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Original article

Floppy mitral valve/mitral valve prolapse syndrome: Beta-adrenergic receptor polymorphism may contribute to the pathogenesis of symptoms

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ABSTRACT

Background: Certain patients with floppy mitral valve (FMV)/mitral valve prolapse (MVP) may have symptoms that cannot be explained on the severity of mitral valvular regurgitation (MVR) alone; hypersensitivity to adrenergic stimulation has been suggested in this group defined as the FMV/MVP syndrome.

Methods: Ninety-eight patients (75 men, 23 women) with mitral valve surgery for FMV/MVP were studied. Of those 41 (42%) had symptoms consistent with FMV/MVP syndrome [29 men (39%), 12 women (52%)]; median age of symptom onset was 30 years (range 10–63 years) and median duration of symptoms prior to valve surgery was 16 years (range 3–50 years). Ninety-nine individuals (70 men, 29 women) without clinical evidence of any disease were used as controls. Genotyping of β_1 and β_2 adrenergic receptors was performed.

Results: β-Adrenergic receptor genotypes (β_1 and β_2) were similar between control and overall FMV/MVP patients. Subgroup analysis of patients, however, demonstrated that the genotype *C/C* at position 1165 resulting in *389 Arg/Arg* of the β_1 receptor was more frequent in women compared to those without FMV/MVP syndrome and to normal control women ($p < 0.025$). This polymorphism may be related to hypersensitivity to adrenergic stimulation as reported previously in these patients.

Conclusion: This study shows a large proportion of patients with FMV/MVP, predominantly women, had symptoms consistent with the FMV/MVP syndrome for many years prior to the development of significant MVR, and thus symptoms cannot be attributed to the severity of MVR alone. Further, women with FMV/MVP syndrome, symptoms at least partially may be related to β_1-adrenergic receptor polymorphism, which has been shown previously to be associated with a hyperresponse to adrenergic stimulation.

Introduction

Certain patients with floppy mitral valve (FMV) associated with mitral valve prolapse (MVP) may have symptoms that cannot be explained on the severity of mitral valvular regurgitation (MVR) alone. Neuroendocrine-cardiovascular or autonomic nervous system functional abnormalities have been postulated as an explanation for the symptoms in this group of patients, which is classified as the FMV/MVP syndrome [1–14]. Many clinical observations during the past 140 years suggested that individuals with irritable heart, soldier's heart, and neurocirculatory asthenia, most likely related to FMV/MVP syndrome, had a disorder of the sympathetic nervous system as a basis for their symptoms [15–17]. Previous studies from our laboratory demonstrated that patients with the FMV/MVP syndrome, mostly females, had a high

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adrenergic tone at rest and a hyperresponse to adrenergic stimulation [9,10]. It is also known that certain polymorphisms of β_1-adrenergic receptors may result in an increased response to adrenergic stimulation [18–22]. It was hypothesized that hypersensitivity to adrenergic stimulation in certain patients with the FMV/MVP syndrome is at least partially related to β-adrenergic receptor polymorphism that results in hypersensitivity to β_1-adrenergic receptors. The present study was undertaken to test this hypothesis.

Materials and methods

Study population

Demographic data are shown in Table 1. Ninety-eight patients (75 men and 23 women) with a mean age of 57 ± 13 years who had mitral valve repair for severe MVR at St Lukas Hospital, Thessaloniki, Greece, due to FMV/MVP from November 2008 to January 2011 were studied. The mean systolic blood pressure was 135 ± 10 mmHg and the mean diastolic blood pressure was 80 ± 5 mm Hg; the resting heart rate was 76 ± 14 beats per minute. The FMV/MVP and the severity of MVR were established prior to surgery with two and three-dimensional transthoracic and transesophageal echocardiogram; FMV also was confirmed in the operating room [23–31]. Mitral leaflet prolapse was posterior in 53, anterior in 4, and bi-leaflet in 41 patients. Diffused thickening of the mitral valve was present in 40 and regional thickening in 58 patients (Table 2). All patients had an apical holosystolic murmur prior to surgery consistent with significant MVR. A detailed history, related to type, onset, and duration of symptoms, especially of those symptoms consistent with the FMV/MVP syndrome, was obtained [1–6,13]. Ninety-nine individuals (70 men and 29 women) with a median age of 63 years (range 31–80 years) without evidence of any disease were used as controls [26]. The study was approved by the Institutional Review Board of St. Lukas Hospital and written informed consent was obtained from all participants.

Table 1
Demographic data of the study population.

