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AYDANO PAMPONET MACHADO

REDEFINING FORME FRUSTE KERATOCONUS AS ECTASIA SUSCEPTIBILLITY

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Research Article

Redefining Forme Fruste Keratoconus as Ectasia Susceptibillity

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Abstract

The term form fruste keratoconus was initially coined by Marc Amsler in 1938 in cases with slightly tilted Java mires and, later on, longitudinal studies using Polaroid Placido photokerastocopy for describing patterns of irregularity that did precede clinical keratoconus. The term fruste is derived from French and means "confused, crude, or unfinished." Fruste refers to an incomplete and abortive form of the disease, in contrast to the concept of the full-blown presentation. Rabinowitz describes forme fruste keratoconus as the eyes with unremarkable biomicroscopy and no visual impairment having good distance corrected visual acuity by glasses, which present a typical keratoconus irregularity on the topographic mapping. In 2009, Klyce proposed that the term forme fruste keratoconus should also apply to the contralateral eye of keratoconus patients with no clinical findings of any sort.

There is no consensus on the current definition of forme fruste keratoconus. The recent 2015 Global consensus states that keratoconus is bilateral disease and that ectasia may occur unilaterally due to purely biomechanical stress. Nevertheless, FFCK has been recognized as the most important risk factor for developing progressive ectasia after refractive laser correction. This article provides a prospective review of the definition of forme fruste keratoconus as the cases with high susceptibility for corneal biomechanical decompensation and ectasia progression.

Keywords: Forme Fruste Keratoconus; Corneal Ectasia; Multimodal Corneal Imaging

Introduction

Keratoconus (KC) is a bilateral, progressive, and habitually asymmetric ectatic corneal disease characterized by biomechanical failure, stromal thinning, and subsequent corneal protrusion causing irregular astigmatism and visual impairment [1]. Although the criteria for KC diagnosis are well defined, identifying milder or subclinical forms of the disease remains challenging [2].

The term fruste is derived from French and means "confused, crude or unfinished" and has been classically used to specify an incomplete phenotypic expression of a condition, being an abortive form that may later progress to full-blown or forme pleine disease. It is used in several medicine fields to describe an atypical or attenuated manifestation of a disease or syndrome. For example, Sigmund Freud often used form fruste to describe incomplete or obscure cases of neurosis and psychosis. Conceptually, a form fruste of any disease might progress or not to a form plaine depending on several factors.

The need to detect the mildest forms of KC has been extensively explored and referred to as "forme fruste keratoconus," "subclinical keratoconus," or "keratoconus suspect" have been proposed. While these terms have been used interchangeably, this might lead to a significant misunderstanding of the natural history of the disease [3]. The term form fruste keratoconus (FFKC) was initially coined by Marc Amsler in 1938 in cases with slightly tilted Java mires and, later on, longitudinal studies using Polaroid Placido photokerastocopy for describing patterns of irregularity that did precede clinical keratoconus [4].

In the 1980s, the introduction of computerized Placido-disk-based corneal topography provided a more reproducible and detailed analysis of the corneal surface [5]. The advent of refractive surgery led to the demand for detecting mild or subclinical forms of keratoconus because these cases have a very high risk for developing iatrogenic ectasia after keratorefractive procedures that typically weaken the cornea, starting with radial keratotomy [6-8]. Rabinowitz describes FFKC as the eyes with unremarkable biomicroscopy and no visual impairment having good distance corrected visual acuity (DCVA) by glasses, which present a typical keratoconus irregularity on the topographic mapping. Randleman and coworkers combined corneal topography, corneal pachymetry, and clinical data to develop the Ectasia Risk Scoring System, considering FFKC a topographic classification with a major risk ectasia after LASIK [9]. This is in agreement with the first case described by Seiler in 1998 of progressive ectasia one month after LASIK in a case with stable refraction but referred to an FFKC because of irregular corneal topography [6]. FFKC was then recognized as the most critical risk factor for the development of progressive ectasia after refractive laser correction.

