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ORIGINAL ARTICLE

Atopy-related skin rash in a normal population of infants: Distribution and rates for 50 separate skin regions: Cohort study from 4 months to 3.5 years

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ABSTRACT

Analysis of the rash in a normal population of infants may give new information that is different from clinical observation of atopic dermatitis (AD). For this purpose, a cohort study was undertaken on infants at 4 months, 10 months and 3.5 years. Infants who attended the local health center for health check were the subjects. Rash related to AD, dryness, scaling, erythema, papules, exudation and crusts was recorded in 50 skin regions and divided into three degrees. Examination was performed twice a month for a year at each age. The 777 infants who attended all three examinations were analyzed in this report. Rash-positive regions were 14.7% on average at 4 months and decreased with age. Prevalence of rash-positive infants was 93.6% at 4 months and also decreased with age. The main findings are as follows. First, rash was more frequent and more severe in younger infants. This seems to suggest that AD in early infancy is initiated and developed by immune immaturity, and is resolved by its maturation. Second, rash involved preferentially air-exposed and air-closed skin in younger infants. This seems to be evidence that the epidermis of young infants is easily responsive to both dryness and wetness. Third, some regions did not show age-dependent reduction of rash rate in younger infants. Those regions are probably irritated by saliva and urine or rubbing and scratching.

Key words: atopic dermatitis, distribution, infants, population surveillance, skin rash.

INTRODUCTION

The distribution and morphology of skin rash in atopic dermatitis (AD) are important in understanding its pathophysiological mechanism.[1] However, the data obtained in clinical patients often include severe cases and therefore may incorporate exaggerated rash in some particular skin regions, and coexisting mild rash, such as slight dryness or redness in other regions, may be overlooked. If we examine the whole skin of infants in a normal population, we may be able to see mild skin rash in preclinical infants. It may provide a different view on the distribution of AD rash we see in clinical patients. In addition, if observation is repeated at three ages, more information on the understanding of skin rash of AD in young infants may be obtained. This is the reason we attempted a cohort study in a normal population of infants at three different ages, starting from 4 M.

In a previous paper, we preliminarily reported a cohort study dealing with infants aged 4–10 M in which age change and seasonal change of rash prevalence was described.[2] Cohort study was extended to 3.5 years (Y), and in this report, location of rash was analyzed in infants who attended all three examinations.

METHODS

By law, infants are requested to visit a health center (HC) for general health check at the ages of 4 M, 10 M, 1.5 Y and 3.5 Y in Japan. On three occasions during these visits, a dermatologist (T. F.) attended Fujiidera HC located in southern Osaka Prefecture. When the accompanying parent agreed, the infant's skin was examined in 50 specific regions to determine whether any skin rash related to infantile AD was present. The study was approved by the official committee in the Disease Prevention Department of Osaka Prefecture.

The examination was performed twice monthly for 12 M and included infants who had reached 4 M of age at each month. Examinations were also performed when the infants reached 10 M and 3.5 Y at 12 M each. The total time required to complete the examinations was 4 Y and 6 M (from September 1990 to October 1994).

Skin rash, including dryness, scaling, erythema, papules, exudation and crusts; were graded as follows: degree 1 (D1), mild erythema or dryness; degree 2 (D2), moderate erythema or papules with scaling; and degree 3 (D3), severe erythema or papules with exudation or crusts.

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Of the total population of 1775 infants born between May 1990 and April 1991 in the two cities (Fujiidera and Habikino), 1487 infants (83.8%) visited the HC between September 1990 and August 1991 at 4 M. The yearly number of visiting infants decreased to 1264 (71.2%) at 10 M and to 817 (46.0%) at 3.5 Y. In this report, 777 infants who attended all three examinations were analyzed, which corresponded to 43.8% of the infant population.

The rash grades for each of 50 regions of individual infants were entered into Microsoft Office software (Microsoft, Redmond, WA, USA) on a personal computer and analyzed. The total number of rashes graded as D1, D2 or D3 at individual skin sites in 777 infants was divided by 777 to obtain the average rash rates (prevalence) per year. There was no statistical difference between 777 infants and wider cohort infants in the composition of three degrees and also of four degrees that included no rash at all three ages.

Sex was not considered in this report.

