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Mitral valve prolapse syndrome and MASS phenotype: Stability of aortic dilatation but progression of mitral valve prolapse☆

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ABSTRACT

Background: Mitral valve prolapse syndrome (MVPS) and MASS phenotype (MASS) are Marfan-like syndromes that exhibit aortic dilatation and mitral valve prolapse. Unlike in Marfan syndrome (MFS), the presence of ectopia lentis and aortic aneurysm preclude diagnosis of MVPS and MASS. However, it is unclear whether aortic dilatation and mitral valve prolapse remain stable in MVPS or MASS or whether they progress like in MFS.
Methods: This retrospective longitudinal observational study examines clinical characteristics and long-term prognosis of 44 adults with MVPS or MASS (18 men, 26 women aged 38 ± 17 years) as compared with 81 adults with Marfan syndrome (MFS) with similar age and sex distribution. The age at final contact was 42 ± 15 years with mean follow-up of 66 ± 49 months.
Results: At baseline, ectopia lentis and aortic sinus aneurysm were absent in MVPS and MASS, and systemic scores defined by the revised Ghent nosology were lower than in MFS (all $P < .001$). Unlike in MFS, no individual with MVPS and MASS developed aortic complications ($P < .001$). In contrast, the incidence of endocarditis ($P = .292$), heart failure ($P = .644$), and mitral valve surgery ($P = .140$) was similar in all syndromes. Cox regression analysis identified increased LV end-diastolic ($P = .013$), moderate MVR ($P = .019$) and flail MV leaflet ($P = .017$) as independent predictors of mitral valve surgery.
Conclusions: The study provides evidence that MVPS and MASS are Marfan-like syndromes with stability of aortic dilatation but with progression of mitral valve prolapse. Echocardiographic characteristics of mitral valve disease rather than the type of syndrome, predict clinical progression of mitral valve prolapse.

1. Introduction

Modern echocardiographic criteria identify mitral valve (MV) prolapse (MVP) with systolic prolapse >2 mm of MV leaflets, and with leaflet thickening ≥5 mm during diastole. MVP is non-classic with isolated presence of leaflet prolapse and classic when combined with leaflet thickening [1]. Classic and non-classic MVP together have a prevalence of 2.4% in the general population [1].

Some individuals with MVP develop severe MV regurgitation, endocarditis, heart failure, and sudden cardiac death [2]. MVP may occur as a familial, and non-familial trait and MVP can manifest with syndromic or non-syndromic phenotype [3]. The etiology of MVP is largely unknown. Several findings argue for involvement of genetic factors in the pathogenesis of MVP: (1) some families with MVP exhibit X-linked or autosomal dominant inheritance with incomplete penetrance [3], (2) genetic studies showed linkage of MVP to chromosomes 3q31.3–q32.1, 11p15.4, and 16p12.11–p11.2, (3) some MVP phenotypes are caused by mutations in the X-linked filamin A gene (*FLNA*) [3,4], or in *DCHS1* [5], and (4) MVP is an established cardiovascular feature of several genetic aortic disorders including Marfan syndrome (MFS), Loeys–Dietz syndrome, aneurysm osteoarthritis syndrome, and thoracic aortic aneurysms caused by mutations in the *TGFB2* and *SMAD3* genes [6]. In this study we examined MVP in Marfan-like syndromes comprising MVP syndrome (MVPS) and MASS phenotype (MASS).

☆ All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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Early descriptions of MVPS suggested atypical chest pain, exertional dyspnea, palpitations, syncope, anxiety, low blood pressure, lean body stature, and electrocardiographic repolarization abnormalities as typical features of MVPS [2], but of these only leaner body mass was confirmed in population-based cohorts [2,7]. Today, the revised version (Ghent-2) [8] of the initial Ghent nosology (Ghent-1) [9,10] defines MVPS as MVP with Marfan-like features including pectus excavatum, scoliosis and arachnodactyly, but with a systemic score on the Ghent-2 nosology <5 points [8]. The Ghent-2 systemic score considers 13 manifestations according to their diagnostic accuracy for MFS comprising MVP, myopia, skeletal manifestations, pneumothorax, dural ectasia, and skin striae. In addition, diagnosis of MVPS requires exclusion of aortic root aneurysm Z-scores ≥2 and of ectopia lentis [8].