Different situations have been denominated as FFKC, including the normal topographic eye of very asymmetric ectasia (VAE) cases (Figure 1-3), or even a normal topographic eye that naturally evolves to clinical ectasia when longitudinally followed. It is important to mention that very mild KC might occur in both eyes from the same patient, and this is described as bilateral FFKC (Figure 4). Keratoconus suspect (KCS) is another term that has been coined to describe an abnormal topographical pattern, which is not yet definitive for KC criteria. These cases may be truly mild forms of KC or eventually present a stable behave and even be candidates for successful laser vision correction (LVC) [10]. Recently, Henriquez and coworkers performed a systematic literature review on KCS and FFKC, concluding that there is a significant lack of unified criteria to define these cases [11].

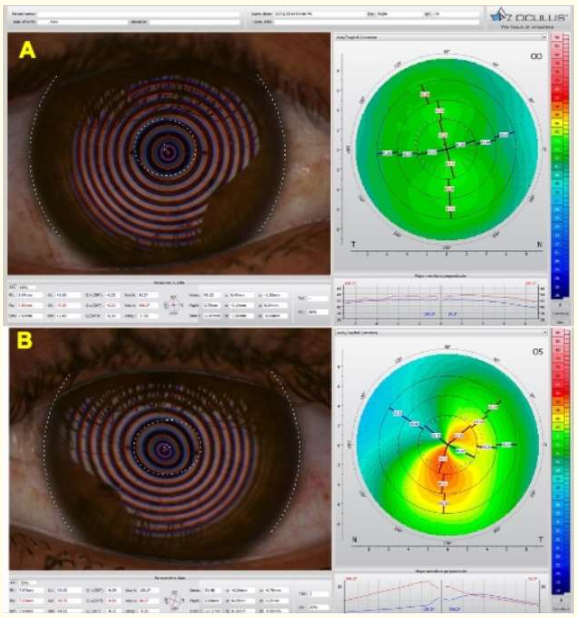

Figure 1: Placido-disk-based corneal topography of OD (A) and OE (B) showing regular astigmatism on axial curvature map in OD and irregular pattern in the left eye with inferior steepening and skewed radial axis (IS-SRA).

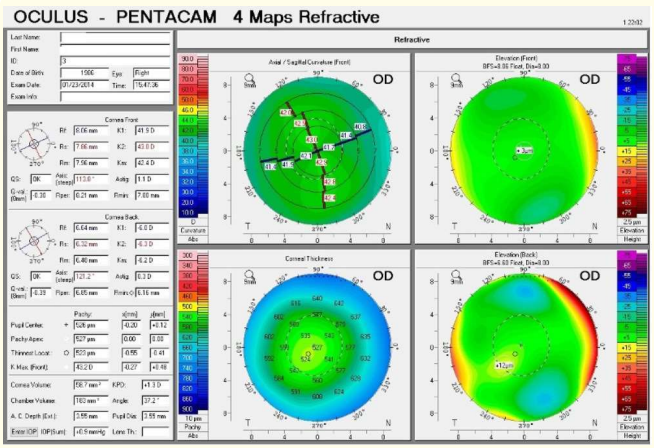

Figure 2: Quad Refractive Map of OD relatively within normal limits with a mild elevation in the posterior surface with 12 microns considering the best-fit-sphere for 8 mm.

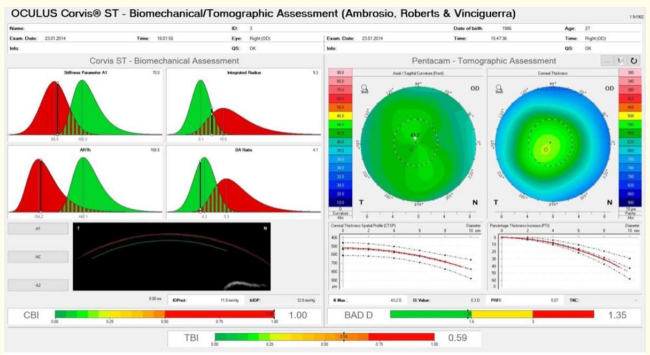

Figure 3: Corvis ST tomographic-biomechanical display from OS shows SPA1 and low ARTh, CBI of 1.0, TBI of 0.59, and BAD-D of 1.35.

