" being statistically significant compared with the reference group.

4 | DISCUSSION

Over a 9-year period (2010-2018) 283 children were referred because of vaccination granulomas. A positive patch test reaction to aluminum was found in 266 (94%). In a similar study from another Danish department of dermatology, patch test data were collected from approximately 70 dermatologists in private practice and other dermatology departments in Denmark. Over a 10-year period (2003-2013) 47 children with vaccination granulomas were registered,¹⁴ of whom 92% reacted to aluminum. Although there is an overlap in the two periods of reporting, there is no overlap in patients and the

TABLE 3 Self-reported evaluation of quality of life, measured using Children's Dermatology Life Quality Index (CDLQI) and a visual analog scale (VAS) from 0 to 10, with 0 being no impact on life quality

	Granuloma N = 172	References N = 58	P-value
CDLQI total			
Mean (SD)	3.10 (3.21)	3.86 (5.20)	.92
Range	0-17	0-27	
CDLQI 10			
Over the last week, how much of a problem has the treatment for your skin been?			
Mean (SD)	0.26 (0.52)	0.52 (0.73)	.009
Range	0-2	0-3	
VAS: Affecting the child in general			
Mean (SD)	4.11 (2.97)	3.25 (2.23)	.061
Range	0-10	0-9	
VAS: Affecting the family in general			
Mean (SD)	3.98 (2.84)	3.0 (2.60)	.017
Range	0-10	0-9	
VAS: Affecting the child when symptoms were worst			
Mean (SD)	6.65 (2.82)	5.25 (3.34)	.007
Range	0-10	0-10	
VAS: Affecting the family when symptoms were worst			
Mean (SD)	6.67 (2.69)	5.55 (3.29)	.046
Range	0-10	0-10	

Notes: Mann-Whitney U test, nonparametric distribution.

Notes: Significant P -values ($<.05$) shown in bold. SD, standard deviation.

considerable larger group of children with vaccination granulomas seen in our department probably reflects an increased awareness among parents due to increased public attention on vaccines and their side effects.

4.1 | Vaccines and aluminum load

Since 2005 there have been changes in the Danish Childhood Vaccination Program concerning vaccine production companies. The amount of aluminum in the DiTeKiPol vaccines has generally been 1 mg aluminum per dose, but from January 2014 to March 2018, two vaccines with 0.625 mg aluminum were also available. In this study it was not possible to distinguish between the vaccines that had been administered, but reports of adverse effects from the Danish Medicines Agency showed that most cases of granulomas were in children vaccinated in 2015 and 2016.²²

Concerning continued vaccinations, Salik et al described that one-third of parents in their study had decided to omit or postpone further vaccination of their child,¹⁴ and a similar behavior was described by Bergfors and Trollfors.¹¹ We observed that 47 (27%) of the parents had delayed further vaccinations, with 26 (15%) even refusing further vaccinations. The main reason was fear of another granuloma or exacerbating symptoms of an existing one. This emphasizes the need for careful advice to these families regarding vaccination.

The induction of granulomas could be associated with the accumulated aluminum load received through vaccines.¹⁴ In our study 75 (42%) children developed granulomas after the second or third vaccine (administered at 5 and 12 months, respectively), supporting this hypothesis; however, in 58 (33%) the granulomas appeared after the first vaccine. The risk of additional granulomas following future vaccinations has until now only been investigated in a study of 25 children, where two (8%) developed new granulomas.¹¹ We found that 63% reported to have more than one granuloma. This is solely based on the questionnaires and not clinically confirmed.

4.2 | Avoidance behavior

A high proportion (up to 67%) of families were trying to avoid contact to aluminum. This is in contrast to the very few known case reports of aluminum contact allergy following external exposure. Axillary eczema following the use of antiperspirants has been described in older children and adults following ASIT,^{16,26,27} and in studies by Bergfors et al and Salik et al, three of 19 and four of 39, respectively, reported a worsening in the skin condition of the child when using an aluminum-containing sunscreen.^{14,21} In our study, reactions to aluminum-containing sunscreens were reported by 81 (46%). These reports are of course subjective and might be biased by the parents' knowledge of the positive test reaction to aluminum during patch testing. Reactions following the use of antiperspirants were reported by 16 (9%). This could be due to the young age of our study population, by whom this type of products is not yet used. In addition, the dermal penetration of aluminum through normal skin is reported to be low. In a study

measuring the transdermal penetration of aluminum chlorohydrate, an absorption of less than 0.07% was shown. A similar result was recently found in a study by the cosmetic industry.^{28,29}