In 1989 Glesby and Pyeritz suggested the acronym "MASS" to describe phenotypes involving MV, aorta, skeleton, and skin [11]. They suggested that individuals with the exclusion of ectopia lentis, with only mild dilatation of the aortic root and with Marfan-like manifestations including MVP, skeletal features, and skin striae should be diagnosed as having MASS [11]. In 1996 the Ghent-1 nosology revised MASS criteria as presence of myopia, MVP, mild aortic dilatation, skin striae, and minor skeletal involvement, where diagnosis required involvement of ≥2 different organ systems [9]. Similar to MVPS, the current Ghent-2 nosology redefined MASS with the presence of MVP and some Marfan-like clinical features and with exclusion of aortic root aneurysm (≥2 Z-scores) and of ectopia lentis. In contrast to MVPS the definition of MASS requires a systemic score ≥5 points. The etiology of MASS remains unknown, although some causative fibrillin-1 (*FBN1*) mutations presented with MASS phenotype [12]. *FBN1* mutations usually cause MFS which carries a high risk for rupture and dissection of the aorta. Some authors consider MASS as the mild end of a continuous spectrum of Marfan-like syndromes [13]. However, detection of a causative *FBN1* mutation in MASS raised concerns about MASS to evolve into outright MFS and overt dissection or rupture of the aorta [8,14].

Today, there is only scarce clinical data on MVPS [15–17] and MASS [11,12,14,18–21], and there is no study to assess MVPS or MASS with recent Ghent-2 criteria. Moreover, prognosis of MVP and aortic disease in MVPS and MASS has not been described. Hence, the Hamburg and Ghent Marfan centers joined to perform a retrospective longitudinal, observational study with the aim to characterize the clinical features of these entities by applying the current Ghent-2 criteria. Furthermore we studied the long-term outcomes of cardiovascular manifestations of MVPS and MASS in comparison with MFS. We wanted to test whether MVPS and MASS remained unaffected by aortic root complications, and we aimed to examine whether MVP evolved with similar severity as known in MFS, where MVP tends to be progressive [22–24].

2. Methods

2.1. Patients

We screened patient records for individuals aged 18 years or older who exhibited MVP diagnosed in MVPS or in MASS, and we compared these with individuals of the same age who exhibited MVP related to MFS. We identified a total of 44 adults with MVPS or MASS of whom 18 were men and 26 were women at a mean age of 38 ± 17 years (range 18–70 years), and 81 adults with MFS, including 34 men and 47 women at a mean age of 35 ± 12 years (range 18–67 years). We identified 80 of these patients in Hamburg and 45 patients in Ghent.

We applied Ghent-2 criteria to establish the final diagnosis of MVPS, MASS and MFS [8]. In brief, MVPS was present with MVP, exclusion of aortic root dilatation with Z-scores ≥2, ectopia lentis, and exclusion of a systemic score ≥5 points. Similarly, MASS was present with MVP, exclusion of aortic root dilatation ≥2 Z-scores and ectopia lentis, but with a systemic score ≥5 points including at least one skeletal feature. MFS was confirmed, first in the absence of a family history of MFS, with aortic root dilatation (Z-scores ≥2) and ectopia lentis, or with systemic score ≥7 points, or with ectopia lentis and a *FBN1* mutation known to cause aortic dilatation, and second, in the presence of a family history, with ectopia lentis, or with systemic score ≥7 points, or with aortic root dilatation (Z-scores ≥2) [8]. All individuals with MFS fulfilled clinical criteria and harbored a causative *FBN1* mutation [8]. We verified the diagnosis of MVPS and MASS clinically in all individuals at the age of >20 years [8], and we did not find a causative *FBN1* mutation in all these individuals. As Ghent-2 recommends, we diagnosed MVP with the presence of ≥1 of the echocardiographic standard criteria as specified below [8,25].

