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Penetrating Keratoplasty for Corneal Amyloidosis in Familial Amyloidosis, Finnish Type

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Purpose: To analyze the outcome of penetrating keratoplasty (PK) to the first eye for corneal amyloidosis in familial amyloidosis, Finnish type (FAF).

Design: Single-center, retrospective, nonrandomized, interventional, noncomparative case series.

Participants: Thirty-one eyes of 31 patients with FAF.

Intervention: All patients with FAF who had their first PK in Helsinki University Eye Hospital between January 1, 1990, and August 1, 2011, were identified and a retrospective analysis of the patient charts was performed.

Main Outcome Measures: Best spectacle-corrected visual acuity (BCVA), intraoperative and postoperative complications, graft survival, reason for graft failure, and frequency of regrafting.

Results: The median follow-up period was 32 months (range, 5−114). After 24 months, the median BCVA was 1.15 on a logarithm of the minimum angle of resolution scale (20/280; mean, 1.1; SD, 0.5) in comparison with the preoperative median BCVA of 1.3 (20/400; mean, 1.3; SD, 0.4). At 24 months, 3 of 18 eyes (17%) had a visual acuity of $\geq$0.5 (20/63) and 13 of 18 grafts (72%) were clear. Rejection occurred in 6 of 31 primary grafts (19%). Graft failure occurred in 16 of 31 eyes and resulted from surface complications in 11 eyes and additionally from rejection in 5 eyes. Seven eyes needed regrafting (twice in 1 eye). Complications were frequent in the early and late postoperative periods. Presence of preoperative corneal or graft neovascularization was an indicator of a high risk of graft failure and poor visual outcome.

Conclusions: In a minority of FAF patients, PK improves vision. Owing to the high failure risk and guarded visual prognosis after PK, it is important that both the surgeon and the patient have realistic expectations. It may be reasonable to limit PK to cases with bilateral advanced disease. It seems reasonable to optimize ocular surface health and to delay PK. *Ophthalmology 2015;122:457-463 © 2015 by the American Academy of Ophthalmology.*

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Amyloidosis refers to a clinically polymorphous group of inherited and sporadic disorders in which protein aggregates known as amyloid are deposited into the affected tissues.[1] Some degree of local deposition of amyloid is part of normal human aging,[2,3] but excessive deposition can disrupt the normal function of tissues. Familial amyloidosis, Finnish type (FAF; OMIM 105120) is an autosomal-dominant condition that is part of Finnish disease heritage and is also known as Meretoja syndrome or hereditary gelsolin amyloidosis. The corneal manifestation of FAF was previously known as lattice corneal dystrophy, type II, or gelsolin type lattice corneal dystrophy, but it is no longer considered a dystrophy, because FAF is a systemic amyloidosis. In Finland, FAF is among the most common inherited diseases and affects 400−600 Finns.[4−6] The syndrome has been reported from several European countries, Japan, Iran, and the United States, and thus it is not exclusive for Finnish disease heritage.[5,7−23]

Familial amyloidosis, Finnish type, arises from a G654A (Finnish type) or G654T (Danish type) point mutation in the gelsolin (*GSN*) gene on chromosome 9q33. Gelsolin is an 83-kDa actin-modulating protein[24] synthesized in most types of cells and tissues. The role of gelsolin in the normal human cornea remains unknown, but it may function in binding and removing actin. In FAF, aberrant degradation of mutated gelsolin causes formation of a 7-kDa degradation product leading to amyloid aggregation.[25] In FAF, the mutated protein is deposited widely in different parts of the eye.[26−28] Usually, the corneal manifestation of FAF develops first.[5,29] The distribution of corneal deposits in the cornea is pathognomonic and accordingly the diagnosis of FAF can be made by histological analysis at the time of corneal transplantation.[27] Immunohistochemical studies in patients with FAF[27,28,30] show strands of amyloid in the anterior and midstroma, deposition of a continuous layer of amyloid under Bowman's layer and occasionally at the level of the epithelial basement membrane, and secondary scarring with occasional amyloid deposits invading the subepithelial space.[27] The subepithelial deposits rather than the lattice lines lead to recurrent corneal erosions and eventual loss of vision requiring corneal transplantation in FAF.