The 50 skin regions were divided anatomically into four groups for convenience: head group (HD; 15 regions), transition group (TS; nine regions including buttocks), trunk group (TK; six regions) and arms/legs group (AL; 20 regions). Transition group includes the areas between HD and TK and between TK and AL.

Statistical analysis was performed by Mann–Whitney *U*-test except when otherwise stated.

RESULTS

Rash number distribution in individual infants

Rash number in individual infants varied greatly, ranging 1–31 at 4 M, 1–32 at 10 M and 1–39 at 3.5 Y. The most frequent number was six in 73 infants at 4 M, three in 95 infants at 10 M and one in 161 infants at 3.5 Y.

Average rash number per infant

The total rash number in 50 skin regions of 777 infants was obtained and averaged for individual infants. Rash number per infant (rash rate) was 7.5 of 50 (15.0%) at 4 M, 5.7 (11.3%) at 10 M and 2.4 (4.8%) at 3.5 Y. At each age, D1 rash was major, D2 rash was minor and D3 rash was rare (Fig. 1). Composition of the three degrees was not different (statistically insignificant) between 4 M and 10 M, and also between 10 M and 3.5 Y. This was the same even when the fourth component of no rash was added.

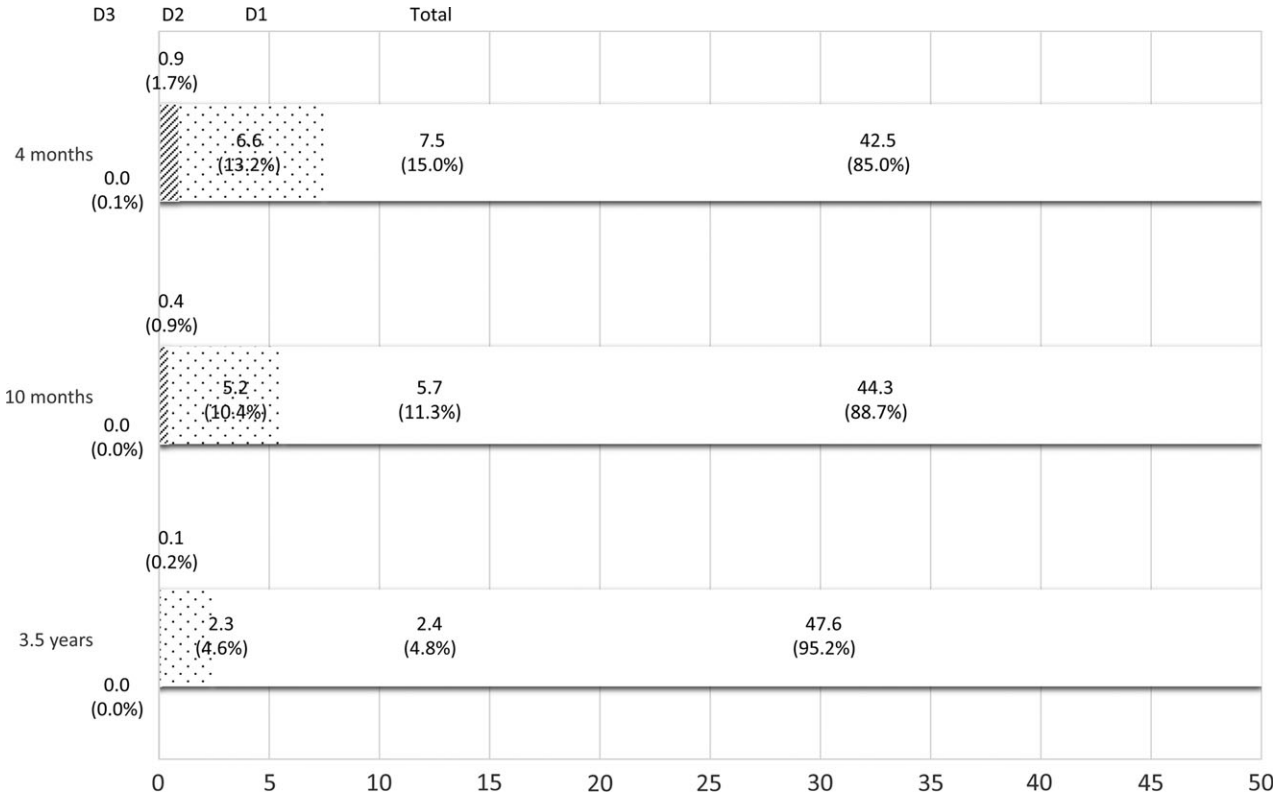

Figure 1. Graded rash number and rate in 50 separate skin regions per infant are shown. D1 (degree 1 rash; mild erythema or dryness) (light shade) was most prominent at 4 months (M), slightly decreased at 10 M and largely diminished at 3.5 years (Y). D2 (degree 2 rash; moderate erythema or papules with scaling) (dark shade) was much less than D1 with similar age change as D1. D3 (degree 3 rash; severe erythema or papules with exudation or crusts) was negligibly few through the three ages.

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Prevalence of total and different degrees of rash

