Keratoconus Associated with Cornea Guttata - Implication for Disease Progression

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Abstract: Purpose: To describe the diagnostic considerations in patients with keratoconus (KC) and concomitant cornea guttata (CG). **Patientsand Methods**: The study included 31 eyesof 31 patients, 12 eyes with KC and CG (group I), 7 eyes with CG only (group II), 6 eyes with KC only (group III), and 6 normal eyes (group IV). Complete ophthalmologic examination was performed, including Scheimpflug rotation tomography, specular microscopy and endothelial cell count. **Setting**: Department of Ophthalmology, Saarland University Medical Center, Homburg/Saar, Germany. **Design**: Retrospective, comparative study. **Results**: The mean age was 49.4 ± 19.7 years, 18 patients were female (58.1%). The mean best-corrected visual acuity (BCVA) in LogMar was 0.5 ± 0.4 in group I, 0.6 ± 0.3 in group II,0.4 ± 0.1 in group III and 0.0 ± 0.0in group IV. The mean corneal thickness of the thinnest point was 479 ± 43 µmin group I,583 ± 49 µmin group II, 475 ± 39 µmin group III and 567 ± 22 µmin group IV. **Conclusions**: KC and CG may coexist in the same patient. Progression of the dystrophy may be masked by corneal ectatic thinning while progression of KC may be masked by endothelial decompensation and thickening. VA cannot be used as a predictor for the presence concomitant KC and CG. The diagnosis should consider complete ophthalmic examination, corneal topography, and tomography, along with specular microscopy.

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Introduction

KCis a bilateral progressive, non-inflammatory corneal stromal thinning disorder that leads to corneal ectasia. It is characterized by progressive myopia and astigmatism leading to decreased uncorrected and spectacle-corrected visual acuity. The etiology is multifactorial, allergic processes and eye rubbing are possible causes in genetically susceptiblepatients.[1, 2]Thyroxin (T4) may also play a role in KC pathophysiology, most likely mediated by T4 receptors.[3]

KC can occur together with corneal dystrophies, and Fuchs endothelialcorneal dystrophy (FECD) is the most common.[4] FECD is also bilateral, may be markedly asymmetric and affects more females (4:1).[5] FECD ranges from asymptomatic cornea guttatato a decompensated cornea with stromal edema, epithelial bullae, and subepithelial fibrosis.[6] Cornea guttata may exist either as a primary, age-related, degenerative type or a secondary, post inflammatory type. Other corneal conditions that may resemble cornea guttae include age-relatedperipheral Hassall–Henle warts and pseudoguttata which may occur post-inflammation orpost-traumatic.[7] The genetic basis of FECD is complex and heterogeneous, demonstrating variable expressivity and incomplete penetrance.[8] Occasionally, the diagnosis of one condition is underestimated or even missed due to considerable overlapping.[9]

The purpose of this study was to describe the diagnostic considerations in patients with KC and concomitant CG.

Patients and Methods

In this retrospective study, 31 patients were included, 12 eyes with KC and CG (group I),7 eyes with CG only (group II), 6 eyes with KConly (group III), and 6 normal eyes (group IV). Complete ophthalmologic examinations were performed in all patients, including best-correctedvisual acuity (BCVA), slit lamp biomicroscopy, tonometry and dilated fundoscopy, Scheimpflug rotational tomography (Pentacam HR, Oculus, Wetzlar, Germany), and specular microscopy (EM 3000, Tomey, USA).

CG and FECD were detected at slit-lamp biomicroscopy, and their degree of severity was subsequently assessed by specular microscopy and Pentacam. We graded CG based on Gottsch's modification of the scale proposed by Krachmer et al.[10, 11](table 1).

KC was diagnosed based on a comprehensive clinical evaluation, including slit-lamp biomicroscopy, corneal tomography, topography, and pachymetry.

KC was graded by Amsler-Krumeich (AK) classification of KC **(**table 2**).** In the AK system, the severity of keratoconus is graded from stage 1- 4 using spectacle refraction, presence or absence of scarring, centralkeratometry, and central thickness.[12]

The main outcome measures included: Age, sex, BCVA, theseverity of CG, keratometric readings [flattest K (K1), steepest K (K2), average K (Km) and K maximum (Kmax)], pachymetric measurements at the thinnest point (TP) and endothelial cell count (table 5). All data were analyzed statistically by SPSS (IBM SPSS Statistics for Windows, Version 19.0. Armonk, NY: IBM Corp.). non parametric Mann Whitney u test was used.

