

Clinical Report

Ichthyosis Follicularis, Alopecia, and Photophobia (IFAP) Syndrome: Report of a New Family With Additional Features and Review

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Two brothers with ichthyosis follicularis, noncicatricial universal alopecia, photophobia, hyperkeratotic psoriasis-like lesions, nails dystrophy, inguinal herniae, cryptorchidism, short stature, seizures, and psychomotor developmental delay are described. These features correspond to the ichthyosis follicularis, alopecia, photophobia (IFAP) syndrome. The youngest brother had in addition a bilateral absence of 4th fingers and camptodactyly, features never reported in patients with IFAP syndromes.

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KEY WORDS: alopecia; ichthyosis follicularis; photophobia; ectrodactyly

INTRODUCTION

Ichthyosis is a congenital dermatological disease that is represented by thick, scaly skin. It has been reported in more than 200 syndromes, of which about 40 are associated with alopecia. The association of ichthyosis follicularis, atrichia, and photophobia (IFAP) was first reported as a syndrome by MacLeod [1909] in three boys.

Grant sponsor: The Genethon Association.

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Received 27 January 2003; Accepted 22 April 2003

DOI 10.1002/ajmg.a.20352

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Since then, nearly 25 patients have been reported with occasional additional features [Zeligman and Fleisher, 1959; Eramo et al., 1985; Hamm et al., 1991; Martino et al., 1992; Keyvani et al., 1998; Cursiefen et al., 1999; Konig and Happle, 1999; Boente et al., 2000; Sato-Matsumura et al., 2000; Bibas-Bonet et al., 2001; Cambiaghi et al., 2002].

Here, we report on two brothers with a severe presentation of the IFAP syndrome, with additional clinical features. A review of the literature was performed leading to a discussion of differential diagnoses and possible modes of inheritance.

CLINICAL REPORTS

The two sibs are the products of a nonconsanguineous Lebanese couple.

Patient 1

Patient 1 is the first child of the family. At the time of his birth, both parents' age was 33 years. Pregnancy had been unremarkable. Delivery was at term by cephalic presentation. At conception, the patient's weight was 2,400 g (5th centile), his length 52 cm (60th centile), and the occipito-frontal circumference (OFC) 32 cm (10th centile). At birth, the lack of scalp and eyebrow hair and eyelashes and generalized ichthyosis were noted. By 4 months of age, the child had developed a bilateral inguinal hernia which required surgery. Photophobia became apparent at the first year of life. Developmental delay was suspected during the 2nd month of life, when the mother noticed that her baby was hypotonic and had difficulties to feed. He held up his head at 2 years, and was able to walk without help and talk at around age 3-1/2 years. By 2-1/2 years of age, he had generalized tonic-clonic seizures that accompanied high fever, and for which he was treated. An EEG was performed and showed slowing of background activity and diffuse

paroxysmal figures. At that time, radiographs of the chest and hands, EKG, and echocardiogram, all were normal. Renal ultrasound disclosed the presence of bilateral discrete dilatation of the renal cavities. Dental development was normal. Sweating and hearing appeared not to be impaired. He repeatedly developed anaphylactic reactions to eggs but no other atopic manifestations were noted.

The patient was examined when he was 8 years. His speech was intelligible with some distortions. He was attending a normal school but his performance was below average. According to his mother, he had repeated upper respiratory infections and pneumonia. His height was 103.5 cm (<3rd centile), weight 17 kg (<3rd centile), and OFC 49.6 cm (3rd centile). He was suffering from severe photophobia leading him to keep looking down with eyes almost closed to avoid the light, in addition to chronic tearing. Physical examination showed that he had a prominent and high forehead, large ears, complete absence of hair, eyelashes and eyebrows, severe angular cheilitis around the mouth (Fig. 1), generalized dryness of the skin with ichthyotic scaling leading to severe itching, eczematous changes of the forearms, dystrophic nails, and hyperkeratotic psoriasis-like lesions localized in the cleft between buttocks. No lesions in the form of spiky follicular hyperkeratoses were found. Sweat pores were present. Teeth were normal. Dermatoglyphic palm patterns were unremarkable. External genitalia exam showed a right cryptorchidism. Neurological examination and auditory brainstem response were normal. Ophthalmologic evaluation revealed that visual acuity was limited bilaterally to counting fingers at no more than 1 m. Slit lamp examination revealed the presence of a diffuse punctate epithelial keratopathy with diffuse vascularizing keratitis and rare areas of partial corneal opacification next to areas with maintained corneal transparency. The anterior chamber, lens, and ocular fundus were normal.



Fig. 1. Photograph of patient 1 (left) and patient 2 (right). Note the photophobia, high forehead, large ears, complete absence of hairs, eyelashes and eyebrows, angular cheilitis around the mouth, dystrophic nails, and ectrodactyly in patient 2.

