Association of Keratoconus and Mitral Valve Prolapse

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Purpose: To compare the prevalence of mitral valve prolapse (MVP) in patients with keratoconus (KCN) with that of normal subjects.
Methods: This study includes 62 individuals with KCN diagnosed by clinical findings and topographic criteria, and 167 age and sex matched controls with no clinical or topographic evidence of KCN. All participants were evaluated by two-dimensional M-mode and color doppler echocardiography. Perloff's criteria were used for diagnosis of definite MVP.
Results: Definite MVP was diagnosed in 22.6% of subjects with KCN and 6.6% of the control group (OR= 4.2; 95% CI, 1.93-11.3; P= 0.009). MVP was more prevalent in patients with KCN based on age and sex stratification. Odds ratio for MVP increased from 2.67 before the third decade of life to 33.44 in the third decade and slightly decreased to 16.52 in the fourth decade and above.
Conclusion: This study disclosed an increased prevalence of MVP in individuals with keratoconus suggesting the necessity of cardiovascular evaluation in these patients.

Iran J Ophthalmic Res 2007; 2 (1): 15-18.

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INTRODUCTION

Keratoconus (KCN) is a progressive noninflammatory ectatic degeneration of the cornea with a prevalence of 50-230 per 100,000 in the general population.[1] The exact etiology of this corneal degeneration is unknown but it seems to be multifactorial. KCN has been reported in association with different systemic disorders such as atopy, Down syndrome, joint hypermotility and mitral valve prolapse (MVP).[1-7] Various abnormalities have been postulated to play a role in the pathogenesis of KCN[1-3,8-16] including defects in corneal collagen fiber synthesis or structure and increased levels of keratan sulfate,[8-11] over-activation or over-expression of lytic enzymes or decreased levels of their inhibitors,[9] increased levels of lyzosomal enzymes in the corneal and conjunctival epithelium,[12,13] decreased collagen type VI,[9] increased elastic fibers named oxytalan which stain with antibodies against collagen type VI[14], and fragmentation of scleral collagen fibers.[15]

KCN manifests with corneal thinning and ectasia which eventually leads to myopia and irregular astigmatism. The diagnosis is usually made clinically, however corneal topography is mandatory for detection of subtle forms. The

severity of this condition increases gradually, reaching a plateau in adulthood followed by stabilization.[3]

MVP is a non-inflammatory degeneration which can be diagnosed based on clinical signs or by echocardiography.[17-19] Its prevalence has been reported from 0.4% to 17%.[18] The severity of MVP also increases gradually reaching a plateau in early adulthood followed by stabilization.[17-21] Well known ocular associations of MVP include progressive external ophthalmoplegia and retinal vascular occlusions secondary to arterial emboli which may result in sudden visual loss.[20] Infectious endocarditis and pulmonary emboli are the cardiac and pulmonary complications of MVP.[5,6] Endocarditis prophylaxis is indicated in surgical procedures associated with bacteremia in patients with MVP.[17]

Both disorders have hereditary and familial forms with similar inheritance patterns and both have been described in association with a number of connective tissue disorders.[4,7] MVP has been reported in up to 58% of patients with advanced KCN[5] and up to 38% of patients at different stages of KCN.[7] However, one study has demonstrated no association between these two conditions.[6] This case-control study was designed to evaluate a possible association between KCN and MVP.

METHODS

This study included 62 cases with KCN and 167 age and sex matched controls. Clinically, KCN was suspected in the presence of central corneal thinning, Fleischer ring, Vogt striae, acute hydrops or its scar, Munson sign on slitlamp biomicroscopy or scissoring reflex on retinoscopy. Exclusion criteria included other degenerative disorders of the cornea (pellucid and Terrien's marginal degeneration), heart disease other than MVP, history of ocular trauma, corneal infections, Marfan syndrome, rheumatic fever, rheumatoid arthritis and systemic lupus erythematosus. A clinical diagnosis of KCN was confirmed by corneal topography (CSO, Italy) after discontinuing soft and rigid gas permeable contact lenses for 2 and 3 weeks respectively.

Topographic criteria for definite KCN included keratometric readings over 42.7 diopters, inferior-superior value (ISV) more than 1.4, skewed radial axis (SRAX) larger than 21 degrees, and simulated keratometry (Sim-K) greater than 45.7 diopters. Age and sex matched controls were selected from subjects who had no evidence of KCN based on the above mentioned clinical criteria.

