Keratoconus in Patients with Macular Stromal Dystrophy

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Objective: *To show the association between keratoconus and macular dystrophy.*
Material and Method: *All patients with macular dystrophy and associated clinical findings leading to a diagnosis of keratoconus by corneal topography were retrospectively reviewed during a 10-year period. Uncorrected and best-corrected visual acuity, automated refraction, manifest refraction, corneal thickness, and corneal curvature by corneal topography were evaluated.*
Results: *Three patients with macular dystrophy exhibiting decreased vision, multifocal white dense deposits, and haze surrounding the deposits in the corneal stroma were evaluated. All had a steep corneal curvature of >47 diopters and a thin cornea consistent with keratoconus. Penetrating keratoplasty was performed in one patient with severely decreased vision. Macular dystrophy was diagnosed based on an Alcian blue-stained pathological specimen.*
Conclusion: *Keratoconus may develop as a result of changes associated with macular dystrophy. Therefore, patients with severely decreased vision should be evaluated for keratoconus to ensure proper management.*

Keywords: *Keratoconus, Macular stromal dystrophy, Corneal topography, Corneal thinning*

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Macular corneal stromal dystrophy is a rare hereditary corneal disease characterized by early onset of blurred vision and stinging eyes at three to nine years of age. Multifocal grayish-white deposits with ill-defined margins and surrounding haze develop in the corneal stroma. These lesions are deposits of acid glycosaminoglycans and extend from the central cornea to the limbus; they are associated with corneal thinning in some patients[1]. The reported prevalence of macular dystrophy in the United States is 9.7:1,000,000[2]. This condition might be caused by a change in the TGFBI gene (CHST6) on chromosome 16 (16q 22.1) with autosomal recessive inheritance[3]. The clinical diagnosis is based on slit lamp biomicroscopy, which demonstrates white opacities in the superficial stroma and corneal thinning. However, pathological specimens stained with Alcian blue definitively confirm the diagnosis.

Keratoconus is a non-inflammatory condition characterized by corneal degeneration with a steep corneal curvature of >47 diopters (D) and corneal thinning associated with cone-like corneal bulging. It is usually bilateral with asymmetric severity in each eye, and onset typically occurs during puberty. Corneal thinning and protrusion occur with slow or rapid progression. Mildly to severely decreased vision results from an extreme degree of irregular astigmatism or corneal hydrops and leukoma formation. The incidence of keratoconus is 3.3 to 4.5:100,000 in Caucasians and 19.6 to 32.2:100,000 in Asians[4]. The cause of keratoconus is unclear. Rabinowitz reported associations of keratoconus with allergy, Down syndrome, and Leber's congenital amaurosis with a history of vigorous eye rubbing[5]. Frequent mild pressure on the cornea may play a role in the progression of this condition. Another theory is that multifactorial influences including both environmental and hereditary causes are involved, the latter of which is based on similar findings in homozygous twins[6-8].

Keratoconus is diagnosed by clinical findings, including Munson's sign (a conical indentation in the lower eyelid during the downward gaze), the presence of Vogt's striae at Descemet's membrane, acute corneal hydrops presenting as localized edema, and a scissoring reflex on retinoscopy. Pathological examination shows a thin cornea, breaks in Bowman's layer, subepithelial scarring, a normal or torn Descemet's membrane in the presence of acute hydrops, and iron deposition in the epithelium (Fleischer rings)[9]. Keratometry in patients with prolonged progression of keratoconus shows an

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irregularity on the corneal surface. Corneal topography can be used to evaluate patients with early onset of keratoconus and shows an asymmetrical bowtie pattern on a curvature map and abnormal anterior and posterior elevation on an elevation map. According to the Belin/Ambrósio Enhanced Ectasia Display, patients with keratoconus exhibit abnormal elevation with corneal thinning, an increased corneal thickness spatial profile, and a rapid change in the percentage thickness increase[10-12].

Keratoconus may also be associated with other corneal diseases. A few cases of the co-occurrence of macular dystrophy and keratoconus have been reported in Iran and Kuwait, but there have been no such reports in Thailand[13-15]. Therefore, the purpose of the present report was to evaluate the association between keratoconus and macular stromal dystrophy in Thailand.

