Received: 5 July 2022 | Accepted: 22 November 2022

DOI: 10.1111/jdv.18811

JEADV JOURNAL OF THE EUROPEAN ACADEMY OF DERMATOLOGY & VENEREOLOGY

ORIGINAL ARTICLE

Adverse reactions after oral provocation with aluminium in children with vaccination granulomas and aluminium contact allergy

Stine Skovbo Hoffmann[1] | **Jesper Elberling**[2] | **Kirsten Skamstrup Hansen**[2,3] | **Jacob P. Thyssen**[1] | **Charlotte G. Mortz**[4] | **Rasmus Overgaard Bach**[4] | **Jeanne Duus Johansen**[1]

[1]National Allergy Research Centre, Department of Dermatology and Allergy, Herlev and Gentofte Hospital, University of Copenhagen, Hellerup, Denmark

[2]Department of Dermatology and Allergy, Herlev and Gentofte Hospital, University of Copenhagen, Hellerup, Denmark

[3]Department of Pediatric and Adolescent Medicine, Herlev and Gentofte Hospital, University of Copenhagen, Herlev, Denmark

[4]Department of Dermatology and Allergy Centre, Odense University Hospital, University of Southern Denmark, Odense, Denmark

Correspondence
Stine Skovbo Hoffmann National Allergy Research Centre Department of Dermatology and Allergy Herlev and Gentofte Hospital, University of Copenhagen Gentofte Hospitalsvej 20A, 1st floor 2900 Hellerup, Denmark.
Email: stine.hoffmann@regionh.dk

Funding information
Kongelig Hofbuntmager Aage Bangs Fond; Miljø- og Fødevareministeriet; the Danish Environmental Protection Agency

Abstract

Background: According to their parents, some children with aluminium contact allergy and vaccination granulomas may react to aluminium-containing foods by developing dermatitis, granuloma itch and subjective symptoms.

Objectives: The objective of this study is to determine whether oral intake of aluminium-containing pancakes can cause adverse events and/or systemic contact dermatitis (SCD) in children with vaccination granulomas and aluminium contact allergy.

Patients/Methods: A total of 15 children aged 3–9 years (mean age, 5 years) with vaccination granulomas and positive patch-test results to aluminium chloride hexahydrate 2%/10% pet. completed a 3-week blinded randomized controlled crossover oral aluminium/placebo provocation study with pancakes. Granuloma itch and other subjective symptoms were evaluated daily on a visual analogue scale (VAS). Dermatitis was evaluated by the primary investigator, and sleep patterns were tracked with an electronic device. Aluminium bioavailability was assessed by measuring aluminium excretion in the urine. The children served as their own controls with the placebo provocations.

Results: All 15 children completed the study. The mean VAS scores were slightly higher during aluminium provocations compared with placebo for granuloma itch (mean VAS, 1.5 vs. 1.4, $p = 0.6$) but identical for other subjective symptoms (0.6 vs. 0.6, $p = 1$). There were no differences in sleep patterns and no significant correlation between urinary aluminium excretion and symptom severity. Three children developed a symmetrical rash on the face or buttocks on day 4 of the aluminium provocations, but not during placebo provocations.

Conclusions: No difference was found between oral aluminium intake and the occurrence of subjective symptoms and granuloma itch, but on a case-basis oral aluminium may be associated with the development of systemic contact dermatitis.

INTRODUCTION

Aluminium is a ubiquitous metal, with numerous industrial and domestic applications. Humans may be exposed to aluminium from various sources including food, antacids, deodorants, and vaccines.[1,2] As an allergen, aluminium is generally considered weak. Aluminium contact allergy is predominantly observed in children, who develop small itching subcutaneous nodules, known as vaccination granulomas, following immunization with aluminium-adsorbed vaccines. These granulomas occur in up to 1% of vaccinated children, usually appear weeks to months after vaccination, and may last for several years.[3–6] Rarely, individuals who are allergic to aluminium may develop

dermatitis or exacerbated granuloma itch when exposed to dermal aluminium products, such as sunscreens and deodorants.[7–10]

Systemic contact dermatitis (SCD) occurs when an individual sensitized through skin exposure develops a rash via the systemic route in response to the same allergen. SCD may occur in individuals who are allergic to metals, medications or foods.[11,12] The only published study on SCD in children who are allergic to aluminium reported that an aluminium-containing toothpaste caused granuloma itch in three children.[13] Nevertheless, parents of children who are allergic to aluminium have reported that their children may develop granuloma itch or dermatitis, as well as subjective symptoms such as headaches, abdominal pain and agitation, after consuming aluminium-containing foods.[5,14,15]

