Case Report

Discordant Keratoconus in Monozygotic Twins

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Abstract
We report a case of discordant keratoconus (KC) in a set of monozygotic twins with contrasting environmental risk factors. Twin one had bilateral, asymmetrical KC. He reported significant eye rubbing using his knuckles during his night-shift work as an emergency doctor. His usual sleeping position on the left side corresponded to the most affected eye. Twin two had normal corneas, with no evidence of KC. He reported mild infrequent eye rubbing, daytime work pattern, and a supine sleeping position. This case report highlights the influence of environmental and behavioural factors in the development of KC, in particular eye rubbing, night work, and sleeping position, in two individuals sharing identical genetic inheritance.

Introduction
Keratoconus (KC) is a progressive corneal condition characterized by thinning and steepening of the cornea usually in the central or inferior paracentral areas. This leads to corneal deformation, irregular astigmatism, and increased higher order aberrations. KC is usually bilateral and often asymmetrical. The pathogenesis is commonly thought to be multifactorial, with both environmental and genetic factors playing a role. A recent review by Rabinowitz et al. [1] summarized the different theories of the influence of the genetic component and of the mechanical factors.

The role of biomechanical factors in patients genetically predisposed to KC is addressed in a small number of case reports of monozygotic (MZ) twins with unilateral or highly
asymmetric KC [2, 3]. We report a case of a discordant KC in MZ twins with contrasting lifestyle risk factors, emphasizing the role of environmental influence.

**Case Report**

This is a case report of MZ twin brothers aged 29 years old, who have lived in the same geographic area for their lifetimes. Both twins have a history of atopy and seasonal allergic rhinitis. There was no family history of KC. Genetic monozygosity had previously been confirmed by DNA analysis.

Twin one had bilateral KC. He is an emergency medicine doctor, left-handed, who works at night, sleeps on his left side, and admitted to regular vigorous eye rubbing, especially on the left side, using his knuckles. The patient started to rub since he was a teenager because of allergies. KC was discovered when he was 21 y.o during a routine consultation where it was found that his corneal astigmatism had increased. His best corrected visual acuity was 20/20 in both eyes with a refraction of +1.25D/−1.00D × 130° in the right eye and +3.0/−1.50 × 80° in the left eye. Slit-lamp examination revealed bilateral Fleischer rings and central corneal thinning in the left eye. Scheimpflug corneal tomography (Pentacam, Oculus, Germany) confirmed asymmetrical KC (Fig. 1a, b), which was more pronounced in the left eye and displayed marked vertical asymmetry. Maximal keratometry in the right eye was 46.4D and

![Scheimpflug tomography (Pentacam, Oculus, Germany).](image-url)
51.1D in the left eye. Minimal corneal thickness (pachymetry at the thinnest point) in the right eye was 495 µm, and 473 µm in the left eye. Corneal hysteresis was 7.6 mm Hg in the right eye and 4.3 mm Hg in the left eye. The Belin Ambrósio Enhanced Ectasia Display (BAD display) with D indices was 4.07 in the right eye and 6.96 in the left eye.

Twin two has a PhD in law, is right-handed, and rubs his eyes infrequently. His best corrected visual acuity was 20/20 in both eyes with a refraction of +0.50D/−0.50D × 95° in the right eye and +0.50DS in the left eye. Slit-lamp examination revealed no signs of KC (e.g., Fleischer ring, Vogt's striae, apical scarring). Multimodal imaging of the cornea showed no abnormalities in either eye (Fig. 1c, d and Fig. 2). Maximal keratometry in the right eye was 43.5D and 44.0D in the left eye. Minimal corneal thickness in the right eye was 524 microns and 515 microns in the left eye.

Corneal topography performed with Scheimpflug tomography and Placido topography (OPDscan III, NIDEK, Gamagori, Japan), revealed bilateral regular, symmetrical corneas. Corneal hysteresis was 9.9 mm Hg in the right eye and 9.7 mm Hg in the left eye. The BAD display with D indices was 1.02 in the right eye and 1.25 in the left eye.

