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Case Report

Avellino Corneal Dystrophy - Case Reports in A Family and Literature Review

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Abstract

Avellino is a corneal dystrophy with granular deposits in the subepithelial and anterior stromal corneal layers, combined with discernible lattice lines in the stroma. Vision decreases with age as the central visual axis becomes affected, and pain may accompany mild corneal erosions. The disease is more severe in homozygous patients than in their heterozygous counterparts, and mutations in TGFBI are responsible for the occurrence. Treatments vary by the depth of the opacities in the cornea and the availability of a graft, and phototherapeutic keratectomy (PTK) or keratoplasty has been used. We examined a family of 10 siblings; 8 were examined, and of these, 7 (3 males and 4 females) had the typical corneal opacities of Avellino dystrophy. Penetrating keratoplasty was performed on 4 eyes and the histopathological analysis of these grafts revealed them to be compatible with Avellino's dystrophy, with focal areas of irregular hyalinization in the anterior and posterior regions of the stroma, which a had tracery appearance and epithelial thickening.

Keywords: Avellino Corneal Dystrophy

Introduction

In ophthalmology, the term “corneal dystrophy” has been used to refer to a group of inherited corneal diseases that are typically bilateral, symmetric, slowly progressive, and without relationship to environmental or systemic factors [1]. The word dystrophy is derived from the Greek (dys = wrong, difficult; trophe = nourishment) [2] and was introduced into the medical literature by Wilhelm Erb (1840 - 1921) in 1884, in describing a disease of the musculature [3].

In 1945 and 1951, Franceschetti and Babel demonstrated that these dystrophies could be distinguished from one another histopathologic ally. The classic study of the histopathologic differentiation of granular, macular, and lattice dystrophies by Jones and Zimmerman appeared in 1961 [4]. Fuchs [5] used the word dystrophy to refer to ophthalmologic disease and postulated that dystrophic tissues resulted from lack of nourishment, hormones, blood, and nerve supply. Uhthoff [6] and later Yoshida [7] continued to use the term in their publications.

Because keratoplasty was seldom performed until well into the 1940s, little was available in the way of satisfactory material for pathologic study. In 1988, a report was published describing the histopathologic examination of corneal buttons from 4 patients who had undergone unilateral keratoplasty because of decreased vision caused by what had been diagnosed clinically as granular dystrophy. The patients came from 3 different families, each of which traced its origin to the Italian province of Avellino. The clinical and histopathological features of the 4 corneas affected by combined granular-lattice dystrophy thereby added to the total of 12 other corneas that have been so-described in the literature [8].

It is an autosomal dominant corneal disease characterized by asymmetric, gray-white, central anterior, stromal opacities of various shapes and sizes and deep lattice-like stromal deposits [9]. In the previously mentioned study, all 4 corneas were studied pathologically, using both conventional hematoxylin and eosin stains as well as special histochemical techniques, and all contained lesions characteristic of both granular dystrophy and lattice dystrophy, a

circumstance that has given rise to the name "combined granular-lattice dystrophy" [10].

Clinical characteristics and diagnosis

Avellino corneal dystrophy is characterized by the presence of gray-white, discrete granular deposits in the subepithelial and anterior stromal corneal layers, with or without discernible lattice lines in the stroma. In the most advanced form of the disorder, stromal haze emerges [11]. These lattice lines develop in the second and third decade of life or even later, and they differ from the ones present in typical lattice corneal dystrophy in being larger, denser, whiter, and more speculated [12].

Three clinical signs characterize combined granular-lattice dystrophy: (1) anterior stromal discrete, grayish-white deposits; (2) lattice lesions located in mid-stroma to posterior stroma; and (3) anterior stromal haze. Both clinically and histopathologic ally, the lattice lesions are of greater diameter than are those that occur in lattice dystrophy type I. In the past few years, striking advances have been made in understanding the genetics of combined granular-lattice dystrophy [10].

In transmission electron microscopy, anterior, stromal rod-shaped, very electron-dense deposits are noted. On higher magnification, the rod-shaped deposits are composed of extracellular masses of fine, electron-dense, highly aligned fibrils. An extremely common ultrastructural finding is the presence of randomly aligned fibrils of amyloid. The confocal microscopy findings are a reflective, breadcrumb-like round deposits with well-delineated borders or highly reflective, irregular trapezoidal deposits, present in the anterior stroma. Linear and branching deposits with changing reflectivity are observed (similar to LCD) [13].

Histologically, these deposits stain with Masson trichrome and Congo red and are seen as discrete hyaline and fusiform deposits of amyloid in the corneal stroma [14-16].

Symptoms include, decreases in vision with age as the central visual axis becomes affected. Pain may accompany mild corneal erosions.

Genetics

Avellino corneal dystrophy is one of the transforming growth factor beta-induced (TGFBI) associated corneal dystrophies. TGFBI associated corneal dystrophies are quite interesting and include lattice corneal dystrophy type 1 (CDL1), granular corneal dystrophy (CDGG1), and Reis–Bucklers dystrophy (CDRB). All are caused by mutations in the TGFBI gene and show white deposition accumulating under the subepithelium of the cornea [9].

