Posterior polymorphous dystrophy and keratoconus: more than a casual association?

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PURPOSE: To report the simultaneous presentation of Posterior Polymorphous Corneal Dystrophy and Keratoconus in a group of patients from the Cornea and External Diseases Clinic at CES University, between 1995 and 2008 and provide a plausible explanation for it.

METHODS: This is a retrospective clinical records review of patients with simultaneous presentation of Posterior Polymorphous Corneal Dystrophy and Keratoconus who had undergone a complete ophthalmological examination; the diagnosis of Posterior Polymorphous Corneal Dystrophy was based on clinical findings on slit lamp examination and the diagnosis of Keratoconus was confirmed by corneal topography.

RESULTS: We identified five patients with a simultaneous clinical presentation of Posterior Polymorphous Corneal Dystrophy and Keratoconus.

CONCLUSIONS: Weighing the facts, there is a possible association between Posterior Polymorphous Corneal Dystrophy and Keratoconus well beyond simple chance, explained on the basis of a common embryological origin together with simultaneous chromosomal alterations, justifying their simultaneous presentation.

KEY WORDS: Keratoconus, Posterior Polymorphous Corneal Dystrophy, chromosome 20, neural crest, VSX1 gene.

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INTRODUCTION

Posterior Polymorphous Corneal Dystrophy (PPCD) is in most of the cases an autosomal dominant, bilateral and asymmetric entity[1,2]. It's a genetically heterogeneous entity, mapped to chromosome 20[2-5] on three different loci and to chromosome 10[6]. It has a wide clinical spectrum, with changes on the corneal endothelium and –less frequently– on the iris and anterior chamber angle[1,2,7]. Some have suggested classifying it as a neural crest anomaly in which there is a defect in the terminal differentiation of the corneal endothelial cells[8]. It's been associated with keratoconus[9-15], Essential Iris Atrophy[12,15], glaucoma[16] and Alport Syndrome[17].

Keratoconus (KC) is a non-inflammatory corneal ectasia[18]; it's bilateral in up to 90% of patients and usually asymmetric, with no sex or race predilection[18-20]. Its presentation is usually sporadic and isolated, although a positive family history can be found in up to 10% of cases[19], and it has been mapped to chromosomes 13, 16, 17, 20 and 21[21-24]. It has been associated with other diseases of genetic origin including Fuchs', Anterior Basement Membrane, Lattice, Granular and Posterior Polymorphous dystrophies[9-14,21-28].

In view of the growing number of reports connecting PPCD and KC[9-14,29], and considering that the statistical probability of this association being casual is remote, an explanation is needed on the basis of a common link.

PATIENTS AND METHODS

We herein report 5 patients with the association of KC and PPCD seen at the Cornea Service of CES University between 1995 and 2008. Inclusion criteria

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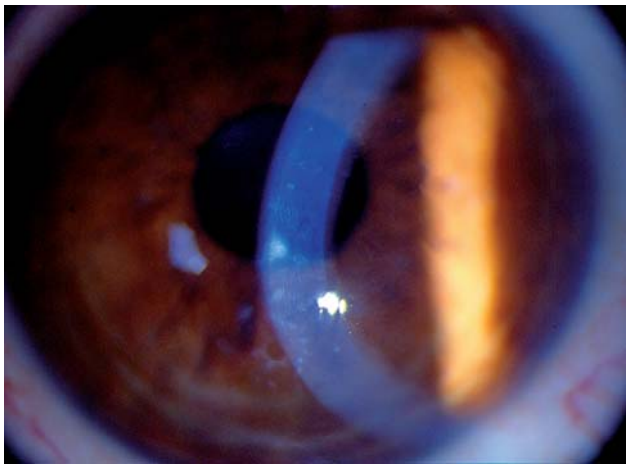

Figure 1A. Slit lamp cornea picture of the right eye of a 25 y.o. male showing coincident Vogt striae, Bowman's membrane ruptures, apical leucomas, and multiple endothelial grayish vesicles and annular lesions.

