

Migratory Ichthyosiform Dermatitis With Type 2 Diabetes Mellitus and Insulin Resistance

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Background: In addition to the well-defined hereditary primary ichthyoses, many sporadic or less well-defined keratinization disorders with or without systemic manifestations have been reported. Herein we describe ichthyosiform dermatosis associated with type 2 diabetes mellitus.

Observations: The patients were members of a large Arab family with heavy consanguinity. Eighteen members were affected with a variously severe scaly disorder. They showed migratory polycyclic keratotic scaly plaques evolving into diffuse generalized scaling or

complete remission. Acanthosis nigricans–like lesions were also noted, and there was an association with type 2 diabetes mellitus. A scarcity of intercorneocyte lamellae and reduction in lamellar body contents were observed.

Conclusions: We could not find a report of a similar dermatosis. Furthermore, an association between ichthyosis and diabetes has not been documented. Therefore, we believe that this may constitute a new entity.

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IN ADDITION to the well-defined groups of hereditary primary ichthyoses, many sporadic or familial ichthyosiform disorders have been described. In the latter group of less well-defined ichthyoses, there may be extracutaneous manifestations. Whereas excessively dry skin of the shins with mild ichthyosiform skin changes has been associated with diabetes,¹ true ichthyosis has not been reported, and, to the best of our knowledge, hereditary ichthyosiform dermatosis has not been associated with diabetes.

Herein described is a heavily consanguineous Arab family, originating in Africa, that displays a unique form of migratory ichthyosiform dermatosis as well as type 2 diabetes mellitus, probably representing a new entity.

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REPORT OF CASES

CASE 1

The proband, a 44-year-old man (II-7 in **Figure 1**) was seen several times for evaluation of a severely itching ichthyosiform dermatosis, which had appeared in early childhood and become worse at the age of 17 years. His mother did not recall the presence of any skin lesions at birth. The patient had type 2 diabetes mellitus that had

been diagnosed 10 years previously and was taking glyburide (an oral hypoglycemic). He also had mild (untreated) hypertension and a past and present history of heavy alcohol consumption.

Skin changes included generalized ichthyosis, sparing the palms, soles, and scalp. On the thighs, buttocks, and lower extremities there were migratory oval keratotic plaques coalescing to form circinate lesions of various sizes (**Figure 2**). In addition, the face showed a diffuse thickening with slight erythema, and marked hyperkeratosis superimposed on lichenification was seen on the anterior aspect of the ankles, on the knuckles, and on the dorsal aspects of the hands. All lesions were migratory within days.

During 3 years of follow-up we observed a cyclical course of the dermatosis; at times migratory lesions predominated, and at other times there was a generalized dermatosis consisting of small and medium-sized scales covering the whole body (**Figure 3**). Hair, nails, teeth, and mucous membranes were normal.

Complete blood cell count and results of blood smear were within normal limits (ie, no intracellular lipid droplets were present). Fasting blood glucose level was 13.2 mmol/L (238 mg/dL) (reference range, 3.3-5.6 mmol/L [60-100 mg/dL]); glycosylated hemoglobin concen-

