Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/survophthal

Major review

A review of keratoconus: Diagnosis, pathophysiology, and genetics

Veronica Mas Tur, FEBO[a], *Cheryl MacGregor, BM*[a], *Rakesh Jayaswal, MBChB, FRCOphth, FRCS (Ed)*[a], *David O'Brart, MD, FRCS, FRCOphth*[b], *Nicholas Maycock, BSc (Hons), MBBS, FRCOphth*[b,*]

[a] *Eye Department, Queen Alexandra Hospital, Portsmouth, Hants, United Kingdom*
[b] *Department of Ophthalmology, St Thomas' Hospital, London, United Kingdom*

ARTICLE INFO

Article history:
Received 8 February 2017
Received in revised form 26 June 2017
Accepted 29 June 2017
Available online 6 July 2017

Keywords:
keratoconus
genetics
review article

ABSTRACT

We discuss new approaches to the early detection of keratoconus and recent investigations regarding the nature of its pathophysiology. We review the current evidence for its complex genetics and evaluate the presently identified genes/loci and potential candidate gene/loci. In addition, we highlight current research methodologies that may be used to further elucidate the pathogenesis of keratoconus.

1. Introduction

Keratoconus (KCN) is an asymmetric, progressive ectatic condition that can lead to significant visual impairment.[114] Although the disease has high prevalence, the cellular etiology of the disease is not well understood. Studies in varied fields such as genetics, genomics, small biomolecule analyses, and gene expression analysis suggest that the disease may be multifactorial in origin. Furthermore, a variety of genome-wide studies in familial KCN implicate differential loci. Therefore, it is even more evident that the disease may be sporadic and dependent on external factors and stimuli that lead to the inception and progression of this complex disease.

KCN is a bilateral and usually asymmetrical disease in which the ectatic cornea becomes conical in shape. It typically presents in adolescence and progress until the third or fourth decade of life and is one of the commonest reasons for keratoplasty in the developed world,[36] although this demand is decreasing with the onset of corneal collagen crosslinking.

The etiology of KCN is not fully understood with several different pathways implicated—biochemical, physical, and genetic—with the condition being a final common pathway for several different diseases. It can occur as a result of genetic

* Corresponding author: Nicholas Maycock, BSc (Hons), MBBS, FRCOphth, Department of Ophthalmology, St Thomas' Hospital, Westminster Bridge Road, London SE1 7EH, United Kingdom.
E-mail address: nicholas.maycock@me.com (N. Maycock).
0039-6257/$ – see front matter © 2017 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.survophthal.2017.06.009

predisposition triggered by environmental factors. It may arise as an isolated condition or in association with ocular and systemic disorders such as atopy, vernal disease, Down syndrome, retinitis pigmentosa, Turner syndrome, connective tissue disorders such as Marfan syndrome, Ehlers-Danlos syndrome, osteogenesis imperfecta, and pseudoxanthoma elasticum. KCN has a strong association with eye rubbing, repeated trauma from contact lenses, and allergic eye disease.[67,114] Between 8% and 10% of cases have a hereditary component and family history, and an inverse relationship between the severity of the condition and diabetes has been described.[45,47,114,117,153] Stromal thinning is thought to be related to a combination of increased activity of proteinase enzymes and decreased proteinase inhibitors with subsequent reduced biomechanical stability.[11]

KCN affects both genders and all ethnicities. The reported prevalence and incidence is variable. This is probably due to different clinical definitions and diagnostic criteria used between studies and populations. The incidence of KCN in the European white population has been determined to be between 5 and 23, with a mean prevalence of 54, per 100,000.[117] There is a higher prevalence in South Asian patients compared with whites.[17,108] Based on a 48-year epidemiological study conducted in the United States, KCN was thought to affect approximately 1 person in 2000, with a mean incidence of 2 new cases per 100,000 per year[51]; however, a recent study by Godefrooij and colleagues has shown both the annual incidence and prevalence to be much higher.[45] They conducted an epidemiological study looking at 4.4 million patients in the Netherlands and found the annual incidence was 1:7500 (13.3 cases per 100,000) and the estimated prevalence was 1:375 (265 cases per 100,000). These values are 5 to 10 fold higher than previously reported in population studies, and this is thought to be a result of a combination of earlier and more advanced detection with tomography and comprehensive data collection in the Netherlands.