2.2. Genetic analysis

We extracted DNA from EDTA blood samples using standard procedures, and amplified the coding region and flanking intronic sequences including 20 nucleotides of the introns at each acceptor (positions −1 to −20) and donor splice site (positions +1 to +20) of the *FBN1*, (NM 000138.4), *TGFBR1* (NM 004612.2) and *TGFBR2* (NM 001024847.2) genes by PCR in all patients. We performed Sanger sequencing of the PCR products with an ABI PRISM 310 Genetic analyzer using the ABI

Table 1
Baseline characteristics in 125 adults with various syndromic forms of mitral valve prolapse.

Variable[a]	MVPS (N = 29)	MASS (N = 15)	MFS (N = 81)	P[b]
Age at initial evaluation (years)	42 ± 19	30 ± 11	35 ± 12	.093
Male gender	14 (48%)	4 (27%)	34 (42%)	.399
Total cholesterol (mg/dl)	194 ± 39	207 ± 47	187 ± 40	.366
HDL cholesterol (mg/dl)	58 ± 15	74 ± 22	55 ± 16	.042
LDL cholesterol (mg/dl)	113 ± 27	117 ± 31	107 ± 36	.406
Systolic blood pressure (mm Hg)	132 ± 17	125 ± 16	126 ± 16	.302
Diastolic blood pressure (mm Hg)	75 ± 11	73 ± 14	73 ± 10	.521
BAB medication	8 (28%)	2 (13%)	40 (49%)	.009
ACEi or ARB medication	3 (10%)	0	17 (21%)	.087
Previous ischemic neurologic event	2 (7%)	0	4 (5%)	.687
Ectopia lentis	0	0	38 (47%)	<.001
Systemic score (points)	1.1 ± 1.3	7.2 ± 3	7.3 ± 3.5	<.001
Aortic sinus diameter (cm)	3 ± .4	2.9 ± .4	4.5 ± 3	<.001
Aortic sinus Z-score	−.8 ± 1.3	−.8 ± 2.1	3.7 ± 2.9	<.001
LV ejection fraction (%)	59 ± 11	58 ± 8	57 ± 11	.900
Indexed LVESD (mm/m^2)	17 ± 4	18 ± 3	17 ± 4	.788
Indexed LVEDD (mm/m^2)	27 ± 4	27 ± 3	27 ± 4	.966
Indexed left atrial diameter (mm/m^2)	21 ± 6	18 ± 3	19 ± 4	.240
Anterior MV leaflet prolapse[c]	22/28 (79%)	11/13 (85%)	75/80 (94%)	.060
Posterior MV leaflet prolapse[c]	15/28 (54%)	2/13 (15%)	53/80 (66%)	.002
Bileaflet MVP[c]	11/28 (39%)	1/13 (8%)	48/80 (60%)	<.001
MV bileaflet thickening	9/26 (35%)	4/13 (31%)	14/80 (18%)	.151
Moderate degree of MVR	11 (38%)	4 (27%)	13 (16%)	.049
Flail MV leaflet	3 (10%)	0	4 (5%)	.488
Tricuspid valve prolapse	3/27 (11%)	1/13 (8%)	26/79 (33%)	.022
NT-proBNP (pg/ml)	67 ± 63 (N = 7)	100 ± 100 (N = 7)	842 ± 2249 (N = 48)	.003

ACEi identifies angiotensin-converting enzyme inhibitors; ARB, angiotensin-receptor blockers; BAB, beta-adrenergic blockers; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LV, left ventricle; LVEDD, LV end-diastolic diameter; LVESD, LV end-systolic diameter; MASS, MASS phenotype; MV, mitral valve; MVR, mitral valve regurgitation; MVPS, mitral valve prolapse syndrome; MFS, Marfan syndrome; np, not performed; NT-pro-BNP, N-terminal pro-brain natriuretic peptide.

[a] Continuous data are presented as mean ± standard deviation.

[b] Kruskal–Wallis test for continuous data and the generalized Fisher's exact test for nominal and categorical data.

