Fewer Melanocytic Nevi Found in Children With Active Atopic Dermatitis Than in Children Without Dermatitis

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Objective: To investigate the effects of atopic diseases on nevus development during childhood.

Design: A descriptive survey of nevi in a cohort of 8- and 9-year-old children combining a skin examination and a validated questionnaire regarding atopic dermatitis, allergic rhinoconjunctivitis, and bronchial asthma.

Setting: Fifty-one primary schools in Sweden.

Participants: A total of 788 children born in 1992 participated in 1999 in a prevalence study of allergic diseases. The present study was restricted to the 545 children from that study who were still living in the community, and 515 (94%) of them participated. The cumulative incidence of atopic dermatitis, allergic rhinoconjunctivitis, and bronchial asthma was 24%, 12%, and 13%, respectively, from birth to age 7 years as reported by questionnaire; 3% reported all 3 diagnoses.

Results: Children with reported atopic dermatitis and findings of active dermatitis on examination had fewer nevi (median, 4; mean, 7.4) than children with no reported atopic disease and no active dermatitis found on examination (median, 9; mean, 11.2) (P<.001). Children who developed active atopic dermatitis after the questionnaire was filled out (ie, during the last 2 years) had fewer nevi than children with no atopic disease (median, 3; mean, 5.3) (P<.001). There was no difference in nevus number between the children with bronchial asthma or allergic rhinoconjunctivitis and children with no atopic disease.

Conclusion: Children with atopic dermatitis had few melanocytic nevi, which suggests that the proinflammatory cytokine network in the atopic skin might inhibit melanocyte growth and/or progression to nevi.

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The incidence of cutaneous malignant melanoma is increasing. There is a strong positive correlation between the number of melanocytic nevi in adults and melanoma risk, and high nevus frequency in early age may predict high risk of melanoma. Most melanocytic nevi are acquired, and UV light is the most obvious environmental agent inducing genetic damage and proliferation of melanocytes in the skin. An increased number of melanocytic nevi, as well as an increased melanoma risk, has been shown to be related to sun exposure, especially during childhood.

Atopic dermatitis is a pruritic inflammatory skin disease that often starts in the first years of life and is commonly treated with moisturizers, topical steroids, and UV light. Treatment with artificial UV light is not routinely used in children and adolescents with atopic dermatitis. Broberg and Augustsson found that adults with severe atopic dermatitis, although most of them had undergone UV treatment regularly, had few melanocytic nevi. With the intention of gaining more knowledge about effects of inflammation on nevus development, we investigated nevi in children with atopic dermatitis.

We have previously described the frequency and distribution of melanocytic nevi in 8- and 9-year-old children living in the Linköping area. The present study examines nevi in children with allergic diseases within that cohort by combining a standardized questionnaire regarding symptoms of allergy with a skin examination.

METHODS

This study was approved by the ethics committee of the medical faculty in Linköping, Sweden. The population from which we enrolled children consisted of 788 children, and...
46% of all children born in Linköping in 1992. In 1998, this population participated in a study of the prevalence of allergic diseases in the community, which involved the parents completing a questionnaire regarding symptoms from the skin, nose, eyes, and bronchi.14 This questionnaire was a Swedish version of a validated protocol for allergy diagnosis from the International Study of Asthma and Allergies in Childhood Committee (ISAAC). An English version of this protocol has been published by Asher et al.15

In the present study, the diagnosis of atopy was based on the parent’s answers in the questionnaire from ISAAC.14,15 The questionnaire consisted of 6 questions regarding symptoms from the skin, 8 questions referring to bronchial symptoms, and 6 questions on symptoms from the eyes and nose. Atopy was defined as the presence of at least 1 of the following diagnoses: atopic dermatitis, allergic rhinoconjunctivitis, or bronchial asthma.

A written consent form was required to participate in the study and was signed by at least 1 of the parents. The skin examination was performed during the winter season (October-March) 2000-2001 by 2 experienced dermatologists (I.S. and I.R.) at 51 primary schools during 38 days.