Advances in molecular genetics could improve the understanding of the role of some specific genes on corneal transparency and the pathogenesis of the disorders and lead to a different classification of the dystrophies [17]. The disease is more severe in homozygous patients than in their heterozygous counterparts [18]. Interestingly, there are two different phenotypes of these homozygous disease types. Type I has a spot-like opacity present in the anterior stroma, in which the lesions are confluent. The type II corneal opacity pattern is a reticular opacity in the anterior stroma, with round translucent spaces (Figure 1). The heterozygous siblings of these two homozygous patients did not show such a clinical variation [19].

Figure 1: Histological sections of the cornea from one of the patients, showing focal areas of non-stroma hyaline irregularities.

Explicit mutations in TGFBI are responsible for specific types of 5q31- linked corneal dystrophies, such as Groenouw type I (R555W), Avellino (R124H), Reis-Bücklers (R124L), Thiel-Behnke (R555Q), and lattice type I (R124C) [20]. The R124H mutation known to be associated with Avellino corneal dystrophy (ACD) (OMIM 121900) was initially described in families originating from an Italian province near Naples [21]. Despite specific TGFBI mutations being associated with each of these corneal dystrophies, atypical and variable phenotypes [22-25] along with extensive intrafamilial and interfamilial variations [13] are seen and genotype-phenotype correlation is not always possible.

The combined features of lattice and granular dystrophies in the same cornea resulting from mutations in the same gene raises the question of validity of relying solely on clinical and histological evidence for classifying disease. Modern genotyping now enables greater accuracy in the nosology, and the International Committee for Classification of Corneal Dystrophies (IC3D) has already incorporated this information into their recent reclassification of these dystrophies [13]. In this classification system, type-2 lattice dystrophy, or granular-lattice, is the eponymous Avellino dystrophy, is related to the locus 5q31 (TGFBI gene) and has an autosomal dominant inheritance.

Homozygote patients initially demonstrate numerous small dots in the superficial cornea in early childhood. By adulthood, there are larger, very dense subepithelial, irregularly shaped opacities, which may become deeper with time [13].

Treatment

To reduce corneal deposits, phototherapeutic keratectomy (PTK) or keratoplasty has been used, depending on the depth of the opacities in the cornea and the availability of a graft [26,27]. Corneal deposits after PTK in patients with heterozygous mutation were mild; the granular opacities occurred as spot lesions in the central cornea. In contrast, the patient with a homozygous mutation showed a more severe pattern, and the recurrent lesions were diffuse. Recurrence was observed even after penetrating keratoplasty (PKP) at 12 to 24 months in homozygotes [28].

Impairment of the interaction between TGFBIp and periostin is believed to be involved in the pathogenesis of 5q31-linked corneal dystrophies. Choi., *et al.* demonstrated that GCD2 primary cultured fibroblasts are more susceptible to oxidative damage induced by decrease of catalase. These findings indicate that additional study of antioxidants is needed to find treatment methods [29].

Case reports in A family

In a family of 10 siblings, 8 were examined and of these, 7 (3 males and 4 females) had the typical corneal opacities of Avellino dystrophy. One reported that the mother of these individuals also had corneal opacity, evolving with low vision but was not diagnosed for having died before being examined. One of the sisters said she had a daughter with low vision.

In this kinship, 4 eyes were subjected to penetrating keratoplasty at the same hospital. The disease recurred in one of them, 3 grafts remained transparent and in one there was graft failure.

Histopathological analysis of four of these grafts revealed Avellino's dystrophy, characterized by the presence of granular dystrophy (hyaline) and lattice (amyloid) deposits. They presented focal areas of irregular hyalinization in the anterior and posterior regions of the stroma, which had tracery appearance and epithelial thickening. This mixed deposit pattern is characteristic of Avellino's dystrophy.

The three nontrans planted eyes presented different patterns of corneal opacity in biomicroscope.

Figure 2: Hyaline deposits in the corneal stroma positive for Congo red (same patient).

Figure 3: A patient's cornea, showing that hyaline deposits under polarized light are refractive.

Figure 4: Biomicroscopy of the same patient before performing corneal penetrating transplantation, showing the linear and granular opacities in the corneal stroma.

Figure 5: Same patient, after 15 days of penetrating corneal transplantation.

Figure 6: Same patient, after 15 days of penetrating corneal transplantation.

Conclusion

Avellino Corneal Dystrophy is a rare autosomal dominant disease with complete penetrance. Although no molecular analysis was performed, the clinical picture was characteristic of a mixed granular and lattice corneal dystrophy.

Although the studies show a relationship between the disease and cellular oxidative damage, there is still no definitive treatment that completely prevents recurrence. For the time being, it is known that penetrating keratoplasty does not prevent the disease from recurring but allows the possibility of avoiding progression and, in some cases, even cure with significant improvement in visual acuity.

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