Prevalence of mitral valve prolapse in keratoconus patients

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Summary

Fifty patients with advanced degrees of keratoconus, requiring corneal transplantation, were screened for mitral valve prolapse by two dimensional echocardiography. The overall prevalence of 58% was found to be statistically higher than the prevalence of 7% found in a group of age and sex-matched controls. It was also found to be higher than the previously reported prevalence of 38% in a group of keratoconus patients with similar age and sex match to our series. The findings of our study in conjunction with the histopathological and biochemical similarities between the two conditions strongly suggest that they may be different manifestations of similar defects in collagen metabolism.

Introduction

Keratoconus is a non-inflammatory corneal thinning disorder that usually starts to manifest itself at puberty and is almost always bilateral. It is characterized in its most advanced form by a localized conical protrusion of the cornea with an area of corneal stromal thinning most marked at the apex of the cone (Figure 1).

These changes lead to high myopia and irregular astigmatism that often prevent adequate spectacle correction, forcing the patient to rely on contact lenses. In severe cases, however, the steep conical protrusion of the cornea prevent adequate contact lens fitting. At this stage surgery in the form of corneal transplantation is indicated to rehabilitate the patient. Many systemic conditions have been associated with keratoconus, although no common aetiology could be found[1,2]. Mitral valve prolapse has also been considered to be associated with many systemic conditions with no specific aetiology that could be identified[3]. Beardsley and Foulks reported in 1982 an association of keratoconus and mitral valve prolapse with an overall prevalence of 38%[4]. The group of patients they studied, had variable degrees of keratoconus, with only 44% of the cases severe enough to require corneal transplantation.

The aim of our study was to detect if the prevalence of mitral valve prolapse in selected cases with advanced degrees of keratoconus, ie those requiring corneal grafting, is higher than its prevalence in a group of age and sex-matched controls, thus supporting the theory that an alteration in collagen metabolism may underlie both conditions. We also wanted to compare our findings with those detected in the above mentioned study that was performed on unselected keratoconus patients.

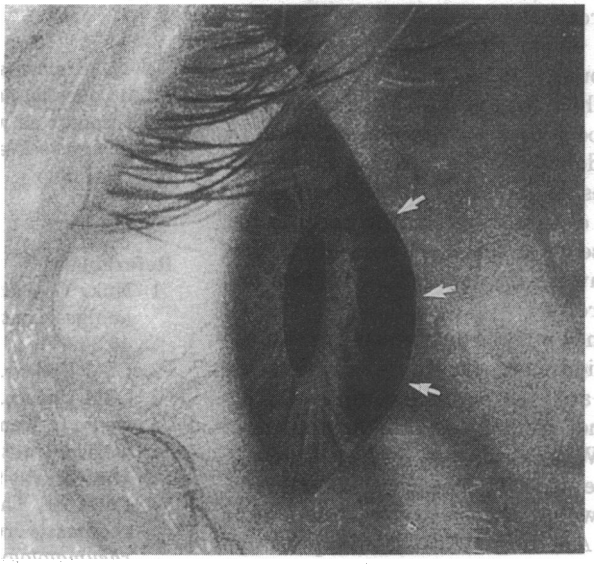

Figure 1. Lateral view of right eye showing advanced keratoconus with a localized conical protrusion of the cornea (arrows) - pre-operative photograph

Patients and methods

Fifty cases were selected for our study from patients with keratoconus presenting to the Corneal-Plastic Unit, Queen Victoria Hospital. The selected cases were patients with severe degrees of keratoconus that required corneal transplantation to achieve visual rehabilitation. These cases were studied echocardiographically for mitral valve prolapse at the Cardiology Department, St Thomas' Hospital.

The patients had no other associated ocular diseases, no systemic collagen disease, and no history of cardiac disease. All the cases were examined by two dimensional echocardiography with colour flow doppler studies without the use of amylnitrate (HP Sonos-cardiovascular imaging system). The results were recorded as either positive or negative for mitral valve prolapse. The features that we recognized as being positive for mitral valve prolapse included posteriorly displaced co-aptation of the mitral leaflets, or a superior movement of either leaflet above the mitral ring. The patients were checked for any sign of mitral regurge or any other cardiac anomalies.

Results

The age of the patients in our study ranged from 17 to 64 years (mean=32 years). There were 32 men (64%)

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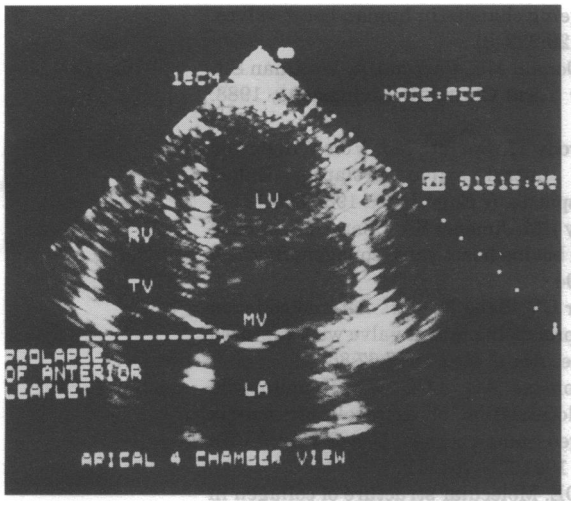

Figure 2. Two-dimensional echocardiogram of the same patient in Figure 1 showing prolapse of the anterior leaflet of the mitral valve (MV - LA, left antrium; LV, left ventricle; RV, right ventricle)

and 18 women (36%) in the series. All the patients had corneal transplantation because their keratoconus was so severe that they could not obtain industrially-useful vision (6/18 or better) with contact lenses or spectacles.

