Subclinical Keratoconus Detection in Identical Twins

ABSTRACT

Purpose: To report clinical keratoconus in only one eye of two identical female twins, along with subclinical disease in the fellow eyes, elaborating on the two-hit hypothesis of ectasia development, which relates to the combination of genetics and the impact of environment.

Methods: Case report and literature review.

Results: Two identical 48-year-old female twins were presented for clinical evaluation. Mild keratoconus was detected in the right eye of twin 1, characterized by classic slit-lamp findings (exacerbated corneal nerves and incomplete Fleischer’s ring) and front surface curvature abnormalities, including asymmetry of the inferior–superior curvature at 6 mm (I–S value) of 2.78 D and a grade 1 Topographic Keratoconus Classification pattern. Topographic Keratoconus Classification was possible in the fellow eye of twin 1 (I–S value = 1.22 D) and negative in both eyes of twin 2 (I–S value = −0.46 OD and −0.13 OS). Ambrósio’s Relational Thickness for the maximal progression meridian was 209 and 354 in twin 1 and 360 and 392 in twin 2 in the right and left eyes respectively. The final deviation value of the Belin–Ambrósio Enhanced Ectasia Display was 4.54 and 1.47 in twin 1 and 1.7 and 1.35 in twin 2.

Conclusion: Corneal tomography data provide a better representation of corneal genotype in detecting mild, subclinical, or forme fruste keratoconus in the fellow eyes with normal topography of these twins. These cases present high risk or susceptibility for ectasia progression if environmental factors are associated (second hit).

Keywords: Corneal tomography, Heritability, Subclinical or forme fruste keratoconus, Twin.


Source of support: Nil

Conflict of interest: Dr. Ambrósio and Dr. Belin are consultants for OCULUS Optikgeräte GmbH.

INTRODUCTION

Keratoconus is a bilateral ectatic corneal disorder that typically presents with moderate asymmetry. It involves progressive corneal thinning, protrusion, and irregular astigmatism. Classically, the disease starts in puberty and progresses throughout the third and fourth decades of life.1,2 There is a strong genetic component in the pathogenesis of keratoconus.3-5 However, studies involving monozygotic (MZ) and dizygotic (DZ) twins also demonstrate that there are environmental factors related to the development of the disease.6,7 The two-hit hypothesis refers to an underlying genetic-related susceptibility coupled with external environmental factors, including eye rubbing and atopy.8,9

This study involved two identical twins; clinical keratoconus was detected in only one of the four eyes. The tomographic findings and clinical history of eye rubbing and ocular allergy illustrate the importance of going beyond of front surface topography to detect subclinical or very mild ectasia, as well as considering the environmental factors for ectasia development.

CASE REPORT

A 48-year-old female patient (twin 1) was referred for ophthalmological evaluation in 2014 due to diagnosis of keratoconus. She complained about bad vision in her right eye and ocular allergy symptoms that were aggravated over the last 2 weeks after starting systemic treatment for chronic allergy with an antihistamine. Uncorrected distance vision acuity was 20/200 OD and 20/40 OS. Manifest refraction provided distance corrected vision acuity of 20/25-2 (+2.00 spher –2.00 cyl 37) in the right eye and 20/20 (+1.50 sph –0.50 cyl 108) in the left eye. She mentioned having an identical twin sister who did not have keratoconus; therefore, her sister was subsequently called for a complete eye exam.

Twin 2 presented with mild complain related to blurred vision for near. Uncorrected distance vision acuity was 20/25 OD and 20/30 OS. Distance corrected vision acuity was 20/20 (+1.00 sph –0.75 cyl 111) in the right eye and 20/20 (+1.00 sph –0.50 cyl 65) in the left eye, with spectacles.