Material and Method

The authors' report was approved by the Siriraj Institutional Review Board (Ethical approval No. 245/2013). The medical records of patients at Siriraj Hospital were retrospectively reviewed during a 10-year period (2002-2012). The inclusion criteria were macular dystrophy and keratoconus. The exclusion criteria were corneal ulcers and no record of visual acuity or corneal topography examination findings. Each patient's history, uncorrected and best-corrected visual acuity, slit lamp biomicroscopy findings, and corneal topography findings (Pentacam; Oculus Optikgeräte GmbH, Wetzlar, Germany) were analyzed. Keratoconus was diagnosed in patients with a steep corneal curvature of >47 D in the central area and corneal thinning of <450 microns[5].

Patients exhibiting corneal opacity with multifocal grayish-white deposits with ill-defined margins and haze around lesions characterized as macular stromal dystrophy were enrolled[16]. Visual acuity of 6/6 was classified as normal vision, 6/9 to 6/12 as mildly decreased vision, less than 6/18 as low vision, and less than 3/60 as blindness.

Penetrating keratoplasty was considered in patients with an average keratometry reading of more than 55 D at baseline.

Results

Patient 1

An 18-year-old female was examined in October 2002 for a 2-year history of non-painful decreased vision in both eyes. Her vision was worse in her left eye (OS) than right eye (OD). Her corrected visual acuity improved with glasses wearing for four years. She had no relevant family history; only her sister had astigmatism and normal corneal curvature. The patient's visual and corneal measurements were shown in Table 1. Both corneas exhibited multiple hazy foci in the stroma; more lesions were present in the central area than in the periphery. The cornea did not exhibit a conical shape (Fig. 1A, B). No fluorescein staining occurred, and the depth of her anterior chamber and iris contour were both normal. Her corneal lesions progressively worsened for seven years (Fig. 1C, D). The best spectacle-corrected visual acuity OD and OS were $6/24^{+1}$ and 6/18, respectively, indicating low vision; her visual acuity in both eyes improved to 6/9 while looking through a pinhole. Her manifest refractions OD were sphere -8.00 D, cylinder -4.00 D, and axis 168°, and those OS were sphere -10.75 D, cylinder -4.00 D, and axis 178°, indicating high myopia and high astigmatism. Asymmetric bowties were present on the curvature map with >47 D in the central area of both eyes on corneal topography (Fig. 2). The central corneal thickness was thin at 418 microns OD and 429 microns OS. She declined to undergo penetrating keratoplasty, and instead underwent correction with glasses and follow-up.

Patient 2

A 33-year-old woman was examined in August 2006. She had a 10-year history of progressively decreasing vision, photophobia, burning, and tearing. Her visual acuity was severely low (Table 1). Stromal

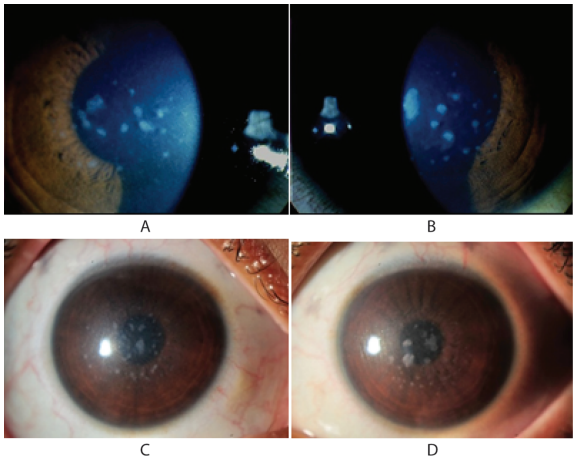

Fig. 1 Corneal opacity in patient No.1, A) right eye, B) left eye. Seven years later, progression of opacity in right eye (C), left eye (D).