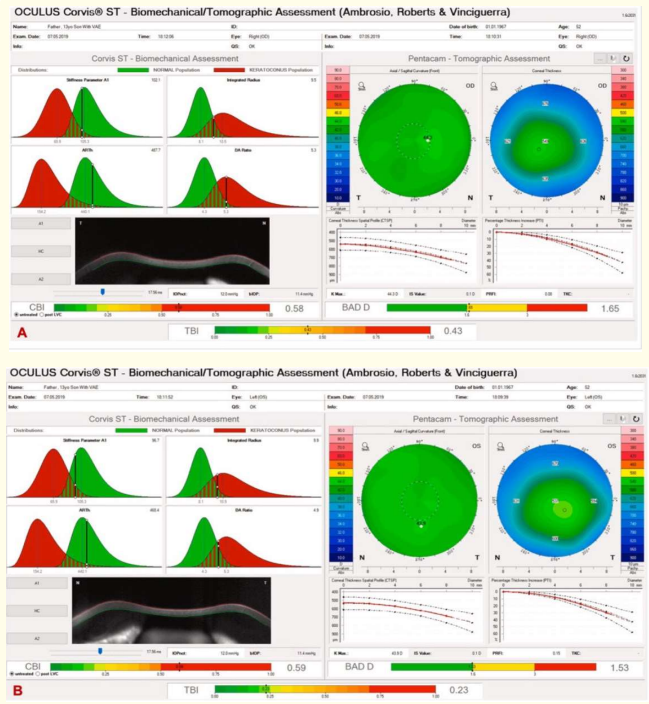

Figure 4A and 4B: Corvis-ST Tomographic-biomechanical display from both eyes of his father. Note that despite an innocent topographic map, we can observe abnormal TBI values of 0.43 and 0.23 in OD and OS, respectively.

Clinical relevance of corneal biomechanics

Considering ectatic corneal diseases, including keratoconus and pellucid marginal degeneration, understanding of corneal biomechanics has a major role and relevance for the diagnosis, staging, and providing prognostic information about the disease [12,13]. The need for depicting the innate susceptibility of each cornea for ectasia progression was recognized, leading to the quest of going beyond and not over classic tests such as computerized topography and central corneal thickness [10]. In fact, understanding the cornea's biomechanical behavior is relevant for the detection of subclinical KC as well as for the detection of ectasia progression. There is a global agreement that while KC may present with a high degree of asymmetry, but the disease is typically bilateral [14]. Conversely, there is also an agreement that an iatrogenic biomechanical process might result in unilateral ectasia, and, in this situation, we should avoid the term KC or KCS. Longitudinal studies have reported cases of unilateral ectasia, documenting long-term stability with advanced diagnostic methods [15].

Corneal biomechanical investigation has become significant in the setting of refractive surgery to identify patients at higher risk

of developing iatrogenic ectasia after LVC, along with enhancing the predictability and efficacy of these elective procedures [7,16].

Unilateral ectasia has also been described in patients who underwent monocular refractive surgical procedures, which remain stable in the unoperated fellow eye [17]. This circumstance is assigned to a biomechanical failure post-LVC, either due to an intrinsic preoperative susceptibility, a detrimental procedure, or even a combination of both [8].

Evolution of corneal imaging and characterization

Corneal topography

In the late 1980s, computerized corneal topography was introduced [5]. Placido disk-based corneal topography represents quantitative anterior surface data through color-coded maps [18]. Rabinowitz and McDonnell proposed topographical indices such as inferior-superior asymmetry, between eyes asymmetry, and central corneal power to detect KC [19]. These indices are still nowadays applied for topographical diagnosis of KC and have proved to be sensitive to identify milder ectatic patterns as well [20]. Rabinowitz describes FFKC as the eyes with unremarkable biomicroscopy and no visual impairment having good distance corrected visual acuity (DCVA) by glasses, which present a typical keratoconus irregularity on the topographic mapping. Randleman and coworkers combined corneal topography, corneal pachymetry, and clinical data to develop the Ectasia Risk Scoring System, considering FFKC a topographic classification with a major risk for ectasia after LASIK. This is in agreement with one seminal report by Seiler of iatrogenic keratectasia after LASIK in a case of FFKC [6]. However, the limitations of this approach were realized after the disclosure of patients that developed post-refractive surgery ectasia, even despite normal anterior curvature maps [17], along with eyes with abnormal preoperative topographic maps, that underwent laser vision correction and present documented stability based on advanced corneal imaging. Furthermore, the subjective classification of these topographic maps represents an important limitation as well [21].

