CASE REPORT

Mild Keratoconus in the Mother of a Patient with Down Syndrome: Case Report and Clinical Hypothesis

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ABSTRACT

The purpose of this study is to report a case of mild or forme fruste keratoconus (FFKC) in the mother of a patient with Down syndrome (DS) who presented for cataract surgery and to propose a possible association of mothers with mild forms of ectasia and higher risk for delivering babies with DS. Advanced corneal imaging including corneal topography, corneal tomography, and the integrated corneal tomography and biomechanical assessment allowed the identification of a mild form of keratoconus in both eyes of this patient, and the correct characterization of the corneal structure and whole optics of the eye were crucial for IOL selection and planning cataract surgery.

Keywords: Corneal tomography, Corneal topography, Down syndrome, Forme fruste keratoconus, Keratoconus.

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INTRODUCTION

Keratoconus (KC) and ectatic corneal diseases represent an important area of research and a true subspecialty in modern ophthalmology. This multifactorial and genetic heterogeneous bilateral ectatic corneal dystrophy has an incidence of approximately 1 per 2000 in the general population, with a presumed interaction between genetics, environmental and other factors.¹⁻⁴ Prevalence of KC might vary between 8.8 and 54.5 per 100.000^{1,2,5,6} and between 50 and 230 per 100.000, depending on the diagnostic criteria used and the study's population ethnicity.^{1,7-9} Moderate and advanced stages of KC are promptly recognized by a trained physician, but the identification of milder or subclinical forms of KC can represent a challenge at times.^{10,11} The introduction of refractive surgery and the paradigm shift related to the development of new treatment modalities have boosted the need to recognize milder forms of the disease and identify inherent predisposition for ectasia progression.¹²⁻¹⁶ Advanced corneal imaging including corneal topography, tomography along with an assessment of biomechanical properties have a fundamental role in this appropriate characterization.^{17,18} However, additional applications for advanced corneal imaging, beyond the identification of forme fruste keratoconus and screening for ectasia risk, can be further explored. For example, the recognition of milder forms of keratoconus called forme fruste (FFKC) in family members of KC patients might be helpful in the study and characterization of familial KC.

Down syndrome (DS) was first described by John Langdon Down in 1866,¹⁹ and is associated with a condition defined as chromosomal nondisjunction, at chromosome 21. Considered one of the major causes of intellectual disability, DS has an estimated incidence of 1 in 1000 to 1 in 700 live births in the general population.²⁰ Several ophthalmic disorders have been reported in DS patients including

epicanthus, ectropion, blepharoconjunctivitis, nystagmus, strabismus, nasolacrimal duct obstruction, high myopia, and lens opacities.^{21,22} The association between Down syndrome and keratoconus is also well established, with a reported prevalence ranging from 0.5% to 15% (10–300-fold that of the normal population).^{1,22-27} This relationship might be explained not only by the fact that DS patients are usually affected by collagen-related disorders,^{2,3,28,29} but also due to a frequent habit of eye rubbing usually found in these patients.²⁸ However, the association between KC or FFKC as a risk factor for a mother having a son with Down syndrome has never been investigated. The purpose of this study was to report a case of FFKC in a mother of a patient with Down syndrome who presented for cataract surgery and to hypothesize a possible association between mothers with FFKC or KC having a higher risk of delivering a baby with DS.

CASE REPORT

An 80-year-old female patient presented because of poor quality of vision for both distance and near activities. She had a previous diagnosis of cataract in both eyes and was seeking for surgery with premium multifocal intraocular lens implantation. Her family history was remarkable for their daughter with Down syndrome with keratoconus, who had a successful triple procedure over ten years ago at this clinic. UDVA was CF 1M in both eyes and manifest refraction was $-4.25 -1.25 \times 84$ in OD and $-4.50 -1.50 \times 96$ in OS, giving 20/30 and 20/40, respectively. Slit lamp examination exhibited and a grade 2 nuclear cataract in both eyes, along corneas within normality but with more evidenced corneal nerves. Intraocular pressure was 16 mm Hg in OU. The dilated retinal exam was unremarkable in both eyes. Specular microscopy documented normal endothelial mosaic with central cell counting of 2,410 and 2,421 cells/mm² in OD and OS, respectively.