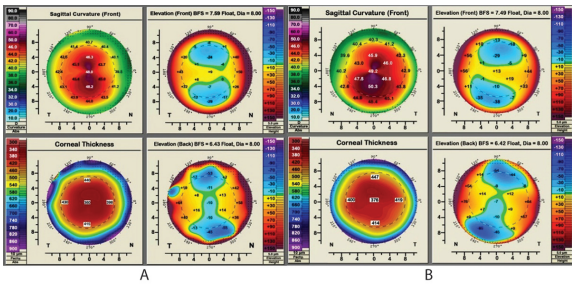

Fig. 2 Asymmetric bowtie in curvature map, thinning cornea in pachymetry map with central keratometric power over 47 dioptered in both eye, A) right eye, B) left eye.

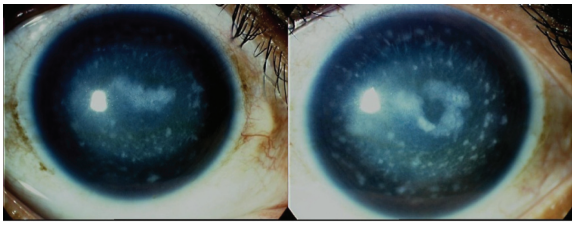

Fig. 3 Multifocal opacity in stroma both eyes with ill-defined margin distributed from central and paracentral area of patient No.2, A) right eye, B) left eye.

corneal opacities in both eyes prevented the performance of autorefraction and measurement of refractive error. No fluorescein staining was observed, and her anterior chamber depth and iris were normal (Fig. 3). Her vision decreased to blindness based on finger counting at 1.0 foot OD and 0.5 foot OS. Inferior steepening was evident on the curvature map OD (54.3 D), and a skewed radial axis and irregular astigmatism was evident OS with an increased corneal thickness spatial profile and percentage thickness increase (Fig. 4).

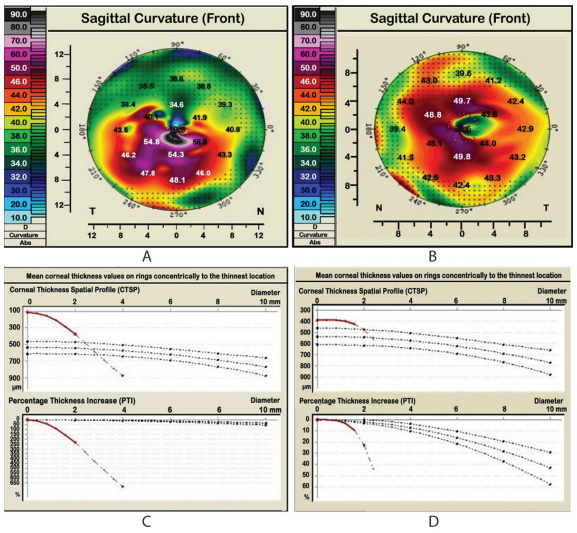

Fig. 4 Curvature map in patient No.2, A) right eye with inferior steepening, B) left eye with skewed radial axis and irregular astigmatism, C and D) demonstrate increased in corneal thickness spatial profile (CTSP) and percentage of thickness increase (PTI) in right eye and left eye.

Penetrating keratoplasty was performed in the left eye in December 2010. Pathological examination of the corneal stroma revealed Alcian blue-stained deposits, and macular dystrophy was diagnosed. Her visual acuity OS at the last follow-up visit (February 2013) was $6/30^{-1}$ and showed improvement to $6/15^{-1}$ while looking through a pinhole. The graft was clear.

Patient 3

A 38-year-old woman presented in August 2008 with a 2-year history of decreased vision, stinging, and burning (Table 1). Multifocal corneal opacities in the stroma of both eyes and irregular corneal surfaces

Table 1. UCVA, BSCVA, corneal refraction, corneal thickness, and corneal curvature of the three patients in the present study

	Patient 1		Patient 2		Patient 3	
	OD	OS	OD	OS	OD	OS
UCVA	$6/9^{+1}$	6/63	5/60	5/60	6/24	$6/24^{-1}$
Pinhole	6/9	$6/36^{+1}$	6/60	6/60	6/9	6/9
BSCVA	$6/9^{-1}$	$6/9^{-3}$	6/60	6/60	6/12	6/9.5
Automated refraction	-3.50 ≈ -3.00x2°	-5.00 ≈ -3.50x175°	N/A	N/A	-0.75 ≈ -3.25x102°	-2.00 ≈ -0.50x70°
Manifest refraction	-1.25 ≈ -1.25x180°	-2.00 ≈ -4.00x170°	N/A	N/A	-0.75 ≈ -1.50x100°	-1.00 ≈ -0.50x70°
Thinnest corneal thickness (microns)	347	351	110	388	448	436
Maximum corneal curvature (diopters)	54.1	55.0	117.6	56.2	55.6	47.2