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**Fig. 2. Multimodal imaging of the cornea of the unaffected twin.**

- **a** Placido topography (OPDscan III, Gamagori, Japan). Sagittal curvature maps reveal normal corneas in both eyes. All calculated values for Klyce/Maeda indices are normal.
- **b** BAD display performed by Pentacam Topographer. There is no difference in the elevation maps of the central points on both the anterior surface and the posterior surface in both eyes. The corresponding values of the “d” indices are normal.
- **c** Optical coherence tomography (Optovue) shows similar central corneal thickness on pachymetry maps and no focal thinning in the epithelial thickness maps in both eyes (left box). Ocular Response Analyzer is normal in both eyes. CH values are within the normal range (right box). CH, corneal hysteresis.
Discussion and Conclusion

Twin studies are invaluable in assessing the relative contribution of genes and environmental factors in the development of a disease. Tuft et al. [4], described the concordance of KC in 18 sets of twins; 13 MZ and 5 DZ twins. Their results showed more concordance in MZ than DZ twins supporting a genetic effect in the development of KC; however, the presence of phenotype variability in MZ twins also suggested an environmental influence on the expression of disease. The study did not, however, extend to analysis of other potential risks or environmental factors.

A genetic contribution to the pathogenesis of KC has been extensively investigated and is supported by reported high concordance rates in MZ twins, and very significantly increased risk of KC in children of consanguineous parents, as reported by Gordon-Shaag et al. [5]. On the other hand, a positive family history of the condition is reported in only 5–20% of cases [6]. In addition, KC has also been associated with genetic disorders such as Down Syndrome, Leber’s congenital amaurosis (although these syndromes are also strongly associated with eye rubbing), and Ehlers-Danlos Syndrome.

The mode of inheritance of KC has been widely debated. Although KC is most frequently sporadic, there is evidence of aggregations of familial KC. Autosomal dominant with reduced penetrance is the mode of inheritance that has best fitted several studies made over the past decades [7].

Multiple linkage analysis has been performed on families with a high prevalence of KC, with a large number of loci described, however few that have been replicated in further studies, supporting the hypothesis of low penetrance of KC and the theory that KC is a complex, heterogenous disorder.

More recently, the multifactorial origin of KC and particularly the significant role of eye rubbing are increasingly accepted [8]. In a recent case-control study, we reported specific environmental risks associated with KC [9]. Eye rubbing, prone sleep position, night work, and screen time were identified as significant associations. We stated in a previous article that eye rubbing, possibly associated with eye compression related to sleeping position, is a sine qua non condition for the appearance and progression of KC, without which the morphological changes seen in KC would not appear spontaneously [10, 11]. This case provides a clear example of two individuals with identical genetic predisposition, where KC only develops in one twin with associated specific environmental risk factors. Indeed, there are a small number of reports where discordance has previously been reported in MZ twins, where otherwise concordance would have been expected [2, 3, 12].

In conclusion, we report a case of discordant KC in a set of MZ twins, emphasizing the impact of environmental influences in the development of KC. This case report highlights the influence of environmental and behavioural factors, in particular eye rubbing, night work, and sleeping position in two individuals sharing identical genetic inheritance. It is clear, however, than many patients rub their eyes and do not develop KC, suggesting that such environmental factors may act as a trigger in certain patients with a potential genetic predisposition. Whether eye rubbing is a risk factor or rather plays an important causative role, it is nevertheless crucial that patients are educated on the deleterious effects of eye rubbing.

Statement of Ethics

The research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. Ethical approval was not required for this study in accordance with local or national guidelines. Written informed consent was obtained from patients for publication of the details of their medical case and any accompanying images.
Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Karen Bitton was involved in data acquisition and manuscript drafting. Mathieu Dubois and Damien Gatinel contributed to critical revision of the manuscript. Damien Gatinel and Sarah Moran revised the manuscript.

Data Availability Statement

All data generated and analysed during this study are included in this published article. Further enquiries can be directed to the corresponding author.

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