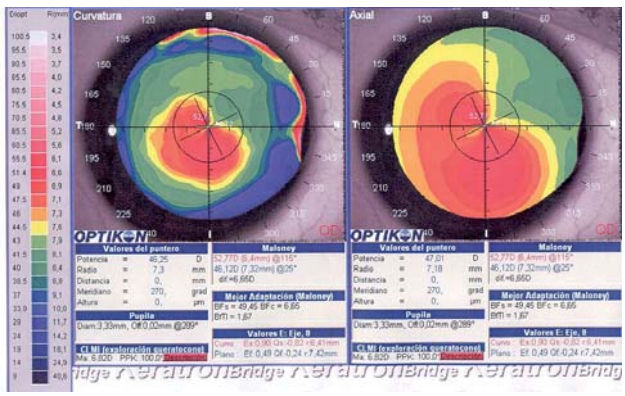

Figure 1B. Same patient's right eye corneal topography showing asymmetric inferior steepening.

were a clinically evident KC confirmed by Corneal Topography and the concomitant presence of any clinical sign of PPCD.

All patients came to office complaining of poor visual acuity secondary to the KC and none had a previous diagnosis of PPCD.

All subjects were male, with a mean age of 16.6 yrs (range 9-26), with clinically evident bilateral KC while 3 had bilateral and 2 had unilateral clinical findings of PPCD.

KC-related clinical findings included apical thinning (5 patients), Vogt striae (3 patients) (figs. 1A, 2A, 3A), Fleischer's ring (3 patients) (fig. 4), prominent corneal nerves (2 patients) (fig. 4) and Bowman's breaks (2 patient) (fig. 2A). All patients had a grossly abnormal corneal topography with inferior steepening (figs. 1B, 2B, 3B).

Regarding endothelial findings related to the PPCD, 4 patients had railroad track lesions (fisg. 3A, 4, 5, 6), 3 had annular lesions with a grayish halo and 2 had vesicles (figs. 1A, 2A, 4, 5).

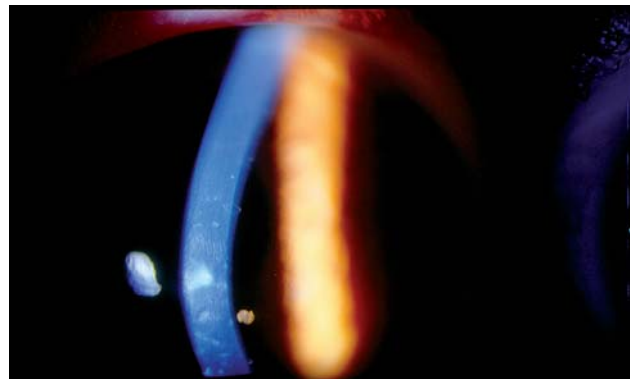

Figure 2A. Slit lamp cornea picture of the left eye of patient of pictures 1A and 1B, showing Vogt striae, and multiple endothelial grayish vesicles and annular lesions.

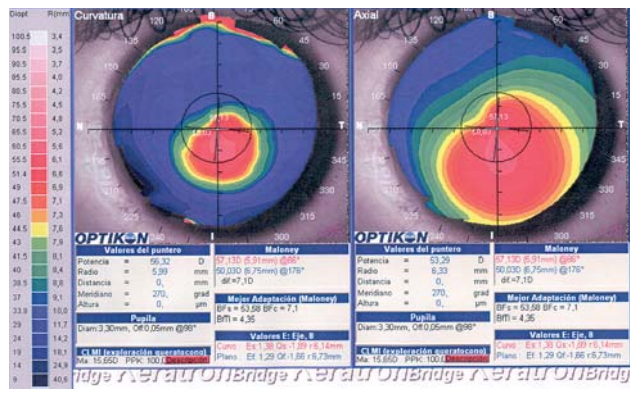

Figure 2B. Same patient's left eye corneal topography showing asymmetric inferior steepening.

