

SHORT COMMUNICATION**Case report**

Keratoconus and Fuchs' heterochromic iridocyclitis: a coincidence or a defect during embryogenesis?

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PURPOSE. We aimed to discuss the possible role of developmental embryologic factors in neural crest cells in the aetiology of keratoconus and Fuchs' heterochromic iridocyclitis by presenting this case.

CASE REPORT. We diagnosed bilateral keratoconus and unilateral Fuchs' heterochromic iridocyclitis in a 19 year old women complaining of progressively blurring vision in her left eye. We also examined most of her first and second degree relatives. One niece had FHI in addition to a choroidal nevus in the inferior temporal quadrant of her left eye.

DISCUSSION. Regarding the common embryological origins of iris stroma, uveal melanocytes and corneal stroma, it might be worth considering that the combination of FHI and keratoconus is not coincidental. A role of embryologic factors in neural crest cells in the etiology of both diseases cannot be excluded. (*Eur J Ophthalmol* 2001; 11: 73-6)

KEY WORDS. Keratoconus, Fuchs' heterochromic iridocyclitis, Etiology, Embryogenesis

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INTRODUCTION

Fuchs' heterochromic iridocyclitis (FHI) is a chronic, unilateral indolent uveitis that has been reported in combination with a retinitis pigmentosa-like clinical picture, ocular trauma, the subclavian steal syndrome, hemifacial atrophy, Horner's syndrome and Moebius syndrome (1). Keratoconus is a non-inflammatory, progressive, non-vascular axial corneal ectasia whose etiology and pathogenesis are not clear. There are several reports of systemic and ocular disorders associated with keratoconus (2). However, to our knowledge there is no report of an association between keratoconus and FHI.

Case report

A healthy 19-year-old woman complained of progressively blurring vision in her left eye. She had had

an extracapsular cataract extraction and posterior chamber intraocular lens implanted in her right eye four months before in another ophthalmology clinic.

The visual acuity was 0.3 in the right pseudophakic eye and 0.05 in the left eye. Slit-lamp examination of the right eye revealed hypochromia and fine, depigmented, evenly distributed keratic precipitates on the corneal endothelium, characteristic of FHI (Fig. 1). The pupil was round and the posterior chamber intraocular lens was centrally located. Slight posterior capsular opacification was noted. There were no cells in the anterior chamber. From old records we saw that the posterior subcapsular cataract and hypochromia existed before the cataract surgery. In the left eye, she had corneal thinning and protrusion at the apex. Topographical analysis confirmed our diagnosis of bilateral keratoconus. Intraocular pressures were normal in both eyes. Fundoscopic examination of the two eyes was unremarkable.



Fig. 1 - Photograph of the patient showing apparent hypochromia and pseudophakia in the right eye. There is a special keratoconus contact lens in her left eye.

The visual acuity of the right eye improved to 0.6 with the aid of $-1.0 -3.50$ 90° spectacle lens and in the left eye it improved to 0.9 with a gas-permeable hard keratoconus contact lens with the base curve 6.70, power -5.0 D and diameter 9.30 mm.

To investigate the possibility of hereditary pattern for either keratoconus or FHI, we planned to examine the patient's first and second degree relatives. One niece had mild heterochromia and fine, depigmented, evenly distributed keratic precipitates on the corneal endothelium in her left eye, giving a diagnosis of FHI. Fundoscopic examination was unremarkable in the right eye, but there was a choroidal nevus in the inferior temporal quadrant of the left fundus.

DISCUSSION

To our knowledge, this is the first report of a patient with bilateral keratoconus and unilateral FHI. Although the exact etiology of FHI is unknown, there are many theories about the pathogenetic mechanisms. Fuchs offered the first theory (3), then an infective etiology became popular after the publication of a number of reports indicating a high incidence of chorioretinal lesions characteristic of toxoplasmosis in patients with FHI (4-7). A few reports presented cases of FHI in family members, suggesting a hereditary predisposition (8). La Hey (1) pointed out the abnormal adrenergic innervation in FHI, but has never been confirmed. Vascular factors (1) and previous ocular trau-

ma (4) have been suggested as etiologic factors in some reports.