The total number of infants with rash (total prevalence) was 726 (93.4%) at 4 M, 727 (93.6%) at 10 M and 466 (60.0%) at 3.5 Y (Fig. 2). Figure 2 summarizes the number of maximum degrees of rash in individual infants, which were averaged for 777 to obtain the prevalence rate. Prevalence of D1, D2 and D3 was compared between 4 M and 10 M and also between 10 M and 3.5 Y. Statistically significant difference ($P < 0.01$) was detected in both tests, indicating that rash was more severe at younger ages.

Total rash rates in each of 50 regions

The total rash number of 777 infants was summed in each of 50 regions and divided by 777 to obtain total rash rates in 50 regions. They were separated into three grades – very high rate (>30%; VR), high rate (10–30%; HR) and low rate (<10%; LR) – and shown in body charts for three ages (Fig. 3).

Very high rate regions were six of HD and three of TS at 4 M but decreased to three of HD at 10 M and never appeared thereafter. HR regions were two HD, three TS, five TK and two AL at 4 M, increased to three HD, six TS, five TK and three AL at 10 M, then decreased to one HD, zero TS, three TK and three AL at 3.5 Y. Others were all LR. Only cheeks remained VR through three ages.

In summary, the change of total rash rate in 50 regions by age preferentially involved HD and TS skin at 4 M, gradually resolved from there, and finally remained in limited regions of HD, TK and AL at 3.5 Y.

Analysis of three degrees of rash in 50 regions

Details of rash rate in 50 regions are described for each rash degree as line graphs in which three ages are shown concomitantly (Fig. 4). The D1 graph (Fig. 4a) shows similar line patterns as the total lines (not shown) through the three ages, though the rates were slightly reduced. The D2 graph shows (Fig. 4b) a much lower rate of rash, and that in the D3 graph (Fig. 4c) is negligibly low.

D1 rash. Degree 1 rash at 4 M was very high in several regions of HD and TS. Eight regions exceeded 30%: head, forehead, cheeks, chin, post-auricular regions, neck, axillae and femoral regions. While most of these regions reduced the

