ORIGINAL ARTICLE

Characterization of Classical Flexural and Nummular Forms of Atopic Dermatitis in Childhood with Regard to Anamnestic, Clinical and Epidermal Barrier Aspects

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Nummular (coin-shaped) and classical (flexural) atopic dermatitis differ morphologically, but no other distinguishing features are known. The aim of this study was to determine differences and similarities of both variants in children. Detailed interviews, clinical examinations, biophysical measurements and electron microscopic analyses were performed on 10 children with nummular atopic dermatitis, 14 with classical atopic dermatitis and 10 healthy controls. Nummular atopic dermatitis affected more boys than girls and manifested less frequently within the first year of life than classical atopic dermatitis. Localization, distribution and morphology of the eczema varied more over time, and expression of keratosis pilaris was more severe in children with nummular atopic dermatitis. Both disease groups showed reduced hydration, increased transepidermal water loss and reduced intercellular lipid lamellae in lesional skin areas compared with non-lesional areas. These findings underline the separate classification of both variants. Further research is necessary to investigate the potential of diverging therapeutic approaches.

Key words: atopic dermatitis; nummular eczema; children; epidermal barrier.

Accepted Dec 22, 2021; Epub ahead of print Dec 22, 2021

Acta Derm Venereol 2022; 102: adv00664.

DOI: 10.2340/actadv.v101.979

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SIGNIFICANCE

Compared with the classical variant of atopic dermatitis with flexural eczema, the nummular subtype with coin-shaped lesions has received little attention. To uncover differences and similarities, this study compared both variants, with a focus on the skin barrier, using biophysical measurements and electron microscopy. It was found that the impaired integrity of the epidermal barrier known to occur in the classical variant can also be detected in the nummular variant. Differences occurred in sex ratio, initial manifestation, variability over time, and expression of keratosis pilaris. These results underline the need to distinguish the nummular variant of atopic dermatitis from the classical one.

Atopic dermatitis (AD) is a chronic, inflammatory skin disease with globally high prevalence. In Europe, the 1-year prevalence of doctor-diagnosed AD in children ranges from 1.8% to 18.6% (e.g. 8.4% in Germany, 18.6% in Spain), varying by study and region (1, 2). It usually begins in early childhood and often leads to a severe reduction in the quality of life of patients and their relatives (3, 4). Clinically, AD is usually characterized by dry skin, severe pruritus, and recurrent eczematous lesions (acute or chronic). The morphology of these skin lesions is highly heterogeneous (5, 6). The classical variant of AD (CAD) manifests in the form of an eczema in the flexures. In contrast, the nummular variant (NAD) manifests with coin-shaped lesions, primarily on the legs, and less commonly on the trunk and arms (7–9). Clinical experience shows that NAD is more often refractory to therapy than is CAD (8). Thus, there may also be differences between both variants, for example, in medical history (including initial manifestation, temporal changes, comorbidities and family history), in other clinical characteristics (including atopic stigmata) or in the structure and function of the epidermal barrier. However, apart from morphology, it is unclear how NAD differs from CAD.

The key factors in the multifactorial pathophysiology of AD, in general, are a dysfunctional skin barrier, dysregulation of the immune system (including TH2-lymphocyte-dominated cutaneous inflammation), and a dysbiosis of the microbiome. The complex interplay of these mechanisms is substantially influenced by genetic and environmental factors (5). The impaired epidermal barrier results from altered expression of epidermal barrier proteins, such as filaggrin and other cornified envelope proteins. In addition, changes in lipid composition, such as altered content and composition of ceramides, and disruption of intercellular lipid lamellar organization in the stratum corneum (SC) play a role (5, 10–12). Skin barrier defects in AD are reflected by decreased skin hydration and increased transepidermal water loss (TEWL). Furthermore, electron microscopy can be used to visualize the disturbed integrity of the skin barrier (10, 13, 14).

