

Clinical Communications

Hyperlinear palms as a clinical finding in peanut allergy

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Clinical Implications

- Hyperlinear palms were found to be more common in children with atopic dermatitis and peanut allergy, suggesting that this may be a clinical finding in food allergy. Clinicians should look for hyperlinear palms on examination.

It is well accepted that atopic dermatitis (AD) and peanut allergy (PA) are associated with filaggrin (*FLG*) mutations.^{1,2} Patients with AD with *FLG* mutations have more severe, more persistent, and earlier onset AD. AD onset typically precedes the development of PA.^{1,3} Recently, published findings by our group demonstrated that the nonlesional skin of children with AD with PA (AD PA+) has significantly lower filaggrin expression than the nonlesional skin of children with AD without PA (AD PA−). This was irrespective of *FLG* gene mutations and consistent with increased type 2 immune activation playing a role in reducing filaggrin expression.⁴ In addition, a birth cohort study of skin barrier function in infants reported that children with food allergy (FA) have increased transepidermal water loss (TEWL) in the newborn period, even if AD is not present, suggesting a role for the skin barrier early on in the development of food sensitizations.⁵ Clinical features of skin barrier abnormality in AD and *FLG* mutation include xerosis, hyperlinear palms (HP), keratosis pilaris (KP), and ichthyosis vulgaris (IV).^{6,7} HP reflect abnormalities in keratinization and can be defined as “more than 5 prominent lines longer than 1 cm running across” the palm, particularly in the area of the thenar eminence.⁸ In a recent study of Japanese children under 5 years, the presence of HP was associated with the development of sensitization to egg as determined by egg white specific IgE levels.⁹ In the current study, we examined associations between physical examination features, including the presence or absence of HP, KP, and IV in AD PA+, AD PA−, and nonatopic (NA) controls.

Children between the ages of 4 and 17 years were selected for this prospective, clinical mechanistic study. Sixty-two children, including 22 NA controls, 21 with AD PA+, and 19 with AD PA−, were enrolled. The groups were balanced based on AD severity, age (pre- vs postpuberty), gender, and race/ethnicity distribution. The mean age of subjects with AD PA+ was 10.8 years, and the mean age of subjects with AD PA− was 12.1 years. There was no difference in age between subjects with AD PA+ and those with AD PA− ($P = .2$). Peanut-allergic children were identified based on the following diagnostic criteria: peanut skin prick test wheal ≥ 8 mm and previous history of positive oral food challenge to peanut or convincing history of an immediate allergic reaction to peanut. Those who were considered NA had no history of a food-allergic reaction and had negative skin prick

tests (<3 mm) to multiple foods, including peanut, milk, egg, wheat, soy, shellfish mix, almond, walnut, hazelnut, cashew, brazil nut, and sesame seed. The children with AD were assessed for AD severity using the SCORing Atopic Dermatitis (SCORAD), Nottingham Eczema Severity Score (NESS), and Eczema Area and Severity Index (EASI), and both AD groups were balanced for AD severity using NESS scores. Physical examinations were performed by a board-certified allergist, and the presence of HP, KP, and IV was identified based on first glance. Severity scoring of these features was not done. Skin tape strip (STS) lipidomic and proteomic analysis was performed. To compare differences between the groups, Pearson's χ^2 test and the Mann-Whitney or Student's t -test were used for categorical variables and continuous variables, respectively. Data analysis was performed and/or validated by the National Institute of Allergy and Infectious Diseases DAIT Statistical and Clinical Coordinating Center at Rho Federal Systems Division.