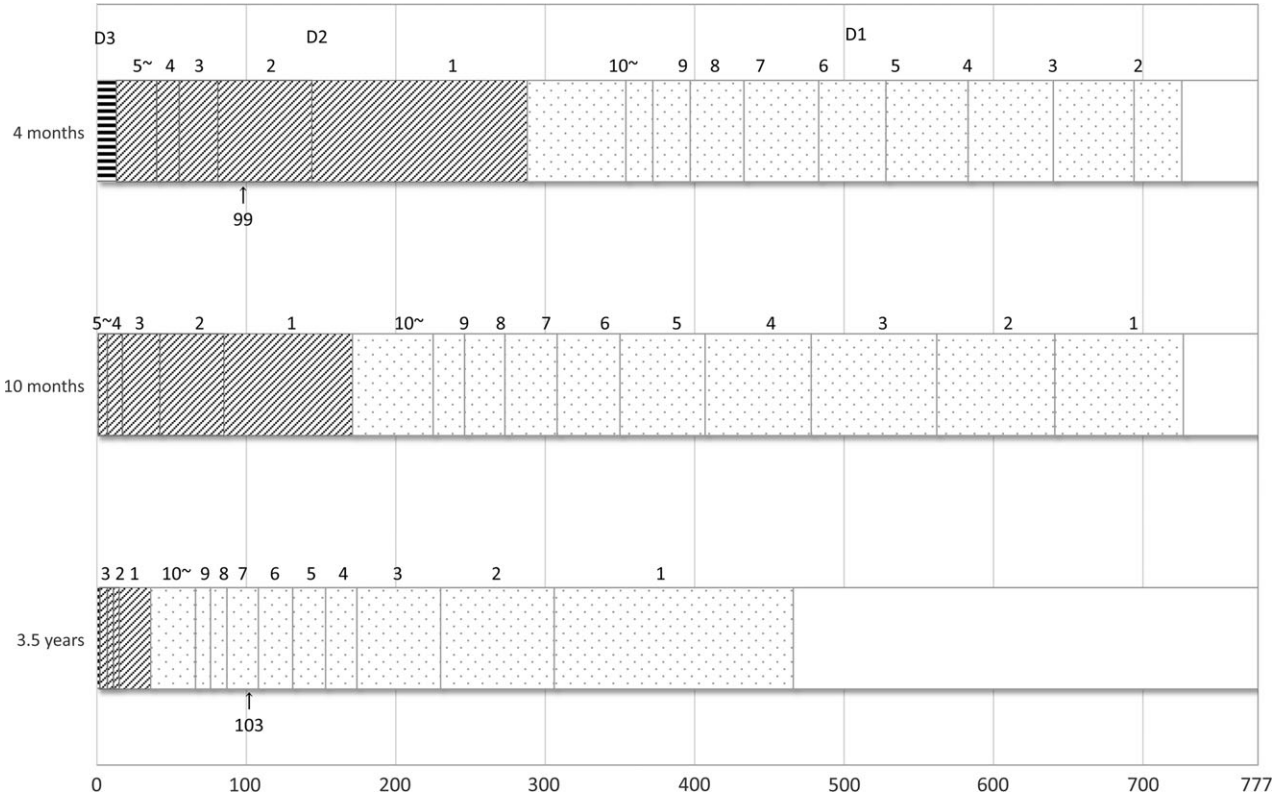

Figure 2. Prevalence of maximum degree rash at three ages are shown. Light shade shows D1, intermediate shade D2 and dark shade D3. Divided sections within each degree column indicate prevalence of different rash numbers that are shown above the column. Note that D1 rash may overlap within the D2 column, and D1 and D2 rash may overlap within the D3 column. Two arrows indicate the number of infants diagnosed with AD at 4 M and 3 Y of age in the Ministry of Health and Welfare (MHW study, 2000–2002) study. D1, degree 1 (mild erythema or dryness); D2, degree 2 (moderate erythema or papules with scaling); and D3, degree 3 (severe erythema or papules with exudation or crusts).

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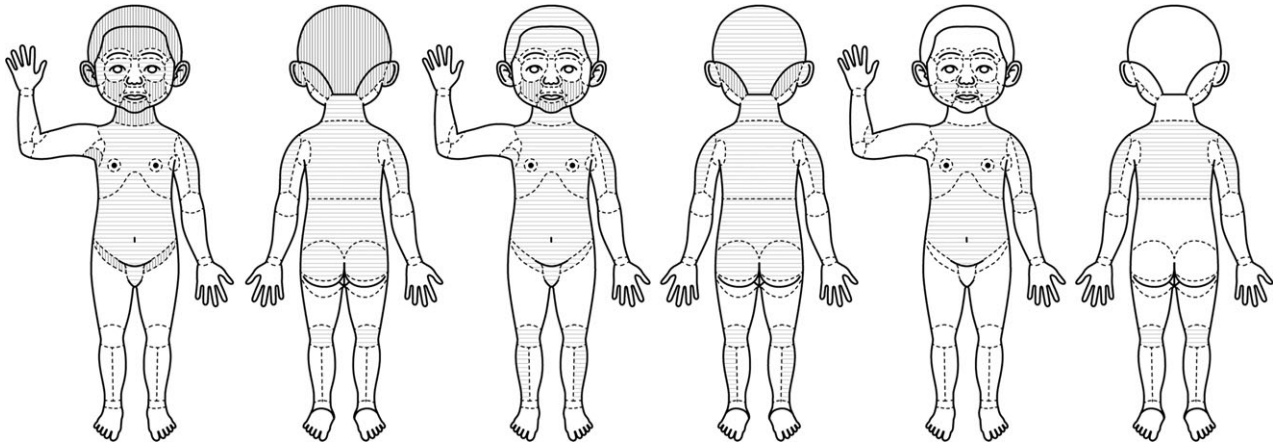

