

REPORT

Clinical detection of ichthyosis vulgaris in an atopic dermatitis clinic: Implications for allergic respiratory disease and prognosis

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Background: Recent genetic studies have demonstrated that filaggrin mutations, shown to underlie ichthyosis vulgaris (IV), may also predispose patients with atopic dermatitis to allergic respiratory disease.

Objective: Our objective was to determine whether the clinical presence of IV influences the severity and age at onset of atopic dermatitis or the probability of having allergic respiratory disease.

Methods: We reviewed data collected from the initial visits of 1187 patients with atopic dermatitis.

Results: Asthma symptoms were more common in atopic dermatitis patients with IV than in those without (39.9% vs 32.9%, odds ratio [OR] = 1.35, $P = .050$) and were most associated with severe IV (OR = 2.52, $P = .002$). This relationship remained after controlling for the baseline severity of atopic dermatitis. Clinical IV was also associated with symptoms of allergic rhinoconjunctivitis, earlier onset of atopic dermatitis, severity of atopic dermatitis, hyperlinear palms, and keratosis pilaris.

Limitations: Our limitations include subjective grading, few data points in some groups, and an inability to demonstrate causality.

Conclusion: These results suggest that clinical evidence of IV, irrespective of filaggrin genotype, serves as a potential marker for those patients with atopic dermatitis who develop allergic respiratory disease and a more severe skin phenotype. (J Am Acad Dermatol 10.1016/j.jaad.2008.03.029.)

BACKGROUND

Past reports indicate that 2.5% to 37% of patients with atopic dermatitis (AD) have clinical evidence of ichthyosis vulgaris (IV).¹⁻⁵ Mutations in the gene encoding filaggrin underlie IV,^{6,7} and these mutations are found more frequently in AD than in control populations.⁷⁻¹⁶ Filaggrin is an epidermal protein

Abbreviations used:

AD: atopic dermatitis
ARD: allergic respiratory disease
IV: ichthyosis vulgaris

critical to the development of an intact skin barrier. Abnormally functioning filaggrin may partially explain the skin barrier defects seen in patients with AD. Mutations in filaggrin may also influence the course and severity of AD. Filaggrin mutations have been associated with early age at onset of AD¹⁰⁻¹⁴ and with disease persistence into adulthood.¹² In addition, several studies have found a higher prevalence of respiratory atopy and allergic sensitization in those AD patients with filaggrin mutations than in those without.⁸⁻¹¹ The mechanisms linking IV and allergic respiratory disease (ARD) are not understood, but together these data suggest allergic sensitization may occur via a compromised skin barrier.¹⁷

The recent studies examining the relationship between IV and ARD have focused primarily on filaggrin genotypes. In clinical practice, genotyping

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is not yet practical and clinicians must rely on phenotypic assessments. No previous studies have examined whether a link exists between ARD and the clinical features of IV, irrespective of genotype. Our objective was to determine whether a clinical diagnosis of IV was associated with the presence of ARD in a large group of patients with AD. We also wished to determine whether a true link exists between IV and ARD that is independent of the underlying skin disease severity.

METHODS

We utilized a cross-sectional study design using data obtained during the initial visit of consecutive patients with AD seen at Oregon Health & Science University from 1978 through 2006. Data were extracted from a standardized patient intake form used for all new patients undergoing evaluation of AD. The intake form facilitates diagnosis by prompting the physician to record major and minor criteria,¹⁸ including age at onset, personal and family history of ARD, and the presence or absence of numerous physical features. Age at onset of AD and previous diagnosis or symptoms of ARD were determined by patient history. Physical features, including IV, hyperlinear palms, and keratosis pilaris, were graded on a 0-3 scale (0 = absent, 1 = mild, 2 = moderate, and 3 = severe). The anterior lower leg is well recognized as the most commonly affected site of involvement in IV.¹⁹⁻²¹ Therefore the presence and severity of IV were assessed solely by the prominence of polygonal plate-like scale on the anterior legs, not by history or the presence of other physical features. The presence of xerotic skin without polygonal scales did not qualify as evidence of IV. Subjects also received an overall AD severity grade on a scale of 0-5 for the initial visit. Scoring was performed by one of two close-working physicians (E. S. or J. H.) for all patients, and the clinical diagnosis and severity were verified together in many patients to ensure consistency.