The aim of this study was to identify characteristics in addition to morphology to distinguish between NAD and CAD, and to identify possible differences in the underlying pathomechanisms. For this purpose, anamnestic, clinical and epidermal barrier aspects were compared between children with NAD and CAD as well as healthy controls (HC). A better understanding of the characteristics of NAD and CAD is the basis for deriving more targeted diagnostics and more precise therapies adapted to the different variants of AD.

MATERIALS AND METHODS

Subjects and study design

The investigation was conducted on 10 children with NAD (age 1–9 years, mean ± standard deviation (SD): 4.50 years ± 2.37, 2 females and 8 males), 14 children with CAD (age 1–10 years, mean ± SD: 5.07 ± 2.84 years, 6 females and 8 males) and 10 healthy controls (age 1–10 years, mean ± SD: 5.40 years ± 3.1, 6 females and 4 males). Patients were selected with consideration for an even age distribution in all study groups, while the sex distribution in the groups was random. The patients were recruited from the patient registry of the Department of Dermatology, Venereology and Allergology, University Hospital Schleswig-Holstein (UKSH), Campus Kiel, Kiel, Germany. The diagnosis of AD was based on the criteria of Hanifin & Rajka from 1980 (15). Subsequently, patients were classified into groups with NAD and CAD, based on the morphology of the eczema (nummular vs flexural). Because the forms of eczema occur on different parts of the body, the examinations had to be performed at different body sites: for the NAD group at the lower leg, thigh, back, lower forearm and gluteal; for the CAD group on the inner sides of arms and legs, mostly in the flexors; for the HC group examinations were carried out at the lower forearm. Biophysical measurements and sampling for electron microscopic examinations were performed on both lesional and non-lesional skin areas directly next to each other (representative images of the investigated skin regions are shown in **Fig. 1**). Patients were instructed to stop topical treatment with glucocorticoid or calcineurin inhibitor-containing products on the day of investigation. Furthermore, they were instructed that the skin should not be washed with soap or treated with skin care products on this day. The study was carried out at the Department of Dermatology, Venereology and Allergology, University Hospital Schleswig-Holstein, Campus Kiel, Kiel between November 2015 and May 2016. Written and informed consent was obtained from the parents of the participants before starting the examinations. The study was approved by the local ethics committee of the medical faculty of the Christian-Albrechts-University of Kiel on 9 November 2015.

Medical history

Personal data, such as sex, age and body measurements, were collected from all patients. Regarding the patients' medical history, information about the initial manifestation of AD and changes in localization, distribution and morphology of the eczema over the patient's lifetime was requested. In addition, patients were asked about doctor-diagnosed atopic comorbidities, such as allergic asthma, allergic rhinitis and food allergies, as well as the family history. For evaluating the disease-related quality of life, we used the age-related quality of life questionnaires (IDQOL, CDLQI) and the family quality of life questionnaire (FDLQI), developed by the Department of Dermatology, Cardiff University (16–18). All questionnaires have a maximum score of 30, equivalent to the greatest possible impairment of quality of life.

Clinical examination

For assessing disease severity, "Severity Scoring of Atopic Dermatitis" (SCORAD) was used. Application of the SCORAD includes the evaluation of spread and intensity of AD as objective parameters, as well as pruritus and sleep loss due to the eczema as subjective parameters (19). The manifestation of atopic stigmata as Hertoghe's sign, Dennie-Morgan-fold or keratosis pilaris was measured in a severity degree from 0 (not present) to 3 (maximal manifestation).

Skin hydration and transepidermal water loss

The function of the epidermal barrier was investigated by instrumental measurements (20, 21): the Corneometer® CM 825 (Courage & Khazaka, Cologne, Germany) was used to determine the hydration of the SC and the Tewameter® TM 300 (Courage & Khazaka, Cologne, Germany) was used to measure the TEWL. For both methods, the conditions recommended by the manufacturers were considered.