The food additive sodium aluminium phosphate (SALP) has been used in studies investigating aluminium bioavailability.[16,17] SALP is labelled E541 and categorized among "additives other than colours and sweeteners." It is used in many baking products, including pancake mix, as a leavening acid to react with baking soda.[18]

We investigated whether aluminium provocations could induce a systemic response in children who are allergic to aluminium. We used a blinded randomized controlled oral provocation study design to compare SALP pancakes with aluminium-free (placebo) pancakes. In addition, we investigated whether there were any associations between the dose of oral aluminium challenge, symptom severity, and the quantity of aluminium excreted in the urine.

MATERIALS AND METHODS

Study design

The study was a randomized blinded placebo-controlled aluminium challenge. All children were followed for 3 weeks and underwent three periods (the first 4 days of each week) of blinded provocation with SALP/placebo pancakes. Each 4-day provocation with SALP/placebo pancakes was followed by a 3-day washout period, before initiating the next provocation or terminating the study. Urine samples were collected on day 4 of each week. Children were randomized to ingest SALP pancakes for 1 or 2 weeks of the 3-week study, and for the remaining 1 or 2 weeks, the children ingested placebo pancakes. There were no restrictions on, or monitoring of, the children's regular food intake during the study.

Participants

A priori assessment showed that 23 participants were needed to obtain a power of 80% and a significance level of 0.05, if 31% of the participants reacted as described in a previous questionnaire study.[14] We made extensive efforts to reach this target, but after 1.5 years we had to close the study. We included a total of 15 children, aged 3–9 years, who had been referred to the Department of Dermatology and Allergy at Gentofte Hospital or the Department of Dermatology and the Allergy Centre at Odense University Hospital due to itching granulomas following immunization with aluminium-adsorbed vaccines. The exclusion criteria were allergy to any ingredients in the pancakes other than aluminium (e.g., egg, wheat, or milk), kidney or bone disease, systemic immunosuppressant treatment, vaccination within the previous week, use of antacid within the previous week, illness during the study period, or a vaccination granuloma that was no longer itching. Inclusion took place from February 2021 to May 2022.

Patch testing

All children were patch tested at the Department of Dermatology and Allergy (Herlev and Gentofte Hospital, University of Copenhagen, Denmark) or the Department of Dermatology and the Allergy Centre (Odense University Hospital) using aluminium chloride hexahydrate 2% pet. (allergEAZE; SmartPractice) and an empty aluminium Finn Chamber (Epitest), in accordance with standard procedures. From 2021, children older than 8 years were tested using aluminium chloride hexahydrate 10% pet., in accordance with new recommendations.[4,19] A total of 20 mg of sample was applied to each 8-mm propylene-coated Finn Chamber, and an empty propylene-coated chamber was used as a control. All chambers were taped to the upper back for 2 days using Scanpor tape (Norgesplaster; Alpharma). Parents were instructed to check the test site for extreme reactions on the day of application and on the following day. The test site was evaluated on day 2 and days 3–4, depending on which department performed the test, and also on day 7. Reactions were classified as negative (0), irritant (IR), doubtful (+?), positive (+), strong positive (++) or extremely strong positive (+++), in accordance with the European Society for Contact Dermatitis recommendations.[20]

Pancakes

Two different pancake mixes that were similar in texture and taste were used. One mix had SALP as an additive, whereas the other mix had no aluminium. The mixes were analysed for aluminium content at ALS Scandinavia (Luleå, Sweden) using inductively coupled plasma mass spectrometry (ICP-MS), which can detect very small quantities of aluminium. ICP-MS detected 1640 mg aluminium/kg mix (±224 mg/kg) in the SALP pancakes but less than 5 mg/kg mix (i.e., the detection limit) in the placebo pancakes. All pancakes were cooked in a cast-iron skillet, packed in plastic bags, and stored at −20°C until they were distributed to the study participants.

Children are predominantly exposed to aluminium via their diet, because they are generally too young to use

aluminium-containing cosmetic products, stomach acid medicines or deodorants. The quantity of aluminium present in a child's diet varies from 0.21–1.02 mg/kg body weight (bw)/week, depending on the child's age.[21,22] Various studies on oral toxicity of aluminium have been used to assess the risk of aluminium exposure, and the European Food Safety Authority (EFSA) defines the tolerable weekly intake of aluminium as 1 mg Al/kg bw/week.[18] The SALP pancakes consumed by our children aimed to provide 3–4 mg Al/kg bw/week, corresponding to up to 4-fold the estimated regular dietary intake, without drastically exceeding recommended tolerable weekly intake.