Allergic rhinoconjunctivitis was considered present if a patient had a physician diagnosis of it or had symptoms of itchy, watery eyes or runny nose with a seasonal predilection or with allergenic exposure. Asthma was considered present if a patient had a physician diagnosis of asthma or had symptoms of recurrent wheezing requiring inhaler therapy. Responses not included as consistent with asthma were one-time events, such as "wheezed once with cold." To maintain blinding, the status of IV was not available during the coding of the respiratory variables. Examining physicians were not blinded to the respiratory status of their patients; however, data were recorded before a time when a link between

IV and respiratory allergy was known. Ambiguous answers and omissions were not included in the analysis.

Logistic regression was used to control for potential confounding variables including age, gender, and underlying AD disease severity. Season of the year at the time of examination was included in an attempt to control for differences in seasonal temperature and humidity that may influence a clinical diagnosis of IV.

Neither genetic testing for filaggrin defects nor any objective test for respiratory disease was performed in this study. The study was performed with the approval of the Oregon Health & Sciences University Institutional Review Board.

Statistical methods

We performed all statistical analyses with the SPSS statistics package (version 14.0). Chi-square tests were used to compare discreet proportions and logistic regressions were used to control for the effects of age, sex, season, and the severity of AD. We used a Spearman correlation to examine the association between the severities of IV and AD. All *P* values are two tailed, with a significance level of .05.

RESULTS

Because these data were not originally collected for study purposes, some data points were missing. Of the 1187 AD intake forms we reviewed, unambiguous information was available for 1007 patients regarding asthma, 1021 for acute rhinoconjunctivitis, 975 for IV, 491 for AD severity, 986 for hyperlinear palms, and 958 for keratosis pilaris. In all calculations, we included every subject with a valid data point; therefore our denominators are not uniform.

Prevalence of IV

The status of IV was recorded for 975 patients with AD who presented to our Department of Dermatology. Of these, 321 (32.0%) patients were found to have coexisting clinical evidence of IV.

AD severity

Both the status of IV and the severity of AD were recorded in 448 of the patients in our population (Table I). Among these, we noticed a significant correlation between the severity of AD and the severity of IV ($r = 0.234$, $P < .001$). No patient with severe IV demonstrated only mild AD.

Asthma. The status of IV and asthma were both recorded in 821 of our patients (Table II). AD severity was recorded in 373 of these patients. AD patients with IV were slightly more likely than AD patients without IV to have concomitant asthma (39.9%

Table I. Severity of atopic dermatitis compared with severity of ichthyosis vulgaris*

IV	No.	Severity of AD (5-point scale) (%)				
		1	2	3	4	5
No IV	305	27 (8.9)	63 (20.7)	175 (57.4)	11 (3.6)	29 (9.5)
IV	143	4 (2.8)	13 (9.1)	91 (63.6)	2 (1.4)	33 (23.1)
Mild	74	3 (4.1)	8 (10.8)	48 (64.9)	0 (0.0)	15 (20.3)
Moderate	44	1 (2.3)	2 (4.6)	33 (75.0)	1 (2.3)	7 (15.9)
Severe	25	0 (0.0)	3 (12.0)	10 (40.0)	1 (4.0)	11 (44.0)

AD, Atopic dermatitis; IV, ichthyosis vulgaris.

*N = 448; $r = 0.234$; $P < .001$. Number of patients with valid data points for the severity of AD and IV.**Table II.** Prevalence of asthma in patients with ichthyosis vulgaris

IV	Prevalence of asthma (n = 821)*					Prevalence of asthma adjusted for AD severity, age, sex, and season (n = 373)		
	No.	% with asthma	Attributive risk	OR (95% CI)	P value	No.	OR (95% CI)*	P value
No IV	550	32.9	0.0	1.00 (NA)	NA	250	1.00 (NA)	NA
IV	271	39.9	21.3	1.35 (1.00-1.83)	.050	123	1.78 (1.10-2.87)	.019
Mild	146	37.0	12.5	1.20 (0.82-1.75)	.376	62	1.64 (0.89-3.02)	.112
Moderate	78	35.9	9.1	1.14 (0.70-1.87)	.600	39	1.47 (0.71-3.05)	.303
Severe	47	55.3	68.1	2.52 (1.38-4.61)	.002	22	3.06 (1.19-7.92)	.021

AD, Atopic dermatitis; CI, confidence interval; IV, ichthyosis vulgaris; NA, not applicable; OR, odds ratio.