We discuss the diagnosis and pathophysiology of KCN. We review the evidence for the complex genetics of KCN and evaluate the currently identified genes/loci and potential candidate gene/loci. In addition, we highlight current research methodologies that may be used to further elucidate the pathogenesis of KCN.

2. Diagnosis

KCN should be suspected in any patient with significant irregular astigmatism, especially if unstable and increasing over time. In the early stages of the disease, there is altered metabolic activity that may lead to biomechanical instability and stretching of the corneal tissues.[89] As the disease progresses, there is accompanying tissue loss. In addition, there is a loss of correlation between the anterior and posterior corneal curvature.[111] Progressive corneal thinning and distortion causes a conical or cone-shaped protrusion, which may be visible at the slit lamp in advanced cases.[46] In early disease, the condition may go undiagnosed unless assessments of the posterior and anterior corneal surfaces are undertaken using corneal tomography.

2.1. *Corneal topography*

The following topographic parameters should arouse suspicion and examination for further evidence of the disease: astigmatism >5 diopters (D), and/or keratometry values (K1/K2) > 48 D[70]; maximum keratometry (Kmax) reading >49 D; central corneal thickness (CCT) <470 μm; and corneal asphericity > −0.50 μm (see Tables 1 and 2).[18] The normal corneal surface is aspherical, ranging from mild oblate to moderate prolate in shape, with most studies suggesting the human cornea Q (asphericity) values range from −0.01 to −0.80 (mean −0.23 ± 0.08) measured in the 4.5-mm optical zone.[142]

Topography maps with high astigmatism or an asymmetrical bowtie pattern are suggestive of KCN.[114] Regular astigmatism will be represented by a bowtie pattern with 2 symmetric segments (see Fig. 1). The symmetrical bowtie is vertical in with-the-rule astigmatism, horizontal if the astigmatism is against-the-rule, and diagonal with oblique astigmatism. Corneal irregularities, or deviations from the symmetrical bowtie pattern, are detected by the curvature map and described in terms of their shape: round, oval, superior steep, inferior steep, irregular, symmetric bowtie with skewed radial axis, inferiorly steep asymmetric bowtie, superiorly steep asymmetric bowtie, or asymmetric bowtie with skewed radial axis (see Fig. 1). These patterns are risk factors for corneal ectatic disorders when accompanied by abnormal tomographic parameters. Within the 5-mm central zone, symmetrically opposite superior and inferior locations are compared. There is a risk of corneal ectasia if the superior value is more than 2.50 D greater than the lower value or the inferior value is more than 1.50 D greater than the upper.[114]

There is a displacement of the corneal apex with localized areas of steepening. In addition, there is vertical asymmetry in corneal power, skewing of radial axes above and below the horizontal meridian, and focal pachymetric thinning localized to the corneal apex. KCN cones can be classified into (1) nipple—the cone has a diameter ≤5 mm, round morphology and is located in the central, paracentral, or inferonasal corneal

Table 1 – Amsler-Krumeich Classification for grading keratoconus

Stage	Findings
1	Eccentric steepening Myopia, induced astigmatism, or both <5.00 D Mean central K readings <48 D
2	Myopia, induced astigmatism, or both from 5.00 to 8.00 D Mean central K readings <53.00 D Absence of scarring Corneal thickness >400 micron
3	Myopia, induced astigmatism, or both from 8.00 to 10.00 D Mean central K readings >53.00 D Absence of scarring Corneal thickness 300–400 micron
4	Refraction not measurable Mean central K readings >55.00 D Central corneal scarring Corneal thickness < 200 micron