Morphometric analysis of intercellular lipid lamellae

Non-invasive SC sampling using the Lipbarvis® method, sample preparation and analysis by transmission electron microscopy (TEM) were performed as described by Dähnhardt-Pfeiffer et al. in 2012 (14). The area of the intercellular space (ICS) and the length

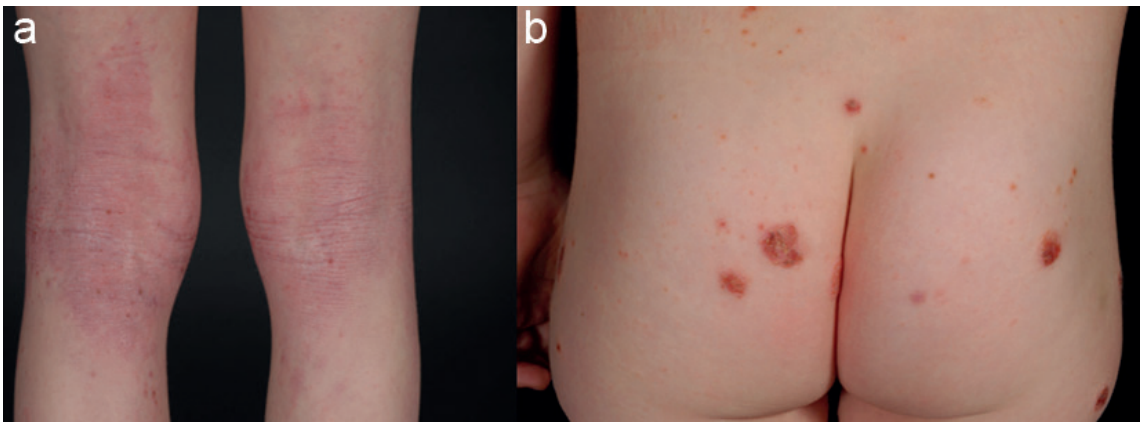

Fig. 1. (a) Classical (flexural) form and (b) nummular form of atopic dermatitis in children. Photographs from the Department of Dermatology, Venereology and Allergology, University Hospital Schleswig-Holstein, Campus Kiel, Kiel.

of the contained lipid lamellae (ICLL) were measured in nm^2 and nm, respectively. Subsequently, the ratio of ICLL to ICS was normalized to an area of 1,000 nm^2 to allow comparability of the samples (then labelled normalized ICLL=nICLL). Samples from 9 patients were analysed for all study groups (NAD, CAD, HC).

Statistical analysis

Statistical analysis and generation of graphs were performed using R 3.2.4 (R Core Team 2019) and SPSS Statistics 24 (IBM SPSS Inc. and IBM Co., Chicago, IL, USA). The χ^2 test and Fisher's exact test (if the expected frequency per cell was not > 5) were used to test for differences between nominal variables. To test for differences between 2 study groups, the 2-sample *t*-test for unpaired samples was used if normal distribution (tested with Shapiro-Wilk test and QQ plots) and homogeneity of variance (Bartlett test) of the compared data sets were given. The Mann–Whitney *U* test was used for not normally distributed data, and the Welch test was performed if variance of homogeneity was not given. In order to test for differences between lesional and non-lesional values within a study group, the 2-sample *t*-test for paired samples was carried out for normally distributed data, and the Wilcoxon test for not normally distributed data. Differences between 3 or more study groups were examined with an analysis of variance (ANOVA) when normal distribution and homogeneity of variance were given or with the Kruskal–Wallis test if the requirements were not met. All statistical tests were conducted 2-sided and at a significance level of 5%. Highly significant results are presented with $p < 0.001$. Mean values are always given with standard deviation (SD), unless otherwise stated.

RESULTS

Medical history

There was a sex imbalance in patients with NAD. Among the patients randomly selected in terms of sex, the proportion of males ($n = 8$) was higher than that of females ($n = 2$). This imbalance also exists in the total number of patients with diagnosed NAD in the pool of patients at the Department of Dermatology of UKSH (74% males, $n = 114$). In contrast, for the CAD, there was a more balanced sex ratio, both among the patients in the study (8 males, 6 females) and among the total number of patients with diagnosed CAD in the patient registry (58% males, $n = 283$). The difference in the sex ratio between NAD and CAD patients in the entire pool of patients was statistically significant ($p = 0.003$, χ^2 test).