[c] We excluded 1 individual with MVPS and MFS, respectively, and 2 individuals with MASS because in these documentations MVP was available without original echocardiographic documentation; we included 2 individuals with MVPS and 1 with MASS, who had original echocardiographic documentation which described buckling of a single MV leaflet according to Freed without specification of MV leaflet. We considered mono-leaflet MVP in these 3 individuals, but we counted prolapse as absent in both the anterior and the posterior MV leaflet.

PRISM BigDye Terminator cycle sequencing kit (Applied Biosystems) [26,27]. To detect single and multiple exon deletions or duplications, we used 100 ng DNA for multiplex ligation-dependent probe amplification (MLPA) [28] with SALSA kits P065 (probes for *FBN1* and *TGFBR2*) and P066 (probes for *FBN1*) (MRC Holland, Amsterdam, The Netherlands) according to the manufacturer's protocol. We separated PCR products on an ABI PRISM 310 or 3130xl Genetic analyzer (Applied Biosystems), and we analyzed MLPA results with the Sequence Pilot algorithm (JSI Medical Systems, Kippenheim, Germany).

2.3. Baseline characteristics

At the time of initial evaluation at our institutions, we obtained age, sex, body surface area according to Du Bois [29], fasting blood lipid levels, and systolic and diastolic blood pressure after 15-min rest on standard sphygmomanometer [30]. We documented intake of beta-blockers (BAB), angiotensin-converting enzyme inhibitors (ACEi), or angiotensin-receptor blockers (ARB) with medication over ≥1 year prior to baseline, previous ischemic neurologic events with cerebral infarction identified as persistence of a focal neurologic deficit for ≥24 h caused by altered cerebral circulation shown on tomographic images or with transient ischemic attack with resolution of a focal neurologic deficit ≤24 h [23,31]. Ectopia lentis was present with any displacement of the lenses, or after surgery for this condition, and we assessed wrist sign, thumb sign, pectus carinatum, pectus excavatum, chest asymmetry, hindfoot deformity, plain pes planus, protrusio acetabuli, reduced upper segment/lower segment ratio, increased arm/height ratio, scoliosis or thoracolumbar kyphosis, reduced elbow, extension, facial features, pneumothorax, dural ectasia, skin striae, myopia >−3 diopters, and MVP in all individuals to calculate the Ghent systemic score [8,32].

We used standard 2-dimensional transthoracic echocardiographic recordings to assess aortic root diameters in the parasternal long-axis view at the level of the aortic sinuses at end-diastole using the leading-edge method with calculation of Z-scores using Devereux's formula [33], left ventricular (LV) ejection fraction according to Simpson [34], LV end-systolic diameters (LVESD), LV end-diastolic diameters (LVEDD), and left atrial diameters with normalization to BSA according to current guidelines [34]. We assessed prolapse of MV leaflets separately with posterior and anterior late systolic prolapse >2 mm on M-mode echocardiography, or on two-dimensional echocardiography from the parasternal long-axis view as leaflet displacement >2 mm, where we also measured the displacement of this leaflet in the apical four-chamber view; however, because of the lateral scallop of the posterior leaflet is most difficult to evaluate from these views, we confirmed the degree of displacement always by examination of the long-axis scans [1]. We considered MV leaflet thickening with a thickness ≥5 mm separately for both mitral leaflets during diastasis. We considered MVP with displacement >2 mm of at least one MV leaflet. We quantified MV regurgitation as moderate (we did not see individuals with severe MV regurgitation at baseline), and we assessed flail mitral leaflet, and tricuspid valve prolapse according to current guidelines. In addition, we measured N-terminal pro-brain natriuretic peptide (NT-proBNP) serum levels with an electrochemiluminescence sandwich immunoassay (Roche Diagnostics GmbH, Mannheim, Germany) on the Elecsys System 2010 with a detection limit ≥5 pg/ml (Table 1) [35].