Abdominal sonography, and echocardiogram were unremarkable. Spine radiographs disclosed the presence of osteosclerosis of the dorsal end-plates and abnormal vertebral bodies of L4 and L5. Other body radiographs were unremarkable. Biopsy specimen obtained from the shoulder showed focal parakeratosis and attenuated granular cell layer. A specimen from the right arm showed follicular parakeratosis and plugging consistent with follicular hyperkeratosis, and one from the scalp

a



b



Fig. 2. a, b: Patient 2. Note the complete absence of scalp hair, and the geographical appearance of the ichthyotic scaling and erythematous and yellowish thick scaly hyperkeratotic plaques.



Fig. 3. Hand radiographs of patient 2 at age 5 years. Note the absence of both 4th fingers.

showed actinic damaged skin. These findings were interpreted as being consistent with ichthyosis follicularis. Complete blood count, aminoacid studies of plasma and urine, liver and thyroid functions, zinc, folic acid, ferritine, and urinalysis, were unremarkable. Immunological screening was within the normal limits except for the IgG2 which were slightly under average. Lymphocyte chromosome study using G- and R-banding (550 bands) revealed a 46,XY karyotype.

Patient 2

Patient 2 was born 2 years after his affected brother. At birth, his weight was 2,200 g (3rd centile), and length 48 cm (10th centile). He presented the same clinical features as his brother, and in addition an absence of both 4th fingers. His clinical course was identical to that of his affected brother except that he did not have inguinal hernia. Early developmental milestones were delayed. He was able to walk without help at 5 years.

He was 6 years old when he was evaluated at the same time as his affected older brother. His weight was 15 kg

(3rd centile), height 100 cm (<3rd centile), and OFC 49.5 cm (5th centile). He has mental retardation, making sounds but no words, though he understood simple commands. He had an elongated face with a narrow bifrontal diameter, a prominent occiput, frontal bossing, complete absence of scalp hair, eyelashes, and eyebrows, red gums, smooth tongue, and normal teeth (Fig. 1). Ectrodactyly and camptodactyly were noted on both hands. Nails were hyperkeratotic. The skin was very dry and harsh and there was typical large platelike ichthyotic scaling over much of the body but particularly marked on the scalp and neck. The lesions on the scalp consisted of erythematous and yellowish thick scaly plaques. They were clearly delineated by an elevated border giving them a geographical appearance. Skin overlying the napkin area was markedly thick, hyperkeratotic, and entirely covered with silver scales, resembling a psoriasis lesion (Fig. 2a,b). Mild hyperkeratotic lesions were also seen over the elbows, knees, palms, and soles. Sweat pores were present. Genital examination was normal. Neurological examination disclosed the presence of hypotonia, and mild gait abnormality. Ophthalmologic evaluation revealed the same ocular findings of those of his brother except that he was slightly less photophobic, and had a moderate left eye esotropia. Visual acuity was not determined.

Abdominal sonography and echocardiogram were unremarkable. Lymphocyte chromosome study revealed a normal 46,XY karyotype. Total body radiographs revealed the bilateral agenesis of the 4th fingers (Fig. 3).

Neither parents presented any of the features of the affected boys. Dermatological examination of the mother (examination of the head with a special attention to the scalp, the neck, and the four limbs) was normal. Further examination was refused by the mother.

DISCUSSION

Generalized ichthyosis and alopecia have been reported in very few syndromes (Table I).

Between those listed, consideration was given to two diagnoses, the IFAP syndrome and the dermatrichic syndrome [Freire-Maia and Pinheiro, 1984]. These two

TABLE I. Major Conditions in Which Ichthyosis and Alopecia are Both Present

Syndrome	Mode of inheritance	MIM or reference
Ablepharon-ichthyosis	Uncertain	Chaurasia and Goswami [1971]
Alopecia-ichthyosis-pseudohermaphroditis	Uncertain	Kauschansky et al. [1998]
Alopecia-skeletal anomalies-mental retardation	Autosomal recessive	203550
Deafness-ichthyosis	Uncertain	Oikarinen et al. [1980]
Dermotrichic	X-linked recessive	308205
Ectodermal dysplasia-alopecia-mental retardation	Uncertain	Steijlen et al. [1994]
Hayden syndrome	Uncertain	Freire-Maia and Pinheiro [1984]
Hereditary mucoepithelial	Autosomal dominant	158310
IFAP	X-linked/autosomal dominant	308205
Ichthyosis-deafness-hirshprung	Uncertain	Mallory et al. [1989]
Ichthyosis-hypotrichosis-hypohidrosis	Autosomal recessive	602400
Keratitis-ichthyosis-deafness (KID) syndrome	Autosomal dominant	242150
Keratosis follicularis spinulosa decalvans	X-linked/autosomal dominant	308800
Sjogren-Larson-like	Autosomal recessive	242510
Trichooculodermovertebral syndrome	Uncertain	Alves et al. [1981]
Woodhouse syndrome	Autosomal recessive	241080

syndromes have overlapping manifestations characterized by ichthyotic lesions and atrichia from birth, and short stature, mental retardation, and seizures. They can be differentiated mainly on the basis of skeletal and intestinal anomalies present in the dermatotrichic syndrome and ocular and respiratory disorders in the IFAP syndrome. Clinical manifestations identified in our patients were felt to be consistent with the IFAP syndrome (Table II), but with severe skin lesions and ectrodactyly and camptodactyly present in the youngest brother, never seen before in any other patients. The severity of the skin manifestations and the hands malformations might be secondary to variable expressivity of the disease. Follicular hyperkeratosis is evident in the first year of life; in most cases thornlike projections were described except in the present patient and the one reported by Boente et al. [2000] (Table II). Nevertheless, it is worth noting that such skin changes could no longer be remarkable after a certain age.