*Number of patients with valid data points for asthma and IV (the adjusted number also required a valid data point for AD severity).

vs 32.9%, $P = .050$); however, the smaller subset of patients with severe IV had a substantially greater prevalence of asthma compared to those without IV (55.3% vs 32.9%, $P = .002$). Mild and moderate IV correlated with asthma to a much lesser degree. The relationships between IV and asthma remained significant after adjusting for age, gender, season of examination, and AD severity (OR = 1.78, $P = .019$).

Allergic rhinoconjunctivitis. Data regarding allergic rhinoconjunctivitis and IV were available for 850 patients (Table III). Of these, 383 patients also had a recorded AD severity rating. A higher likelihood of concomitant allergic rhinoconjunctivitis symptoms was found if there was clinical evidence of IV (61.8% vs 53.2%, $P = .018$). We did not see a significant association with increased severity of IV. After adjustment for the severity of AD, age, gender, and season, the relationship between IV and allergic rhinoconjunctivitis remained significant. Similar to the relationship between IV and asthma, a much stronger, significant association was seen between severe IV and allergic rhinoconjunctivitis symptoms (OR = 2.84, $P = 0.048$).

Age at onset. The age at onset of AD and IV status were available for 849 patients (Table IV). In general, patients with IV reported developing AD at an earlier age than those without. In patients

with IV, 71.1% developed AD before 2 years of age, whereas 61.7% of those without IV developed AD before the 2 years of age ($P = .009$). Looking at the data another way, 35% of patients who developed AD before the age of 2 years demonstrated clinically evident IV compared with 28% of those who developed AD between the ages of 2 and 18 years. Severe IV, in particular, appears to significantly increase one's risk for early-onset AD. Among 53 patients with severe IV, 42 developed AD before the age of 2 years, and all developed AD by the age of 13 ($P = .016$). Adult-onset AD occurred more often in patients without evidence of IV. Adult-onset AD occurred in 4.1% and 8.6% of patients with and without IV, respectively. Examining all patients with adult-onset AD, only 18% of patients had evidence of IV.

AD persistence. The age of evaluation for AD and the status of IV were available for 963 patients (data not shown). Patients with AD presented to our clinic at ages ranging from zero to 83 years, with a mean age of 21.4 years and a standard deviation of 17.9 years. Patients presenting for an initial evaluation with active AD who were older than 18 years of age (ie, patients with persistent AD) were no more likely to demonstrate IV than those 18 years of age and younger (31.7% vs 32.1%, respectively). To

Table III. Prevalence of allergic rhinoconjunctivitis in patients with ichthyosis vulgaris

IV	Prevalence of AR (n = 850)*					Prevalence of AR, adjusted for AD severity, age, sex, and season (n = 383)*		
	No.	% with asthma	Attributive risk (%)	OR (95% CI)	P value	No.	OR (95% CI)*	P value
No IV	575	53.2	0.0	1.00 (NA)	NA	261	1.00 (NA)	NA
IV	275	61.8	16.2	1.42 (1.06-1.91)	.018	122	2.14 (1.32-3.47)	.002
Mild	152	60.5	13.7	1.35 (0.94-1.94)	.107	63	2.15 (1.16-3.98)	.015
Moderate	75	62.7	17.9	1.48 (0.90-2.42)	.122	39	1.85 (0.88-3.86)	.103
Severe	48	64.6	21.4	1.60 (0.87-2.96)	.129	20	2.84 (1.01-8.00)	.048

AD, Atopic dermatitis; AR, allergic rhinoconjunctivitis; CI, confidence interval; IV, ichthyosis vulgaris; NA, not applicable; OR, odds ratio.

*Number of patients with valid data points for AR and IV (the adjusted number also required a valid data point for AD severity).

Table IV. Prevalence of ichthyosis vulgaris according to atopic dermatitis age at onset (n = 849)*

IV	AD age at onset				P value
	No.	<2 y/o	2-18 y/o	>18 y/o	
No IV	579	357 (61.7%)	172 (29.7%)	50 (8.6%)	NA
IV	270	192 (71.1%)	67 (24.8%)	11 (4.1%)	.009
Mild	148	100 (67.6%)	39 (26.4%)	9 (6.1%)	.357
Moderate	69	50 (72.5%)	17 (24.6%)	2 (2.9%)	.121
Severe	53	42 (79.2%)	11 (20.8%)	0 (0.0%)	.016

AD, Atopic dermatitis; IV, ichthyosis vulgaris; NA, not applicable; y/o, years old.

