BRIEF ARTICLE

Heritable Malignant Mitral Valve Prolapse

Prolapso de válvula mitral maligno familiar

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Mitral valve prolapse may result from two different structural alterations: myxomatous degeneration (Barlow's disease) and fibroelastic deficiency. In addition to mechanical complications, it may be associated with complex ventricular arrhythmia and sudden death. We describe a family case, that reveals that there may be a mechanism responsible for arrhythmias not associated with the hemodynamic stress caused by the valvular dysfunction, with sudden death events occurring even in the pediatric age group, without significant valvular regurgitation or evidence of macroscopic fibrosis on magnetic resonance imaging.

INTRODUCTION

Mitral valve prolapse (MVP) is currently defined as the systolic excursion of any segment of its leaflets >2 mm above the annular plane. This condition affects 2.4% of the general population.(1) It may result from two different structural alterations, although most publications do not distinguish between them: myxomatous degeneration (Barlow's disease) and fibroelastic deficiency.(2) The former has a much slower and insidious time course over decades, while the latter has a later onset, usually after the sixth or seventh decade of life, but with a more rapid clinical course.

In addition to the mechanical complications, the chordal rupture and the chamber volume overload caused by the valvular defect, MVP may be associated with complex ventricular arrhythmia and sudden death (SD). This disease state has been described for decades, but the valve disease spectrum to which it is related, and the pathophysiological mechanism to which it can be attributed, have yet to be identified.

CASE

A familial case is described below. It includes positive findings, summarized in Table 1 for easier understanding. The age mentioned is that of the first visit. The family consists of father (F), mother (M), and the following children: the eldest child (C1): female; the second child (C2): male; and the third and fourth children (C3 and C4) are fraternal twins, both female. Mitral involvement was present in the father and all his children.

During the annual follow-up, C2 suffered from SD. The rest of the family group was studied, and an implantable cardioverter defibrillator (ICD) was placed in C3 and C4. C1 refused ICD implantation based on a personal decision. Six months later, C3 presented ventricular fibrillation aborted by two ICD shocks.

Thanks to a free program provided to Latin America by a genetic diagnostics company, all living family members were screened for 100 target genes in a panel associated with arrhythmia and sudden death. Sequencing of those genes was performed using Illumina next generation sequencing method. The results are described in Table 2. No pathological variants were observed. Two variants of uncertain significance were observed in the mother, one of them was non-sense in the TRPM4 gene, the latter inherited by C3. In turn, the 3 daughters presented a variant of uncertain significance inherited from the father related to RBM20 gene.

The association between ventricular arrhythmia and SD in patients with myxomatous mitral valve disease has been described since the 1960s. Although certain related factors have been found, the medical community has not yet understood the reasons for this association, the mechanisms involved, and, therefore, how to identify patients at higher risk in order to provide SD primary prevention.

Several signs associated with MVP and SD have been described: ventricular repolarization disturbance in the ECG, QT interval prolongation and dispersion, fibrosis in papillary muscles or in the inferolateral region of the left ventricle, mitral annular disjunction, and high velocity on tissue Doppler in the basal segments (Pickelhaube sign).(3-5) However, the studies performed on this context have not separated the causes of MVP due to fibroelastic deficiency from myxomatous degeneration; besides, the characteristics found to be linked to SD are those usually present in the latter morphology. So, if we only examined the group of patients with MVP due to myxomatous degeneration, we would not be able to discriminate,

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Table 1. Familial clinical case summary

	Age	History	Symptoms	Physical characteristics	ECG	Echocardiography	Holter	MRI	ICD	Events
F	51	-	-	Thinness, pectus carinatum, gingival hyperplasia	No alterations QTc 390 ms	Bileaflet, myxomatous MVP, severe MR Preserved LVSF	No arrhythmia	-	-	Suicide
C1	19	Mitral valve repair at 16 years old	-	Thinness, pectus carinatum, gingival hyperplasia	T wave –DII-III-aVF QTc 390 ms	Redundant leaflets, mitral repair with mild residual regurgitation Preserved LVSF	No arrhythmia.	No LGE	Indicated, not accepted by patient	-
C2	15	-	-	Thinness, pectus carinatum, gingival hyperplasia	Biphasic T wave –DII-III-aVF QTc 400 ms	Bileaflet, myxomatous MVP, mild MR. Preserved LVSF	PVC 2600/ day NSVT	No LGE Mitral annular disjunction	-	SD
C3	12	-	Syncope, presyncope	Thinness, mild pectus carinatum, gingival hyperplasia	Biphasic T wave DII-III-aVF and V1-V3 QTc 410 ms	Bileaflet, myxomatous MVP, mild to moderate MR Preserved LVSF	VEB PVC 1600/day NSVT	No LGE, Mitral annular disjunction	Implanted	VF-ECV
C4	12	-	-	Mild pectus carinatum	Biphasic T wave DII-III-aVF and V1-V5 QTc 410 ms	Bileaflet, myxomatous MVP, mild MR Preserved LVSF	PVC 1600/day bigeminal	No LGE, Mitral annular disjunction	Implanted	-

ECG: electrocardiogram; MRI: magnetic resonance imaging; ICD: implantable cardioverter defibrillator; QTc corrected QT; LVSF: left ventricular systolic function; MVP: mitral valve prolapse; MR: mitral regurgitation; PVC: premature ventricular complexes; NSVT: nonsustained ventricular tachycardia; LGE: late gadolinium enhancement; VF: ventricular fibrillation; ECV: electrical cardioversion; SD: sudden death.