The eye is an immunologically privileged site, as shown by the ACAID (anterior chamber associated immune deviation). Some aspects of antigen-driven T-cell function are inhibited by the cytokine transforming growth factor (TGF- β) which is secreted by the iris and ciliary body parenchymal cells. La Hey (1) suggested the possibility of diminished function of ACAID and a low concentration of TGF- β causing anterior uveitis in FHI. Apart from La Hey's adrenergic defect theory, the same defect causing heterochromia by affecting neural crest cells during embryogenesis might affect the development of iris parenchymal cells, leading to low levels of TGF- β and an anterior chamber reaction. However, no specific abnormalities or immune deposits were observed in the irises of patients with FHI (9, 10).

Murray et al (11) analysed aqueous humor from 23 patients with FHI and suggested that their findings added further evidence to the theory of immune dysregulation; In addition, interleukin 6 (IL-6) may play a role as an inflammatory mediator in uveitis including FHI (12, 13). Muhaya et al (14) found significantly lower IL-2 and higher IL-10 production by vitreous-derived T-cell lines from FHI than in intermediate uveitis patients, suggesting these cytokines were important in the pathogenesis of chronic uveitides. In another paper (15), they established that aqueous humor cytokine profiles were different in FHI and idiopathic anterior uveitis. Interferon gamma and IL-10 levels were higher, while IL-12 levels were lower in the FHI group, suggesting that different local mechanisms might underlie clinical differences in these disorders.

In FHI, in cases of congenital hypochromic heterochromia, the iris melanocytes are reduced in number or deficient in pigment, and in acquired cases atrophy of the stroma is responsible (16). Atrophy of the anterior border layer, stroma and pigment epithelium occurs in irises of FHI patients. During embryogenesis, the iris pigment epithelium is derived from the surface ectoderm, and the neural crest cells differentiate into the iris stroma and uveal melanocytes. Heterochromia is one of the features of Waardenburg syndrome and its cause lies in the neural crest. Therefore, during embryogenesis a problem affecting neural crest cells might damage developing stromal cells and uveal melanocytes and cause heterochromia.

Several theories have been proposed regarding the etiology of keratoconus. Teng (17) suggested it is primarily a disease of the ectodermal layer of the cornea. However, Galin and Berger (18) sustained that in keratoconus a defect should exist in mesenchymal development or maintenance. A hereditary etiology is also reported, though in fact the exact cause of keratoconus is still unknown (2) and one can not totally exclude the possible role of developmental factors in its etiology.

There are no reports, as far as we know, of an association between keratoconus and FHI. However, keratoconus may be associated with various disorders of the iris (19, 20). Blair et al (19) reported a case of bilateral essential iris atrophy and keratoconus and proposed a new hypothesis similar to the genetics of retinoblastoma for the pathogenesis of the iridocorneal endothelial syndrome with keratoconus and/or posterior polymorphous dystrophy. Eiferman et al (20) reported a case of iridoschisis and keratoconus in the same eye and suggested a related pathogenesis since the posterior layers of the cornea and the iris stroma have a common embryological origin. Like in Eiferman's case possibly a deviation in neural crest cells

during embryogenesis could lead to a defect in mesenchymal development or maintenance that causes keratoconus, this could also cause heterochromia and low-grade anterior uveitis, as discussed above. Regarding the common embryological origins of iris stroma, uveal melanocytes and corneal stroma, it is conceivable that the pathogenesis of FHI and keratoconus might be interrelated.

The presence of FHI and choroidal nevi in patient's niece is in favour of a hereditary and developmental predisposition as choroidal nevus is composed of atypical uveal melanocytes that are also derived from the neural crest. It might be worth considering that the combination of FHI and keratoconus is not coincidental. A role of embryological factors in neural crest cells in the etiology of both diseases cannot be excluded.

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