DISCUSSION

The association of KC and PPCD is well documented, with multiple case reports going back to 1974[9-11,14, 29], making it hard to deem it a casual association. Such a linkage can have two non-necessarily excluding explanations: an alteration on the embryologic development and a chromosomal mutation.

The hypothesis of an alteration on the embryologic development is based on a disruption of the neural crest cells[8]. Corneal endothelial cells originate from a group of cells of mesodermal origin called the primary mesenchyme. Subsequently neural crest cells migrate into this primary mesenchyme and constitute the secondary mesenchyme; then, the neural crest cells from this secondary mesenchyme, migrate into the developing eye in three successive waves, originating the corneal endothelium and trabecular meshwork (1st wave), stromal keratocytes (2nd wave) and iris stroma (3rd wave).

The anatomical and embryological proximity of the corneal endothelium cells (1st wave; DPP) and stromal keratocytes (2nd wave; KC) during the whole previously described process, tolerates a suspicion on some kind of common injury to both cellular groups which will be

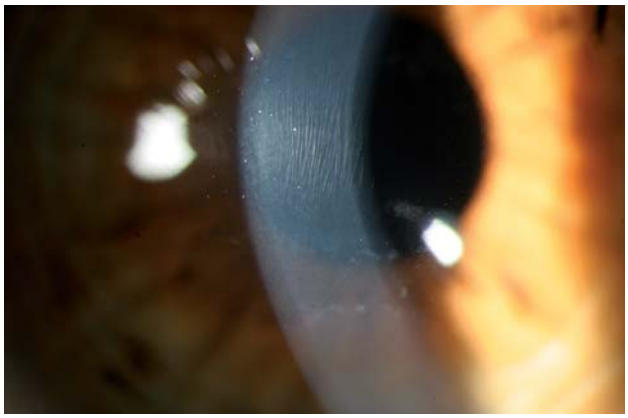

Figure 3A. Slit lamp cornea picture of the right eye of a 26 y.o. male showing coincident Vogt striae and an inferior horizontal railroad track image with thickened and irregular borders.

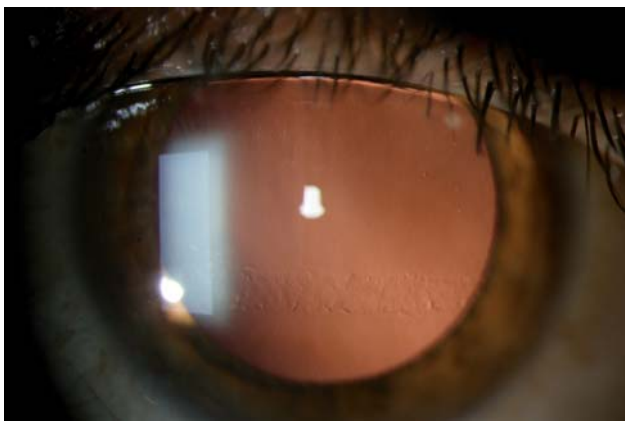

Figure 3B. Same patient's railroad track image seen on retroilumination.

expressed by a simultaneous anomaly later on during the corneal development.

Regarding the hereditary/chromosomal component of this association, it is important to note the high expression variability of both KC and PPD[2,3,5,19,32-37].

Even though most KC cases are sporadic, up to 10% of these patients have a family history; its genetics are extremely complex and heterogeneous. Regarding PPCD, it has a wide range of expression with an increasingly evident multiplicity of chromosomal locations[3,4,32,35,36,38,39].