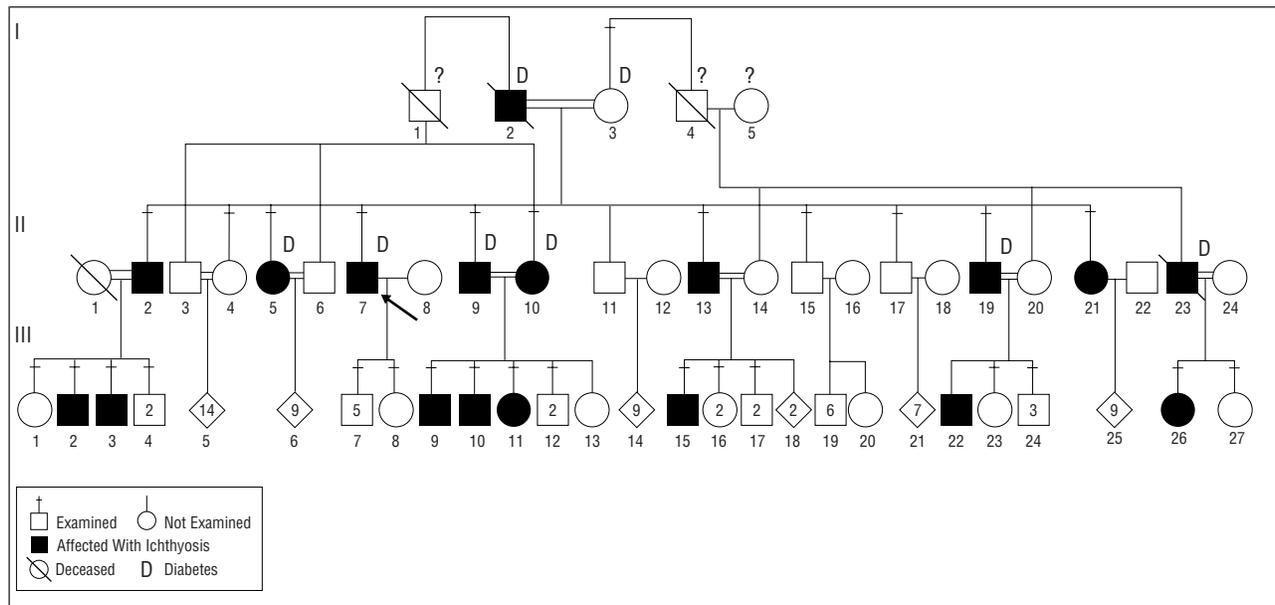


Figure 1. Pedigree of the family with ichthyosiform dermatosis and type 2 diabetes mellitus. Arrow indicates the proband.



Figure 2. Case 1. Circinate hyperkeratotic lesions of buttock.



Figure 3. Case 1. Generalized scaling on buttocks and trunks (compare with Figure 2).

tration, 0.08 (reference range, 0.04-0.06); creatine kinase level, 313 U/L (reference range, 24-203 U/L); aspartate aminotransferase level, 33 U/L (reference range, 7-40 U/L); alanine aminotransferase level, 48 U/L (reference range, 7-40 U/L); and γ -glutamyltransferase level, 118 U/L (reference range, 11-50 U/L). Radiographic studies of the thorax were normal, while abdominal ultrasound disclosed a fatty liver. There was diabetic retinopathy. Neurologic and otologic function were normal.

CASE 2

A 19-year-old, mentally retarded man (patient III-9) had suffered from an itchy ichthyosiform dermatosis from early childhood. There had been no bullae nor a collodian membrane at birth. Thereafter he had a localized migratory scaly itchy dermatosis. A year before the current examination, new lesions had appeared, involving most of the body.

Physical examination showed a generalized symmetrical ichthyosiform dermatosis. Lesions started with tiny keratotic papules that slowly spread centrifugally, forming large polycyclic keratotic and scaly plaques, as in the proband (**Figure 4**). The large circinate plaques had a raised ery-

thematous, crusted, and scaly border. These lesions migrated within weeks, and any area of the integument could be involved at various times. Ankles and knuckles showed marked hyperkeratosis superimposed on lichenification. Hyperkeratosis was also noted on the soles but not on the palms. Diffuse scaling covered the scalp, without hair involvement. Nails were normal. Oral examination disclosed multiple dental caries. No mucous membrane, ocular, or genital organ abnormalities were noted. Serum creatine kinase level was markedly elevated at 643 U/L, but all other biochemical measures, including results of blood chemistry studies; levels of glycosylated hemoglobin, cholesterol, triglycerides, and thyrotropin; and complete blood cell count and blood smear, were within normal limits. Fasting blood glucose level was normal, but fasting blood insulin level was significantly elevated at 534 pmol/L (reference range, 62-118 pmol/L).

CASE 3

The 49-year-old brother of the proband (patient II-9) displayed a localized and migratory pruritic scaly dermatosis.



Figure 4. Case 2. Polycyclic, keratotic, and scaly area with active borders on the trunk.



Figure 5. Case 3. Localized, keratotic scaly lesion of right elbow.

sis, aggravated in winter, that first appeared in childhood. The patient also suffered from type 2 diabetes mellitus, well controlled with oral hypoglycemics. The physical examination showed erythematous keratotic and scaly areas on both buttocks, similar to those described above, and hyperkeratosis resembling lichenification on the hands and elbows (**Figure 5**). Laboratory tests showed the fasting blood glucose level to be 15.2 mmol/L (273 mg/dL), with a glycosylated hemoglobin concentration of 0.09. Complete blood cell count, results of liver function tests, and lipid profile were within the normal range.