2.4. Clinical events

We assessed all MV-related clinical events during clinical evaluation at our institutions and upon interviews during follow-up, where we documented both the age of initial occurrence of each clinical event, and the time interval between the initial evaluation at our institutions and the final contact. We considered clinical events as related to the MV only with documentation of clinical and echocardiographic criteria of infective endocarditis involving the MV, heart failure related to the MV with clinical signs and symptoms of congestive heart failure according to classical criteria [36], and surgery of the MV that was performed as an isolated procedure for severe MVR as diagnosed by echocardiographic standard criteria in all patients. Finally, we assessed aortic surgery or intervention, and death with unknown cause (Table 2).

2.5. Statistical methods

We performed an exploratory data analysis and therefore we made no adjustments for multiple testing. We compared baseline characteristics with the Kruskal–Wallis test for continuous data and the generalized Fisher's exact test for nominal and categorical data (Tables 1 and 2). For time-to-event analysis of study variables with MV surgery we performed univariable Cox regression analysis and we included variables with $P < .05$ in a multivariable Cox regression model with backward elimination to determine independent predictors of prognosis within these sets (Table 3). To investigate the influence of age assessed from birth to the time of MV surgery depending on MV morphologic characteristics, we used the Kaplan–Meier estimator to calculate the cumulative probability of event displayed as 1 − the cumulative event-free functions, and with the Log rank to screen for statistical differences (Fig. 3). We considered *P*-values as descriptive measures with values <.05 only as an indicator of inhomogeneity between groups. Unless otherwise specified, we expressed quantitative data as means ± standard

Table 2
Clinical events in 125 patients with mitral valve prolapse.

Outcome variables[a]	Age at event (years; range)	MVPS (N = 31)	MASS (N = 13)	MFS (N = 81)	*P*[b]
Age at baseline (years)	36 ± 14 (18–70)	42 ± 19 (18–70)	30 ± 11 (19–51)	35 ± 12 (18–67)	.093
Age at final contact (years)	42 ± 15 (21–79)	47 ± 20 (21–79)	35 ± 12 (22–55)	42 ± 13 (21–72)	.095
Follow-up interval (months)	66 ± 49 (1–183)	50 ± 41 (1–151)	58 ± 42 (1–135)	73 ± 51 (1–183)	.134
Patients lost to follow-up	24 ± 3 (22–28)	1 (3%)	2 (15%)	1 (1%)	.037
Non-MV-related clinical events					
– Death	56 ± 20 (34–77)	1 (3%)	0	4 (5%)	1.000
– Aortic surgery[c]	39 ± 12 (19–69)	0	0	35 (43%)	<.001
MV-related clinical events					
– MV endocarditis	32 ± 9 (19–39)	0	1 (7%)	3 (4%)	.292
– Heart failure	51 ± 14 (31–72)	3 (10%)	0	8 (10%)	.644
– MV surgery[d]	44 ± 15 (21–72)	6 (21%)	0	16 (20%)	.140
– Patients with MV-related events	45 ± 16 (19–72)	8 (28%)	1 (7%)	21 (26%)	.227

MV identifies mitral valve.
[a] Continuous data are presented as mean ± standard deviation.
[b] For comparison between all three groups we employed the Kruskal–Wallis test for continuous data and the generalized Fisher's exact test for nominal and categorical data.
[c] Aortic surgery comprised composite valve grafting according to Bentall, aortic valve-sparing re-implantation techniques according to David, wrapping of the ascending aorta, and placement of a stent-graft in the descending thoracic aorta.
[d] MV surgery comprised replacement of the MV or surgical reconstruction procedures.

Table 3
Predictors of mitral valve surgery as outcome.