Symptom assessment

From a previous questionnaire study and parental reports,[14,15,23] we created a diary with a list of subjective symptoms to be evaluated each day during the 3-week study. The symptoms included headache, irritability/agitation, stomach ache, and tiredness; in addition, parents had the opportunity to choose symptoms not listed in the diary.[14] Parents chose three symptoms they wished to evaluate during the 3-week study period, and each was scored daily on a visual analogue scale (VAS) ranging from 0 to 10.

All children were given a Garmin Vivofit Junior activity watch (Garmin Ltd), and they were instructed to wear the watch overnight to gather data (e.g., duration asleep and awake). Parents downloaded the matching app on their smartphones.

Additionally, cutaneous reactions were subdivided into the following categories:

- Flare-up reactions in previously patch-tested areas.
- Any large- or small-scale clinical skin eruptions on previously affected and unaffected skin.
- Granuloma itch.

After the 3-week study period, parents were asked to identify the weeks during which their child consumed aluminium pancakes, based on the child's symptoms.

Urine samples

The bioavailability of aluminium from the diet is low, and only approximately 0.1% of ingested aluminium is absorbed.[24] The absorbed aluminium is excreted in the urine within days, and the aluminium content of the urine is a sensitive marker of general aluminium absorption.[16,17,25] To measure the potential increase in aluminium uptake during the weeks when SALP pancakes were consumed, and to evaluate possible correlations between excreted aluminium and VAS symptom scores, all participants provided urine samples after each of the three provocations. The urine samples were analysed for aluminium using ICP-MS by ALS Scandinavia (Luleå, Sweden).

Statistical analysis

Patient characteristics were described as frequencies (%) for categorical variables and as means with standard deviations (SDs) for continuous variables. For each of the 3 provocation weeks, the mean VAS scores for granuloma itch and for all other three subjective symptoms combined were calculated in each participant. Cutaneous reactions and parental guesses regarding the weeks during which aluminium pancakes were consumed (correct or incorrect) were analysed as binary categories (yes or no). Binary variables were analysed using the chi-square test for independence, or by using Fischer's exact test for counts less than five. Non-parametric statistical methods were used to analyse the VAS scores, and the Friedman test was used to compare the 3-week reactions. The Wilcoxon signed-rank test was used for pairwise comparisons between pooled aluminium and placebo provocations. The correlation between VAS scores and urinary aluminium excretion was assessed using Spearman's rho. p-values <0.05 were considered statistically significant. Data were analysed using IBM SPSS software for Windows (ver. 25.0; SPSS).

Ethics

This study was approved by the Danish Data Protection Agency and the regional ethics committee in Denmark (H-20060917), and conducted according to the declaration of Helsinki. The study was prospectively registered at www.clinicaltrial.gov (NCT04921163).

RESULTS

Characteristics of the participants are shown in Table 1. In total, 15 children with a mean age of 5.7 years (SD = 1.8) participated in the study. Of the 15 participants, 8 children (53%) were girls, and parents of 3 of the children (20%) had clear suspicions of previous cutaneous reactions to aluminium in food.

Granuloma itch, VAS scores and oral exposure

We evaluated the granuloma itch and symptomatic VAS scores during each of the three provocation weeks using Friedman's test; the results were not significant for granuloma itch (p = 0.86) or other subjective symptoms (p = 0.23).

The ingested pancakes provided a dose of aluminium equivalent to 3.7 (SD = 0.5) mg/kg bw/week (Table 1).

Next, due to the small number of participants, we pooled data from the aluminium provocations and placebo provocations to create two groups for comparison, and we used the Wilcoxon signed-rank test for pairwise comparisons (Table 2). The mean VAS scores for granuloma itch were 1.5 (SD = 1.4) for aluminium provocations and 1.4 (SD = 1.2) for placebo

TABLE 1 Characteristics of the participants.

Participant	Age (years)	Sex	Patch test result 2%/10%[a] pet.	Atopic dermatitis	Mg al/kg bw/ week[b]	Previous parental-reported cutaneous reaction
1	6	Female	++	Yes	4.6	No
2	8	Male	++[a]	No	2.6	Yes
3	6	Male	++	Yes	4.0	No
4	8	Female	++	Yes	3.1	No
5	9	Female	++[a]	No	3.3	No
6	3	Female	+++	No	4.3	No
7	5	Male	++	Yes	3.7	No
8	7	Female	++	No	4.0	No
9	3	Male	++	No	3.4	No
10	5	Female	++	No	4.5	Yes
11	6	Female	++	No	3.7	No
12	5	Male	+	Yes	3.7	Yes
13	6	Female	++	No	3.8	No
14	5	Male	++	Yes	4.2	No
15	3	Male	++	Yes	3.7	No

[a]Children older than 8 years has from 2021 been patch tested with aluminium chloride hexahydrate 10% pet instead of 2% pet.
[b]Mg aluminium per kilogram bodyweight per week (aluminium provocation weeks only).

