Primary gelatinous drop-like keratopathy

D S GARTRY,¹ M G FALCON,¹ AND R W COX²

From the ¹Department of Ophthalmology, St Thomas's Hospital, London SE1 7EH, and the ²Institute of Ophthalmology, 17-25 Cayton Street, London EC1V 9AT

SUMMARY This paper describes three siblings, the only affected members of the family, with gelatinous drop-like keratopathy. This rare form of primary corneal amyloidosis has been reported almost exclusively in Japanese literature, and to our knowledge this is the first report of the condition seen in the United Kingdom. Clinical and histological details are presented. The nature and possible aetiology of the amyloid deposits are discussed and the literature is fully reviewed.

The family described here came originally from Teheran and consisted of four siblings whose parents were first cousins. Two of the three boys and the only girl were affected, but no other members of the family or their relatives had a history of eye disease.

The clinical presentation in the three patients was strikingly similar. In each of the three children visual difficulties had begun at the age of 6 years and they had become virtually blind within the ensuing 10 years. There was also extreme photophobia and a characteristic tendency to sneeze violently and repeatedly on exposure to light. There appeared to have been no other history of eye disease or trauma. All three siblings had had a corneal graft in 1981, the oldest boy at that time being 20, his brother 12, and his sister 17. Full clinical details are not available, but 'failure' was said to have occurred after two years in the case of the young men and after only two months in the case of the girl.

At the time of presentation in 1986 the older brother was aged 26, the younger 18, and their sister 24. The clinical features in all six eyes were very similar, but examination was extremely difficult (even under local anaesthesia) because of the intense photophobia. Vision was reduced to barely navigational levels. Both the grafted and non-grafted corneae were opaque, with confluent jelly-like nodules extending throughout, and superficial vascularisation (Fig. 1). The grafted eye in the girl was more opaque than the other eye and was therefore regrafted; in the two men the converse was the case.

All three siblings underwent penetrating keratoplasty. The operations were uneventful except that it was considered helpful to excise the peripheral

nodules in the host anterior stroma to reduce the gross corneal thickness (which was approximately twice normal) to a manageable level. There was a striking early improvement not only in vision but also in the disabling photophobia that existed preoperatively, in spite of one eye still being involved with the keratopathy in each patient.

Two of the three excised discs were fixed in formol saline and examined histologically.

Histology

Microscopic examination of the two corneal discs disclosed areas of irregular epithelial hyperplasia, areas of epithelial atrophy, epithelial oedema, destruction of Bowman's layer, stromal fibrosis, stromal vascularisation and large, mainly superficial, deposits of hyaline, eosinophilic material that gave

Fig. 1 Preoperative appearance of gelatinous drop-like keratopathy (the sister).

Fig. 2 Corneal disc from the sister showing epithelial atrophy, epithelial hyperplasia, and the considerable extent of the subepithelial and superficial stromal deposits of hyaline material. (Haematoxylin and eosin, $\times 90$).

the reactions of amyloid, namely, positive staining with the periodic acid Schiff and Congo red methods, orange-green dichroism with Congo red when examined in polarised light, and bright greenish yellow fluorescence with thioflavin T. In the second of the discs examined (the brother) the eosinophilic deposits penetrated as deeply as two-thirds of the corneal thickness. There was evidence of the previous corneal graft in the first disc examined, and Descemet's membrane and associated endothelial cells were clearly visible in both cases. Electron microscopy in the second specimen revealed fibrils that measured 10 nm in diameter and were consistent with amyloid. The morphological findings in both patients were considered to be compatible with the diagnosis of primary gelatinous drop-like corneal dystrophy (Figs. 2, 3).