Variable	Hazard ratio	Lower 95% CI	Upper 95% CI	P[a]
Age at initial evaluation (years)	1.028	1.000	1.058	.051
Male gender	1.582	.681	3.675	.285
Body surface area (m^2)	.254	.037	1.722	.160
Total cholesterol (mg/dl)	1.003	.992	1.014	.633
HDL cholesterol (mg/dl)	.987	.957	1.017	.386
LDL cholesterol (mg/dl)	1.002	.989	1.016	.724
Systolic blood pressure (mm Hg)	1.001	.975	1.027	.953
Diastolic blood pressure (mm Hg)	.968	.928	1.010	.130
BAB medication	1.150	.488	2.710	.749
ACEi or ARB medication	.485	.130	1.806	.281
Previous ischemic neurologic event	.045	.000	143.969	.451
Ectopia lentis	.725	.282	1.862	.503
Systemic score (points)	.885	.782	1.000	.051
Aortic sinus diameter (cm)	.753	.461	1.228	.256
Aortic sinus Z-score	.924	.810	1.055	.242
LV ejection fraction (%)	.975	.939	1.012	.184
Indexed LVESD (mm/m^2)	1.094	1.014	1.181	.021
Indexed LVEDD (mm/m^2)	1.159	1.076	1.247	<.001
Indexed left atrial diameter (mm/m^2)	1.142	1.068	1.229	<.001
Anterior MV leaflet prolapse	.383	.126	1.160	.090
Posterior MV leaflet prolapse	12.734	1.700	95.400	.013
Bileaflet MV prolapse	2.493	.908	6.845	.076
MV bileaflet thickening	2.734	1.127	6.630	.026
Moderate degree of MV regurgitation	4.518	1.778	11.482	.002
Flail MV leaflet	5.015	1.802	13.959	.002
Tricuspid valve prolapse	2.157	.910	5.114	.081
MVPS/MASS vs MFS	.725	.274	1.921	.518

ACEi identifies angiotensin-converting enzyme inhibitors; ARB, angiotensin-receptor blockers; BAB, beta-adrenergic blockers; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LV, left ventricle; LVEDD, LV end-diastolic diameter; LVESD, LV end-systolic diameter; MASS, MASS phenotype; MV, mitral valve; MVR, mitral valve regurgitation; MVPS, mitral valve prolapse syndrome; and MFS, Marfan syndrome.
[a] Univariate Cox regression analysis.

deviation and qualitative data as numbers (percentage). We used IBM-SPSS software (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp) for all statistical tests.

3. Results

3.1. Baseline characteristics

MVPS and MASS were unrelated to *FBN1*, *TGFBR1* and *TGFBR2* mutations in all individuals. Age, sex, lipid levels, blood pressures and medication were similar in all groups, but BAB medication was less frequent in MVPS and MASS ($P = .009$), and systemic score points were lower in MVPS and MASS than in MFS ($P < .001$; Figs. 1 and 2). Moderate MV regurgitation was somewhat more prevalent in MVPS than in MFS ($P = .049$), but tricuspid valve prolapse was less frequent in MVPS and MASS than in MFS ($P = .022$). NT-pro-BNP levels were lowest in MVPS, higher in MASS and highest in MFS ($P = .003$; Table 1).

3.2. Clinical events

The average age at baseline evaluation was 36 ± 14 years. The age at final contact was 42 ± 15 years, where only 4 individuals were lost during 65 ± 48 months of follow-up. Death occurred in four individuals with MFS where severe aortic disease was the most likely cause of death, and in one individual with MVPS where the cause of death was unclear. In contrast to MFS, no single individual with MVPS or MASS required aortic surgery or intervention ($P < .001$). Conversely, the incidence of endocarditis ($P = .292$), heart failure ($P = .644$), and MV surgery ($P = .140$) was similar in all syndromes.

Kaplan–Meier curve analysis showed that at the age of 47 years already 51% of MFS had undergone aortic surgery or intervention, whereas no individual with MVPS or MASS required aortic surgery ($P < .001$). In contrast, 56% had undergone MV surgery at the age of 69 years with MVPS or MASS as compared with 58% at the age of 58 years with MFS ($P = .168$; Fig. 3).