SKIN EXAMINATION

Prior to the start of this study, the investigators together reviewed numerous nevi in children with the goal to standardize the counting. No intranidividual counting was performed. All children had a total body skin examination. All well-circumscribed brown flat or raised lesions with a distinct border and a diameter of 2 mm or larger (measured by overlaying a 2-mm stencil of a circle) and clinically diagnosed as melanocytic nevi were counted on all body sites including skin folds, palms, soles, scalp, and genital skin areas. The regional distribution of nevi was registered using a schematic body chart divided into 16 areas (A-P), and the number of nevi was registered separately in each area (Figure 1). The areas were outlined taking clothing habits and general UV exposure pattern into account. Areas A (face) and F (dorsal surfaces of the hands) were considered to be chronically UV exposed, and areas C (medial aspect of the arms), H (lower abdomen and genitalia), and J (buttocks), rarely UV exposed. With the exceptions of areas B, E, and P (scalp, palms, and soles), the remaining areas were considered intermittently exposed to UV light. These latter areas are usually covered by clothes and are UV exposed only in the short summer period or during holidays in summer climates. Active atopic dermatitis on the day of examination was diagnosed by the criteria of Hanifin and Rajka.11 Hypopigmentation and areas with atopic dermatitis were registered in a schematic figure, and the extension was estimated by using the size of the child’s own palm to represent approximately 1.25%16 of his or her total body surface. Fitzpatrick skin types were used for categorization. Hair color was registered in 4 categories: blond, brown, black, or red; eye color was registered in 3 categories: blue/gray, green, or brown. Skin types I and II were pooled when analyzed as were types III and IV.

STATISTICAL ANALYSIS

For comparison between groups we used the Wilcoxon rank-sum test (Mann-Whitney); for comparison between more than 2 groups, we used the Kruskal-Wallis test. The statistical analyses were performed with Stata version 7.0 (Stata Corp, College Station, Tex).

RESULTS

We decided to limit our study to those 545 children living within 25 km of the city of Linköping. In all, 515 (94%) of 545 were examined, 275 boys and 240 girls (Figure 2). One of us (I.S.) examined 442 subjects, and another (I.R.), 73. There was no significant difference in nevus counts between these 2 subpopulations; therefore, the data were pooled.

Figure 1. The regional distribution of nevi was registered using this schematic body chart divided into 16 areas (A-P), and the number of nevi was registered separately in each area.

Figure 2. Flow diagram of study design. Atopic dermatitis (AD) was reported by parents when children were 7 years old.
REPORTED ATOPIC DERMATITIS, ALLERGIC RHINOCONJUNCTIVITIS, AND BRONCHIAL ASTHMA

Details of the questionnaire-reported prevalence of atopic dermatitis, allergic rhinoconjunctivitis, and bronchial asthma at age 7 years are given in the Table. Forty-five children (9%) reported both atopic dermatitis and either allergic rhinoconjunctivitis or bronchial asthma, and 15 (3%) reported all 3 diagnoses. Most of these children had active atopic dermatitis on examination (27 of 45 and 10 of 15, respectively; Table) and a wide extension of eczema. A total of 283 children (55%) did not report any of these diagnoses and did not have an active atopic dermatitis on examination. This group of children was used as the reference group and compared with other groups of children in all analyses except for the analysis of the correlation between the extension of atopic dermatitis and total nevus counts in which the reference group consisted of the 405 children without active atopic dermatitis on examination.

A total of 110 (21%) of 515 children had active dermatitis on examination. Of the 124 children with atopic dermatitis reported during their first 7 years of life, 55 (44%) displayed atopic dermatitis and 55 children with no report of atopic dermatitis had active atopic dermatitis on examination. The dermatitis was itchy and primarily situated at typical locations for atopic dermatitis such as the flexures. Ninety-five of 110 children had dermatitis either around the arm or knee folds or both. The other 15 subjects had involvement of the trunk, buttocks, thighs, or face.

