Ocular Findings in Ichthyosis Follicularis, Atrichia, and Photophobia Syndrome

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Ichthyosis follicularis, atrichia, and photophobia (IFAP) are typical features of a rare neuroichthyosis termed IFAP syndrome. We demonstrate the ultrastructural findings of the eyes from a 33-year-old patient with IFAP syndrome. Clinically, eyebrows and eyelashes were absent from birth, and photophobia was noted at the age of 1 year. The globes measured 28 and 29 mm, respectively, and both eyes showed a posterior staphyloma. Histopathologically, bilateral centrally located subepithelial avascular corneal scarring with secondary corneal amyloid deposition was found. In addition to already described ocular abnormalities in IFAP syndrome we demonstrate ultrastructural anomalies of desmosomes and tonofilaments in corneal epithelium; defects of basement membrane, Bowman layer, and anchoring fibrils; secondary corneal amyloid deposition; and keratocyte degeneration. A defective tear film, recurrent atopic keratoconjunctival inflammations, or a primary anomaly of corneal epithelial adhesion are potential causes for the corneal defects. Photophobia is most likely due to corneal abnormalities.

The syndrome of ichthyosis follicularis, atrichia, and photophobia (IFAP) was first recognized by MacLeod in 1909. Since then, 10 patients with this rare, probably X-linked syndrome have been described. The syndrome belongs to a group of ichthyosiform skin diseases with ocular signs and symptoms such as photophobia and corneal scarring. This is, to our knowledge, the first clinicopathologic study of eyes from a patient with IFAP syndrome.

**REPORT OF A CASE**

The patient was the firstborn of 3 children from nonconsanguineous parents with an unremarkable family history. Lack of eyebrows and eyelashes was noted shortly after birth (Figure 1). The skin was red and scaly. Photophobia and atrichia were noted at the age of 1 year. Whereas mental and motor development seemed to be normal until 2 years of age, the following years were characterized by generalized seizures and severe retardation of growth and psychomotor development. From age 14 years the patient lived in an institution for severely handicapped persons. Visual acuity and detailed ophthalmologic examination were not obtainable because of poor compliance. At age 25 years, an external ophthalmologic examination noted corneal scarring and a myopic fundus. The patient died at age 33 years of bronchopneumonia, with postmortem studies confirming the diagnosis of IFAP syndrome. Other neuropathologic and dermatopathologic findings are described by Keyvani et al.

Both eyes were enucleated 25 hours post mortem. The globes measured 28 and 29 mm, respectively, with a posterior staphyloma in both eyes. Histopathologically, subepithelial scarring was noted in both corneas centrally with secondary corneal amyloid deposition in the left eye (Figure 2). Retina showed stratified architecture and signs of autolysis with retinal ganglion cells only scarcely detectable. The optic nerve exit was oblique without marked signs of atrophy (Figure 3).

Ultrastructurally, the corneal epithelium showed reduced numbers of desmo-
somes, dispersed and irregularly arranged bundles of tonofilaments particularly at the desmosomal junction, and dilated intercellular gaps with segregated cytoplasmic globules containing desmosome remnants (Figure 4, A and B). Cell splitting did not occur within the desmosomal plaque, but along cytoplasmic protrusions. The irregular basal surface of epithelial cells displayed rarefied hemidesmosomes, dispersed tonofilament bundles, and bundles of anchoring fibrils within surface invaginations (Figure 5, A and B). Basement membrane was focally absent and focally markedly thickened up to 12 µm, displaying a multilayered network composed of reduplicated fragments and interwoven bundles of anchoring fibrils (Figure 5, A-D). The Bowman layer was also partly missing. Diffusely arranged electron-dense material, degenerated keratocytes with cytoplasmic vesicles, and thinned collagen fibrils (20-30 µm in diameter) were found in the corneal stroma (Figure 6).