3.3. Predictors of MV surgery

Cox regression analysis identified that the risk for the need of MV surgery was related to increased indexed LV end-systolic (*P*.021), LV end-diastolic ($P < .001$), and left atrial diameters ($P < .001$), posterior

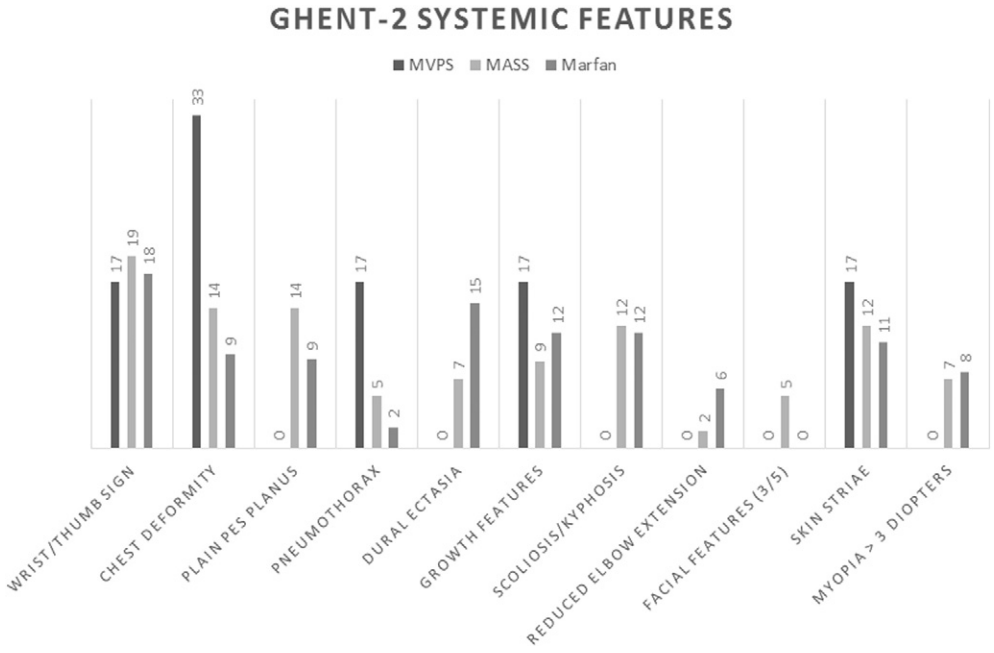

Fig. 1. Analysis of systemic features comprising wrist/thumb sign, chest deformity, pes planus, pneumothorax, dural ectasia, growth/anthropometric features, scoliosis/kyphosis, reduced elbow extension, facial features (3/5), skin striae, and myopia > 3 diopters as defined in the Ghent-2 nosology [8]. We only present results from individuals with complete assessment of all signs, where we identified 6, 57 and 234 systemic signs in 11, 13 and 59 individuals with mitral valve prolapse syndrome (MVPS), MASS phenotype (MASS), and Marfan syndrome (MFS), respectively. We present the frequency of each clinical feature relative to the total number of features found in each syndrome (percent).

MVP ($P = .013$), MV bi-leaflet thickening ($P = .026$), moderate MV regurgitation ($P = .002$), and flail mitral leaflet ($P = .002$; Table 3). Multivariate Cox regression analysis of all univariately significant variables identified that increased LV end-diastolic (HR = 1.118; 95% CI 1.023–1.222; $P = .013$), moderate MVR (HR = 3.146; 95% CI 1.207–8.199; $P = .019$) and flail MV leaflet (HR = 3.698; 95% CI 1.265–10.808; $P = .017$) as independent predictors of MV surgery.

4. Discussion

With the application of current Ghent-2 criteria and with no evidence of a causative mutation in *FBN1*, *TGFBR1* and *TGFBR2*, our study provides novel insights into the clinical characteristics and long-term prognosis of MVPS and MASS. As expected, MVPS- and MASS-affected individuals exhibited similar systemic features as those with MFS. Unlike in MFS, no individual with MVPS or MASS developed aortic complications. In contrast, the incidence of endocarditis, heart failure, and MV surgery was similar in all syndromes. The risk for MV surgery depended exclusively on the presence of classical echocardiographic predictors of MV disease progression such as LV diameters and MV dysfunction at baseline.