CASE 4

The 15-year-old daughter of the proband's cousin (patient III-26) displayed keratotic and scaly migratory lesions similar to the ones present on the proband (Figure 3).

RESULTS

Similar changes of varying severity and extent were seen in several affected members of this kindred. Those with generalized ichthyosis suffered from severe generalized pruritus unrelieved by antihistamines, while others with milder forms or during periods of spontaneous regression had only minimal itch.

Acanthosis nigricans-like lesions were present in the axillae, palms, and inguinal regions in 9 affected members and in 4 without skin lesions. In 2 of the patients there were achromia-like pigmentary changes and, in 1, papules resembling seborrheic keratosis on the shins, neither of which was seen in unaffected members of the family.

The general physical examination disclosed moderate obesity in many of the family members without other anomalies. Hair, nails, teeth, mucous membranes, and

genital organs (in males) were normal, and there was no hepatosplenomegaly or lymphadenopathy.

Type 2 diabetes mellitus was documented in 7 (38%) of the 18 family members with ichthyosiform dermatosis (see Figure 1). After the age of 43 years, all subjects with ichthyosis also had diagnosed diabetes. Subjects considered to have diabetes were those with diagnosed diabetes according to World Health Organization criteria and treated with oral hypoglycemic agents, insulin, or a specific diet. Most of the other patients with ichthyosis were still too young to manifest type 2 diabetes mellitus. Only 1 member of the kindred had diabetes but not ichthyosis.

Other associated findings included mental retardation in 3 of 18 individuals with ichthyosis, as opposed to only 1 of the 60 subjects without ichthyosis. One patient with ichthyosis had undergone surgery for craniopharyngioma.

CLINICAL LABORATORY FINDINGS

Complete blood cell count, blood smears, glucose level, glycosylated hemoglobin concentration, results of liver function tests, and levels of thyrotropin, creatine kinase, cholesterol, and triglycerides were determined in 12 patients with ichthyosis. Five affected members had elevated serum creatine kinase values ranging from 227 to 654 U/L (reference range, 24-203 U/L) without suffering from any symptomatic myopathy or hypothyroidism. Analysis of isoenzymes showed that the elevations reflected increased muscle enzymes. In the proband, serial measurements of creatine kinase showed waxing and waning unrelated to drug intake or physical condition, skin disease, or diabetes control. A mild elevation in liver enzyme levels was noted in 5 patients, 1 of whom was an alcoholic. Fasting blood insulin levels were determined in 5 nondiabetic patients who had ichthyosis with acanthosis nigricans, by means of enzyme-linked immu-

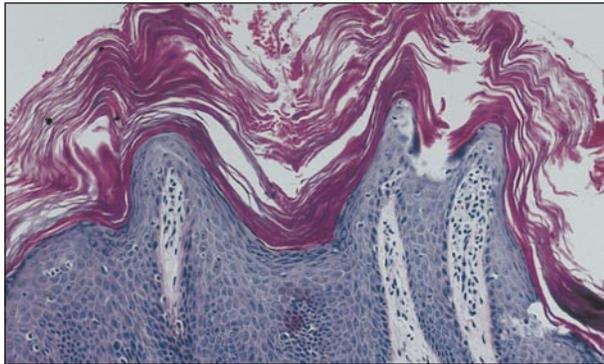


Figure 6. Light microscopy of hyperkeratotic plaque demonstrating acanthosis, papillomatosis, hyperkeratosis with focal parakeratosis of the epidermis, and focal hypogranulosis (hematoxylin-eosin, original magnification $\times 50$).