Corneal tomography

Corneal topography evolved to a complete corneal analysis with corneal tomography [22]. This approach provides a 3-dimensional reconstruction of the cornea with measurements of both anterior and posterior corneal surfaces. Different systems, including slit-scanning, rotational Scheimpflug, very high-frequency ultrasound, and optical coherence tomography, allow this approach.

The Orbscan (Bausch and Lomb; Rochester, US) was the first instrument introduced in the market. Reports have demonstrated good sensitivity and specificity of Orbscan indices to discriminate early forms of KC, even in cases with innocent Placido-disk-based topography [23]. More recently, special software developed using linear regression analysis was designed for the Orbscan to objectively classify topographic maps as positive or negative for ectasia risk. The Screening Corneal Objective Risk of Ectasia (SCORE) Analyzer has been tested and validated in FFKC cases and post-LASIK ectasia cases as well [24,25].

The Galilei Dual-Scheimpflug Analyzer (Ziemer; Port, Switzerland) is a system that unites Scheimpflug imaging to Placido disk-based corneal topography. Investigators have demonstrated the ability of this technique not only to differentiate normal and KC eyes [26], but to detect abnormalities in fellow normal topographical eyes from patients with very asymmetric ectasia as well.

The Pentacam (Oculus, Wetzlar, Germany) was the first rotating Scheimpflug system available, and several indices have been proposed to improve the diagnosis of KC using this device. One of the main displays available for preoperative screening is the Pentacam Belin-Ambrósio Enhanced Ectasia Display (BAD). This clinical tool combines pachymetric and elevation data to assist KC diagnosis. Tomographic parameters are displayed as standard deviation from normality (d values) and a linear regression analysis applies different weights to each parameter and calculates a final D value [27]. Studies involving normal and KC eyes have found high sensitivity and specificity values using this approach. Additionally, studies involving highly asymmetric cases have also been conducted and

the ability of this method to detect abnormalities in these cases has been evidenced as well [28]. Retrospective studies evolving eyes that developed ectasia after LASIK were also performed, and researchers found higher accuracy of this technology to identify susceptible cases, which have formerly been deliberated as good candidates, based on the corneal topography [17,29].

Machine learning algorithms and AI methods have been effectively used to combine Pentacam parameters. The Pentacam Random Forest Index (PRFI) was developed in a study including groups of normal eyes, clinical KC eyes, normal topographic eyes from very asymmetric ectasia, and ectasia susceptibility eyes (preoperative data of post LASIK ectasia) [30]. The PRFI demonstrated high performance in discriminating against the four groups. Ambrósio and coworkers applied logistic regression analysis to investigate the benefit of integrating clinical and tomographical data to distinguish between stable LASIK eyes and eyes that developed iatrogenic ectasia after LASIK. This retrospective analysis demonstrated higher sensitivity and specificity of the combination of parameters than individual parameters alone to identify preoperative ectasia susceptibility [31].

Segmental or layered tomography

The next step in corneal tomography evaluation was the characterization of the individual corneal layers. Reinstein and collaborators pioneered corneal epithelial measurements with very high-frequency ultrasound (VHF-US) [32]. Corneal epithelial indices derived from VHF-US have also been proposed as a valuable tool for detecting KC, even in milder forms of the disease [33].

Huang and collaborators developed a parallel approach with optical coherence tomography (OCT) technology. The authors explored an extended epithelial thickness map, which along with different epithelial indices, was able to detect KC, even in milder stages as well [34].

Additionally, Sinha-Roy and coauthors developed a new Bowman's roughness index derived from OCT technology. The authors found significant differences between the level of the irregularity of the Bowman's layer in healthy and KC eyes. The authors demonstrated even higher sensitivity to identify mild forms of KC combining this index with epithelial thickness data and BAD-D value [35].