The mean age of the first manifestation of AD was lower in patients with CAD (7.79 ± 9.07 months) than in patients with NAD (16.30 ± 15.36 months), but no significant difference was found between both groups ($p = 0.164$, Mann–Whitney *U* test). However, while in 12 of 14 CAD children AD manifested within the first year of life, in the NAD group only 5 of 10 children developed eczema within this period. When comparing whether the first manifestation was reported before or after completion of the first year of life, the difference between the NAD and CAD patients was significant ($p = 0.028$, Fisher's exact test).

Patients with NAD showed significantly more frequent changes in the localization, distribution, and morphology of eczema over time than patients with CAD ($p < 0.001$, Fisher's exact test). The appearance of the eczema had changed in 9 of 10 patients with NAD over time since the first manifestation: on the one hand in the morphology of the eczema (e.g. earlier in life more extensive eczema or flexural eczema), on the other hand in the localization (e.g. first arms and chest area affected, later the legs and at the time of examination exclusively back and face). In the CAD group, in only 1 of 14 patients did the appearance of the eczema change over time (in localization).

With regard to atopic comorbidities and the family history, there were no significant differences between the patients in the NAD and CAD groups. The survey of disease-related quality of life also showed similar results in both groups without significant differences (Table SI).

Clinical examination

The mean severity of AD, measured by the SCORAD, was, only slightly lower in patients with NAD (36.29 ± 12.17) than in patients with CAD (41.84 ± 13.70) with no significant difference between the 2 groups (**Fig. 2**).

In the survey of atopic stigmata, 6 of 10 patients with NAD and only 1 of 14 patients with CAD had a keratosis pilaris, but the frequency of occurrence was not significantly different. However, in the degree of keratosis pilaris, the patients with NAD were significantly more affected (0.90 ± 0.88) than the patients with CAD (0.07 ± 0.27; $p = 0.005$, Mann–Whitney *U* test). In the manifestation of the other atopic stigmata, there was no significant difference between the groups.

Skin hydration and transepidermal water loss

In both the NAD and the CAD groups, skin capacitance was significantly reduced at lesional regions compared with non-lesional regions (NAD lesional: 24.57 ± 10.17 AU, NAD non-lesional: 38.84 ± 9.82, $p = 0.001$; CAD lesional: 22.41 ± 12.22, CAD non-lesional: 36.39 ± 12.64, $p < 0.001$, t-tests for paired samples) and to the HC group (38.18 ± 8.96, NAD: $p = 0.005$, CAD: $p < 0.001$, *t*-tests for unpaired samples). TEWL was significantly higher for both NAD and CAD patients in the lesional areas than in the non-lesional areas (NAD lesional: 32.80 ± 18.27 g/h/m^2, NAD non-lesional: 8.42 ± 2.79 g/h/m^2, $p = 0.001$; CAD lesional: 30.28 ± 10.63 g/h/m^2, CAD non-lesional: 11.39 ± 3.93 g/h/m^2, $p < 0.001$, *t*-tests for paired samples) and compared with the HC group (9.70 ± 2.66 g/h/m^2, NAD: $p = 0.003$, CAD: $p < 0.001$, Welch tests). There were no significant differences when comparing skin capacitance and TEWL of the lesional regions from the NAD and CAD patients. Furthermore, there were no significant differences in skin capacitance and TEWL between the non-lesional areas of the NAD and CAD patients compared with the HC group (Fig. 2).