Hyperlinear palms were identified in a total of total 16 patients, including 11 with AD PA+ (68.8%), 4 with AD PA− (25%), and 1 NA subject (6.2%) ($P < .01$, unadjusted logistic regression model) (see Table I). The occurrence of HP remained significantly greater in children with AD PA+ than in those with AD PA− even after adjustment for AD severity (either NESS, SCORAD, EASI score), age, gender, race, and body mass index ($P = .04$). In contrast, no association was found between KP and PA with 3 of 21 (14.3%), 4 of 19 (21.1%), and 7 of 22 (31.8%) subjects identified as KP+ among AD PA+, AD PA−, and NA subjects, respectively ($P = .38$). Also, no association was found between IV and PA with 1 of 21 (4.8%), 1 of 19 (5.3%), and 1 of 22 (4.5%) identified as IV+ among AD PA+, AD PA−, and NA subjects, respectively ($P = .99$). HP+ patients had a larger peanut wheal size, as the HP− group had a high proportion of AD PA− and NA subjects, who, by the study definition, were peanut skin test negative. However, no difference in peanut wheal size was found between HP− AD PA+ and HP+ AD PA+ subjects (peanut wheal size, mm [standard deviation]: 15.4 [5.4] and 20.1 [6.2], respectively).

In addition, all HP+ subjects (a group enriched for AD PA+ subjects) had significantly greater keratin 5 expression in STS ($P < .01$) of nonlesional skin (see Table I). They also had a significantly reduced EOS CER/NS CER ratio (ω -esterified fatty acid sphingosine ceramide/nonhydroxy fatty acid sphingosine ceramide) ($P < .01$) in STS layers 15-16 of nonlesional skin (see Table I). Of note, KRT5 expression was the highest in the HP+AD PA+ group and statistically different from HP− AD PA− subjects ($P = .02$) (KRT5 [median (1st, 3rd quartile)]: HP+ AD PA+ subjects 136.6 (115.9, 149.7); HP− AD PA+ subjects 102.2 (92.9, 130.8); HP+ AD PA− subjects 101.1 (94.9, 105.9); and HP− AD PA− subjects 97.5 (75.5, 103.7)). The EOS CER/NS CER ratio was only significantly different between the HP+ AD PA+ and HP− AD PA− groups ($P = .02$) (EOS CER/NS CER ratio [median (1st, 3rd quartile)]: HP+ AD PA+ subjects 0.34 [0.23, 0.45]; HP− AD PA+ subjects 0.32 [0.12, 0.59]; HP+ AD PA− subjects 0.32 [0.23, 0.57]; and HP− AD PA− subjects 0.81 [0.51, 1.10]).

In this study, *FLG* genotyping was done only in Caucasian AD patients for 5 major mutations (R501X, 2282DEL4,

TABLE I. A comparison of clinical features associated with hyperlinear palms (HP)

	HP		Total (n = 62)	P value
	No (n = 46)	Yes (n = 16)		
Group				<.01*
AD with peanut allergy (AD PA+)	10 (21.7%)	11 (68.8%)	21 (33.9%)	
AD without peanut allergy (AD PA–)	15 (32.6%)	4 (25%)	19 (30.6%)	
Nonatopics (NA)	21 (45.7%)	1 (6.2%)	22 (35.5%)	
Race				.83*
Caucasian	37 (80.4%)	13 (81.2%)	50 (80.6%)	
Black or African American	8 (17.4%)	3 (18.8%)	11 (17.7%)	
Native Hawaiian or Pacific Islander	1 (2.2%)	0 (0.0%)	1 (1.6%)	
Peanut wheal size (mm), mean (SD)	3.4 (6.9)	13.8 (10.9)	6.1 (9.2)	<.01†
FLG mutation:‡ yes	0/20 (0.0%)	5/12 (41.7%)	5/32 (15.6%)	<.01*
FLG,§ mean (SD)	107.6 (78.5)	82.8 (49.1)	101.2 (72.5)	.24†
FLG2§	101.8 (36.2)	95.5 (27.9)	100.2 (34.1)	.53†
KRT5,§ median (1st, 3rd quartile)	89.9 (74.2, 104.0)	117.2 (102.4, 142.7)	96.9 (76.0, 114.3)	<.01
EOS CER/NS CER ratio§	0.75 (0.36, 1.15)	0.37 (0.23, 0.49)	0.59 (0.29, 1.07)	<.01

AD, atopic dermatitis; EOS CER, ω-esterified fatty acid sphingosine ceramide; FLG, filaggrin; NS CER, nonhydroxy fatty acid sphingosine ceramide; PA, peanut allergy; SD, standard deviation.