Figure 3. Body charts show rates of total rash at 50 regions at 4 months (M), 10 M and 3.5 years (Y). Vertical line shade indicates very high rate (VR; >30%), horizontal line shade high rate (HR; 10–30%) and no line low rate (LR; <10%). Note that rash predominantly involves head group (HD) and transition group (TS) skin at 4 M but they become less at 10 M and least at 3.5 Y. Trunk and flexural and external involvement was similar at the three ages.

rate to approximately half at 10 M, three regions – cheeks, post-auricular regions and chin – maintained the same rate. Other regions were high (10–30%) or low (<10%) at 4 M and also decreased to approximately half at 10 M. All regions except cheeks strikingly reduced in rate to only a few percent at 3.5 Y. Two regions of the diaper area, genital and perineal, were 15–20% at 4 M, went slightly up or down at 10 M, and dropped to a few percent at 3.5 Y.

Four TK regions – upper chest, upper back, lower frontal trunk and lower back – maintained relatively high rates of approximately 20% from 4 M to 10 M, and slightly decreased to approximately 10% at 3.5 Y.

In AL, outer upper arms and outer lower legs and also cubital and popliteal fossae showed relatively high rates in all three ages but others were low throughout the three ages. Popliteal and cubital fossae were the second and third top regions at 3.5 Y.

D2 rash. Degree 2 rash was much lower than D1 at all ages. Among them, scalp and cheeks exceeded 10% at 4 M. Other VR regions of D1 were 2–7% at 4 M and less than 2% at 10 M. Femoral and two diaper regions were low at 4 M but more than doubled at 10 M. Upper trunk (chest and upper back) was also relatively higher at 4 M. AL were all low and near 2% or lower through the three ages. At 3.5 Y, only cubital and popliteal fossae exceeded 1.5% and hips, backs of wrists and ankles were the third to fifth highest regions with rates of approximately 1%.

D3 rash. Degree 3 rash was very low in all 50 regions except cheeks, which was over 1%.

Short summary

The overview given in Figure 4 suggests that there is a general tendency of the rash to appear in at a high rate in selected regions of HD and TS at 4 M and, while the rate reduced, the rash gradually moved to TK and flexural and extensor regions of AL at 3.5 Y.

DISCUSSION

The purpose of this paper is to analyze skin rash observed in a normal infant population to better understand the rash in AD. Although real AD infants were thought to be included in this study, far more infants with milder rash formed the majority who may not be referred to as having been diagnosed with AD from a clinical point of view. The mild rash observed in this study may correspond to preclinical rash and more severe sections (D2 plus D3) may correspond to clinical AD rash.

Figure 4. Detailed description of rash rates at three ages in the 50 skin regions in order of skin groups: head group (HD), transition group (TS), trunk group (TK) and arms/legs (AL). All regions are shown in the body chart. (a) D1 rash was as follows: very high rate (VR; >30%) rash was noted in five regions of HD and three of TS at 4 months (M), of which three regions of HD maintained the rate till 10 M. High rate (30–10%) rash was noted in HD, TS, TK and in limited regions of AL at 4 M and 10 M. At 3.5 years (Y), all regions of HD and TS except the cheeks became low (<10%), and three regions of TK and three regions of AL were high; two of the latter – the cubital and popliteal fossae – are typical atopic dermatitis regions. Most of the AL regions were low rate through the three ages. (b) D2 rash in 50 regions were generally low rate except two regions of HD, the head and cheeks at 4 M, but several regions corresponding to high rate regions of D1 were relatively high within low rate range. Diaper regions were also so at 10 M. AL skin was very low at the three ages throughout. (c) D3 rash was negligibly small anywhere at any ages except the cheeks at 4 M.