In our patients, manifestations of the dermatotrichic syndrome were present as well, mainly large ears, frontal bossing, dystrophic nails, and skeletal malformations. Overlapping of both syndromes had already been noted in another patient [Martino et al., 1992] showing that they could one and the same entity. Different possibilities including pleiotropism of a single gene resulting in the two disorders, allelic mutations and a contiguous gene syndrome could explain variations in clinical features.

The etiology of the IFAP syndrome is still unknown. The quite variable phenotypes among reported patients suggest a deletion of contiguous genes. However, karyotypes performed in few patients and the present family did not show any abnormalities. Mode of inheritance is also not definitely determined. Most of the reported patients were males, and in some families milder effects were noted in possible transmitting females. Furthermore, lesions following the lines of Blaschko were noted in heterozygous women [Konig and Happle, 1999], and male-to-male transmission was never been observed. All this suggests an X-linked recessive inheritance of this rare syndrome. This family, with two affected boys and nonconsanguineous normal parents confirms this hypothesis. Recently, a mother and daughter [Sato-Matsumura et al., 2000], and two unrelated female patients [Cambiaghi et al., 2002] with an IFAP syndrome have been reported. They did not have a linear distribution of skin lesions suggesting an autosomal dominant transmission. Nevertheless, they were all less affected than most of male ones, and no female-to-male transmission was observed. Thus, beside the autosomal dominant inheritance, we can assume that this syndrome may also be inherited as an X-linked dominant or recessive trait depending on the mutation, as it has been reported in the NEMO gene for instance [Zonana et al., 2000].

In conclusion, the two brothers reported herein presented the IFAP syndrome with additional features. We anticipate that other reports of similar cases will enable further delineation of the clinical spectrum of this entity, and show whether we are dealing with clinical or genetic heterogeneity of the disorder.

TABLE II. Review of Clinical Features Associated With IFAP Syndrome

	Personal report	MacLeod [1909]	Zeligman and Fletscher [1959]	Freire-Maia and Pinheiro [1984]	Eramo et al. [1985]	Hamm et al. [1991]	Martino et al. [1992]	Keyvani [1998]	Konig and Happle [1999]	Boente et al. [2000]	Bibas-Bonet et al. [2001]	Sato-Matsumura et al. [2000]	Cambiaghi et al. [2002]
Sex	2M	3M	2M	M	2M	M	M	M	M/2F	M	M	2F	2F
Congenital alopecia	+	+	+	+	+	+	+	+	+	+	+	+	+
Developmental delay	+	-	+	+	+	+	+	+	-	+	+	+	-
Hypotonia	+	-	+	+	+	+	+	+	-	+	+	+	-
Short stature	+	-	-	-	±	+	+	+	-	+	+	-	-
Microcephaly	+	-	-	-	±	+	+	+	-	+	+	-	-
Frontal bossing	+	?	?	+	+	+	+	+	+	?	+	+	±
Photophobia	+	+	+	+	+	+	+	+	+	+	+	+	+
Seizures	+	+	+	+	±	+	+	+	+	+	+	+	-/+
Mental retardation	+	-	+	+	+	+	+	+	+	+	+	+	+
Ichthyosis	+	-	+	+	+	+	+	+	+	+	+	+	+
Psoriasisiform plaques	+	-	+	+	+	+	+	+	+	+	+	+	+
Cheilitis	+	-	+	+	+	+	+	+	+	+	+	+	+
Lack of sebaceous glands	+	-	+	+	+	+	+	+	+	?	+	+	+
Dystrophic nails	+	-	+	+	+	+	+	+	+	+	+	+	+
Hypohydrosis	+	-	+	+	+	+	+	+	+	+	+	?	+
Hyperkeratosis	+	-	+	+	+	+	+	+	+	+	+	+	+
Spiny follicular projections	+	-	+	+	+	+	?	?	+	+	+	+	+
Recurrent infections	+	-	+	+	+	+	+	+	+	+	+	+	+
Atopic manifestations	+	-	+	+	+	+	+	+	+	+	+	+	+
Mild vertebral changes	±	-	+	+	+	+	+	+	+	+	+	+	+
Inguinal hernia	+	-	+	+	+	+	+	+	+	+	+	+	+
Cryptorchidism	+	-	+	+	+	+	+	+	+	+	+	+	+
Other malformations	+	-	+	+	+	+	+	+	+	+	+	+	+
Possible mode of inheritance	Hands XLR	XLR	Cerebral; hernia XLR	Megacolon; anemia XLR	XLR	XLR	Intestinal XLR	Renal XLR	XLR	Neonatal tooth XLR	Cerebral XLR	AD/XLR	AD/XLR

M, male; F, female; AD, autosomal dominant; XLR/D, X-linked recessive/dominant.

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