*Number of patients with valid data points for AD age at onset and IV.

examine whether IV is associated with early onset of AD, persistent AD as reported previously,¹² we compared the prevalence of IV in AD patients with both disease onset before the age of 2 years and disease persistence past the age of 18 years against all other AD patients in our sample. Clinical evidence of IV was not associated with early onset, persistent AD (33.9% vs 31.0%, $P = .419$).

Hyperlinear palms and keratosis pilaris. The status of hyperlinear palms and IV were recorded in 915 of our patients (Table V). Patients with IV were much more likely to demonstrate hyperlinear palms than patients without IV (81.3% vs 43.0%, hyperlinear palms ($P < .001$). This relationship remained significant after controlling for the severity of AD, age, gender, and season (data not shown). Additionally, keratosis pilaris was seen more commonly in patients with IV than in those without (52.9% vs 28.4%, $P < .001$, $n = 898$) (see Table V). Again, this relationship persisted after controlling for potential confounders. The increased prevalence of hyperlinear palms and keratosis pilaris in our IV population supports the accuracy of our clinical diagnosis of IV.^{5,22}

DISCUSSION

This study documents clinical evidence of IV in 32% of a large group of university-based patients with AD. This prevalence is consistent with previous clinical observations that showed IV present in 2.5% to 37% of patients.¹⁻⁵ This also agrees with recent genetic studies that have reported loss-of-function filaggrin mutations in 5.6% to 56% of AD patients,^{7-16,23} a meta-analysis of which confirmed an association between filaggrin mutations and AD (OR = 3.51, 95% confidence interval [CI] = 2.24-5.50).²⁴ Our data reveal that the presence of IV diagnosed by clinical examination can be an indicator of respiratory atopy, consistent with recent studies using filaggrin genotyping.⁸⁻¹¹ In addition, we found that those patients with a severe IV phenotype were most likely to demonstrate ARD. Finally, we report the novel finding that the clinical severity of IV correlates with the severity of AD.

Palmer and colleagues⁸ were first to suggest that IV may predispose to respiratory disease when his group reported that filaggrin mutations were associated with the presence of asthma in the setting of AD. Weidinger and colleagues^{9,10} and Marenholz and colleagues¹¹ both reported that loss-of-function filaggrin mutations correlate with increased IgE levels and a higher prevalence of asthma and hay fever within a population of patients with AD. Because AD disease severity is known to be an independent risk factor for the development of asthma,²⁵⁻²⁷ allergy,²⁸ and increased IgE levels,^{27,29-31} controlling for the underlying AD disease severity was necessary to establish an independent link between IV and ARD. After controlling for confounders, the link between IV and ARD remained strong, confirming an association independent of AD severity.

Within our population, not only the presence, but also the severity, of IV influenced the probability of concomitant ARD. This correlation supports the hypothesis that the degree of barrier dysfunction influences the degree of allergic sensitization. Patients

Table V. Prevalence of hyperlinear palms/keratosis pilaris in patients with ichthyosis vulgaris

IV	Prevalence of HLP (n = 915)*					Prevalence of KP (n = 898)*			
	No.	% with HLP	OR (95% CI)	P value		No.	% with KP	OR (95% CI)	P value
No IV	621	43.0	1.00 (NA)	NA		620	28.4	1.00 (NA)	NA
IV	294	81.3	5.76 (4.13-8.04)	<.001		278	52.9	2.83 (2.11-3.80)	<.001
Mild	163	77.9	4.68 (3.13-7.00)	<.001		157	52.2	2.76 (1.93-3.95)	<.001
Moderate	81	85.2	7.62 (4.05-14.4)	<.001		78	50.0	2.52 (1.57-4.06)	<.001
Severe	50	86.0	8.14 (3.61-18.4)	<.001		43	60.5	3.86 (2.04-7.29)	<.001

CI, Confidence interval; HLP, hyperlinear palms; IV, ichthyosis vulgaris; KP, keratosis pilaris; OR, odds ratio.