4.3 | Systemic allergic dermatitis

Many patients with contact allergy/dermatitis speculate on the influence of food intake on symptoms. Aluminum is naturally present in both plants and animals. It is also used as a food additive, and especially dried products such as fruit and tea leaves contain a high amount of aluminum. The same is true for foodstuff prepared or stored in aluminum utensils.^{30,31} In addition, the concentration of aluminum in various milk- and soy-based formulas is much higher than in human breast milk.^{32,33}

Systemic allergic dermatitis is well known, but a rare entity, where a person sensitized by skin contact develops symptoms from systemic exposure (eg orally). The symptoms vary from a local flare of previous dermatitis to the so-called baboon syndrome.³⁴ However, gastrointestinal bioavailability of aluminum in general is considered low³⁵⁻³⁷ and at least in some cases, a more general flare with characteristic symptoms of systemic allergic dermatitis would be expected if certain food items were involved. This has not (yet) been reported. In nickel-allergic individuals previous studies have indicated that oral nickel contact via dental braces leads to a reduced frequency of nickel contact allergy.³⁸ Early nutritional exposure to aluminum could potentially create tolerance, causing the children who were bottle-fed to be less prone to develop the granulomas. However, we found no difference between the groups regarding nutrition during the first 6 months of life ($P = .75$).

4.4 | Impact on quality of life

Looking at the CDLQI data, we found that the reference group had a slightly higher score compared with the granuloma group (5.44 vs 4.25), although not significantly so ($P = 0.21$). Studies on children with psoriasis showed a similar score with a mean 5.05 (SD $\pm$ 5.0),³⁹ but a higher score in children with AD (7.1 [SD $\pm$ 4.4]).⁴⁰ Although the CDLQI focuses on the skin, chronic disease is a confounder and might contribute to the higher score in the reference group, along with the significantly higher prevalence of AD. As the granulomas tend to disappear over time, another explanation of the lower score in the granuloma group could be the follow-up time. On the VAS, the granuloma group had a significantly higher score than the reference group. This difference in VAS and CDLQI could be because CDLQI questions are quite specific and concern only the child, whereas the VAS we created addressed both the children and their parents. The mean VAS score when symptoms were worst in the granuloma group was similar in the child and the families (6.7), indicating that the parental subjective feeling of the impact of everyday life is very much affected, with all probability due to the changes and precautions they feel they must take.

4.5 | Strengths and limitations

To our knowledge, this the most extensive questionnaire study regarding vaccination granulomas and aluminum contact allergy, and the first published one with a reference group for at least partial comparisons. Overall, our response in the granuloma group was 72%, similar to the response in other printed questionnaire studies.⁴¹ Response in the control group was 49%, which might be because only 24% of these children had a positive patch test and the parents therefore did not find it relevant to participate. Another weakness is the subjective nature of answers in a questionnaire, especially regarding worsening factors and the number of granulomas. A clinical aspect instead of only subjective description would have strengthened our results.

There is a significant age difference between the groups, which makes the comparison difficult, especially regarding quality of life. Older children tend to be more self-conscious concerning the perception on how a disease affects their life. There is also a significant difference in the follow-up period, with more time passed since patch testing of the reference group. This could be another reason for the lower response, as the symptoms might have vanished over time, just as it might be a cause of recall bias in both groups. The reference group itself is heterogeneous concerning diagnoses, but instead of choosing healthy children, we decided to use a group of children with various forms of dermatitis. This allowed us to compare quality of life based on skin conditions.

The study design is limited by its retrospective nature. Only children referred due to granulomas are tested for aluminum allergy routinely in our clinic. The frequency of granulomas and aluminum allergy in the reference group are expected to be at the level as generally noted among children, around 1%, which is less than one person in our control sample. In addition, none in the control group reacted to the metal disk (Finn Chambers). Even though studies have shown that not all positive children react to both the salt and the metal,^{42,43} the risk of them having granulomas and aluminum allergy was considered low and therefore we decided to use these children as the reference group.