TABLE 2 Aluminium intake, excretion, and symptom assessment for aluminium and placebo provocations.

	Aluminium provocation(s)	Placebo provocation(s)	*p*-value
Oral aluminium mg/kg bw, mean (SD)	3.7 (0.5)	-	-
Urine aluminium excretion µg/L, mean (SD)	12.7 (8.3)	6.7 (2.1)	*0.006*[a]
Urine creatinine excretion mmol/L, mean (SD)	7.5 (2.7)	6.3 (2.6)	*0.041*[a]
Symptom assessment			
Granuloma itch, VAS mean (SD)	1.5 (1.4)	1.4 (1.2)	0.6
Subjective symptoms, VAS mean (SD)	0.6 (0.6)	0.6 (0.8)	1.0
Dermatitis (% of total)	3 (20%)	0 (0)	-
Flare-up of patch test reaction (% of total)	0 (0)	0 (0)	-
Sleep pattern			
Total sleep (hours: minutes (SD))	8:59 (0:26)	09:08 (0:39)	0.59
Awakenings (% (SD) of total sleep)	1.7 (2.2)	1.7 (2.2)	0.68
Parental assessment			
Previous cutaneous reaction (% of total)[b]	3 (20%)	-	-
Correct parental identification (% of total)[c]	8 (53%)	-	-
Previous reaction vs. correct identification (% of total)	2 (13%)		0.55

Note: Difference between mean VAS scores, urine excretion, and sleep patterns between aluminium and placebo provocations were assessed with Wilcoxon Signed Ranks Test for non-parametric paired data. Fischer's exact test was used to evaluate the association between previous suspected reaction to aluminium in food and correct parental identification of the aluminium week(s).
[a]Statistically significant *p*-value.
[b]Parents have suspected previous reaction to aluminium-rich food.
[c]Correct identification of the week of aluminium provocation.

provocations. The slight difference was not statistically significant ($p = 0.6$). The mean VAS scores for other subjective symptoms were identical, 0.6 ($SD = 0.6$) for aluminium provocations and 0.6 ($SD = 0.8$) for placebo provocations, $p = 1$.

The distribution of each child's VAS scores during aluminium and placebo provocations is shown in Figure 1.

Three children (participant 2, 7 and 12) developed dermatitis on day 4 of a week in which they consumed aluminium pancakes (Figure 2). Two of the rashes were on the face and the other was on the buttocks, all symmetrical. The rashes were similar to previous rashes that parents had suspected were triggered by aluminium in food. The rashes were slightly

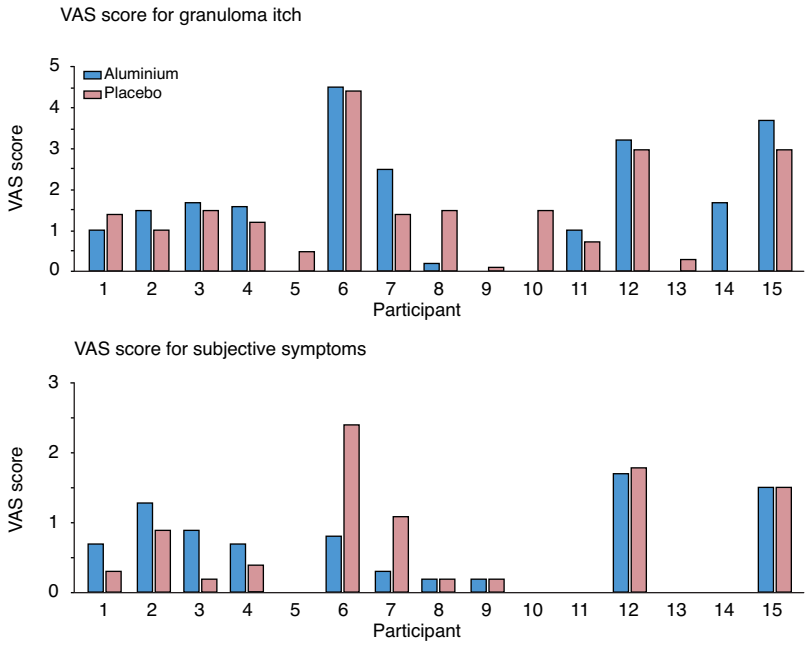

FIGURE 1 VAS scores for each participant for both granuloma itch and other subjective symptoms during aluminium and placebo provocations