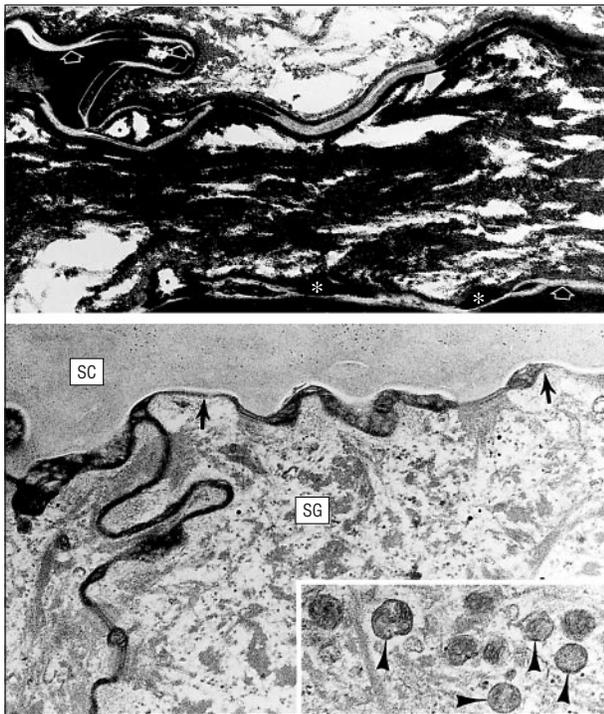


Figure 7. Electron microscopy showing ultrastructure of papular lesion. Top, Stratum corneum, postfixated with ruthenium tetroxide, shows both a scarcity of lamellar membrane structure (solid arrows; white arrow shows normal-appearing lamellae) and multiple areas of phase separation (asterisks) (original magnification $\times 110\,000$). Bottom, Stratum granulosum (SG) shows marked reduction in secreted lamellar body contents at the SG–stratum corneum (SC) interface (arrows). Keratohyaline and fibrillar contents of SG cytosol are reduced, and most lamellar bodies display abnormal contents (inset, arrowheads) (osmium tetroxide, original magnification $\times 30\,000$; inset, original magnification $\times 85\,000$).

nosorbent assay (Boehringer Mannheim, Penzberg, Germany). Four of the subjects had elevated fasting blood insulin levels, suggesting insulin resistance.

Several potassium hydroxide preparations and cultures (at least 2 in each member) from circinate polycyclic lesions repeatedly yielded no evidence of fungal infection.

LIGHT MICROSCOPY

Biopsy specimens from full-blown cases showed acanthosis, papillomatosis, hyperkeratosis, and focal parakerato-

Table 1. TEWL and Stratum Corneum Hydration in Patients With Generalized Ichthyosiform Dermatitis vs Healthy Family Members and Healthy Controls in 3 Body Areas*

Body Site	Patients With Ichthyosis (n = 4)	Unaffected Family Members (n = 4)	Normal Controls (n = 20)†
TEWL Values, g/m² per Hour			
Shin	10.4 \pm 7.2	11.0 \pm 3.4	11.0 \pm 7.0
Forearm	7.3 \pm 1.4	10.3 \pm 4.6	12.3 \pm 4.6
Abdomen	8.0 \pm 3.2	11.0 \pm 5.5	10.3 \pm 4.3
Stratum Corneum Hydration, AU			
Shin	26 \pm 9	40 \pm 0	41 \pm 13
Forearm	26 \pm 14	64 \pm 14	63 \pm 9
Abdomen	13 \pm 9	51 \pm 16	49 \pm 10

*TEWL indicates transepidermal water loss; AU, arbitrary units.

†Normative data from our laboratory from a similar age group.

sis of the epidermis (**Figure 6**). The granular layer was well preserved except for some areas of focal hypogranulosis. A few perivascular lymphocytes were present in the upper dermis. Several biopsy specimens from patients with scales and minimal expression of skin lesions showed only mild hyperkeratosis and focal parakeratosis.

ELECTRON MICROSCOPY

The biopsy specimen from a papular lesion on the shoulder of a patient with a full-blown case was examined by electron microscopy. The specimen showed both a scarcity of lamellar membrane structures and marked reduction in secreted lamellar body contents, as well as abnormal secreted contents (**Figure 7**).

Ultrastructure of a hyperkeratotic plaque from the same patient showed a similar appearance, ie, decreased quantities of extracellular lamellae in the stratum corneum. In addition, granular cells in keratotic lesions showed an apparent reduction in the content of keratohyaline granules and keratin filament bundles with abnormal lamellar body contents.