The prevalence of chronic diseases was higher in the reference group, especially diabetes. This correlates with our chosen reference group suffering from various forms of dermatitis and suspected contact allergy, and the tendency of contact allergy to the medical devices used by diabetes patients (eg, insulin pumps), which is increasingly becoming a problem.⁴⁴

In the reference group questionnaire, it was not possible to include questions regarding aluminum-containing products and the specific questions concerning the granuloma. This means we are unable to tell if the reported reactions in the granuloma group to, for example, sunscreens are specific for the granuloma group or more generally seen in children.

It is important to emphasize that the granuloma group in this questionnaire is a selected group, and given the easy access to online information, it is likely that many parents have sought information regarding aluminum allergy. During consultations with dermatologists at Herlev and Gentofte hospital following patch tests, parents are informed that generally no precautions are needed,

except if the child has a reaction to a certain product. The information and advice parents obtain by using the Internet might not always have a scientific background and could be a risk factor of further avoidance behavior.

In our material it was not possible to evaluate the number of undiagnosed children with vaccination granulomas, who might be unaware of the possible aluminum contact allergy and therefore have no expectations regarding exacerbating factors and avoidance behavior. Because this study was questionnaire based, we have not been able to repeat patch tests on children in whom the granulomas have disappeared; therefore, no conclusions can be drawn on the course of their aluminum allergy.

5 | CONCLUSION

This study showed that although the granulomas and aluminum allergy are benign, the condition has a considerable impact on more than half of the group. They lead to avoidance of further vaccines, precautions in use of sunscreen, and/or dietary restrictions, which are perhaps unnecessary and negatively affect overall quality of life. Omission of vaccines should be taken seriously, as it puts the child at risk and lowers the vaccination coverage in the population. Based on the findings in this study, experimental provocation studies will be designed.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

AUTHOR CONTRIBUTIONS

Stine Hoffmann: Formal analysis; investigation; methodology; writing-original draft; writing-review and editing. **Jacob Thyssen:** Methodology; supervision; writing-original draft; writing-review and editing. **Jesper Elberling:** Methodology; supervision; writing-original draft; writing-review and editing. **Kirsten Hansen:** Methodology; supervision; writing-original draft; writing-review and editing. **Jeanne Duus Johansen:** Conceptualization; funding acquisition; methodology; supervision; writing-original draft; writing-review and editing.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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Supplementary table 1. Baseline demographic characteristics of responders versus non-responders in both groups

Granuloma				
	Responders 177/245	Non-responders 68/245	Odds ratio (95% confidence interval)	P-value
Male	83/177 (47%)	29/68 (43%)	1.19 (0.68-2.09)	.55
Age at test, years (standard deviation)	3.61 (1.88)	3.9 (1.9)	-	.08
Follow-up, years (standard deviation)	2.17 (1.39)	2.15 (1.48)	-	.57
Atopic dermatitis†	21/177 (12%)	10/68 (15%)	0.78 (0.35-1.76)	.55
Positive patch test	177/177 (100%)	68/68 (100%)	-	-
References				
	Responders 61/124	Non-responders 63/124	Odds ratio (95% confidence interval)	P-value
Male	29/61 (48%)	36/63 (57%)	0.67 (0.32-1.33)	.24
Age at test, years (standard deviation)	9 (3.24)	10.5 (3.0)	-	.014
Follow-up, years (standard deviation)	1.75 (0.97)	1.67 (0.82)	-	.85
Atopic dermatitis†	39/61 (64%)	43/63 (68%)	0.78 (0.37-1.66)	.52
Positive patch test	19/61 (32%)	11/63 (18%)	2.1 (0.9-4.9)	.08

†Based on MOAHLFA

Chi-square-test.

Mann-Whitney U-test used for age and follow-up (skewed data).

Significant p-values (<0.05) shown in bold.

Supplement table 2. CDLQI score and severity banding

<i>Very much</i>	<i>Scored 3</i>
<i>Quite a lot</i>	<i>Scored 2</i>
<i>Only a little</i>	<i>Scored 1</i>
<i>Not at all</i>	<i>Scored 0</i>
<i>Question unanswered</i>	<i>Scored 0</i>
The severity banding for CDLQI scores	
<i>0-1</i>	<i>No effect on child's life</i>
<i>2-6</i>	<i>Small effect on child's life</i>
<i>7-12</i>	<i>Moderate effect</i>
<i>13-18</i>	<i>Very large effect</i>
<i>19-30</i>	<i>Extremely large effect</i>