The Placido-disk-based topography studies from both patients are presented in Figure 1. Front surface curvature maps from rotating Scheimpflug tomography are presented in Figure 2. The Belin/Ambrósio Enhanced Tomography Classification was possible in twin 1 (I–S value = 1.22 D) and negative in twin 2 (I–S value = −0.46 OD and −0.13 OS). The final deviation value of the Belin–Ambrósio Enhanced Ectasia Display was 4.54 and 1.47 in twin 1 and 1.7 and 1.35 in twin 2.
Ectasia Display from Pentacam HR (Oculus, Wetzlar, Germany) are presented in Figures 3 and 4. Table 1 includes all topometric (front surface-derived) and tomographic variables analyzed, along with their respective cut-off values, sensitivity, and specificity for detecting keratoconus and forme fruste keratoconus.\textsuperscript{10,11}

Slit-lamp biomicroscopy revealed mild papillae in the superior tarsus from both eyes of twin 1. Both eyes from both patients had exacerbated corneal nerves. Only the right eye of twin 1 had an incomplete Fleisher’s ring inferiorly. Goldmann’s applanation intraocular pressure was 9 and 10 mm Hg in OD and OS of twin 1 and 12 mm Hg in both eyes of twin 2. Fundus exams were unremarkable for all eyes. Specular microscopy revealed normal endothelium in all eyes, with central endothelial cell counts of 2,847 and 2,689 cells/mm\(^2\) in OD and OS of twin 1 and 2,649 and 2,636 cells/mm\(^2\) in OD and OS of twin 2.

Front surface corneal curvature maps from Placido-disk-based topography (Oculus Keratograph 5, Wetzlar, Germany) and from rotating Scheimpflug tomography (Pentacam HR) demonstrated similar findings in all eyes studied (Figs 1 and 2). Moderate inferior steepening of the cornea with \(K_{\text{max}}\) 49.6 D and Oculus topographic keratoconus classification (TKC) positive for keratoconus grade 1 was presented in the right eye of twin 1 with suspicious keratoconus in the left eye (index of high decenteration: 0.017 and TKC: possible). Both eyes of twin 2 had normal topographic findings with negative TKC for ectasia (Fig. 2).

Tomographic analysis using the Belin–Ambrósio Enhanced Ectasia Display (BAD) is presented in Figures 3 (twin 1) and 4 (twin 2). The right eye of twin 1 shows a moderate change in the enhanced elevation of the anterior and posterior corneal surfaces (Fig. 3A). The right eye of twin 2 had a posterior elevation value at the thinnest point, considering the 8 mm best fit sphere of 14 µm. The percentage thickness increase (PTI) graph of the right eye of twin 1 (Fig. 3A) had a complete deviation from the mean of normality. The PTI graphs of the other eyes demonstrated a mild deviation in the peripheral cornea. The final deviation value of the BAD (BAD-D) was 4.54 and 1.47 in OD and OS of twin 1 and 1.7 and 1.35 in OD and OS of twin 2.

Glasses were prescribed to both twin patients, according to their needs and refraction findings. Both patients were educated about ectasia and keratoconus so that they understood the risk of eye rubbing. Oral nutritional supplementation with omega-3 essential fatty acids was prescribed to both patients, along with nonpreserved artificial tears. Topical antiallergic treatment was prescribed to twin 1.

**DISCUSSION**

Detection of mild ectatic disease (and its susceptibility) became paramount due to the advent of refractive surgery, as these cases are at very high risk for keratectasia progression after laser vision progression.\textsuperscript{12,13} Considering ectasia risk assessment, the concept that any cornea can undergo ectasia progression is fundamental. As in the right eye of twin 1, ectasia only occurred because of environmental factors, such as ocular trauma and eye...
Fig. 2: Topometric (front surface curvature) maps from Pentacam HR of twin 1 (A-OD and B-OS) and twin 2 (C-OD and D-OS)

Fig. 3: Belin–Ambrósio Enhanced Ectasia Display of twin 1 (A-OD and B-OS)
Therefore, our goal is not solely to detect or screen for mild or subclinical keratoconus, but to lengthily assess individual’s susceptibility for ectasia progression, which also depends on the biomechanical impact of the laser vision correction procedure.