ATOPIC DERMATITIS AND NEVUS COUNTS

Children with questionnaire-reported atopic dermatitis and active dermatitis on examination had significantly fewer nevi (median, 4 nevi) than the group of children with no reported allergy and no dermatitis on examination (median, 9) (P < .001) (Table). Similarly, children with no reported atopic dermatitis but active dermatitis on examination had fewer nevi than the reference group (median, 3 nevi) (P < .001). Children with active dermatitis at the time of examination (n = 110) had a wide variation in number of nevi (0-42) with a median of 4.3 nevi. Seventy-five percent of these children had 8 or fewer nevi. The corresponding range for the children with no atopic disease was 0 to 79, and 47% had 8 or fewer nevi. When the nevus count was related to present extent of dermatitis, it was found that children with approximately 2.5% of their body surface or more affected by dermatitis had significantly fewer nevi than the children without atopic disease (Table).

LOCAL EFFECTS OF ACTIVE ATOPIC DERMATITIS ON NEVUS COUNT

Fewer nevi were found on children with active atopic dermatitis (n = 110) in most body regions than on children without atopy (n = 283). However, significance was reached only for areas A, C, D, G, I, K, M, and O (Figure 1). Children with active atopic dermatitis had lower nevus counts in area C (the medial aspect of the arms including the arm fold) (mean, 0.3) than did the children with no atopic disease (mean, 0.5) (P < .05).

BRONCHIAL ASTHMA AND ALLERGIC RHINOCONJUNCTIVITIS AND NEVUS COUNT

There was no significant difference in nevus number between children with the diagnosis bronchial asthma or allergic rhinoconjunctivitis and those without any allergic diseases (Table).

PHENOTYPE AND HYPOPIGMENTATION

Of the children with any of the allergic diseases reported, or active dermatitis on examination, 79% were blond, 77% were blue eyed, and 96% had skin types I or II. There were no significant differences in these phenotypic features compared with the group of children without active atopic disease (n = 283, 74% blond, 72% blue eyed, and 91% skin type I or II).

Local hypopigmentation in the skin was seen in 32 (6.2%) of 515 children. These areas were mainly situated on arm and knee folds corresponding to the localization of the former dermatitis and dry skin. The median total nevus count in these 32 children was 4.5. Twenty-four (79%) of those children had a reported atopic dermatitis, and 20 of them also had dermatitis on examination.
DISTRIBUTION OF NEVI IN RELATION TO UV EXPOSURE

Nevi distribution in relation to UV exposure was compared between the group of children with dermatitis (n = 110) and the children with no atopic disease (n = 283). Children with dermatitis had significantly fewer nevi in rarely exposed areas (C, H, and J; Figure 1) than did children without atopic disease (mean number of nevi, 0.6 and 1.0, respectively; P < .05). In chronically UV-exposed areas (areas A and F; mean number of nevi, 0.9 for children with dermatitis and 1.5 for those without), as well as in intermittently UV-exposed areas (areas D, G, I, K, L, M, N, and O; mean number of nevi, 4.7 for children with dermatitis and 8.6 for those without), children with dermatitis also had fewer nevi than children without atopic disease (P < .001). Areas B, E, and P were excluded from the analysis because it was not possible to classify these areas according to exposure pattern and because of the different nature of the skin in these regions.

COMMENT

This study examined nevi in 8- and 9-year-old children with atopy by combining a standardized, validated questionnaire regarding symptoms of allergy with a skin examination. Similar to previous findings in adults, we found children with active atopic dermatitis to have significantly fewer nevi than children without atopy. In a recent article by Dellavalle et al., 3-year-old children with a parental report of history of eczema were found to have more nevi than those without eczema. Unfortunately, our results cannot easily be compared with these findings because the diagnosis of eczema in the earlier study was based only on parental report, and no registration of eczema status was done at examination. In addition to children with atopic dermatitis, Dellavalle et al. included children with a history of other types of eczema as well. This might have had a profound impact on their results, since the profile of inflammatory mediators varies between different types of eczema and/or dermatitis, and so nevus development might also vary. Dellavalle and colleagues counted all nevi regardless of size, but it is not clear if any body sites were excluded. In addition, only 39% of the initially enrolled children were examined, compared with 94% in the present study.

There are also 2 limitations to the present study: (1) To minimize misclassification and to be able to compare our results with counts from children in European centers, we only counted nevi 2 mm across or larger. Certainly, it is much easier to count nevi in children than in adults; all the same, it is our experience that it is difficult to differentiate 1-mm nevi from freckles, especially if localized on the face or the lateral aspect of the arms. Most nevus studies in adults and children have limited the counts to 2 mm or larger, but in none of these studies are the reasons for this cutoff given. Neither is there any systematic study published on diagnostic accuracy for nevi of various sizes. (2) Some criticism might be raised that interrater reliability tests were not performed for nevus counts and assessments of eczema.