BASELINE TRANSEPIDERMAL WATER LOSS AND STRATUM CORNEUM HYDRATION

Measurements were performed with a combined transepidermal water loss (TEWL) and stratum corneum hydration device (Tewameter and Corneometer CM825; Courage & Khazaka, Köln, Germany) in 4 members with generalized lesions and compared with those in 4 age- and sex-matched unaffected family members, as well as with normative laboratory data from 20 normal controls of similar age (**Table 1**). Measurements for all family members were done in the same room after an acclimatization period of 20 minutes; measurements were taken in the ventral part of the shin, flexor part of the forearm, and the midabdomen above the umbilicus. The TEWL measurements of patients with ichthyosis did not significantly differ from those of unaffected family members and normative values, suggesting that their barrier function was competent. However, stratum corneum hydration values of subjects with ichthyosis were 2-fold

Table 2. Distinguishing Features of Differential Diagnosis of Migratory Ichthyosiform Dermatitis*

Characteristics	Migratory Ichthyosiform Dermatitis	EKV ^{2,3}	EKP ⁴	Annular Epidermolytic Ichthyosis ⁵	Zunich-Kaye Syndrome ⁶	Dorfman-Chanarin Syndrome ^{7,8}
Mode of inheritance	?† (Arab descent)	Autosomal dominant	Autosomal dominant	Autosomal dominant	Autosomal recessive	Autosomal recessive (Arab descent)
Clinical	Migratory polycyclic lesions evolving into generalized scaling with cyclical course, acanthosis nigricans-like lesions in flexures	Fixed keratotic plaques, migratory erythema unassociated with keratotic plaques	Psoriasiform plaques with involvement of palms and soles	Migratory annular and polycyclic hyperkeratotic plaques	Migratory hyperkeratotic erythematous plaques with distinct facial involvement and sparse hair	Generalized fine scales with occasional hyperkeratosis of palms and soles
Associated findings	High association with type 2 diabetes mellitus, obesity, elevated CK level	None	None	None	Neurologic abnormalities, severe mental retardation, coloboma, and congenital heart defects	Myopathy, hepatomegaly, cataracts, lipid vacuoles in white blood cells
Histopathological findings	Hyperkeratosis with focal parakeratosis, presence of granular layer, acanthosis, and papillomatosis	Mild hyperkeratosis and acanthosis	Hyperkeratosis with focal parakeratosis, acanthosis, and occasionally perinuclear vacuolation of keratinocytes	Epidermolytic hyperkeratosis	Hyperkeratosis, with follicular plugging	Hyperkeratosis, focal parakeratosis, acanthosis, lipid droplets in basal cells
Electron microscopy	Scarcity of intercorneocyte lamellae and reduction in lamellar body contents	No abnormalities in lamellar body content	Corneocytes show lipidlike vacuoles, and granular cells contain swollen mitochondria	Typical changes of epidermolytic hyperkeratosis with thickened tonofilaments that form pernicular ring	Incompletely cornified cells and lipid droplets, perinuclear edema and few keratohyaline granules in granular layer	Normal number of lamella, electron-lucent droplets

*EKV indicates erythrokeratoderma variabilis; EKP, erythrokeratoderma progressiva; and CK, creatine kinase.

†At the present time, the mode of inheritance is not clear (see the "Comment" section).

lower in comparison with unaffected members and historical controls on all body sites, suggesting that skin hydration is very low in this disease.

RESPONSE TO TREATMENT AND CLINICAL COURSE

Topical emollients containing urea and/or lactic acid were applied, with no beneficial effect. Systemic retinoids were not prescribed because of abnormal liver function tests in the proband; moreover, patients refused to take other systemic medications and declined further medical follow-up.

COMMENT

The ichthyosiform dermatosis in this family presents the following salient features: (1) onset in early childhood with aggravation in adolescence; (2) more or less pronounced itching; (3) migratory skin lesions, beginning as erythematokeratotic papules that evolve peripherally to form small plaques with a grayish brown scale or crust at the margin and fine scales in the center; the small plaques tend to coalesce, forming large polycyclic lesions; (4) a clearly cycli-

cal course with polycyclic lesions evolving into diffuse generalized scaling or complete remission, only to reappear later (5) acanthosis nigricans-like lesions in flexures; (6) high rate of association with type 2 diabetes mellitus and insulin resistance; (7) high degree of consanguinity; (8) elevated creatine kinase levels with no muscle symptoms; (9) light microscopic findings of lesions characterized by marked hyperkeratosis with focal parakeratosis, presence of granular layer, acanthosis, and papillomatosis; and (10) ultrastructural findings of a scarcity of intercorneocyte lamellae and a reduction in lamellar body contents.