**Forme fruste** in French means “crude,” “abortive,” or “unfinished form” that can or cannot progress. This is an attenuated manifestation of a disease that has an opposite term in medicine – **forme pleine** refers to the full-blown or complete form of a disease. Forme fruste keratoconus was first reported by Amsler in 1961 as an aborted or attenuated form of the disease. Forme fruste keratoconus typically has no or minimal clinical signs of the disease and also has normal best spectacle corrected visual acuity and a relatively normal Placido-disk-based corneal topography. Interestingly, Klyce referred to

Table 1: Summary of clinical parameters from Scheimpflug-based corneal tomography analysis of both twins (obtained from the U12 raw data)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Twin 1 OD</th>
<th>Twin 1 OS</th>
<th>Twin 2 OD</th>
<th>Twin 2 OS</th>
<th>Cut-off</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>KKS</td>
<td>1</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>IVA (mm)</td>
<td>0.42</td>
<td>0.18</td>
<td>0.16</td>
<td>0.11</td>
<td>&gt;0.23</td>
<td>97.11</td>
<td>98.12</td>
</tr>
<tr>
<td>IHA (mm)</td>
<td>36.0</td>
<td>10.4</td>
<td>9.2</td>
<td>6.3</td>
<td>&gt;8.2</td>
<td>80.89</td>
<td>95.11</td>
</tr>
<tr>
<td>IHD (mm)</td>
<td>0.052</td>
<td>0.017</td>
<td>0.012</td>
<td>0.009</td>
<td>&gt;0.015</td>
<td>97.11</td>
<td>98.87</td>
</tr>
<tr>
<td>ISV (mm)</td>
<td>43</td>
<td>18</td>
<td>18</td>
<td>13</td>
<td>&gt;28</td>
<td>98</td>
<td>97.37</td>
</tr>
<tr>
<td>KISA</td>
<td>58.29</td>
<td>6.17</td>
<td>0.41</td>
<td>4.10</td>
<td>&gt;63.7</td>
<td>88.22</td>
<td>98.12</td>
</tr>
<tr>
<td>KISA AST (D)</td>
<td>4.30</td>
<td>0.81</td>
<td>1.26</td>
<td>1.05</td>
<td>&gt;1.33</td>
<td>86.89</td>
<td>73.31</td>
</tr>
<tr>
<td>SRAX</td>
<td>14.65</td>
<td>15.15</td>
<td>0.01</td>
<td>11.73</td>
<td>&gt;14.75</td>
<td>82.22</td>
<td>48.50</td>
</tr>
<tr>
<td>CENTRAL K</td>
<td>45.23</td>
<td>44.20</td>
<td>44.02</td>
<td>44.14</td>
<td>&gt;45.10</td>
<td>76.44</td>
<td>80.08</td>
</tr>
<tr>
<td>KI</td>
<td>1.11</td>
<td>1.05</td>
<td>1</td>
<td>1</td>
<td>&gt;1.05</td>
<td>95.78</td>
<td>96.62</td>
</tr>
<tr>
<td>CKI</td>
<td>1.02</td>
<td>1.01</td>
<td>1</td>
<td>1</td>
<td>&gt;1.01</td>
<td>73.56</td>
<td>97.74</td>
</tr>
<tr>
<td>I–S value</td>
<td>2.78</td>
<td>1.22</td>
<td>–0.46</td>
<td>–0.13</td>
<td>&gt;1.21</td>
<td>96.22</td>
<td>95.86</td>
</tr>
<tr>
<td>$K_{\text{max}}$ (front)</td>
<td>49.60</td>
<td>45.10</td>
<td>45.30</td>
<td>45.30</td>
<td>&gt;47.17</td>
<td>91.56</td>
<td>89.10</td>
</tr>
<tr>
<td>Posterior elevation at thinnest point using BFS 8.0 mm</td>
<td>39</td>
<td>10</td>
<td>14</td>
<td>11</td>
<td>&gt;14</td>
<td>96.22</td>
<td>98.87</td>
</tr>
<tr>
<td>$RPI_{\text{max}}$</td>
<td>2.49</td>
<td>1.52</td>
<td>1.50</td>
<td>1.35</td>
<td>&gt;1.51</td>
<td>95.56</td>
<td>98.50</td>
</tr>
<tr>
<td>$RPI_{\text{avg}}$</td>
<td>1.54</td>
<td>1.12</td>
<td>1.12</td>
<td>1.09</td>
<td>&gt;1.04</td>
<td>97.56</td>
<td>94.74</td>
</tr>
<tr>
<td>Thinnest value</td>
<td>502</td>
<td>521</td>
<td>531</td>
<td>520</td>
<td>≤514</td>
<td>89.33</td>
<td>90.98</td>
</tr>
<tr>
<td>Central (APEX) thickness</td>
<td>518</td>
<td>536</td>
<td>544</td>
<td>529</td>
<td>≤522</td>
<td>85.11</td>
<td>86.47</td>
</tr>
<tr>
<td>$ART_{\text{max}}$</td>
<td>209</td>
<td>354</td>
<td>360</td>
<td>392</td>
<td>≤473</td>
<td>95.78</td>
<td>98.50</td>
</tr>
<tr>
<td>$ART_{\text{avg}}$</td>
<td>341</td>
<td>463</td>
<td>444</td>
<td>508</td>
<td>≤473</td>
<td>96.89</td>
<td>97.37</td>
</tr>
<tr>
<td>BAD-D (FFKC)</td>
<td>4.59</td>
<td>1.47</td>
<td>1.70</td>
<td>1.35</td>
<td>&gt;2.05</td>
<td>100</td>
<td>98.50</td>
</tr>
<tr>
<td>BAD-D (FFKC)</td>
<td>4.59</td>
<td>1.47</td>
<td>1.70</td>
<td>1.35</td>
<td>&gt;1.33</td>
<td>93.62</td>
<td>94.56</td>
</tr>
</tbody>
</table>

