Ichthyosis follicularis, alopecia and photophobia syndrome (IFAP): report of the first case with ocular and cutaneous manifestations in Brazil with a favorable response to treatment

Síndrome de ictiose folicular, alopécia e fotofobia (IFAP): relato do primeiro caso com acometimento ocular e cutâneo do Brasil e da resposta favorável ao tratamento

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ABSTRACT

Ichthyosis follicular, alopecia, and photophobia (IFAP) syndrome is a rare disease, with possible X-linked mode of inheritance. The patient presented with ocular findings of photophobia, corneal scarring and erosions, superficial and deep corneal vascularization and myopia. He was treated with artificial tears and punctal occlusion with small improvement of photophobia. After three months using systemic retinoid (Acitretina) and posterior amniotic membrane transplantation in the left eye, there was a significant improvement of photophobia, corneal erosions and neuropsychomotor development.

Keywords: Ichthyosis/diagnosis; Alopecia/diagnosis; Photophobia/diagnosis; Ichthyosis/genetics; Alopecia/genetics; Photophobia/genetics; Ichthyosis/drug therapy; Alopecia//drug therapy; Photophobia/drug therapy; Retinoids/therapeutic use; Amnion/transplantation; Chromosomes, human, X

RESUMO

A síndrome de ictiose folicular, alopecia e fotofobia (IFAP) é uma doença rara, com possível modo de herança ligado ao cromossomo X. O paciente apresentou achados oftalmológicos de fotofobia, cicatrizes e erosão corneanas, neovascularização superficial e profunda da córnea e miopia. Foi iniciado uso de lubrificantes e oclusão do ponto lacrimal com discreta melhora da fotofobia. Após uso de retinóide sistêmico (Acitretina) por três meses e posterior transplante de membrana amniótica no olho esquerdo apresentou melhora importante da fotofobia, das erosões corneanas e do desenvolvimento neuropsicomotor.

Descritores: *Ictiose/diagnóstico; Alopecia/diagnóstico; Fotofobia/diagnóstico; Ictiose/genética; Alopecia/genética; Fotofobia/genética; Ictiose/quimioterapia; Alopecia/quimioterapia; Fotofobia/quimioterapia; Retinóides/uso terapêutico; Âmnio/transplante; Cromossomos humanos X; Relatos de casos*

INTRODUCTION

The ichthyosis follicular, alopecia, and photophobia (IFAP) syndrome was first described by MacLeod in 1909[1]. Up to now nearly twenty-five cases were described. This is the first ophthalmology case described in detail in Brazil. The X-linked recessive mode of inheritance was at first considered, though lately an autosomal pattern has been suggested[2]. More recently Oeffner et al. showed the mutation of the gene MBTPS2 associated with the IFAP phenotype[3].

This syndrome shows ocular findings such as photophobia, corneal scarring and corneal erosion[1,4-5]. The photophobia seems to be due to corneal defects such as central leucoma, recurrent epithelial erosions, neovascularization and potential ulcers[5].

This report describes a case of ichthyosis follicularis, alopecia and photophobia (IFAP), its ocular findings and discusses therapeutic treatment approaches.

CASE REPORT

A three-year and three-month-old white male patient was referred to the ophthalmology department with alopecia, loss of eyelashes and eyebrows, xerosis and photophobia since 4 months of age. The intense photophobia made impossible for him to open his eyes before the end of the day.

The boy was born at term by natural birth, weighing 3,300 g. He presented sickle cell trait. He showed delayed speech and low weight. His family history shows that he had non-consanguineous caucasian parents. There was no history of similar illness in the family.

The dermatological examination showed skin phototype II, areas of capillary rarefaction, thin and brittle hair with the presence of follicular papules, severe xerosis, residual hypochromic macules and no evidence of traction, therefore excluding a diagnosis of psoriasis. He presented loss of eyelashes and eyebrows (Figure 1A). Under optical microscopy the hair presented *trichorrhexis nodosa* (Figure 1B). A skin biopsy showed hyperkeratosis with follicular plugging (Figure 1C). Vitamin A deficiency was excluded by direct determination.

On examination the child showed intense photophobia (Figure 1C) and visual acuity of 20/130 measured by Teller Acuity Cards in both eyes. At biomicroscopy, a more severe diffuse bilateral corneal erosion was observed on the left eye, bilateral central leucoma and bilateral superficial and deep corneal neovascularisation (Figure 2 A). His eyelids had no abnormalities, the tear strip had 0.2 mm in both eyes, no Schirmer's test was performed. The intraocular pressure was of 8 mmHg in both eyes and cycloplegia of -1.00 diopter in

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The authors have no commercial interest in the medication used by the patient. The medication used was the one available in the Public Health System.