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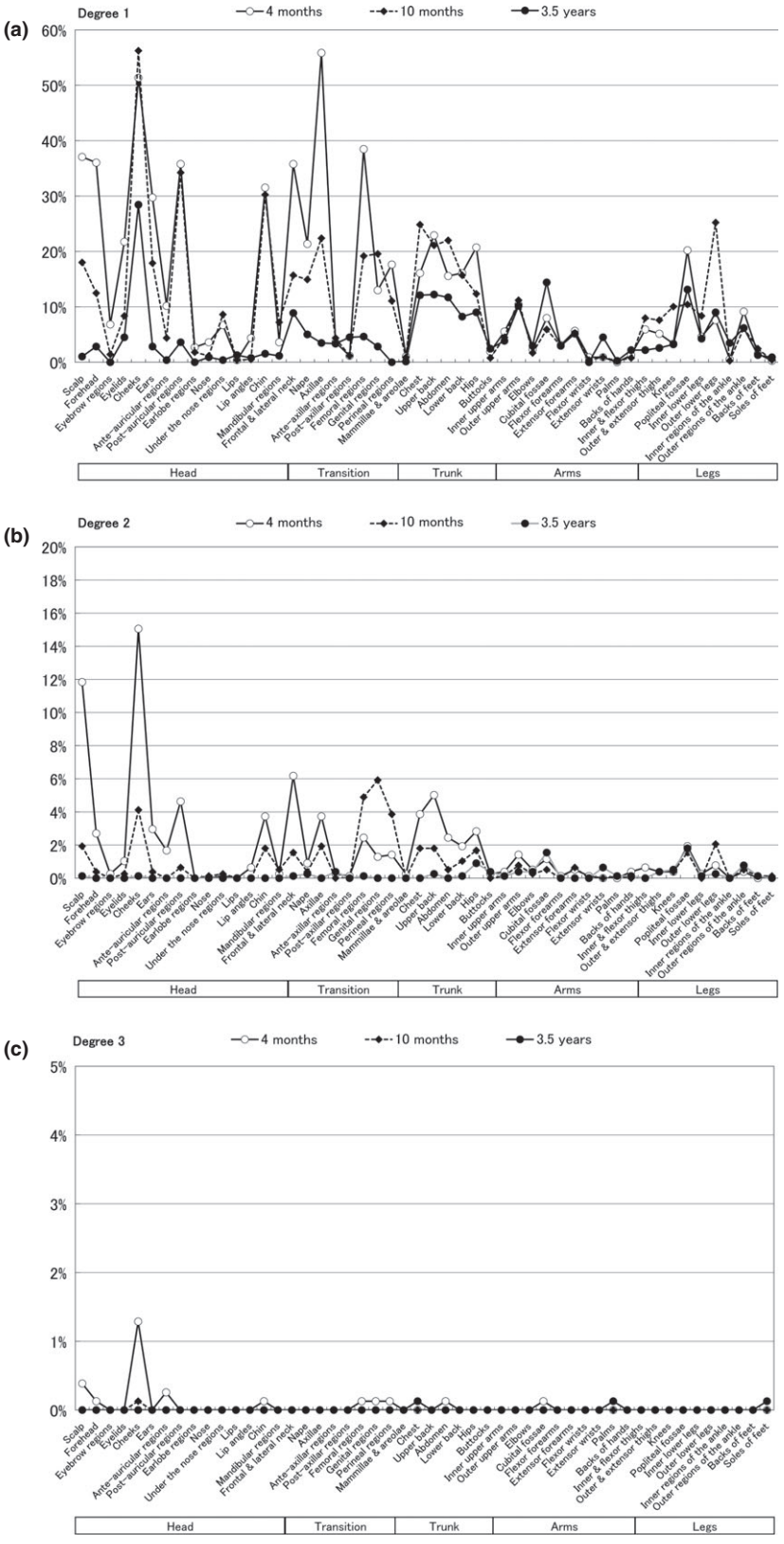

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Relation to AD prevalence rate in a population study

To give global understanding of the rash detected in this report, comparison was made with AD diagnosis rates in a country-wide population study of the Ministry of Health and Welfare (MHW study, 2000–2002) in this country where the prevalence rate was reported to be 12.8% at 4 M and 13.2% at 3 Y.[3] This corresponds to 99 infants at 4 M and 103 infants at 3.5 Y in this study, respectively. If AD diagnosis was applied to infants from the severe rash side of this study, the 99th infant had two D2 rashes at 4 M and the 103rd infant seven D1 rashes only at 3.5 Y, respectively (indicated by arrows in Fig. 2). This means that some of the infants with two D2 rashes in this study were excluded from AD diagnosis at 4 M, while infants with seven D1 rashes were included in AD at 3.5 Y.