The control group in our study consisted of another 50 individuals, who were healthy volunteers with no ocular disorders, that were matched with regards to age and sex to our keratoconus patients. The matching was used to equalize the distribution of age and sex in the cases and the controls to eliminate the potential for biased comparisons due to higher prevalence of mitral valve prolapse in women than men[5].

The echocardiography was performed in both groups by the same operator using the same echomachine. All of these 29 cases, except one, had anterior leaflet prolapse (Figure 2). No other valve anomalies were detected except in one patient who had a bicusped aortic valve with normal opening. Out of the 50 patients in the keratoconus group, 29 cases (58%) were found to have mitral valve prolapse. Sex distribution showed mitral valve prolapse in eight out of 15 women (53%) and in 21 out of 35 men (60%).

Mitral valve prolapse was found in only 7% in our control group (11% women, 3% men).

Discussion

Both keratoconus and mitral valve prolapse are non-inflammatory conditions the aetiology of which has not been clearly identified yet. In keratoconus there is thinning and ectasia of the central cornea with subsequent progressive reduction of vision in most cases. The clinical signs of this condition can be detected with slit-lamp biomicroscopy, corneoscopy and keratometry. Mitral valve prolapse can be non-invasively detected by echocardiography or by auscultation of a midsystolic click and late systolic murmur. Gilbert *et al.*[6] have demonstrated that the two-dimensional time mode echocardiogram is more sensitive in detecting mitral valve prolapse than the M-Mode studies.

In unselected healthy individuals, the prevalence of mitral valve prolapse was reported to be between 4% and 6%[7-9]. In a previously reported echocardiographic study the healthy subjects in the control group who had similar sex and age match as the patients in our series, had a prevalence rate of 13%[4]. Both keratoconus and mitral valve prolapse have been associated with systemic collagen diseases such as pseudoxantherma elasticum, Marfan's syndrome, Ehlers-Danlos syndrome, and osteogenesis imperfecta[1,3,10]. The aetiology of mitral valve prolapse in its primary or idiopathic form is unknown. The histopathological change known as myxomatous degeneration occurs and consists of replacement of the normal collagen matrix of the fibrosa layer with acid mucopolysaccharides, specifically hyaluronic acid and chondroitin sulphate[3]. Electron microscopic studies have shown an alteration in the ratio of collagen to ground substance and breakage of collagen cross-links[3]. These studies indicate that the aetiology of mitral valve prolapse is related to an alteration in collagen metabolism. This has supported the hypothesis that underlying abnormalities of the mesenchymal connective tissue are responsible for the development of mitral valve prolapse[3,11].

It is well known that human heart valves, like the cornea, are composed of collagen types I and V with a small proportion of type III collagen[12,13]. Type V collagen was present in the striated collagen fibrils in Bowman's layer, in the corneal stroma and in a thin non-bonded zone of Descemet's membrane[14]. With regard to striated fibrils in the corneal stroma it has been postulated that type V collagen may control fibril diameter through its longer helix[15]. It has been demonstrated in a study of severe mitral prolapse with ruptured chordae tendenae that there was an absence of collagen types AB and III in most cases[13]. The aetiology of keratoconus is also unknown. The mechanism of stromal thinning is poorly understood. Contrary to prior beliefs[16], the corneal lamellae are of normal thickness. Stromal thinning appears to be the result of a decrease in the number of the lamellae as demonstrated by Pouliquen *et al.*[17]. Biochemical analysis has revealed decreased total collagen, increased glycoproteins, decreased glucose-6-phosphate dehydrogenase, decreased hydroxylation of lysine, decreased glycosylation of hydroxylysine, and abnormal distribution of collagen crosslinking[18,19].

Cultures of stromal cells, obtained form corneae affected with keratoconus, have shown an abnormal distribution of newly synthesized glycosaminoglycans between the growth medium and the cell layer, and reduced cell production of heparin sulphate[20]. In addition there was an alteration in the relative proportion of type I collagen and V collagen produced by these cells in comparison with normal cells[21].

All these findings have stimulated Robertson[22] and Davis *et al.*[23] to suggest that the corneal changes occurring in keratoconus may be the final common pathway for a variety of disorders in normal synthesis of corneal collagens.

In Beardsley and Foulks' report on the association of keratoconus and mitral valve prolapse, the overall prevalence was 38%. However, the group of patients they recruited for their study had variable degrees of keratoconus, with only 44% of the cases severe enough to require corneal transplantation[4].

By selecting patients in our study so that all of them had severe keratoconus, ie all required corneal transplantation, we were able to detect significantly higher prevalence (58%) of mitral valve prolapse ($P < 0.05$). The findings of our study strongly suggest that the clinical, histopathological, and biochemical similarities between keratoconus and mitral valve

prolapse are not coincidental and might represent different clinical manifestations of a subtle defect in the mesenchymal system. As the alteration of collagen subtypes occurs in both keratoconus and mitral valve prolapse, it may be conceivable that a single event during embryogenesis might affect these two structures as both corneal stroma and atrioventricular valves form during the sixth to seventh week of fetal life[1,2,4].

In summary, our study indicates that the prevalence of mitral valve prolapse is significantly high in patients with advanced degrees of keratoconus. We believe that this association between two seemingly unrelated disorders should be brought to the attention of both the physicians and the ophthalmologists involved in managing these cases. Although a common aetiological factor has yet to be determined, the higher prevalence of mitral valve prolapse in patients with severe keratoconus than that found in the normal population, strongly suggests that the two conditions may be different manifestations of similar defects in collagen metabolism.

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