Corneal biomechanical assessment

The theory of multimodal corneal imaging was introduced to pivot the many diagnostic tools available [13]. Placido disk-based corneal topography does enhance the ability to detect mild abnormalities typical of ectasia in patients with good distance-corrected visual acuity and unremarkable slit lamp examinations [12,20]. Consequently, the advent of corneal and anterior segment tomography, with the 3-dimensional reconstruction of the cornea, offered more detail about corneal architecture, providing quantitative indices derived from the front and back elevation and the pachymetric maps [13,36,37]. The capability of corneal tomography to further improve the accuracy of detecting subclinical ectatic disease was illustrated in different studies involving eyes with typically normal topography from patients with clinical ectasia recognized in the fellow eye [12,23,28,38]. Such eyes with regular topography from patients with very asymmetric ectasia (VAE-NT) represent the most valuable template for developing and testing novel diagnostic strategies for improving ectasia detection [13]. Furthermore, corneal tomographic parameters shown a superior ability to recognize susceptibility to develop ectasia after LASIK in retrospective studies involving patients with such a complication [29,39].

The Ocular Response Analyzer (ORA- Reichert Ophthalmic Instruments, Depew, NY) was the first commercially available instrument to measure corneal biomechanical properties. This noncontact tonometer generates two main biomechanical parameters, the corneal hysteresis (CH) and the corneal resistance factor (CRF). Studies have demonstrated that despite CH and CRF have a significantly different distribution among healthy and ectatic eyes, the use of this technology in KC diagnosis is limited once a significant overlap has been found in the comparisons [40].

The Corvis ST (Oculus, Wetzlar, Germany) is also a noncontact tonometer, and internationally, it is approved for biomechanical assessment of the cornea. During its measurement, the cornea deforms inward and outward while passing through two applanation moments. This approach allows a more comprehensive evaluation of the corneal deformation response [41].

A multicentric international investigation group was created in 2014 with the goal to increase knowledge about Corvis ST technology with a unique focus on the investigation of the ectatic corneal disease using Scheimpflug imaging [12,42]. One of the outcomes of this collaborative work was the Vinciguerra Screening Report that provided correlations of normality values and a biomechanically-corrected intraocular pressure. The horizontal Scheimpflug image of the undisturbed cornea also supplies data for calculating the profile or the proportion of increase of corneal thickness from the apex towards the nasal and temporal sides. The characterization of the thickness data on the horizontal Scheimpflug image (the division between corneal thickness at the thinnest point and the Pachymetric Progression Index) enables the calculation of the Ambrósio Relational Thickness over the horizontal meridian (ARTh) [43]. The investigators used linear regression analysis to combine ARTh with corneal deformation parameters to generate the Corvis Biomechanical Index (CBI) [44]. Vinciguerra and coworkers demonstrated that a cut off value of 0.5 CBI was able to correctly identify 98.2% of keratoconic cases among normal with 100% specificity [44].

Later, Ambrósio and coworkers continued this multicenter study to improve ectasia detection and used artificial intelligence to develop a new index combining tomographic and biomechanical data, the tomographic biomechanical index (TBI) [7,12]. This study involved one eye randomly selected from each of the 480 normal patients, 204 "bilateral" KC cases and 72 unoperated ectatic eyes (VAE-E) from 94 (VAE-NT) patients with very asymmetric ectasia, who presented fellow eyes with normal topographic maps based on precise, objective criteria. The random forest will leave-one-out cross-validation using the best machine learning function for the TBI. The cutoff of 0.79 provided 100% sensitivity and specificity to detect clinical ectasia (KC + VAE-E cases). For the eyes with a normal topographic pattern, an optimized cutoff of 0.29 provided 90.4% sensitivity and 96% specificity with an area under the ROC curve of 0.985 [7].