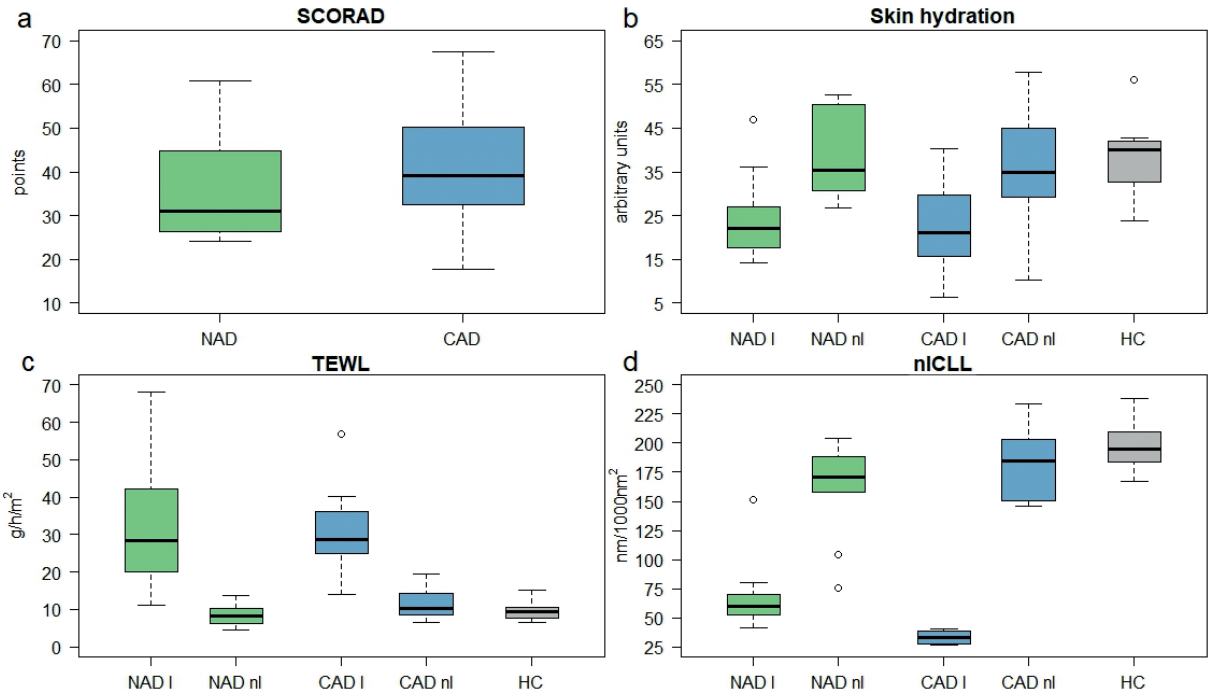

Fig. 2. Measurements from patients with nummular (NAD) and classical (CAD) form of atopic dermatitis (a–d) and healthy controls (HC) (b–d). (a) Severity of atopic dermatitis (SCORAD). (b) Skin hydration. (c) Transepidermal water loss (TEWL). (d) Normalized intercellular lipid lamellae length (nICLL). (b–d) All measurements for NAD and CAD patients on lesional (l) and non-lesional (nl) skin. For (a–c) $n = 10$ in NAD group, $n = 14$ in CAD group, $n = 10$ in HC group; for (d) $n = 9$ in all groups.

Morphometric analysis of intercellular lipid lamellae

The length of intercellular lipid lamellae (nICLL) was significantly reduced in the samples of lesional areas of both NAD and CAD groups compared with the corresponding non-lesional skin areas (NAD lesional: 68.40 ± 33.24 nm/1,000 nm², NAD non-lesional: 161.90 ± 44.12 nm/1,000 nm², $p = 0.008$; CAD lesional: 33.10 ± 5.84 nm/1,000 nm², CAD non-lesional: 182.40 ± 32.87 nm/1,000 nm², $p = 0.008$, Wilcoxon tests). Comparing lesional skin areas, nICLL lengths were significantly more reduced in patients with CAD than in patients with NAD ($p < 0.001$, Mann–Whitney U test). The length of nICLL in non-lesional skin in patients with NAD was significantly lower compared with HC subjects (198.50 ± 21.53 nm/1,000 nm², $p = 0.040$, t-test for unpaired samples). There were no differences in the lengths of nICLL between non-lesional skin of patients with NAD and patients with CAD, and between CAD non-lesional skin and HC subjects (Fig. 2). TEM images of the NAD, CAD and HC subjects are shown in **Fig. 3**.