Potential macular visual acuity with the McIntyre's super pinhole was 20/20 in both eyes.

Placido-disk corneal topography was performed with the keratograph 5 and with rotating Scheimpflug tomography with Pentacam HR (Oculus GmbH; Wetzlar, Germany). Corneal front curvature maps derived from Placido and Scheimpflug presented with similar aspects. Figure 1 illustrates the front curvature axial maps from the Pentacam, with the Smolek/Klyce absolute 1.5 D scale, demonstrated a relatively regular pattern, with no asymmetry of inferior steepening in OU. Maximal keratometry (K Max) was 44.6 D and 45.1 D in OD and OS, respectively. Interestingly, the topometric keratoconus classification on Pentacam demonstrated a borderline keratoconus index (KI) value in OD of 1.07 and abnormal value, 1.69 in OS (Fig. 1). No topometric keratoconus classification (TKC) was detected OU. The Belin/Ambrósio enhanced ectasia display (BAD)^{30,31} from OD and OS demonstrated abnormal front and back elevation maps, along with abnormal deviation values, including Df, Db, Dt, and final D (Figs 2 and 3). The biomechanical assessment was performed with the Corvis ST (Oculus; Wetzlar, Germany) and the tomographic-biomechanical index (TBI)¹⁸ was 0.68 in OD and 0.50 in OS (Figs 4 and 5).

The diagnosis of mild or forme fruste keratoconus was made in both eyes, based on the described findings. The patient was then advised for a bilateral monofocal aspheric IOL implantation (Zeiss Asphina 509 M), and the Haigis formula was selected for IOL calculation. Surgeries were performed with no intercurrents aiming for partial monovision (aim -0.6 D OD and plano OS). The patient recovered well and was very satisfied after the procedure. Ultimate uncorrected distance visual acuity was 20/70 J1 in OD and 20/25 J5 in OS. Final manifest refraction was $-1.25 -1.00 \times 85$ in OD and plano -0.50×100 in OS, giving 20/20 in OU.

Fig. 1: Pentacam topometric axial maps from both eyes. No inferior–superior asymmetry was observed. Note topometric keratoconus classification on Pentacam which shows a borderline KI value in OD and abnormal value in OS

Fig. 2: Belin/Ambrósio enhanced ectasia display from the right eye. Note abnormal front and back elevation maps, along with abnormal deviation values, including Df, Db, Dt, and final D

Fig. 3: Belin/Ambrósio enhanced ectasia display from the left eye

Fig. 4: Integrated corneal tomography and biomechanical display from Corvis ST and Pentacam with CBI and TBI from OD. Note an abnormal TBI value of 0.68

DISCUSSION

As the average population age is increasing, the number of cataract patients will also increase, and patients with

KC are more likely to develop cataracts.^{32,33} Corneal topography is an indispensable tool for investigating the anterior corneal surface and studies have demonstrated

Fig. 5: Integrated corneal tomography and biomechanical display from Corvis ST and Pentacam with CBI and TBI from OS. Note an abnormal TBI value of 0.50

that this technology enhances the ability to detect the ectatic disease even before the development of slit lamp signs or loss of DCVA.³⁴ Nevertheless, in recent years we witnessed a true revolution in corneal imaging with the emergence and development of new technologies capable of investigating not only the corneal shape but also clinical biomechanical behavior. This approach has been a critical tool in the investigation of keratoconus, and ectatic corneal diseases and studies have demonstrated the ability of these technologies to identify early forms of ectatic disease, even in cases undetected by Placido-based topography alone.³⁵⁻⁴⁰ This approach has special relevance when screening candidates for laser vision correction, but also when evaluating patients for cataract surgery.