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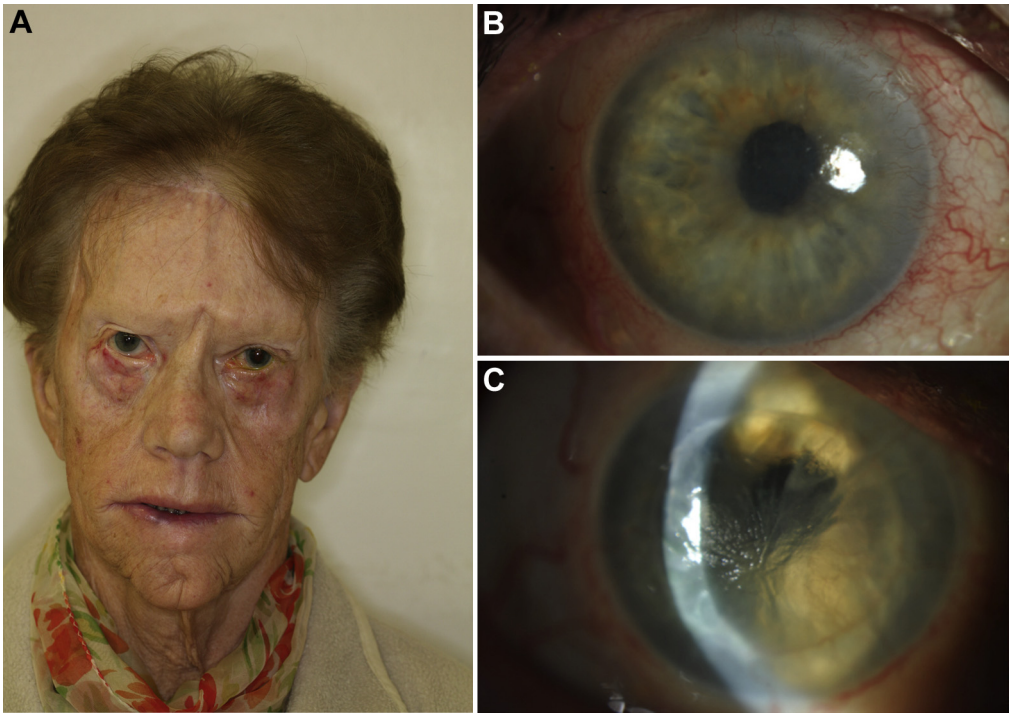

Figure 1. **A**, Typical clinical facial image of a familial amyloidosis, Finnish type (FAF) patient. This patient had several oculoplastic operations to correct lid malposition. **B**, Corneal image before penetrating keratoplasty showing poor quality of the corneal surface, diffuse corneal scarring, and amyloid deposition. **C**, Clinical corneal photograph after penetrating keratoplasty. The image shows leather-like and thickened corneal epithelium after a long-lasting, persistent erosion.

The diagnosis of FAF can be confirmed with genetic testing.[6] In advanced disease, patients suffer from corneal epithelial erosions and neurotrophic keratitis because of corneal sensory nerve damage,[31] visual acuity decreases, and FAF can lead to corneal blindness.[4,5] The visual acuity usually remains adequate until the seventh decade,[32] at which time it often deteriorates because of loss of corneal transparency. Advanced corneal opacification can be treated only by keratoplasty, usually with penetrating keratoplasty (PK). However, the efficacy and safety of this intervention remain unknown. Specifically, FAF affects cranial nerves and neuropathy of the facial nerve is a typical finding. Other neuropathies are also found and sensory defects of the cornea and the face are clinically significant.[6,31,33–37] Blepharochalasis, entropion, ectropion, and lagophthalmus are frequent[6] and complicate the management of ocular surface diseases. Figure 1 shows a typical clinical presentation of a FAF patient.

It is believed that all lattice dystrophies have a similar and generally favorable prognosis after PK.[38] However, only 1 case report of a patient with FAF who had a previous PK has been published.[39] The patient had received 4 keratoplasties in 3 years, roughly after the age of 40, and a fifth keratoplasty 10 years later. The use of keratoplasty in the treatment of FAF has not been evaluated systematically. In Finland, nearly all FAF patients undergoing corneal transplantation are treated at the Helsinki University Eye Hospital. Over the years, we have observed that advanced corneal lattice-like amyloidosis in FAF is challenging to treat. We performed a retrospective analysis of consecutive PK surgeries for FAF.

Methods

This study was reviewed by the Helsinki-Uusimaa Hospital District ethics committee and followed the tenets of the Declaration of Helsinki. We analyzed the patient records of all FAF patients that underwent first PK at the Helsinki University Eye Hospital between January 1, 1990, and August 1, 2011. The diagnosis of FAF was verified by typical histopathology of excised corneal disks together with characteristic facial features, typical age relative to the stage of disease, and a positive family history. Most patients were also referred from Kymenlaakso, a region with a high prevalence of FAF. One patient had additional confirmation of the diagnosis through genetic testing. The only exclusion criterion was a follow-up period of <3 months. Only the first eye undergoing PK of each patient was included in this analysis.

Forty-two eyes of 33 patients who had a PK because of FAF were identified from the patient registry. Two patients (2 eyes) were excluded because of a follow-up period of <3 months, resulting in 31 patients (31 eyes) whose charts were analyzed. One eye of 1 patient with an unsuccessful deep anterior lamellar keratoplasty was also identified, but because it was the only eye that had a deep anterior lamellar keratoplasty it was not included in the analysis.

The following data were recorded: medical history, previous ocular and oculoplastic surgeries, ocular comorbidity,