FIGURE 2 Symmetrical, infiltrated, itching, non-fluctuant rash on the face and buttocks of three participants (2, 7 and 12, respectively), occurring on day 4 in the aluminium provocation week and gradually disappearing within 3–5 days.

palpable, non-fluctuant and itchy, and they gradually disappeared after 3–5 days. All affected children continued in the study and followed the protocol. No children had flare-up reactions in areas that had previously been patch tested.

Finally, we investigated the correlation between the oral aluminium intake defined as mg aluminium per kg bodyweight and VAS scores. The results are shown in Figure 3, with no significant relationship between oral aluminium intake and neither subjective symptoms (Spearman's rho, $p = 0.31$) nor granuloma itch (Spearman's rho, $p = 0.76$).

Aluminium in urine samples and symptom scores

We were unable to stratify our study population to account for the aluminium that children received in their regular diet, which may have affected total aluminium intake. Instead, we investigated any correlation between aluminium excretion in the urine and the VAS scores for both granuloma itch and other subjective symptoms. As shown in Table 2, the mean urinary aluminium excretion was 12.7 µg/L ($SD = 8.3$) during aluminium provocations and 6.7 µg/L ($SD = 2.1$) during placebo provocations ($p = 0.006$). For all children, creatinine measurements were within the normal range.[26] The three children who had rashes during aluminium provocations exhibited aluminium excretion levels of 5–16.1 µg/L.

We investigated the relationship between aluminium bioavailability during aluminium provocations and VAS severity scores (Figure 4); we found no correlation between urinary aluminium excretion and VAS scores (Spearman's rho, $p = 0.6$ for granuloma itch and $p = 0.71$ for other subjective symptoms). Adjusting for creatinine in the urine did not change these results.

Changes in sleep patterns

Because an itching granuloma may affect sleep patterns, we analysed differences in both the mean duration of sleep per week and the proportion of this sleeping time that was spent awake per week, using the data collected via the Garmin Vivofit Junior watches. The results are shown in Table 2. The total mean duration of sleep per night was shorter during aluminium provocation than placebo provocation weeks (8 h 59 min vs. 9 h 8 min per night, respectively), although the difference was not significant ($p = 0.59$). The proportion of the total sleeping time that was spent awake was the same in each case (1.7% of total sleeping time, $p = 0.68$).

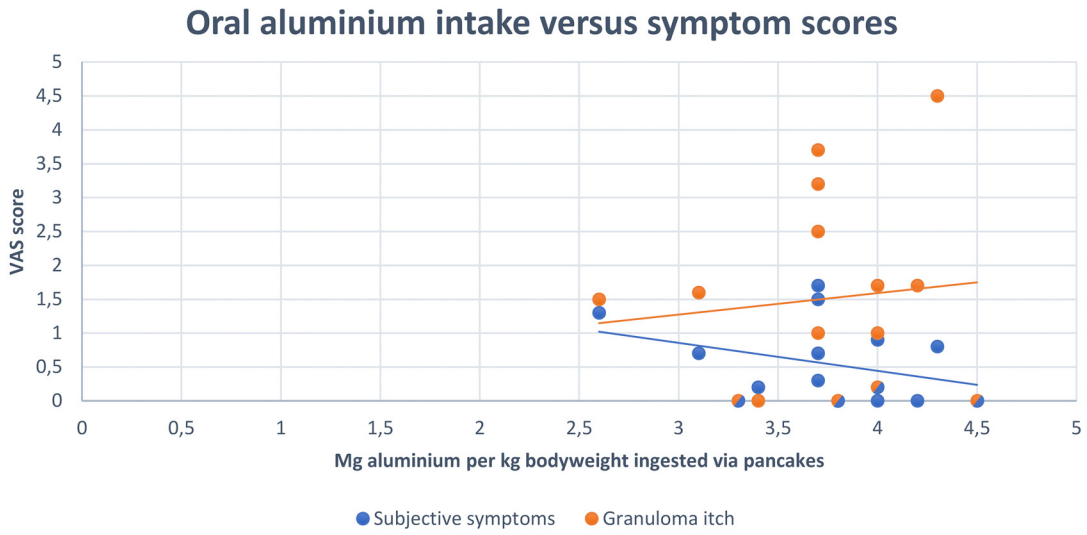

FIGURE 3 Association between aluminium intake as mg aluminium/kg bodyweight of each participant, and VAS scores for both subjective symptoms and granuloma itch.