All data for the results described are listed in Table SI.

DISCUSSION

Medical history

Based on the large patient register of the Department of Dermatology of UKSH, the results of this study emphasize that boys are slightly more affected by NAD than girls. As far as we know, no comparative data analysis exists for NAD in the literature. However, it is known that the sex ratio in AD is, in general, approximately balanced (22), which was also observed for the patients with CAD in the current study. Thus, the sex imbalance in patients with NAD could be a distinguishing feature of both variants, and further studies are needed to determine the underlying reasons. For other atopic diseases, such as allergic rhinitis and allergic bronchial asthma, a more frequent occurrence in boys has also been reported (23).

AD manifestation in the current study was more frequent within the first year of life in children with CAD than in those with NAD. Thereby, the initial manifestation of patients with CAD is, on average, earlier, and that of patients with NAD slightly later, than the general average reported for AD with a frequency of first manifestation of AD in the first year of life of 60% (24). Specific data on the initial manifestation of NAD do not exist in the literature.

Changes in localization, distribution or morphology of the eczema over time (since first manifestation) were reported to occur more frequently in the patients with NAD than in those with CAD. On the one hand, the current results suggest greater variability in the appearance of NAD compared with CAD. On the other hand, some variability in AD in general (especially with respect to age) is not uncommon (25).

The fact that the patients in both groups (NAD and CAD) also had other atopic diseases (allergic rhinitis, allergic asthma) with approximately the same frequency