In this case report, advanced diagnostic parameters derived from three-dimensional corneal tomography and biomechanical assessment were fundamental instruments for the identification of a mild form of keratoconus in both eyes. The correct preoperative characterization of the corneal structure was critical for the best IOL indication since patients with irregular corneal surfaces and significant higher order aberrations have poor outcomes with premium multifocal IOLs since these lenses divide light energy.³³

Interestingly, different conditions have been proposed as FFKC, such as a normal topographic eye that naturally becomes ectatic over time, or the normal topographic eye of high or very asymmetric ectasia (VAE) cases.⁴¹ Suspect, incomplete and subclinical are additional terms proposed to refer to this condition, but modern corneal imaging with tomography and biomechanics has made them nonspecific and obsolete.

There is a consensus that both environmental factors and genetics play a role in the pathogenesis of keratoconus and ectatic corneal diseases.^{35,42} Despite extensive

research, the genetic characterization in keratoconus is still challenging and different genes have been implicated in the development of the disease, including SOD1, VSX1, miR-184, DOCK9, RAB3GAP1, and HGF.⁴² Although most KC patients appear to have a sporadic form of the disease, reports of familial KC are increasing, indicating that family members of KC patients have a higher risk to develop the disorder, and both autosomal dominant and recessive patterns might be implicated.⁴²⁻⁴⁶ Hopefully, the development of new genetic technologies such as whole exome or genome sequencing, might change our knowledge about the etiology of keratoconus, and even guide the therapeutic orientation.⁴²

Down syndrome is related to trisomy of chromosome 21. Chromosomes are structures composed of DNA and proteins that present in every cell of the body and carry our genetic information. Humans normally have 46 chromosomes in each cell, divided into 23 pairs. Human cells undergo division in two possible ways—mitosis and meiosis. In the first method, one cell becomes two cells which have the same number and type of chromosomes as the parent cell. In the second method, which occurs for example in ovaries and testicles, one cell splits into two, with the resulting cells having half the number of chromosomes of the parent cell. In meiosis, there is an event called “disjunction”, in which the pairs of chromosomes are supposed to split and merge to different spots in the dividing cell. However, many errors can occur in cell division and eventually, one pair does not divide and the whole pair goes to one spot. This is called “nondisjunction,” and in this case, in the resulting cells, one will have 24 chromosomes and the other will have 22 chromosomes. In DS, 95% of cases are related to this situation in which one cell (from sperm or an egg) has two entire 21st chromosomes instead of one, so the resulting fertilized egg will have three 21st chromosomes.⁴⁷

In the vast majority of the cases, the extrachromosomes are maternally derived, mainly due to non-disjunction in meiosis II (75%) rather than meiosis I (25%).^{47,48} Maternal age is also strongly associated with 21st chromosome trisomy, which is probably related to an increase in maternal meiotic nondisjunction.

We propose a possible association of mild forms of keratoconus as a potential risk factor along with older age, for mothers delivering babies with DS. Nevertheless, before any conclusion is taken, further studies are necessary to investigate the association of mild ectatic diseases as a risk factor, along with age, for a mother having a son with DS. Cohorts of mothers of patients with DS would probably represent an adequate study design to perform this investigation, and this needs to be done in different populations and in different countries.

CONCLUSION

In this case report, the mother of a patient with Down Syndrome and keratoconus presented for cataract surgery, seeking premium multifocal IOL implantation, Advanced corneal imaging allowed the detection of a mild form of ectasia in both eyes, which was a relative contraindication for multifocal IOL. The correct characterization of the corneal structure was fundamental for correctly choosing the intraocular lens model, as patients with corneal irregularities have frequently poor outcomes with multifocal IOLs.³³ We recommend a detailed evaluation of the cornea before cataract surgery and advanced corneal imaging technologies have a relevant role on this investigation. We also propose a possible association of mild ectatic corneal disease as a risk factor along with age for mothers have a child with DS. Further studies, including cohorts of mothers of patients with DS, are necessary to explore this association.

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