*Pearson's χ^2 test.

†Student's *t*-test.

‡Analysis done in Caucasian AD PA+ and AD PA– subjects only.

§Nonlesional skin tape strip samples were analyzed.

||Mann-Whitney *U* test.

R2447X, S3247X, and 3702DELG) described in Caucasians. Five Caucasian AD subjects with *FLG* mutations were found to have HP; all were heterozygous, and all were from the AD PA+ group. A significant association between HP and *FLG* mutations was found with 5 of 12 Caucasian HP+ AD patients (41.7%) identified as HP+ with *FLG* mutations, and no *FLG* mutations identified in 20 Caucasian HP– AD patients (0%) ($P < .01$, Table I), but *FLG* mutations could not account for HP in the majority of patients. We examined filaggrin and filaggrin 2 protein expression in STS samples in HP+ and HP– subjects as detected by STS proteomics analysis. We did not observe differences in filaggrin and filaggrin 2 protein expression in subjects with or without HP (Table I). No differences in filaggrin and filaggrin 2 protein levels were found among HP+ AD PA+, HP– AD PA+, HP+ AD PA+, and HP– AD PA– subjects (data not shown). Because of the small sample size of patients with *FLG* mutations, further subgrouping and analysis was not feasible.

To determine if HP are a distinguishing feature in AD PA+, we estimated the sensitivity, specificity, and area under the curve (AUC) of HP positivity in predicting AD PA+ subjects. In the current study cohort, the AUC for HP positivity being the predictive feature of AD PA+ is estimated as 0.66 (95% confidence interval [CI]: 0.51, 0.79), with the sensitivity of 0.60 (95% CI: 0.39, 0.79) and the specificity of 0.73 (95% CI: 0.45, 0.92), suggesting that subjects with HP have a slightly larger chance to be AD PA+ and could be potentially considered by clinicians as one of the factors associated with AD PA+.

Children with AD and FA represent a unique endotype with distinct skin barrier function, including differences in *FLG* breakdown products, TEWL, and stratum corneum lamellar bilayer structure.⁴ Interest has turned toward the identification of clinical features, which may distinguish those with AD who are more prone to FA. HP may be seen in individuals with FA and

**FIGURE 1.** Hyperlinear palms in a patient with peanut allergy. Line markings are more prominent in the area of the thenar eminence.

AD and can be identified by increased linear markings or markings of increased depth across the palmar surface of the hand and the fingers (see Figure 1).⁸ This is the first study to show HP as a physical feature in AD PA+ irrespective of *FLG* mutations.

Little is understood about the mechanism of the development of HP. Previous studies suggest that HP are only found in a

minority of patients with AD at 2 years of life.⁸ Our study suggests that HP are more common among subjects with AD than previously thought, as it was present in 37.5 % of subjects with AD, compared with 3% in other studies, though it may be related to the longer duration of disease in our subjects.⁷ Molecularly, this is seen as differences in keratin 5 expression, indicative of hyperproliferative, undifferentiated keratinocytes.

The clinical finding of HP was associated with differences in skin barrier composition. AD subjects with HP had an altered ratio of EOS CER to NS CER. This ratio of ultralong-chain lipids to short-chain lipids reflects deficiencies in the skin integrity as these ultralong-chain lipids bind with epidermal structural proteins, such as involucrin, loricrin, and periplakin.⁴ An altered lipid composition results in loss of epidermal hydrophobicity and increased allergen penetration.

We observed here an association of HP with PA in children with AD. This association was seen regardless of AD severity. The limitation of this study is that HP grading was not performed; in addition, this was a small single-center study that used a rigorous definition of PA. Larger prospective studies using a less rigorous definition of PA are needed to evaluate this relationship further. HP may be due to keratin dysregulation, skin lipid abnormalities, and *FLG* mutation, and in a previous study were associated with egg allergy.⁹ In conclusion, clinicians should examine children with AD for HP, as when combined with patient history they may be an important clinical finding in children with FA.

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