Discussion

Primary gelatinous drop-like dystrophy is a rare form of primary familial corneal amyloidosis first described in Japan by Nakaizumi in 1914.¹ About 60 cases have been reported in the Japanese literature since then,¹⁻²¹ and various names have been given to the condition, such as diffuse gelatinous punctate keratitis,² gelatinous drop-like corneal dystrophy,³ familial diffuse gelatinous drop-like corneal dystrophy,⁴ and colloid drop-shaped familial degeneration of the cornea.⁵

Outside Japan reports of the condition are extremely rare, the first being that by Lewkojewa writing from the Helmholtz Institute in Moscow.²² Since then only a handful of clearly indisputable occidental cases of gelatinous drop-like dystrophy

Fig. 3 Higher power view of subepithelial accumulations of hyaline material with atrophy of the overlying epithelium. It is this type of morphology that produces the gelatinous drop-like appearance seen clinically. (Haematoxylin and eosin, $\times 195$).

have been reported, including three cases from the USA,²³⁻²⁵ one from Switzerland,²⁶ and one from France.²⁷ In the Swiss case, the patient was a 12-year-old Tunisian boy, and no family history was found. Other reports of proved corneal amyloidosis with appearances similar to gelatinous drop-like dystrophy seem to have been *secondary to pre-existing disease*. Stafford and Fine²⁸ reported on an 11-year-old girl in whom an eye that was enucleated because of retrolental fibroplasia was found to have gelatinous drop-like amyloid deposits. McPherson *et al.*²⁹ reported similar bilateral corneal changes in a 20-year-old Negro and included four further case reports of similar changes, concluding that all were due to pre-existing chronic corneal disease. Interestingly, they went on to examine 200 eyes submitted for pathological examination for other reasons and found that 3.5% had corneal amyloidosis which had not been apparent prior to removal. Similarly Garner³⁰ reported five cases of corneal amyloidosis related to previous corneal pathology. Two of these were related to trauma, one to trichiasis and senescent change, one was found to be lattice dystrophy, and the fifth had an atypical sub-epithelial fibrous plaque. Kanai and Kaufman²⁵ likewise reported on a patient who developed gelatinous drop-like amyloid following primary band-shaped keratopathy. The amyloid was not found histologically in the first specimen but was present two years later in the subsequent corneal disc. One of two North African patients presented by Pouliquen *et al.*²⁷ developed gelatinous drop-like keratopathy after long-standing trachoma, while the other appeared to be a case of primary gelatinous amyloid.

Parents of affected patients are rarely affected, and the inheritance of the condition is regarded as being autosomal recessive with a low degree of penetrance.^{13,14} The clinical manifestations usually begin between the ages of 8 and 18 and initially consist of photophobia, lacrimation, redness, a sensation of grittiness, and intermittently blurred vision. On examination of the cornea numerous small subepithelial gelatinous excrescences are seen across the corneal surface, giving the whole an appearance variously described as 'mulberry like' or 'toad skin' like. In advanced cases (often before age 20), the symptoms are very severe, with profound photophobia and visual loss. At this stage there may be stromal neovascularisation. No systemic associations have been reported.

It was not possible, with such advanced cases as ours, to comment on the possible origin of the amyloid fibrils other than to state that the histology suggested that the major site of deposition was anterior stroma with erosion of Bowman's layer. There has been some debate as to the origin of the

amyloid. Hohki *et al.*²⁰ have postulated that it may be produced by both keratocytes (as would appear to be the case with lattice dystrophy³¹) and basal epithelial cells. Nagataki *et al.*¹⁷ consider that the keratocytes are not involved, and along with Ohnishi *et al.*²¹ consider that the basal epithelial cell layers are solely responsible.

Some of the reports discussed above have clouded the issue by describing conditions similar to primary gelatinous drop-like keratopathy, but there is no doubt that this strange and most disabling condition is a discrete entity that can be separated from other forms of familial amyloidosis by the absence of systemic involvement, the unique ocular appearances (which occur early and advance rapidly),³² and the characteristic localisation of the larger amyloid deposits in the superficial cornea.

The precise type of amyloid found in gelatinous drop-like keratopathy has yet to be fully elucidated. Further definition of chemical structure may be possible by immunohistochemical techniques such as those applied by Hida *et al.*³³ to lattice dystrophy types I and II and a newly recognised form, type III. So far attempts at precise chemical description of lattice dystrophy type I by these techniques have produced conflicting results, which are thought³³ to be due to differences in immunohistochemical techniques and the antibodies used or to reflect heterogeneity inherent in type I. Evolution of newer methods applied to unfixed, freshly excised cornea may allow further definition of the amyloid material, including the deposits of gelatinous droplet keratopathy.

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