The TBI has been suggested to epitomize the intrinsic ectasia susceptibility for ectasia progression. Shetty and coworkers reported a case of ectasia after small incision lenticule extraction (SMILE) that was classified preoperatively as normal considering a standard evaluation [45]. Exceptionally, the retrospectively calculated TBI was within the range of abnormality, indicating moderate ectasia susceptibility [46]. Besides the TBI data, the SMILE lenticules from both eyes of this patient that developed ectasia were retrieved and compared with five eyes from three stable-SMILE patients that were matched for age, sex, and duration of follow-up. Gene expression analysis demonstrated reduced expression of lysyl oxidase (LOX) and collagen types I alpha 1 (COLIA1) in the SMILE lenticules that developed ectasia, which may point to the confirmation of clinical predisposition for ectasia development in the molecular domain, confirming ectasia susceptibility [45].

Ocular wavefront analysis

Besides corneal analysis, ocular aberrometry has been widely applied in refractive surgery for the investigation of low and higher-order aberrations, particularly for designing wavefront-guided refractive surgery [47].

The investigation of higher-order aberrations has proven to be valuable in different corneal disorders as well, including KC. Comparative studies have demonstrated that corneal and total higher-order aberrations are significantly higher in KC eyes compared to healthy eyes [48]. Interestingly, the ocular wavefront has proven to be valuable in detecting milder forms of KC as well [49].

Future

While we contemplate the advances in multimodal corneal and refractive imaging into the multimodal domain, this is predictable that molecular biology and genetics will play a higher role. For example, in the characterization of KC, considering the molecular and cellular changes associated with the pathogenesis of ectasia, including extracellular matrix degeneration. An up-regulation of degradative enzymes, oxidative stress, and inflammation may further enhance the ability for ectasia characterization [50]. In fact, the future is bright for refractive surgery and imaging technologies.

Clinical examples

Case 1 - Very asymmetric ectasia with FFKC

We report a case of a 27-year-old female patient presenting with a very asymmetric ectasia (VAE). The manifest refraction was

-2.75/-1.0 x 11° (20/15) in the right eye (OD), and -1.75/-4.0 x 129° (20/25) in the left eye (OS) and central corneal thickness was 529 and 490 microns OD and OS. We can note the typical, relatively normal axial topography in the right eye and mild keratoconus OS. Figure 1 reveals the Placido-disk-based corneal topography of both eyes with regular astigmatism on axial curvature map in OD and irregular pattern in the left eye with inferior steepening and skewed radial axis (IS-SRA), maximal keratometry of 51.4D, and TKC grade 2.

The quad map in OD is relatively within normal limits with a mild elevation in the posterior surface with 12 microns considering the best-fit-sphere for 8 mm (Figure 2). The integrated biomechanical and tomographic display in OD (Figure 3) reveals low SPA1 (stiffness parameter at first applanation) and low ARTh (horizontal Ambrósio Relational Thickness), CBI of 1.0, TBI of 0.59, and BAD-D of 1.35.

This example demonstrates a case of very asymmetric ectasia with FFKC in OD, which could only be diagnosed with multimodal corneal imaging and integration of different approaches with artificial intelligence.

Case 2 - Bilateral FFKC

The 54-year-old man, father of a 13-year-old KC patient who came to the consultation, and we decided to perform a comprehensive examination on both of his eyes. The UDVA was 20/20 on both eyes. Patient had no glasses for distance, but used +2.00 add correction for reading J1. Despite having a relatively normal topographic map, both eyes demonstrated high (abnormal) TBI values (Figure 4A and 4B), indicating. Only because of the tomographic and biomechanical approach he was diagnosed as a bilateral FFKC. This case demonstrates the role of tomography and corneal biomechanics to diagnose milder forms of ectatic disease better.

Conclusion

The global consensus states that KC may present with a high degree of asymmetry, but the disease is typically bilateral [14]. Contrariwise, there was also an agreement that unilateral ectasia may occur secondary to a mechanical process. In this case, the term unilateral ectasia and not KC should be applied. Interestingly, studies have documented instances of unilateral ectasia with long-term stability followed by advanced diagnostic methods [15].

The redefinition of FFKC is intrinsically associated with refractive surgery and KC management, and FFKC is not a topographical or even a tomographical classification and should be defined as very high susceptibility for ectasia progression. Screening for ectasia risk among refractive candidates goes beyond disease diagnosis into understanding inherent susceptibility or vulnerability. Advances in corneal imaging with a multimodal approach allow for augmenting sensitivity and specificity to identify this susceptibility.

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