Neither were any intrarater reliability measurements performed. However, 2 experienced dermatologists performed the examinations. Before starting this study, the investigators clearly defined the diagnostic criteria for eczema and nevi and together assessed numerous nevi in children with the goal to standardize the procedure. It is unlikely that systematic differences in counting or diagnosing eczema between the examiners explain our results, since they remained the same whether data were pooled or analyzed separately.

Why children with atopic dermatitis have few nevi is not known, but the reason might involve genetic factors, altered immune responses, or influence of various treatments including topical steroids and UV irradiation. The time during which the child has had atopic dermatitis or been exposed to treatments might have some impact, and our finding that children with extensive atopic dermatitis have very low nevus counts might indicate that the eczema activity has some significance on the nevus profile. Interestingly, children with atopic dermatitis reported in the questionnaire but with no active dermatitis found on examination had counts not significantly different from children without atopic disease. This might be a group of children who had only minor dermatitis, but it cannot be excluded that the items targeted in the questionnaire were not specific enough to differentiate from other eczematous skin problems during the first years of life.

Children without atopic dermatitis but with reported bronchial asthma or allergic rhinoconjunctivitis had total nevus counts in the same range as the children with no atopic diseases. Therefore, we speculate that the formation of melanocytic nevi is influenced by a local and continuous inflammation in the skin. The T lymphocytes are key cells involved in the development of active dermatitis. T helper cells produce various cytokines such as interleukin (IL) 1, IL-4, IL-5, interferon γ, and tumor necrosis factor (TNF-α). Several of these cytokines inhibit melanocyte growth in vitro and have been shown to be paracrine inhibitors of human melanocyte proliferation. Interleukin 1, IL-3, IL-6, TNF-α, and granulocyte-macrophage colony-stimulating factor are produced in human melanocytes, and IL-1α, IL-1β, IL-6, and TNF-α are produced in melanocytic nevi. These cytokines might be involved in the regulation of melanocyte homeostasis. An altered balance between proinflammatory mediators might disturb the control of melanocyte proliferation and differentiation and influence formation as well as the maturation and elimination of nevi. Surprisingly, even children who had developed atopic dermatitis during the last 2 years had low nevus counts. An enhanced elimination of nevi in children with active atopic dermatitis during such a short time is less likely. Therefore, we suggest that the formation of nevi, which has been shown to be very active during this period of life, is rapidly slowed down by the inflammatory process in the skin.

In our previous study, we found children with light eye colors, blond hair, and skin types I and II to have more nevi than children with darker pigmentation. In the present study, most of the children with active dermatitis were blond haired and blue eyed and had skin type I or II, and there was no significant difference in these phenotypic
variables between children with and without eczema at examination. Despite the fair pigmentation, the children with active dermatitis had very low nevus counts.

In numerous studies, presence of a large number of nevi in childhood has been identified as a risk factor for melanoma. Furthermore, UV light plays an important role in the development of nevi. Data on UV exposure have not been targeted in the present study, but it is our experience that children with active dermatitis in Sweden are exposed to natural sunlight more than other children of their age. Despite this possibility, they have a low number of nevi and therefore probably a low risk of developing melanoma. However, strong evidence that subjects with active dermatitis have a reduced risk of developing melanoma is still lacking. That subjects with atopy might have a low risk of melanoma is suggested by the fact that only 4.2% of patients with melanoma reported atopic symptoms compared with 10% of healthy controls. However, Beral et al. found no difference in the cumulative incidence of eczema in patients with melanoma and age-matched controls.

In the present study, we have shown that children with active dermatitis have very few nevi compared with nonatopic children. This seems to be due to local effects in the skin, since nevus counts in children with bronchial asthma and allergic rhinoconjunctivitis are similar to nevus counts in children without any atopic disease. We hypothesize that the proinflammatory cytokine network in the atopic skin influences melanocytic growth and the progression to nevi.

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