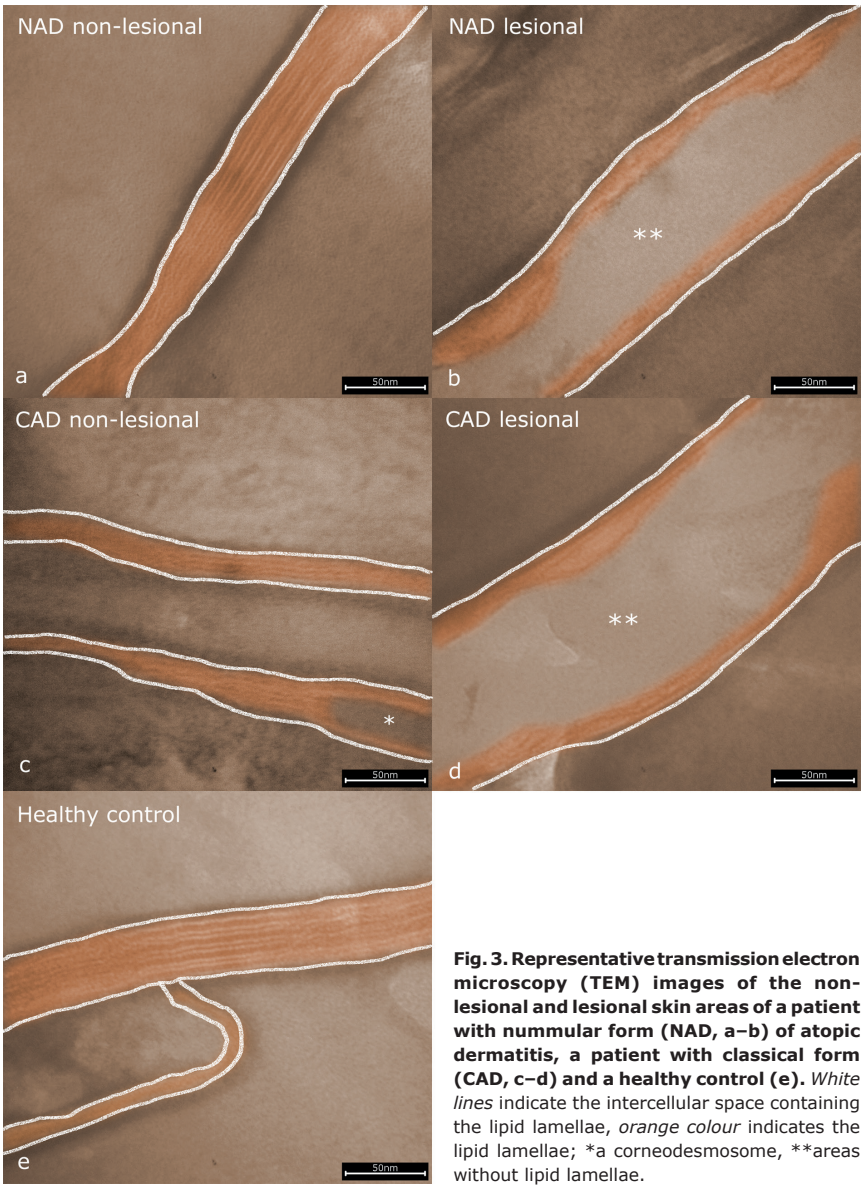

Fig. 3. Representative transmission electron microscopy (TEM) images of the non-lesional and lesional skin areas of a patient with nummular form (NAD, a–b) of atopic dermatitis, a patient with classical form (CAD, c–d) and a healthy control (e). *White lines* indicate the intercellular space containing the lipid lamellae, *orange colour* indicates the lipid lamellae; *a corneodesmosome, **areas without lipid lamellae.

and also had first-degree relatives with AD or other atopic diseases with a similar frequency underlines the common background of both disease manifestations and the clear affiliation of nummular eczema in childhood with atopy.

The examination of quality of life did not reveal any differences between NAD and CAD patients. Compared with data from the literature (available only for AD in general, not specifically for NAD), the levels of the quality of life indices of the NAD and CAD patients (IDQOL and CDLQI) were similar to those of other patients with AD (16, 17, 26, 27). Due to the different morphology, distribution and localization of the 2 forms of AD, as well as the partly different response to therapy, more different degrees of impairment of quality of life could have been suspected. However, the results imply that children with both variants suffer similarly from AD.

Clinical examination

The comparably high SCORAD scores in NAD and CAD patients indicate that children with both variants have similar severity of AD. At the same time, this improves the comparability of our other study results, as many of the parameters collected may be influenced by the severity of the AD. For example, severe AD is known to lead to greater impairment of quality of life (27) or biophysical parameters (28) than mild AD.

Patients with NAD had a more severe expression of keratosis pilaris than did patients with CAD. Keratosis pilaris is a keratinization disorder of the hair follicles, which is typical for AD as an atopy stigma, but not specific (7). The cause of the increased incidence of keratosis pilaris in NAD remains unclear for now, and requires further investigation. In particular, a filaggrin gene analysis could be informative, since an association of keratosis pilaris with mutations of the filaggrin gene is also known in ichthyosis vulgaris as well as in AD (29).

Skin hydration and transepidermal water loss

Decreased hydration and increased TEWL in the lesional areas of both NAD and CAD patients could be expected as an expression of a disturbed skin barrier compared with the non-lesional areas and the HC subjects (28, 30). However, to our knowledge, measurements specifically on patients with NAD were performed for the first time in this study. Surprisingly, not only the patients with AD showed dry skin in Corneometer® measurements, but also the controls. Here, a normal hydration state of the skin with values >40 arbitrary units would have been expected (31). This effect could be due to increased skin dryness caused by the climate in winter (7, 32). It might also be that the differences in both hydration and TEWL between non-lesional skin of patients with AD and skin of healthy controls are not yet as pronounced in children as in adults. A study by Eberlein-König et al. in 2000 (33), which was also performed in children, was also unable to show these differences. Most other comparative studies, which often showed differences between non-lesional skin of patients with AD and healthy skin,

were performed on adults (28, 30, 34, 35). Finally, the more intensive skin care in patients with AD (NAD and CAD) compared with HC subjects may have masked a potential difference in measurements.