All participants were referred to a masked cardiologist for a comprehensive cardiovascular examination. MVP was diagnosed clinically based on hearing the characteristic systolic click and murmur on auscultation. The clinical examination was followed by two-dimensional, M-mode, traditional, and color Doppler echocardiography (Wingmed-750 device, England). Definite MVP was diagnosed in the presence of one or more of Perloff's major criteria[21] including: (1) auscultation of a mid to late systolic click, late systolic murmur or whoop (separately or with each other) on the apex of the heart; (2) prominent upward displacement of mitral valve leaflets during systole with coaptation point at the level of the annulus or higher; (3) mild to moderate upward displacement of mitral valve leaflets with tears in chordae tendineae, mitral insufficiency, or annulus dilation; and (4) mild to moderate upward displacement of mitral leaflets during systole accompanied by holosystolic or late systolic murmurs in the apex of heart in young subjects or late systolic whoop.

The results were analyzed using unpaired T, Chi square, Mantel Haenszel, and Fisher exact tests. Statistical significance was tested at $P<0.05$.

RESULTS

The KCN group included 43 male and 19 female subjects with mean age of 28.1±8.9 (range 18-55) years and the control group consisted of 112 male and 55 female subjects with mean age of 30±13.2 (range 15-65) years. The prevalence of MVP was 22.6% in the KCN

group and 6.6% in the control group (P= 0.009, table 1). The odds ratio for MVP in the KCN group versus control group was 4.2 (95% CI, 1.93-11.13; P= 0.009).

After categorizing subjects into three age groups of younger than 22, 22 to 31, and older than 31 years, the prevalence of MVP was shown to increase with older age in both groups. The prevalence of MVP was higher in the KCN group in all age categories. Odds ratios for MVP in patients with keratoconus increased from 2.67 under age 22 years to 33.44 in the 22-31 years age group and decreased to 16.52 over age 31 years (table 2).

The prevalence of MVP was 31.5% in female vs 18.6% in male subjects (P= 0.21) in the KCN group and 1.8% in female vs 8.9% in male subjects (P= 0.1) in the control group. The prevalence of MVP in both genders was significantly higher in the KCN group than controls (18.6% vs 8.9% in males and 31.5% vs 1.8% in females, respectively; P<0.05).

Table 1 Distribution of participants based on presence of mitral valve prolapse (MVP)

Groups	Number (%)		Total
	MVP	No MVP	
Keratoconus	14 (22.6)	48 (78.4)	62 (100%)
Control	11 (6.6)	156 (93.4)	167 (100%)
Total	25 (10.9)	204 (89.1)	229 (100%)

Table 2 Age stratified prevalence and odds ratio of mitral valve prolapse in cases versus controls

Age group (years)	Prevalence of MVP (%)		Odds ratio	95% Confidence interval	P Value*
	KCN group	Control group			
< 22 (n= 76)	10.0	3.6	2.67	1.7-81	0.008
22-31 (n= 70)	18.1	6.2	33.44	3.3-821	< 0.001
> 31 (n= 83)	40.0	9.5	16.52	3.9-152	< 0.001
Total (n= 229)	22.6	6.6	4.2	1.9-11.1	0.009

* Fisher exact test; MVP, mitral valve prolapse

DISCUSSION

The current study showed that the prevalence of MVP in patients with KCN is higher than age and sex matched controls. The prevalence of MVP in patients with KCN was 22.6% which is less than corresponding figures reported by Beardsly et al[2] (38%) and Sharif et al[5] (58%). This difference seems to be due to different diagnostic methods and criteria; the previous authors did not exclude suspicious cases of MVP. Although our findings demonstrate an association between KCN and MVP, they indicate neither an etiologic relationship nor a common pathophysiology.

The increased odds for MVP in KCN patients from 2.67 in patients aged less than 22 years to 33.44 in the 22-31 years age group and its decrease to 16.52 in patients over age 31 years is compatible with the prevalence pattern of both diseases.[1,2,17,18]

Our results show no statistically significant difference between males and females for MVP. This finding is compatible with present epidemiologic studies on MVP.[20,21] However, the number of male subjects was twice that of female subjects in the KCN group. Recently, a possible role for androgenic hormones has been suggested for the pathogenesis of KCN.[16] The prevalence of MVP in control group was higher in male subjects than in females which may be an accidental finding due to the small sample size.

Previous reports[1,4,12] have associated connective tissue disorders with both KCN and MVP. We excluded subjects with history of connective tissue disorders. It would have been preferable to exclude these cases based on clinical examination and laboratory data.

In conclusion, the current study revealed a relatively high prevalence of MVP in patients with KCN, it is prudent for ophthalmologists to

advise these subjects to be examined by a cardiologist to rule out MVP. The rationale behind this suggestion is the need for endocarditis prophylaxis before instrumentation or surgical procedures leading to bacteremia.

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