*Number of patients with valid data points for hyperlinear palms/keratosis pilaris and ichthyosis vulgaris.

with a severe IV phenotype may represent those patients who are genetic homozygotes or compound heterozygotes for the mutant filaggrin alleles, whereas mild and moderate IV phenotypes may represent heterozygous genotypes.^{6,7} Previous genetic studies have suggested that individuals homozygous for mutated filaggrin, the ones most likely to have a severe phenotype, were more likely to have concomitant respiratory disease, consistent with our clinical findings.^{8,9,11} Caution should be used when attempting to accurately predict genotype using the clinical severity of IV as environmental factors, such as ambient humidity, and the use of moisturizers can significantly alter disease expression. Our results corroborate previous findings that the presence of keratosis pilaris and particularly hyperlinear palms adds support to a diagnosis of IV, but are not essential to the diagnosis.^{6,22}

The mechanisms by which IV may lead to respiratory allergy are unknown. Mouse models suggest a potential link between epicutaneous antigen inoculation and respiratory disease. In these models, protein antigen occluded on mouse skin leads to antigen-specific IgE production and subsequent lung inflammation upon rechallenge with allergen via the respiratory route.^{32,33} The damaged stratum corneum barrier of IV may facilitate and amplify transcutaneous Th2 reactivity, leading to elevated levels of IgE and subsequent respiratory tract sensitivity.^{34,35} Given the suspected epicutaneous route of allergen sensitization, it comes as no surprise that filaggrin mutations are only associated with asthma in the presence of skin disease,³⁶ particularly given the absence of filaggrin expression in the lung.³⁷

The association with IV in our population extended beyond respiratory disease. Consistent with previous genetic work by Weidinger and colleagues¹⁰ and Stemmler and colleagues,¹⁴ the presence of IV in our cohort was linked to earlier onset disease and a more severe AD phenotype. We found a significant linear correlation between the severity of IV and the severity of AD. Lastly, in contrast to the results of Barker and colleagues,¹² we did not

observe a convincing relationship between IV and AD disease persistence into adulthood.

One limitation of our study was that many variables relied on subjective grading made by the examining physician. Because genetic testing for filaggrin was not performed in our study, we are unable to draw conclusions regarding the relationship between filaggrin mutations and AD in the absence of clinically evident IV. As with previous epidemiologic studies,^{9,10} the designation of asthma or allergic rhinoconjunctivitis relied on patient history, rather than on a strict definition of asthma or allergic rhinoconjunctivitis. Similarly, we were unable to distinguish between patients with varying IgE levels. Our study was also dependent on intake forms that were sometimes incomplete. As a result, some subgroups of our large population, such as those with severe IV, were limited in number. This most substantially limited our sample size when controlling for the severity of AD. Although this limited the power of our data, when AD severity was included in our model, the significance of our findings was not lost. Additionally, our population of patients may not represent a larger population of patients with AD as our institution is a tertiary referral center. Not all patients were referrals, however, and 23.6% of our patients had only mild AD. As with all cross-sectional studies, our study was unable to definitively address causation. Because data were recorded at one point in time, we do not know whether IV predisposes a person to the development of eczema and respiratory symptoms or, alternatively, whether the xerotic IV phenotype might result from the underlying inflammatory condition. We also used the age of evaluation as a rough surrogate for disease persistence. A prospective cohort study design using genetic testing would be best for confirming the relationship between filaggrin mutations, clinical signs of IV and AD onset and persistence.

In conclusion, our findings offer clinical confirmation of previous genetic studies that identify IV as a predisposing factor in the development of AD-related ARD. In addition, we have confirmed recent genetic

findings that IV predisposes to earlier onset of AD. We have also found a novel correlation between IV severity and AD disease severity. Together, these findings suggest that evidence of IV, either from clinical examination, genetic testing, or possibly family history may identify a subset of children at higher risk for the development of more severe AD and associated respiratory allergy. Identification of these patients may justify early therapeutic interventions focusing on skin barrier repair and allergen reduction strategies in this specific population. Although there are no generally accepted asthma prevention strategies, removing known promoters of asthma may theoretically be protective.³⁸ Therefore, specifically counseling parents of patients with AD and concomitant IV to avoid pet ownership, eliminate tobacco smoke in the household, and reduce dust mite exposure may help prevent the development of ARD.

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