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both eyes. He was prescribed glasses with photochromic lenses and started regular use of lubricant eye drops and lubricant gel.

After two months using regularly lubricant eye drops there was no improvement in erosion, neovascularization and leucoma, however, photophobia had a small improvement. After that, the use of therapeutic contact lenses was an option but the frequent lens drop-out prevented their use. So, a permanent occlusion of the lower lachrymal point of both eyes was performed with mild bilateral corneal erosion improvement. As the patient still complained of photophobia, Acitretin at 10 mg/day was administered orally. After 2 months of use of this medication an improvement of the fluorescein pattern and photophobia was noted, with no change in neovascularization and leucoma. The use of systemic retinoid (Acitretin) was suspended due to lack of supply of this medication by the Public Health System. As there was still a significant phothophobia in the left eye, with the child closing it and preventing him from carrying out his normal activities, after 1 year and 4 months of the beginning of the treatment, an amniotic membrane graft in the left eye was an option. This eye had greater epithelium erosion and worse response to the previous treatment. The technique used was to suture the membrane with continuous stitch on the cornea with 10.0 nylon and on the conjunctiva with vicryl 8.0, covering the entire cornea and limbal area. There was an improvement in epithelialization and leucoma (Figure 2 B), and photophobia in this eye. The patient made use of topical corticosteroid for 2 months after surgery and since then until the follow-up of 8 months makes use of lubricant, showing stability. The child showed improvement in mood, behavioral change, increasing his activities and gaining weight.

DISCUSSION

Characteristics of the IFAP syndrome are cutaneous manifestations such as significant xerosis and follicular papules[6]. Total alopecia and, in some cases, thin and sparse hair are also a finding in this syndrome[1]. Differential diagnoses are made with otherwise rare diseases and several clinical and epidemiological characteristics must be considered (Table 1).

The ocular findings are photophobia, corneal scars, punctate keratopathy, corneal erosion, allergic keratoconjunctivitis, superficial and deep corneal neovascularization, horizontal nystagmus, and myopia[1,5-6]. Myopia appears to be caused by deprivation of the adequate growth of the eyeball[1,6]. Corneal changes are caused by modification of the tear film and recurrent atopic keratoconjunctivitis[1,6]. Photophobia may exist since birth or may have developed later[1,6]. Vision is generally low[5] and appears to be due to central leucoma. Fundus findings may vary from vascular tortuosity, staphyloma and no change[5].

Regarding neurological findings, delayed neuropsychomotor development is a common feature of most patients. There are reported cases of mental retardation, epilepsy and other neurological findings[4].

Retinoids, such as Acitretin, have been used in genetic disorders from keratinization in children[7] due to action in the mechanisms of cell proliferation and differentiation. Different aspects of the favorable clinical response occurred, in average, after the third month of the beginning of the treatment[8]. There are reports of improvement in the fluorescein pattern in IFAP with 6 months of use of Acitretin. However, photophobia and corneal neovascularization showed no improvement[3]. Photophobia shows to have spontaneously improved in some cases. In the present study, the use of Acicretin showed an improvement in the fluorescein pattern, as described in the literature[4]. Clinical response was observed in the second month of treatment, before what was previously described[8].

Persistent epithelial defects are difficult to treat and are caused by inflammation of the ocular surface, damage to stem cells and the epithelium basement membrane. Although less frequently applied

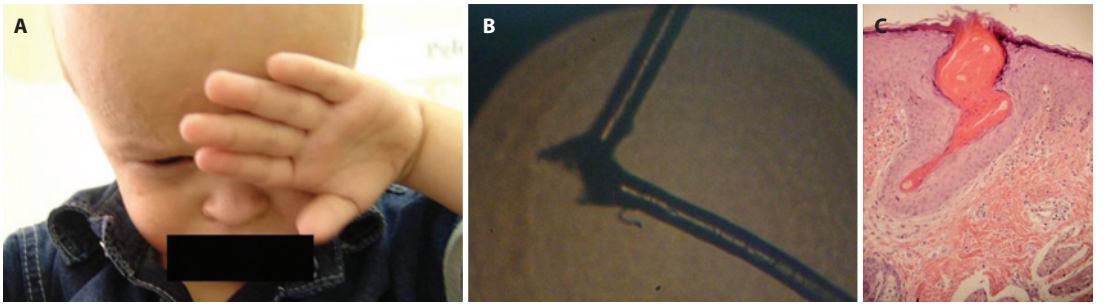

Figure 1. A) Loss of eyebrows and eyelashes. Intense photophobia; B) Optical microscopy 100X. Hair with *Trichorrhexis nodosa*; C) Optical microscopy Hematoxylin and Eosin 100X. Back skin biopsy with hyperkeratosis and follicular plugging.