	Control ($n=99$)	FMV/MVP ($n=98$)
Male	70	75
Female	29	23
Age	64 ± 13	57 ± 13
Systolic blood pressure	27 ± 9	135 ± 10
Diastolic blood pressure	82 ± 6	85 ± 5

FMV, floppy mitral valve; MVP, mitral valve prolapse.

Table 2
Clinical and echocardiographic data in patients with FMV/MVP ($n=98$).

Male (n)	75
FMV/MVPS (n; %)	29 (38.6)
Female (n)	23
FMV/MVPS (n; %)	12 (52.2)
Leaflet prolapse (n)	
Posterior	53
Anterior	4
Bi-leaflet	41
Chordae tendinae rupture (n)	46
Flail leaflet (n)	32
Diffuse thickening of MV (n)	40
Regional thickening of MV (n)	58
LVEDD (mm)	55 ± 5
LA (mm)	46 ± 6
LVEF (%)	61 ± 9
RVSP (mmHg)	38 ± 13
4+ severity of MVR (n; %)	98 (100)

FMV/MVPS, floppy mitral valve/mitral valve prolapse syndrome; LA, left atrium; LVDD, left ventricular end diastolic diameter; LVEF, left ventricular ejection fraction; MV, mitral valve; MVR, mitral valve regurgitation; RVSP, right ventricular systolic pressure. The incidence of symptoms related to FMV/MVP syndrome were more common in women compared to men, $p < 0.05$.

Determination of β-adrenergic receptor polymorphisms

Genomic DNA was isolated from lymphocytes in whole blood using a commercially available kit (Qiagen DNA Blood Isolation Kit, Qiagen, Valencia, CA, USA). DNA samples were genotyped for two β_1-adrenergic receptors (*ADRB1*) including: *49 Ser/Gly* [amino acid substitution of serine for glycine at position 49 resulting in the nucleotide substitution of adenine for guanine at position 145 (*145 A/G*), rs1801252]; and *389 Arg/Gly* [amino acid substitution of arginine for glycine at position 389 resulting in the nucleotide substitution of cytosine for guanine at position 1165 (*1165C/G*), rs1801253]. In addition, DNA samples were genotyped for two β_2-adrenergic receptors (*ADRB2*) including: *16 Gly/Arg* [amino acid substitution of glycine for arginine at position 16 resulting in the nucleotide substitution of guanine for adenine at position 46 (*46 G/A*), rs1042713]; and *27 Gln/Glu* [amino acid substitution of glutamine for glutamic acid at position 27 resulting in the nucleotide substitution of cytosine for guanine at position 79 (*79C/G*), rs1042714]. Single-nucleotide polymorphisms (SNPs) were determined by polymerase chain reaction (PCR) followed by pyrosequencing using a PSQ HS96A SNP reagent kit according to the manufacturer protocol (Biotage AB, Uppsala, Sweden) and TaqMan allelic discrimination (Applied Biosystems, Foster City, CA, USA). The PCR primers and probes for *ADRB1 49 Ser/Gly* and *389 Arg/Gly* (IDs C___8898508_10 and C___8898494_10), and *ADRB2 16 Gly/Arg* and *27 Gln/Glu* (IDs C___2084764_20 and C___2084765_20) used in assays were purchased from Applied Biosystems (Applied Biosystems); 5 mL reactions in a 384-well plate were prepared and the assays were performed and analyzed according to the manufacturer's recommendations. The PCR and pyrosequencing primers for above-mentioned SNPs have been previously reported. Genotype accuracy was verified by genotyping 5–10% randomly selected duplicate samples for each SNP on the alternate platform [19,32].

Statistical analysis

Genotypes of β_1 and β_2-adrenergic receptors between the control group and the FMV/MVP patients were compared using a Chi-square or a Fisher exact test. Further, patients who had symptoms consistent with the FMV/MVP syndrome were compared with the control group and to those patients with FMV/MVP who did not have symptoms. A p-value of <0.05 was considered to be statistically significant.

Results

Forty-one patients (42%) had symptoms consistent with the FMV/MVP syndrome. Twenty-nine out of 75 men (39%) and 12 out of 23 women (52%) had symptoms consistent with the FMV/MVP syndrome (Table 2). The incidence of FMV/MVP syndrome was higher in women compared to men ($p < 0.05$). Twenty-one out of 40 patients (52%) with diffuse thickening of the mitral valve and 19 out of 58 patients (33%) with regional thickening of the mitral valve had symptoms consistent with the FMV/MVP syndrome. The median age of symptom onset was at 30 years (range 10–63 years) and the median duration of symptoms was 16 years (range 3–50 years). Symptoms with age of onset and duration are shown in Table 3. Twenty-five of the patients had a history of palpitations with a median age of onset at 20 years (range 10–55 years) and