Identifying the chromosomal location of an associated condition can give a clue to the genetic alteration. In some cases both diseases can be allelic variables of the same alteration, with greater genetic heterogeneity for them, such as suggested one in the VSX1 gene (located on 20p11-q11) which links PPD and KC[3]; different groups have reported mutations involving the VISX1 gen in patients with PPCD[38,39] and KC[20,34,38] or a combination of both phenotypes[38,40]. This gene seems to play a role in up to 4.7% of patients with isolated KC, and in up to 9% of patients with PPCD[38].

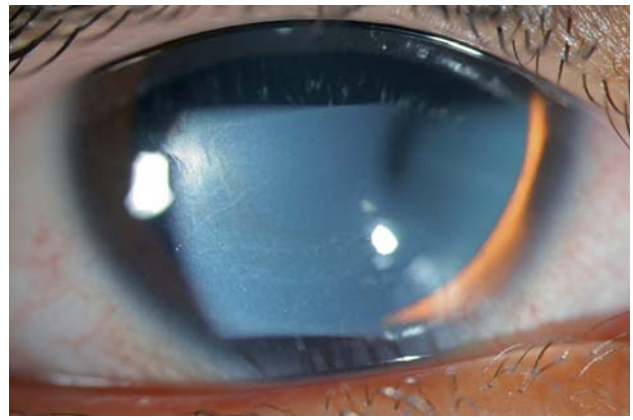

Figure 4. Slit lamp cornea picture of the right eye of a 15 y.o. male showing prominent corneal nerves, Fleischer's ring, an inferior horizontal railroad track image and endothelial vesicles.

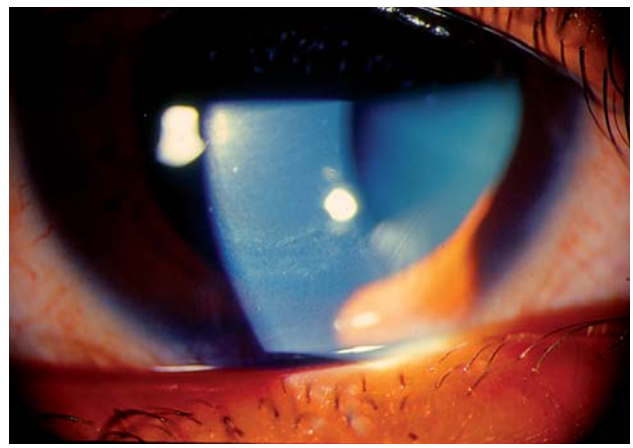

Figure 5. Slit lamp cornea picture of the right eye of a 9 y.o. male showing an inferior horizontal railroad track image delineated by multiple endothelial vesicular images.

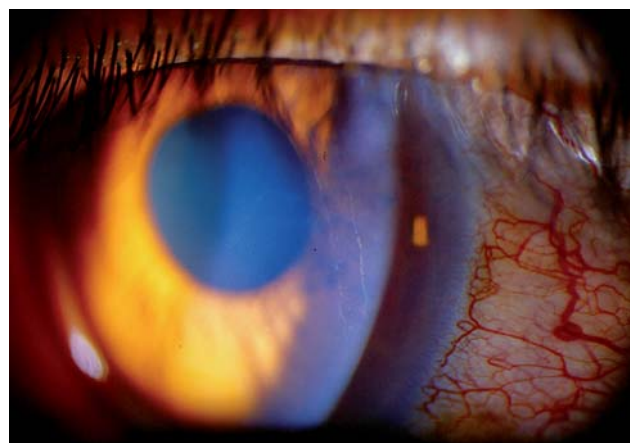

Figure 6. Slit lamp cornea picture of the right eye of a 13 y.o. male showing an unusual vertical railroad track image.

It appears that VSX1 plays a pathogenic role only in a subgroup of PPCD1 mapped families and not in every patient with PPCD[3,41].

In conclusion, we think that the association between KC and PPCD is more than just chance and not due to independent mutational events; the variability and multiplicity of clinical expression and chromosomal alteration of both entities make it very difficult to localize an alteration in a single gene responsible for their concurrence on any one patient.

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