UCVA = uncorrected visual acuity; BSCVA = best spectacle-corrected visual acuity; OD = right eye; OS = left eye

were found (Fig. 5). The anterior chamber depth, lens, and retina were normal. Corneal topography revealed a thin cornea and steep curvature (Fig. 6). In January 2013, glasses correction resulted in improvement in the patient's visual acuity to 6/9.5 in both eyes. The patient thus elected to postpone penetrating keratoplasty.

Discussion

The earliest findings in patients with keratoconus, namely the scissoring reflex on retinoscopy and a conical shape on the nasal side after flashing a light on the temporal side of the cornea (Rizzuti sign), allow for the detection of an overall conical shape of the cornea[16]. In patients who do not exhibit these abnormal findings, as in the present report, keratoconus is difficult to detect based on corneal opacities. Corneal opacities due to deposits in the stroma may be the only sign of dystrophy. However, worsening visual acuity can also lead to an investigation for the cause of decreased vision. Corneal topography can detect subclinical keratoconus, allowing the clinician to plan proper management.

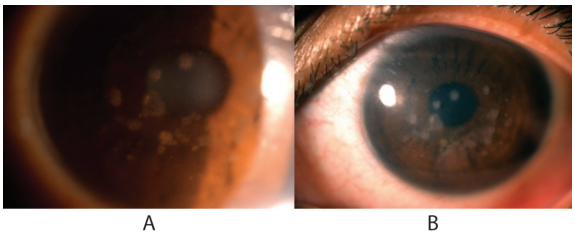

Fig. 5 Patient No.3 with ill-defined margin of corneal opacity in stroma, A) right eye, B) left eye.

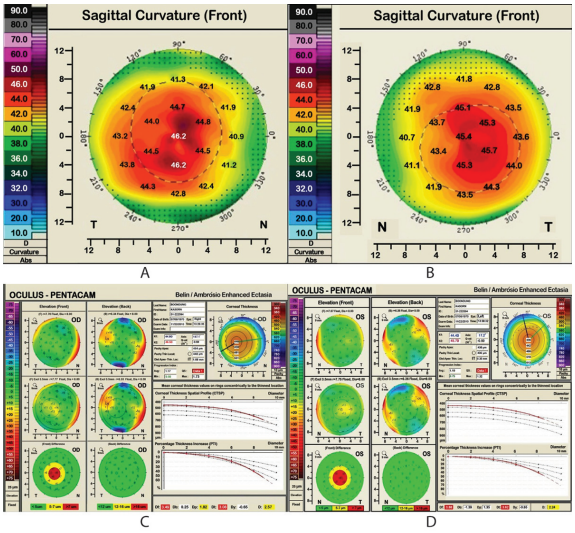

Fig. 6 Curvature map of patient No.3, A) right eye with inferior steepening, B) left eye with skewed radial axis, C and D) Belin/Ambrósio Enhanced Ectasia Display demonstrate steep curvature with high elevation in anterior elevation and increase in Percentage of Thickness Increase (PTI) both eyes.

The pathological findings in Patient 2 after penetrating keratoplasty were characterized by Alcian blue-stained material, and she was diagnosed with macular dystrophy without any signs of early keratoconus.

Among the patients with macular stromal dystrophy in the present report, both corneal opacities and refractive error secondary to keratoconus caused the decreased vision. Proper investigation using corneal topography is important to identify this rare condition. Penetrating keratoplasty can be delayed until it is confirmed that the corneal dystrophy or keratoconus will not improve with glasses correction. Keratoconus has no definitive cause. Some reports have postulated hereditary or environmental factors such as frequent rubbing of the eyes[17]. The mechanism of the co-occurrence of keratoconus and macular dystrophy remains unclear. Javadi et al speculated that changes in the size and distribution of the collagen fibrils in the corneal deposits of patients with macular dystrophy result in subsequent corneal thinning and bulging[13].