Comparison with clinical studies

Rash recorded in hospital studies usually have very high rates.[4] For example, rash in cheeks reached over 80% at 3–5 M,[4] but this rate should not be compared with 67.7% of total rash recorded in cheeks at 4 M. Rash comparable with clinical AD is thought to be D2 in this study, which was 15.1% in cheeks at 4 M.

Degree 2 rash corresponding to well-known atopic makers in Hanifin and Rajka's diagnostic criteria,[5] cheilitis and nipple eczema was 0% (lips) at all ages and 0.3% (nipple) only at 4 M, respectively. However, "facial and extensor involvement in infants"[5] and involvement of face and scalp in young babies[6] were observed at very high frequency both in mild and more severe rash in our results. Facial involvement (all HD skin) of D2 was very high as 28.1% at 4 M but decreased to 8.1% at 10 M and to 0.3% at 3.5 Y. Extensor involvement of D2 in four regions (outer upper arm, extensor forearms, outer and extensor thighs, and outer lower legs) was rather low at 1.8% at 4 M, increased to 8.1% at 10 M and returned to 1.5% at 3.5 Y.

In addition, "flexural" involvement in younger infants[7] was also substantiated in this report. However, involvement of D2 in two flexures (cubital and popliteal) was also not very high at 2.8% at 4 M and 1.9% at 10 M but again increased to 2.6% at 3.5 Y.

MAIN FINDINGS

We propose three main findings which the authors believe useful for understanding the rash in AD. Discussion will be given to each, separately.

Rash was more frequent and more severe in younger infants. One of the important findings of this paper is that rash was more frequent and more severe in younger infants. This was noted in the number of D3 rashes in 50 regions (Fig. 1), in the prevalence rate of D3 rash in 777 infants (Fig. 2) and rash rate of D3 in 50 regions (Fig. 4).

Possible explanation. Initiation, development and resolution of AD in early infancy is mysterious and its process is not yet fully understood.

There does not seem to have been any specific population study on the initiation and development process of AD or related rash before 4 M.[8]

However, immaturity of immunity[9] and epidermal structure[10] and function[11] are without doubt the basis for the afferent process.[12] In fully developed AD, T-helper 2-dependent reactions[13] including food allergy[14,15] are working but this process may be only partial in milder cases.

The resolution process of infantile AD also occurs in early infants. More than half of AD-related rash at 4 M were cleared at 10 M[2] and more than 70% of AD diagnosed at 4 M disappeared at 3.5 Y.[3]

It is apparent that dramatic events of rash development and resolution are being preceded in early infancy.

Rash involved preferentially air-exposed and air-closed skin in younger infants. Very high rate rash of D1 in HD and TS at 4 M were characteristic regions. They could be classified either as air-exposed (dry) and air-closed (wet) skin. In addition, flexural skin, such as cubital and popliteal fossae, can be wet skin, while extensor skin, such as the outer upper arms and outer lower legs, can be dry skin. Diaper skin can also be wet skin.

It seems reasonable to think that VR rash of D1 in HD and TS at 4 M is an unusual phenomenon occurring in these regions in addition to the internal reasons described in the previous section. We believe that there should be some special local reasons for this.

Possible explanation for the rash in air-exposed skin. HD skin is always exposed to the air and is easily affected by high and low humidity or by high and low temperature. These may cause flushing or dryness of the skin resulting in D1 rash recorded in this report.

The barrier function of infant skin has been reported to be immature,[16–18] suggesting that air-exposed skin loses water more easily. However, infant subjects were often aggregated into one study group or are included within a larger age range, resulting in infants aged 4 M and 10 M rarely being dealt with separately.

On this subject, Nikolovski *et al.*[19] presented valuable data on the function of the stratum corneum (SC) of infants aged 1–12 M in comparison with those aged 14–73 M. However, the data does not seem adequate to prove increased permeability of the SC at this age, with regard to the study of Saijo *et al.*[20] who demonstrated that "larger values of transepidermal water loss (TEWL) and conductance in the first year of life" can be caused by sweating. Consequently, no data were obtained about easier loss of water from healthy infant skin.