Table 2. Variants found on sequencing of 100 genes of interest in SD

	CACNA1Da (VUS)	CACNA1Db (VUS)	TRPM4 (VUS)	GAAa (Benign)	GAAb (Benign)	RBM20 (VUS)
F	X		X	X	X	
C1	X	X		X	X	X
C2	X	X	X	X	X	X
C3				X	X	X

VUS: variant of uncertain significance. CACNA1D: calcium voltage-gated channel subunit alpha1 D. TRPM4: transient receptor potential cation channel subfamily M member 4. GAA: alpha glucosidase. RBM20: RNA-Binding motif protein 20.

based on these points, those at higher risk since a considerable proportion would have several or even all of these signs, but only a few would develop fatal arrhythmia.

Regarding the evidence of myocardial fibrosis in patients with MVP, it has become increasingly relevant and has been proposed as one of the crucial issues to determine the risk of arrhythmia in this condition. It is unclear, however, when fibrosis arises in the course of the disease, which may only be a late marker of physical stress on the subvalvular apparatus. According to the experience reported in this article and contrary to this postulate, events were observed in two family members without evidence of late gadolinium enhancement (LGE) on magnetic resonance imaging (MRI).

Besides, there are signs that suggest a specific pathophysiological substrate related to ventricular repolarization. This is evidenced by the inverted T waves mainly in the inferior leads, which were often found in patients with SD or ventricular arrhythmia and MVP, QT interval prolongation and dispersion. (3) In the studies combining MVP and ventricular arrhythmia or SD, it would be extremely useful to observe the qualities of the valve morphological type for a better understanding and estimation of its prevalence. Furthermore, the incidence of arrhythmia is not directly related to the degree of valvular regurgi-

tation or hemodynamic overload and is not resolved by performing a valvuloplasty. It occasionally occurs early in life and without evidence of fibrosis. This indicates that the arrhythmic mechanism is probably not associated, at least in part, with the valvular dysfunction.

There are multiple genes implicated in the MVP by myxomatous degeneration, described both in syndromic cases and point mutations. Since 1999, the loci 16p11.2p12.1 (MMVP1), 11p15.4.96 (MMVP2), 13q31.3-q32 (MMVP 3), related to autosomal dominant myxomatous mitral valve prolapse, and the X-linked X28q locus related to the cytoskeletal structural protein filamin A have been described.(6-8) In addition, associations have been described between myxomatous degeneration and trisomies 13, 15 and 18, and connective tissue disorders such as Marfan, Loeys-Dietz and Ehler-Danlos syndromes, among others. (7,8)

Therefore, the alteration in the extracellular matrix is not limited to its structural proteins, such as collagen, but may also be due, for example, to complex mechanisms of extracellular signaling and mechanotransduction. Alterations in proteins such as filamin A (intracytoplasmic protein) show that, by transitive effect, it can alter the extracellular matrix. (8) It can also be hypothesized that a structural alteration might alter the permeability or density of ion channels in the myocyte and make arrhythmia more likely to occur.

To date, the issue of MVP and its association with SD has been addressed as a disorder related to the valve and the myocardial stress induced by it. Taking into account the large number of genes involved and the fact that they generate multiple and very different pathologies in several organs or systems, but which converge in a myxomatous phenotype of the mitral valve, perhaps, we should redirect our search for an arrhythmic pathology with a concomitant valve disease and discover which genetic alterations may be more closely related to the arrhythmic event.

Currently, this is being studied by some groups and we hope that they will be able to find, at least, a partial answer. Perhaps, we might better understand the reasons why in a condition that affects 1-2% of the general population, such as myxomatous mitral valve disease, with a substantial proportion of patients presenting fibrosis and the morphological features described above, only a small proportion develop malignant arrhythmias. It may be that within this group of patients with a common valvular phenotype, some of the very varied genetic alterations may provide early recognition of the patients more likely to suffer from complex arrhythmic events and SD.

CONCLUSIONS

This family case reveals that there may be a mechanism responsible for arrhythmias which is not associated with the hemodynamic stress caused by the valvular dysfunction, with SD events occurring even in the pediatric age group, without significant valvular regurgitation or evidence of macroscopic fibrosis on MRI.

Conflicts of interest

None declared.

(See authors' conflict of interests forms on the web/Additional material.)

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