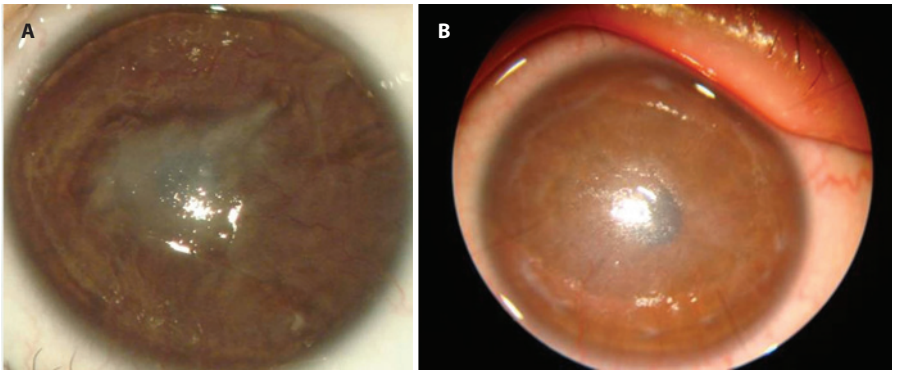

Figure 2. A) Left eye: Corneal leucoma, epithelial erosion, superficial and deep neovascularisation; B) Left eye: Improvement of corneal leucoma, epithelial erosion and neovascularisation.

Table 1. Differential diagnoses of IFAP syndrome

Syndrome	Dermatological and systemic findings	Mode of inheritance	Ocular findings	Reference
Ichthyosis, photophobia, alopecia (IFAP)	Follicular hyperkeratosis, congenital alopecia, hyperkeratosis. Onset at birth or during the first year.	X-linked/autosomal dominant. Deficiency of MBTPS2.	Photophobia, punctate keratopathy, erosion, corneal scarring	Cursiefen C, 1999
Nonbullous congenital ichthyosiform erythroderma (CIE)	Fine white scales, erythroderma, palmoplantar keratoderma, alopecia, loss of eyebrows. Onset at birth or during the first year.	Autosomal recessive. Loci 2q33-q35; 14q11.2, 17p13.1; 19p13.1-p13.2; 19p12-q12.	Ectropion	Akiyama M, 2003
Classic lamellar ichthyosis	Large, dark, platelike scales, erythroderma, hyperkeratosis. Onset at birth or during the first year.	Autosomal recessive Loci 14q11 and 2q33-35.	Severe ectropion, cicatricial lagophthalmos, blepharitis	Pinna A, 2004
Sjogren-Larsson	Congenital ichthyosis, Intellectual disability, spastic diplegia or tetraplegia. Onset in the first year of life.	Autosomal recessive. Aldehyde dehydrogenase (FALDH) deficiency Locus 17p11.	Pigmentary changes in the retina	Aslam AS, 2007
X-linked ichthyosis	Generalized desquamation of large, adherent, dark brown scales, cryptorchidism. Onset at birth.	Steroid sulfatase (STS) deficiency. Locus Xp22.3.	Corneal opacity	Hernández-Martín A, 1999
Keratosis follicularis spinulosa decalvans (KFSD)	Follicular hyperkeratosis, progressive cicatricial alopecia, fissuring of the palms and soles. Onset on childhood.	X-linked/autosomal dominant Locus Xp22.1.	Photophobia, blepharitis, ectropion, and corneal degeneration	Bellet JS, 2008

in children, amniotic membrane was a useful option here to revert chronic epithelial defect. Moreover, it could also be considered as a carrier of limbal stem cells, as recently reported[9-10].

The results remain the same until the moment when 8 months of follow-up was completed. The child showed behavioral changes, adequate growth and weight gain. The treatment as a whole had a positive impact on the child's quality of life, as the left eye was the one that was closed for the most time of the day before the surgery.

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