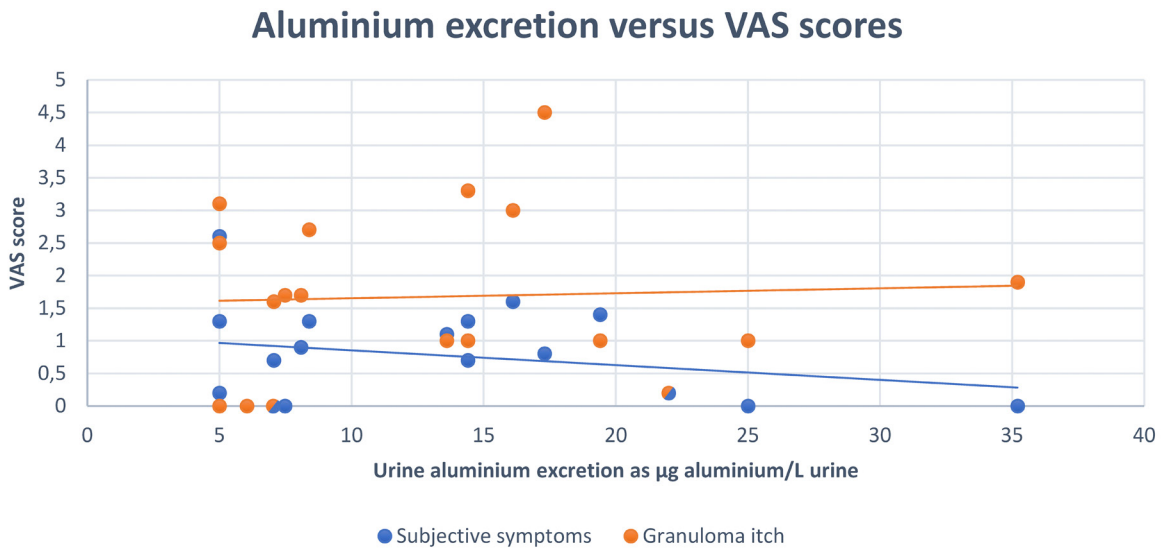

FIGURE 4 Aluminium bioavailability expressed as urinary aluminium excretion vs. VAS scores of subjective symptoms and granuloma itch during the aluminium provocations. Detection level of aluminium in urine samples are 5, all samples with the result of <5 are defined as 5 in this plot.

Parental guess

We assigned binary variables for previously suspected aluminium reactions (yes/no, 3/12) and correct identification of aluminium provocation (yes/no, 8/7), as shown in Table 2. The parents of two of the three children who had previously experienced cutaneous reactions correctly identified the weeks during which aluminium provocation was provided ($p = 0.55$).

DISCUSSION

In this study, we investigated whether children who were allergic to aluminium exhibited reactions when systemically exposed to aluminium in food. We evaluated outbreaks of dermatitis, exacerbation of granuloma itch and other subjective symptoms using a single-blinded controlled study design. We found that significantly more aluminium was excreted during the aluminium provocations, but there

were no significant associations between granuloma itch and other subjective symptoms scored by parents and the amount of bioavailable aluminium.

Some metals do cause SCD.[11,12] Patients who are allergic to nickel may experience flare-ups in areas that have been previously patch tested, following oral challenge.[27] Such patients may also exhibit dermatitis, both flare-ups and de novo, as a result of following a high-nickel content diet.[28] Other cutaneous eruptions include the "baboon syndrome", which is characterized by symmetrical patches of erythema on the buttocks, and vesicular hand eczema.[27–29] Additionally, patients might experience general symptoms such as headache, malaise and stomach ache.[28] Three participants developed a rash during aluminium provocation in this study. These rashes occurred on either the buttocks or the face, and could not be explained by any other obvious exposure. Two of the three children who developed rashes had a history of atopic dermatitis but no flare-ups within the previous year, and in two of the three cases, the parents had suspected that aluminium-rich food may cause skin symptoms in their children.

Interestingly, we did not observe any flare-ups in areas that had been patch tested previously, not even in children who were recently patch tested. A study by Hindsén et al showed that in patients who were allergic to nickel, a previous strong patch test reaction (+2 or +3) was correlated with flare-up reactions during oral nickel challenge.[27]

Other studies have shown that both dose and time elapsed since patch testing influence the risk of SCD reactions.[27,28] Perhaps the dose we used was too low and the exposure time too short to provoke significant symptoms.