**ART:** Ambrósio’s Relational Thickness calculated for the average and maximum progression indices ($ART_{\text{avg}}$ and $ART_{\text{max}}$); **BAD:** Belin/Ambrósio deviation index; **BFS = 8 mm:** Best fit sphere to 8.0 mm zone; **CKI:** Center keratoconus index; **IHA:** Index of height asymmetry; **IHD:** Index of high decentration; **I–S value:** Inferior–superior asymmetry in keratometry; **ISV:** Index of surface variance; **IVA:** Index of vertical asymmetry; **$K_{\text{max}}$ (front):** Maximum axial curvature of the front surface; **KI:** Keratoconus index; **KISA%:** Keratoconus percentage index; **KISA AST:** keratometric astigmatism; **KKS:** Keratoconus stage; **RIP:** Relative pachymetric progression, calculated for the average and maximal progression indices ($RPI_{\text{avg}}$ and $RPI_{\text{max}}$); **Sens:** Specificity; **Spec:** Specificity; **SRAX:** Relative skewing of the steepest radial axes.
the eyes with relatively normal topography of patients with clinical ectasia detected in the fellow eye as forme fruste keratoconus.

There is global consensus that keratoconus is a bilateral disease. Also, there is agreement that ectasia may occur (in one or both eyes of a patient) due to a mechanical process. The two-hit hypothesis is accepted as there is a combination of environmental factors, such as eye rubbing and atopy, and genetic predisposition. In these presented cases, the genetics for both patients are the same. However, clinical keratoconus occurred only in one eye, which the patient referred to have rubbed more aggressively over her entire lifetime. While twin 2 had a moderate susceptibility detected by tomography, she did not develop ectasia progression because of the lack of the second hit. Even though the etiology of keratoconus remains not fully elucidated, the genetic component indubitably plays a major role. The majority of MZ twins are affected in an identical way. Interestingly, a twin study by Mahroo et al analyzed the impact of heritability on anterior and posterior corneal curvature in MZ and DZ twin pairs. As a result of this study, it was found that the genetic factors were responsible for the characteristics of the posterior surface of the cornea in more than 90% of the cases, showing significantly higher correlation between MZ twins. Environmental factors were responsible for the impact on the anterior surface of the cornea once the posterior corneal surface was less exposed. Thereby, changes on the posterior corneal surface are strongly influenced by genetic factors with high heritability cases of MZ twins.

This report illustrates the possibility for enhancing the sensitivity for detecting subclinical ectasia using corneal tomography, which is very relevant for screening ectasia risk prior to laser vision correction. Corneal tomography also helps the long-term follow-up of patients who took to the intracorneal ring segment implantation, as reported by de Oliveira Correia et al.

This case demonstrates that subclinical orforme fruste disease may occur in both eyes.

REFERENCES


39