It should be noted that various influencing factors can affect the measurements of hydration and TEWL (36). Efforts were made to reduce the effect of confounding factors, such as room temperature and humidity, in this study. However, even small variations, which are unavoidable in everyday practice, can lead to measurement inaccuracies. For both hydration and TEWL, a dependence on body site has also been described (37–39). Due to the different distribution patterns of NAD and CAD, performing the measurements on different body regions was unavoidable. At least with regard to TEWL, the deviations described predominantly concern the areas of palm, sole of foot, forehead or axilla. However, for the investigation areas mainly chosen in this study, i.e. forearm, upper arm, lower leg, thigh and back, largely comparable measured values are to be expected (38, 40).

The results show that decreased hydration and increased TEWL, as an expression of a disturbed integrity of the epidermal barrier, are as pronounced in NAD as in CAD.

Morphometric analysis of intercellular lipid lamellae

For healthy skin, mean nICLL values are reported as 200 nm/1,000 nm^2 (14) and are consistent with the results of the HC group in the current study. The NAD and CAD groups both had reduced nICLL lengths on lesional skin, as has been shown on atopic skin in previous studies (14, 41). These nICLL values were slightly higher in patients with NAD and slightly lower in those with CAD than the comparative values from the literature (40 nm/1,000 nm^2 to 50 nm/1,000 nm^2).

The reduction in intercellular lipid lamellae in both variants probably contributes to increased water loss through the skin and associated reduced hydration, as also shown by the measured hydration and TEWL values in the patients in the current study. The lower nICLL values in lesional than in non-lesional skin in NAD and CAD patients correspond to the results of biophysical measurements, which also show a greater impairment in lesional than in non-lesional skin for both groups.

Decreased nICLL values at non-lesional skin compared with the HC group have been shown only in NAD patients, not in CAD patients, although, in AD, damage to the epidermal barrier is generally assumed to occur not only in lesional skin, but also in non-lesional skin (13). It would be conceivable that differences in SC structure in paediatric patients with AD are not yet as obvious in TEM as in adulthood, because the damage to the skin by eczema has not yet lasted long enough. In principle, the results of the Lipbarvis® method are considered transferable from adults to children (14). A dependence of the method on different body sites does not seem to exist, in contrast to other measurement methods such as hydration and TEWL (14).

This study shows, for the first time, that the disrupted intercellular lipid lamellar organization known for AD in general is also detectable in NAD.

Strengths and limitations

The main strength of the current study is the focus on the nummular form of AD, which has hardly been studied before. New insights into this variant could be gained, and it was shown how great is the need for further research in this field. However, this pilot study has some limitations. Firstly, since it is difficult to recruit children for studies, the major limitation of this study was the small sample size. Secondly, since children need a special protection in clinical trials, not all patients were able to completely abstain from their therapy before the studies were conducted. Therefore, an influence of the previous treatment on the results cannot be excluded. Only on the day of the examination itself, no topical treatment was applied to any of the test patients. Thirdly, not all factors necessary for a more profound understanding of NAD could be considered in the current study. An additional investigation of the genetic level (e.g. role of the filaggrin gene), the immunological level (e.g. influence of immunological mechanisms) and the role of the microbiome could lead to further insights.

Conclusion

To our knowledge, NAD was extensively investigated in comparison with CAD in children for the first time. The current study highlights differences between both variants of AD in addition to morphology. For example, there was more frequent occurrence of NAD in boys and a greater variability of localization, distribution and morphology of eczema in NAD over time. Furthermore, the skin barrier impairment known to occur in CAD was also measurable in NAD. Since this is a pilot study, no diagnostic or therapeutic consequences can be drawn. Nevertheless, the results underline the separate classification of both variants. Follow-up studies are necessary, with a larger number of patients and investigations into genetics, immunology and microbiome.

ACKNOWLEDGEMENTS

The authors thank the patients and healthy volunteers for participating in this study. Furthermore, the authors would like to thank the staff of the AD outpatient department of UKSH Kiel for their support.

The authors have no conflicts of interest to declare.

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