Measuring daily exposure to a given metal is difficult, and many variables must be taken into account including bioavailability, individual sensitivity and mode of administration.[11,30] Because of the ubiquity of aluminium and the wide range of sources of aluminium exposure, we were unable to estimate the level of additional aluminium exposure due to the participants' regular diets. We sought to take this possible bias into account by performing urine analyses, showing an overall higher amount of bioavailable aluminium during our aluminium provocations compared with placebo.

Because only 15 children wished to participate, the statistical power of our study was limited. In addition, we could have used increasing aluminium doses to evaluate any dose dependency in VAS scores and cutaneous eruptions. However, we wished to mimic a realistic dose of aluminium and not to drastically exceed the recommended tolerable weekly intake.

CONCLUSION

We observed no statistically significant difference in neither granuloma itch, other subjective symptoms nor sleep duration between aluminium and placebo provocations, in our single-blinded controlled crossover study. Three children did develop a symmetrical rash on the buttocks or the face during aluminium provocations only. This indicates that cutaneous reactions following increased oral aluminium intake may occur in a minority of children.

ETHICS STATEMENT

The patients' guardians/parents in this manuscript have given written informed consent to the publication of their case details.

FUNDING INFORMATION

This study was funded by a grant from Kongelig Hofbundtmager Aage Bangs Foundation and by a grant to the National Allergy Research Centre from the Danish Environmental Protection Agency under the Ministry of Environments and Food.

CONFLICT OF INTEREST

None.

DATA AVAILABILITY STATEMENT

The data presented in this manuscript are available from the corresponding author upon reasonable request. The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ORCID

Stine Skovbo Hoffmann https://orcid.org/0000-0002-3983-2264
Jesper Elberling https://orcid.org/0000-0002-8925-4722
Jacob P. Thyssen https://orcid.org/0000-0003-3770-1743
Jeanne Duus Johansen https://orcid.org/0000-0002-3537-8463

REFERENCES

1. Fernandez-Lorenzo JR, Cocho JA, Rey-Goldar ML, Couce M, Fraga JM. Aluminum contents of human milk, cow's milk, and infant formulas. J Pediatr Gastroenterol Nutr. 2018;28(3):270–5.
2. Corkins MR, AAP Committee on Nutrition. Aluminum effects in infants and children. Pediatrics. 2019;144(6):e20193148.
3. Bergfors E, Hermansson G, Nyström Kronander U, Falk L, Valter L, Trollfors B. How common are long-lasting, intensely itching vaccination granulomas and contact allergy to aluminium induced by currently used pediatric vaccines? A prospective cohort study. Eur J Pediatr. 2014;173(10):1297–307.
4. Bergfors E, Inerot A, Falk L, Nyström U, Trollfors B. Patch testing children with aluminium chloride hexahydrate in petrolatum: a review and a recommendation. Contact Dermatitis. 2019;81(2):81–8.
5. Gente Lidholm A, Bergfors E, Inerot A, Blomgren U, Gillstedt M, Trollfors B. Unexpected loss of contact allergy to aluminium induced by vaccine. Contact Dermatitis. 2013;68(5):286–92.
6. Gente Lidholm A, Inerot A, Gillstedt M, Bergfors E, Trollfors B. 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. Contact Dermatitis. 2018;79(1):26–30.
7. Hoffmann SS, Elberling J, Thyssen JP, Hansen KS, Johansen JD. Does aluminium in sunscreens cause dermatitis in children with aluminium contact allergy: a repeated open application test study. Contact Dermatitis. 2022;86(1):9–14.