The limitations of the present report included the small number of patients, the accuracy of the diagnostic labels, and the search methods for identification of cases in the hospital records. The authors did not investigate genetic data, possible causes of keratoconus, or correlations of other conditions with keratoconus. However, the significance of these cases is that keratoconus as a cause of such vision changes is rare. Further studies are crucial for proper management of these conditions.

Conclusion

Keratoconus may develop as a result of changes associated with macular dystrophy. Therefore, patients with severely decreased vision should be evaluated for keratoconus to ensure proper management.

What is already known on this topic?

Keratoconus occasionally occurs along with other corneal diseases, including macular stromal dystrophy. Such an association has potentially important clinical implications. However, no such cases have been reported in Thailand.

What this study adds?

In the present study, the authors investigated the association between keratoconus and macular dystrophy in Thailand. In a retrospective review of records between 2002 and 2012, the authors identified three patients with both macular dystrophy (decreased vision and multifocal corneal deposits with surrounding haze) and associated clinical findings that led to a diagnosis of keratoconus by corneal topography (steep corneal curvature of >47 diopters and a thin cornea). Detailed review of these cases indicated that keratoconus might develop secondary to changes associated with macular dystrophy.

The immediate clinical impact is that patients with visual deficits, especially those with corneal changes, should be evaluated for keratoconus to ensure proper management.

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Potential conflicts of interest

None.

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กระจกตาเสื่อมรูปกรวย ในผู้ป่วยโรคกระจกตาเสื่อมแมคคิวลา

พนิดา โกสียรักษ์วงศ์, ปณตศม เง่ายุธากร, วิภาวี บูรณพงศ์

วัตถุประสงค์: *เพื่อแสดงอาการพบร่วมระหว่างกระจกตาเสื่อมรูปกรวยและกระจกตาเสื่อมแมคคิวลา*
วัสดุและวิธีการ: *ผู้ป่วยโรคกระจกตาเสื่อมแมคคิวลาร่วมกับอาการทางคลินิก ซึ่งนำไปสู่การวินิจฉัยกระจกตาเสื่อมรูปกรวย จากการทบทวนย้อนหลังดูภาพถ่ายวิเคราะห์ความโค้งกระจกตาเฉพาะส่วนด้วยคอมพิวเตอร์ในช่วงเวลา 10 ปี และประเมินระดับการมองเห็นด้วยตาเปล่า ระดับการมองเห็นที่แก้ไขด้วยแว่นสายตา การวัดสายตาด้วยคอมพิวเตอร์ การวัดสายตา ความหนาของกระจกตา และความโค้งของกระจกตา จากภาพถ่ายวิเคราะห์ความโค้งกระจกตาเฉพาะส่วนด้วยคอมพิวเตอร์*
ผลการศึกษา: *พบผู้ป่วยกระจกตาเสื่อมแมคคิวลา 3 ราย ที่แสดงอาการตามัวลง มีหย่อมสีขาวสะสมอยู่หลายตำแหน่ง และกระจกตาขุ่นโดยรอบรอยโรคในโครงกระจกตา ทุกรายพบความโค้งกระจกตาชันมากกว่า 47 ไดออปเตอร์ และกระจกตาบางเข้าได้กับกระจกตาเสื่อมรูปกรวย ผู้ป่วย1 ราย ที่มีอาการตามัวมากได้รับการผ่าตัดเปลี่ยนกระจกตา ซึ่งส่งตรวจทางพยาธิวิทยา ย้อมติดสีแอลเซียนบลูวินิจฉัยยืนยันว่าเป็นกระจกตาเสื่อมแมคคิวลา*
สรุป: *กระจกตาเสื่อมรูปกรวย อาจเป็นผลจากการเปลี่ยนแปลงที่พบร่วมกับกระจกตาเสื่อมแมคคิวลา ดังนั้นผู้ป่วยที่มีอาการตามัวมากควรได้รับการประเมินตรวจว่ามีกระจกตาเสื่อมรูปกรวย เพื่อให้การดูแลเหมาะสมต่อไป*