Results

The mean age was 49.4± 19.7 (from 15 to 86) years, 18 patients were female (58.1%). The mean best-corrected visual acuity (BCVA) in LogMar was 0.5 ± 0.4 in group I, 0.6 ± 0.3 in group II, 0.4 ± 0.1 in group III and 0.0 ± 0.0in group IV.

In group I (2 eyes CG grade IV, 2 eyes CG grade III, 4 eyes CG grade II, 4 eyes CG grade I) while in group II (1 eye with CG grade IV, 2 eyes CG grade III, 2 eyes with CG grade II, 2 eyes with CG grade I). In group III and IV, CG grade was 0(Table 3).

In group I (2 eyes KC grade IV, 2 eyes KC grade II, 8 eyes KC grade I) while in group III (1 eye KC grade IV, 2 eyes KC grade II, 3 eyes KC grade I). In group II and IV, KC grade was 0(Table 4).

In group I, we detected Fleischer ring (pigmented rings in the peripheral cornea) in 5 cases, Vogt's striae (fine, roughly vertically parallel striations in the of Descemet's membrane) in 3 cases and corneal scarring (superficial, para-central) in 2 cases. CGwere most densely distributed in the central cornea. Examination of all four mid-peripheral quadrants identified the superior cornea as being least severely affected in the all of our cases. Pentacam analysis of corneal thickness at the thinnest point of the affected eye in group I (KC+CG) was 479 ± 43 µm,583 ± 49 µmin group II (CGonly), 475 ± 39 µm in group III (KC only), and 567 ± 22 µm in group IV. The mean pachymetry in group I was (479 µm) which in comparison with group II (583 µm) is considered relatively low, but it is close to the mean pachymetry (475 µm) in group III.

The average central keratometric reading (Km) in group I was 47.6 ± 5.1 diopters (D), in group II was 43.8 ± 2.3 D, in group III was 49.3 ± 3.6 D, in group IV was 43.6 ± 1.6 D. The average keratometry in group I is relatively between that in group II, IV and group III.

Specular microscopy performed in group I (KC+CG) revealed abnormal endothelial mosaic with large dark areas consistent with guttata, pleomorphism, and polymegethism. Average endothelial cell count in the affected eyes was2224 ± 35/mm^2in group I,1862 ± 1120 /mm^2in group II,2641 ± 268/mm^2in group III and 2875 ± 260 /mm^2in group IV (Table 5).

Table 1: Cornea guttata classification based on Gottsch's modification Krachmer scale.[8, 11]

Grade 0	No apparent disease. Up to 11 central guttae on each cornea;
Grade 1	Definitive onset of the disease. Twelve or more central, non-confluent guttae in at least one eye;
Grade 2	A zone of confluent central guttae 1 to 2 mm in horizontal width
Grade	A zone of confluent central guttae 2 to 5 mm wide
Grade	A zone of confluent central guttae greater than 5 mm wide
Grade	A zone of confluent central guttae greater than 5 mm wide plus edema of the corneal stroma and/or corneal epithelium

Table 2: Amsler-Krumeich classification of KC.

Stage I	Eccentric steepening Myopia and or astigmatism < 5.00 D Mean central K reading < 48.00 D No central corneal opacity
Stage II	Myopia and or astigmatism 5.00 - 8.00 D Mean central K reading ≤ 53.00D Minimum corneal thickness ≥ 400 µm No central corneal opacity
Stage III	Myopia and or astigmatism 8.00 -10.00 D Mean central K reading < 55.00 Minimum corneal thickness <300 – 400 µm No central corneal opacity
Stage IV	Refraction not measurable Mean central K reading< 55.00 Minimum corneal thickness 200 µm Central corneal scar

Table 3: Classification of Guttata patients.

	CG grade 0	CG grade I	CG grade II	CG grade III	CG grade IV
Group I (KC+CG)	0	4	4	2	2
Group II (CG)	0	2	2	2	1
Group III (KC)	6	0	0	0	0
Group IV (Normal)	6	0	0	0	0

Table 4: Classification of keratoconus patients.

	KC grade 0	KC grade 1	KC grade 2	KC grade 3	KC grade 4
Group I (KC+CG)	0	8	2	0	2
Group II (CG)	7	0	0	0	0
Group III (KC)	0	3	2	0	1
Group IV (Normal)	6	0	0	0	0

Table 5: Visual acuity, keratometry and pachymetry results of patients with keratoconus and cornea guttata in comparison with keratoconus only, cornea guttata only and normal.