On the other hand, TEWL was reported to decrease in a dry environment,[21] associated with an increased number of SC layers and increased epidermal thickness. This suggests that the primary step of AD-related rash in air-exposed skin may be an exaggerated defense mechanism of immature SC to a dry environment.

Possible explanation for the rash in air-closed skin. All TS are skin-to-skin contact regions closed to the air, because of short

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neck, fixed arms and legs in early infancy. TK and AL skin is always covered with clothes at 4 M, except the legs that may be exposed in summer or at later ages.

For many years, skin occlusion has been known to damage epidermal barrier function and to increase percutaneous absorption.[22] Electron microscopy has revealed that the horny layers of the human skin are swollen with both water and urine,[23] forming many vacuolated pools. Thus, the high rash rate in the air-closed wet portions is thought to be the result of damage to the SC caused by high humidity. The high absorbency of water by the skin of infants aged 3–12 M[19] supports this view. Soaps and detergents damage air-closed skin further raising the rash rate there.[24] Microbes, especially *Staphylococcus aureus*, are also important as a secondary aggravating factor.[25]

Some regions did not show age-dependent reduction of rash rate in younger infants. Most regions with VR rash of D1 in HD and TS steeply dropped from 4 M to 10 M, exempting three regions: cheeks, chin and post-auricular skin. This is not an anecdotal event but suggests that the rash at particular regions can be modified by external causes in younger infants that might often be overlooked in clinics dealing with severe AD.

Possible explanation. As stated before, VR rash at 4 M itself is possibly related to immaturity of immunity, but the limited location of high rate rash seems to require additional explanation. We need to find some new factors inhibiting the reduction of rate. Possible factors are saliva and sweat. Saliva discharge usually starts at approximately 3 M of age and lasts till approximately 7 M. At the same time, babies start sucking and licking of their fingers, toys, clothes and everything around them. In addition, babies start taking solid food at approximately 7 M. These induce saliva contacting the skin, and change dry skin to wet skin, particularly the cheeks and chin.

The delay of rate reduction at post-auricular regions may be explained by increased sweating. Marked rate elevation of D2 at 10 M in the femoral and two diaper regions is probably due to increased urination.

Strength and limitations of the study

Examination of infants was performed twice monthly for 12 M and was repeated three times (a total of 72 occasions) by an expert dermatologist (T. F.). Therefore, there is no inter-examiner difference in rash evaluation but intra-examiner variation may exist between evaluation of different infants and also at different times during the examination period ranging 4.5 Y. Also, repeatability of rash evaluation was not tested.

As already mentioned, there was no statistical difference in composition of the three degrees between 777 infants and infants of the larger cohort at all three ages, however, D1, D2 and D3 rash was more frequently observed in the 777 infants than infants who did not attend later examination ($P < 0.01$) at 4 M, when infants without rash were first added to the statistical testing. This indicates that infants with rash attended the HC more frequently than infants without rash at 10 M and 3.5 Y.

In addition, a larger cohort at 4 M covered only 83.7% of the birth population. The possibility remains that infants who were already diagnosed with AD did not come to the HC at 4 M, or inversely they came more eagerly to the examination through the three ages. This cannot be determined.

Concluding remarks

Our analyses showed standard rash distribution and rate of AD-related rash in a normal infant population in this country. This report gives new insight underlining the rash of AD in young infants under 1 Y of age. It disclosed a high rate of mild rash in various locations of the body possibly overlooked in clinical observation. Rate change of rash by age suggests importance of environmental factors that affects initiation, continuation and persistence of AD in early infants.

We hope that similar studies will be undertaken in other countries to allow international comparisons and reveal the factors that influence the occurrence of AD skin rash.[26]

ADDENDUM

Eczematous rash occurring in wet regions have been termed intertrigo that means “between” plus “to rub” in Latin. However, no particular term has been given to the rash occurring at outer and dry regions. It is our proposal to call it *extersicco* that means “outside” plus “dry” because the term is useful to understand the remaining half of the characteristic location of AD-related rash.

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CONFLICT OF INTEREST: The authors declare no conflict of interest

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