8. Kullberg SA, Ward JM, Liou YL, Atwater AR, Hylwa S, Neeley AB, et al. Cutaneous reactions to aluminum. Dermatitis. 2020;31(6):335–49.
9. Garg S, Loghdey S, Gawkrodger DJ. Allergic contact dermatitis from aluminium in deodorants. Contact Dermatitis. 2010;62(1):57–8.
10. Hoffmann SS, Wennervaldt M, Alinaghi F, Simonsen AB, Johansen JD. Aluminium contact allergy without vaccination granulomas: a systematic review and meta-analysis. Contact Dermatitis. 2021;85(2):129–35.
11. Veien NK. Systemic contact dermatitis. Int J Dermatol. 2011;50(12):1445–56.
12. Jacob SE, Zapolanski T. Systemic contact dermatitis. Dermatitis. 2008;19(1):9–15.
13. Veien NK, Hattel T, Laurberg G. Systemically aggravated contact dermatitis caused by aluminium in toothpaste. Contact Dermatitis. 1993;28(3):199–200.
14. Hoffmann SS, Thyssen JP, Elberling J, Hansen KS, Johansen JD. Children with vaccination granulomas and aluminum contact allergy: evaluation of predispositions, avoidance behavior, and quality of life. Contact Dermatitis. 2020;83(2):99–107.
15. Salik E, Løvik I, Andersen KE, Bygum A. Persistent skin reactions and Aluminium hypersensitivity induced by childhood vaccines. Acta Derm Venereol. 2016;96(7):967–71.
16. Glynn A, Lignell S. Increased urinary excretion of aluminium after ingestion of the food additive sodium aluminium phosphate (SALP) – a study on healthy volunteers. Food Addit Contam Part A. 2019;36(8):1236–43.
17. Yokel RA, Hicks CL, Florence RL. Aluminum bioavailability from basic sodium aluminum phosphate, an approved food additive emulsifying agent, incorporated in cheese. Vol 46. Bethesda, MD: NIH Public Access; 2008. p. 2261–6.
18. Younes M, Aggett P, Aguilar F, et al. Re-evaluation of aluminium sulphates (E 520–523) and sodium aluminium phosphate (E 541) as food additives. EFSA J. 2018;16(7):e05372.
19. Bruze M, Lundh K, Gruvberger B, Hindsén M. Aluminium chloride hexahydrate at 2% is insufficient to trace contact allergy to aluminium. Contact Dermatitis. 2008;59(3):183–4.
20. Johansen JD, Aalto-Korte K, Agner T, Andersen KE, Bircher A, Bruze M, et al. European Society of Contact Dermatitis guideline for diagnostic patch testing - recommendations on best practice. Contact Dermatitis. 2015;73(4):195–221.
21. Tietz T, Lenzner A, Kolbaum AE, Zellmer S, Riebeling C, Gürtler R, et al. Aggregated aluminium exposure: risk assessment for the general population. Arch Toxicol. 2019;93(12):3503–21.
22. Willhite CC, Karyakina NA, Yokel RA, Yenugadhati N, Wisniewski TM, Arnold IMF, et al. Systematic review of potential health risks posed by pharmaceutical, occupational and consumer exposures to metallic and nanoscale aluminum, aluminum oxides, aluminum hydroxide and its soluble salts. Crit Rev Toxicol. 2014;44(Suppl 4):1–80.
23. Bergfors E, Björkelund C, Trollfors B. Nineteen cases of persistent pruritic nodules and contact allergy to aluminium after injection of commonly used aluminium-adsorbed vaccines. Eur J Pediatr. 2005;164(11):691–7.
24. Krewski D, Yokel RA, Nieboer E, Borchelt D, Cohen J, Harry J, et al. Human health risk assessment for ALUMINIUM, ALUMINIUM oxide, and ALUMINIUM hydroxide. J Toxicol Environ Health B Crit Rev. 2007;10(Suppl 1):1–269.
25. Gräske A, Thuvander A, Johannisson A, Gadhasson I, Schütz A, Festin R, et al. Influence of aluminium on the immune system – an experimental study on volunteers. Biometals. 2000;13(2):123–33.
26. Cocker J, Mason HJ, Warren ND, Cotton RJ. Creatinine adjustment of biological monitoring results. Occup Med (Lond). 2011;61(5):349–53.
27. Hindsén M, Bruze M, Christensen OB. Flare-up reactions after oral challenge with nickel in relation to challenge dose and intensity and time of previous patch test reactions. J Am Acad Dermatol. 2001;44(4):616–23.
28. Jensen CS, Menné T, Lisby S, Kristiansen J, Veien NK. Experimental systemic contact dermatitis from nickel: a dose–response study. Contact Dermatitis. 2003;49(3):124–32.
29. Andersen KE, Hjorth N, Menné T. The baboon syndrome: systemically-induced allergic contact dermatitis *. Contact Dermatitis. 1984;10(2):97–100.
30. Yokel RA, McNamara PJ. Aluminium Toxicokinetics: an updated MiniReview. Pharmacol Toxicol. 2001;88(4):159–67.

How to cite this article: Hoffmann SS, Elberling J, Skamstrup Hansen K, Thyssen JP, Moertz CG, Overgaard Bach R, et al. Adverse reactions after oral provocation with aluminium in children with vaccination granulomas and aluminium contact allergy. J Eur Acad Dermatol Venereol. 2023;00:1–8. https://doi.org/10.1111/jdv.18811