COMMENT

The presence of ocular abnormalities is important for the diagnosis of IFAP syndrome. Besides photophobia, which may be present at birth or develop later, other known features of IFAP syndrome are punctate keratopathy, erosion, corneal scarring, atopic keratoconjunctival inflammation, horizontal nystagmus, myopia, and absence of eyebrows and eyelashes. Myopia may be caused by defective control of eye growth owing to reduced visual input (form deprivation myopia). Gray stromal opacities, known to occur in
Figure 4. Electron microscopy of corneal epithelium in ichthyosis follicularis, atrichia, and photophobia syndrome. A, Dilated interepithelial gaps filled with cytoplasmic globules (scale = 3 µm). B, Higher magnification of interepithelial gaps showing globules with remnants of desmosomes (dense plaques) and dispersed bundles of tonofilaments (t). Some cell-cell contacts are still in place (arrows) (scale = 0.5 µm).

Figure 5. Electron microscopy of corneal epithelial-stromal junction (A, B, and D: scale = 1 µm; C: scale = 5 µm). A, Irregular basal epithelial cell surface with dilated intercellular gaps (large asterisk), large dispersed tonofilament bundles (t), multiple basement membrane defects (arrowheads), and anchoring fibrils (small asterisks) lacking contact to anchoring plaques in absent Bowman layer. B, Multilamellar fragments of basement membrane (arrowheads) in an area of missing Bowman layer (anchoring fibrils [asterisks]). C, Basement membrane (bm) thickness is increased up to 12 µm in an area of intact Bowman layer (bl). D, Detail of part C showing multilayered network of basement membrane lamellae and bundles of anchoring fibrils.
patients with X-linked ichthyosis,4,5 or an ectropion, a typical feature of lamellar ichthyosis, were not seen in our patient.

In addition to already known ocular features of IFAP syndrome, we demonstrated anomalies of desmosomes and tonofilaments in the corneal epithelium, basement membrane defects, and focal multilamellar reduplications significantly increasing basement membrane thickness, unanchored anchoring fibrils, defects of Bowman layer, keratocyte cytoplasmic segregation, and secondary corneal amyloid deposition.

Possible causes for the corneal abnormalities include a defective tear film and recurrent atopic keratoconjunctival inflammations, known to occur in patients with IFAP syndrome.1-3 Almost complete absence of sebaceous glands was noted in skin biopsy specimens of the described patient2 (scalp, thorax, inguinal region, toe); whether meibomian glands were also lacking is not known. Deficiency of lacrimal fluid and lack of sebaceous glands have been noted in other patients with IFAP syndrome.2,3 But the observed ultrastructural changes in the epithelial-stromal junction could also be the primary defect in this ectodermal dysplasia causing other secondary corneal abnormalities. In patients with autosomal-recessive lamellar ichthyosis a defect in transglutaminase 1, which is responsible for cross-linking of keratinocytes, was detected. In addition, transglutaminases (type 2) seem to be involved in cross-linking of anchoring fibrils in the dermal-epidermal junction.6 These findings could explain defects in epithelial adhesion to Bowman layer. Basement membrane thickening could possibly be due to hyperactive turnover of epithelial basal cell layer as known to occur in X-linked ichthyosis, which may in part be facilitated by the abnormalities in the desmosomal-cytoskeletal interaction. Histopathologically, it is not possible to determine whether the described ultrastructural changes are secondary to recurrent erosion, ulceration, reepithelialization due to a defective tear film, atopic inflammations, or a primary defect of epithelial adhesion.

Photophobia in IFAP syndrome is most likely due to corneal abnormalities such as the described central corneal scarring and the potentially preceding erosion and ulceration; defects of the central visual system cannot be ruled out as additional causes.1-3 Retinal anatomy was normal in our patient except for signs of autolysis.

The ultrastructural findings demonstrated in this patient could suggest a primary abnormality at the corneal epithelial-stromal junction with anomalies of desmosomes, tonofilaments, and, subsequently, basement membrane and anchoring fibrils causing secondary changes in the corneal stroma. Photophobia in IFAP syndrome is most likely explained by corneal abnormalities.

Accepted for publication December 29, 1998.

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REFERENCES