Analysis of the pedigree shows 2 possible modes of inheritance: an autosomal dominant mode with incomplete penetrance as well as an autosomal recessive mode with incomplete penetrance. When there is a fourth generation, it may be possible to be more precise about the mode of inheritance.

We have not encountered any keratinization disorder similar to that present in our kindred, nor any association between ichthyosis and type 2 diabetes mellitus. **Table 2** summarizes dermatoses that should be considered in the differential diagnosis of our cases. Our patients' disorder differed from erythrokeratoderma vari-

abilis because the migratory erythema was always associated with hyperkeratotic plaques and the ultrastructure showed substantial abnormalities of lamellar body content. It also differed from erythrokeratoderma progressiva symmetrica for similar reasons. Clinically it resembles a kindred described by Sahn et al⁵ with an annular epidermolytic ichthyosis, but histologically and ultrastructurally none of our cases had epidermolytic hyperkeratosis. Another congenital migratory ichthyosiform dermatosis was described by Zunich et al⁶ but was associated with mental, neurologic, ophthalmologic, and heart abnormalities lacking in our cases. Dorfman-Chanarin syndrome, an autosomal recessive syndrome that has been reported in Arab families, was included in the differential diagnosis. However, both the clinical and histological appearance and the lack of lipid vacuolation in circulating polymorphs and monocytes, which is the hallmark of this syndrome, rules out this diagnosis in our kindred.

The prevalence rate of type 2 diabetes mellitus in our dermatosis of 38% is much higher than that of the Arab-Israeli population, which is approximately 6% (Michael Kofler, MD, oral communication, April 1999), suggesting that there is a high association between this dermatosis and type 2 diabetes mellitus. Type 2 diabetes mellitus is characterized by hyperglycemia caused by impaired insulin secretion, insulin resistance in muscle, and elevated hepatic glucose production.⁹ The causes of type 2 diabetes mellitus are poorly understood, but its familial clustering implicates genetic factors.¹⁰ The susceptibility to type 2 diabetes mellitus in our pedigree and the high prevalence of obesity and acanthosis nigricans in young affected members may suggest insulin resistance. It is known that among African Americans, acanthosis nigricans is a marker for substantial hyperinsulinemia and insulin resistance and identifies a subset with a much higher prevalence of type 2 diabetes mellitus than in the general population.¹¹ Since our family originates from Africa, the high frequency of acanthosis nigricans in affected nondiabetic members could imply that they are prone to develop diabetes. The high fasting blood insulin levels lend further support to this possibility.

The elevated creatine kinase level in some affected members suggests muscle involvement, but we did not find any clinical anomalies that could explain this finding in our patients. Elevated creatine kinase levels are also common in hypothyroidism,¹² but the latter was ruled out in this family.

It is well established that normal barrier function requires a competent stratum corneum.¹³ Because of the lamellar body anomalies in our patients, we expected to find increased TEWL values. Surprisingly, these values were normal at baseline in our patients. Frost et al¹⁴ reported a 1.2- to 1.4-fold increase in TEWL level in a cohort of patients with ichthyosis. Lavrijsen et al¹⁵ analyzed the water barrier function in different types of keratinization disorders and showed that an elevated TEWL level discriminates differences in skin function between most patients with ichthyosis and normal volunteers.

However, in X-linked recessive ichthyosis and lamellar ichthyosis (transglutaminase I gene mutation deletion), TEWL level is only slightly elevated, and baseline TEWL level is normal in ichthyosis vulgaris.¹⁵⁻¹⁷ In most of these

studies, including our own, TEWL was measured solely at baseline. Even in situations where TEWL levels are normal or near normal at baseline, an underlying defect often becomes apparent after the presence of stress, as in aging,¹⁸ psychological stress,¹⁹ environmental stress,²⁰ and in X-linked recessive ichthyosis.¹⁷ Future studies of this dermatosis should measure the barrier kinetics, which may be a more accurate evaluation of the barrier function. We also found significantly low stratum corneum hydration in comparison with controls, suggesting that in this form of ichthyosis the stratum corneum water reservoir may be very small.

In conclusion, we have described a kindred with migratory ichthyosiform dermatosis in association with type 2 diabetes mellitus and insulin resistance, to the best of our knowledge not previously described. Studies are currently in progress on the molecular genetics of this syndrome and its association with type 2 diabetes mellitus.

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