		Age	V.A. LogMar	K2	K1	K mean	K max	Pachymetry
(Group 1) KC+CG N = 12	mean	50.7	0.5	49.7	45.7	47.6	57.0	479
	SD	16	0.4	5.1	5.3	5.1	11.0	43
	Min	31	0.05	43.2	39.3	42.7	43.8	407
	Max	86	1.3	58.3	54.0	55.9	79.0	557
(Group II) CG Only N = 7	mean	72.2	0.6	45.0	42.7	43.8	47.1	583
	SD	11.5	0.3	2.6	2.6	2.3	3.6	49
	Min	55	0.2	42.5	40.2	41.7	43.5	538
	Max	81	1.0	49.4	47.0	48.2	52.9	665
(Group III) KC Only N = 6	mean	34.8	0.4	51.8	47.3	49.3	56.4	475
	SD	16.7	0.1	3.7	3.5	3.6	5.0	39
	Min	15	0.2	47.1	43.3	45.1	51.9	421
	Max	60	0.5	58.4	52.6	55.3	65.4	516
(Group IV) Normal N= 6	mean	34.5	0.0	44.7	43.15	43.6	44.8	567
	SD	7.1	0.0	1.08	1.7	1.6	1.5	22
	Min	25	0.0	42.9	40.3	41.8	42.5	539
	Max	43	0.0	45.6	45.0	45.2	46.4	593

Discussion

In the present study, thinning of the cornea caused by KC and endothelial corneal thickening secondary to endothelial dysfunction may combine to false normal corneal pachymetry and relatively higher VA in group I in comparison to group II. The average VA LogMar in group I was 0.5 whilein group II was 0.6 and in group III was 0.4 (p=0.01).

Thus, VA cannot be used as a predictor for the presence concomitant KC in the case of CG and the reverse is true. Consequently, despite the presence of two concomitant corneal pathologies, the visual acuitybeingmuch worth than in normal eyes, was less severely impaired than in KC only.

In our study, the normal mean central corneal thickness was 567 ±22 µm. If we look only at the thinnest location measurements, one or both diagnosis may be missed, or the severity of either may be underestimated. This is critical in establishing aproper diagnosis. In group I, although CG grade IV was present, the corneal thickness was below normal limits. Consequently, the presence of KC masked the change in corneal thickness made by CG.

Tomography allows for the construction of maps that characterize the front and back elevation of the cornea, along with a full corneal thickness map. Ramos *et al* reported KC with a pattern of more abrupt thickening from the thinnest point toward the periphery, while the opposite is observed in the evaluation of corneal edema. The combination of KC and Fuchs, however, may mask or even pseudonormalize these changes as long as both pathologic conditions are relatively mild.[13]

It is may be difficult to assess the progression of both diseases adequately. Increasing endothelial decompensationrelated thickening of the central cornea may mask the increasing thinning due to the progression of KC. In contrast, the increasing thinning of the paracentral cornea of progressive KC may mask the increasing corneal thickening due to severe

concomitant CG. Consequently, pachymetry should not be the only method in the evaluation of endothelial function in a case of KC. Likewise, if we only consider specular microscopy analysis of the corneal endothelium, the disease severity may be underestimated.

Genetic studies have evaluated the association of KC with FECD, but the details of both have not been fully explained. Mutations in a variety of genes have been proven or suggested to play a pathogenic role in FECD. The International Committee for Classification of Corneal Dystrophies (IC3D) classifies FECD in three categories: Category 1: A well-defined corneal dystrophy in which the gene has been mapped and identified and the specific mutations are known.; Category 2: A well-defined corneal dystrophy that has been mapped to one or more specific chromosomal loci, but the gene (s) remain (s) to be identified.; Category 3: A well-defined corneal dystrophy in which the disorder has not yet been mapped to a chromosomal locus.[14]

Conclusions

KC and CG can coexist in the same patient. This association can 'neutralize' pathologic changes that occur in both diseases, but it does not normalize tomographic properties. In particular, the progression of both entities may be masked by simultaneous fellow disease. It is critical to evaluate the endothelium in eyes with KC progression and surgical approachshouldonly bemade after complete ophthalmic examination, supplemented by corneal tomography, and corneal microscopy of the endothelium. Future examinations and gene analyses may provide the clues needed for better understanding of the underlying mechanisms that cause these associations of both corneal diseases in one eye.

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