The diagnostic criteria of MVPS and MASS underwent substantial changes since their initial description [11,17,37]. These changes may be explained by a combination of factors that have significantly evolved over time: molecular testing has become more widely available and now plays a more important role in the new nosology as compared with the initial Berlin nosology [10,38], more reliable 2D echocardiography has replaced the former M-mode echocardiography to diagnose MVP [39], and new entities such as the Loeys–Dietz syndrome caused by *TGFBR1* or *TGFBR2* mutations have been added to the phenotypic

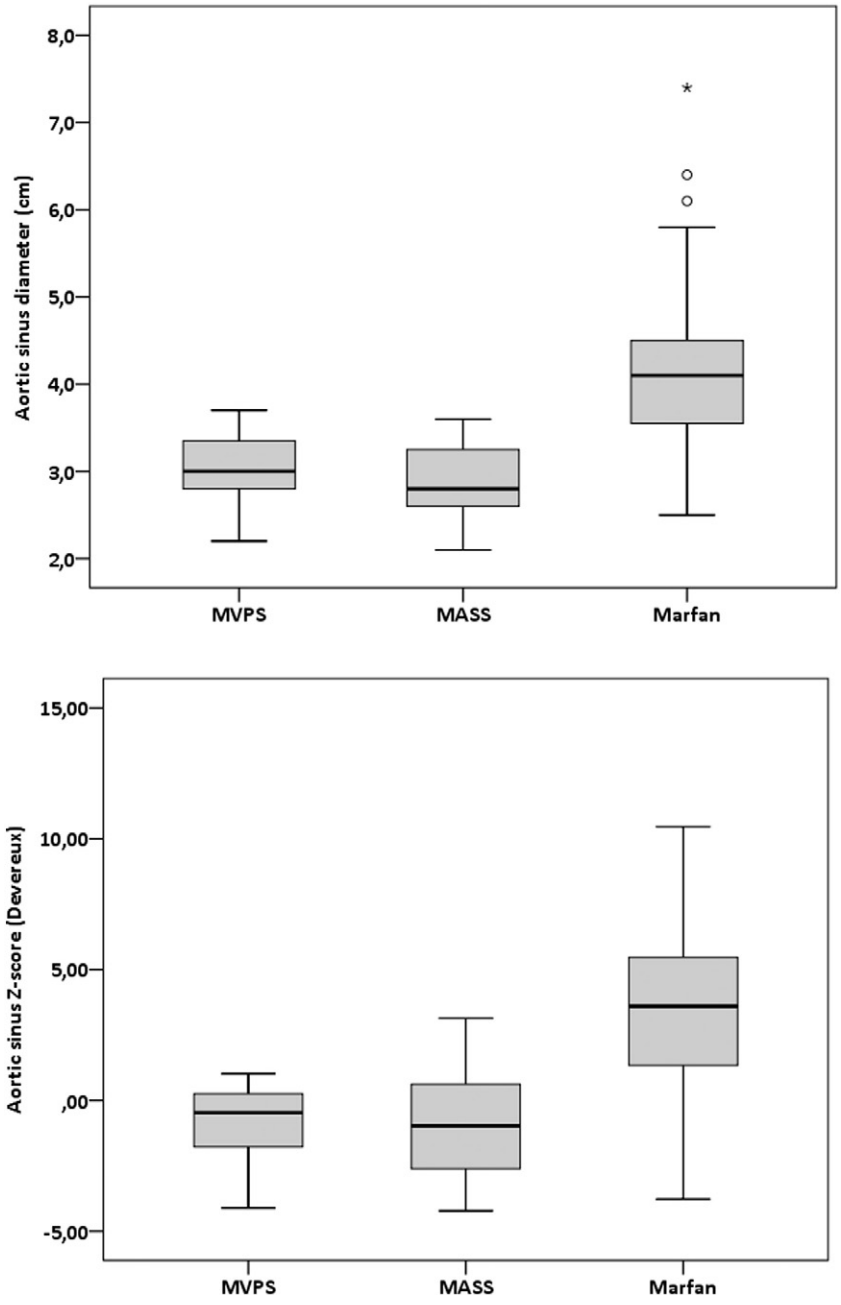

Fig. 2. The box-and-whisker plots of aortic sinus diameters (upper panel) and of aortic sinus Z-scores (lower panel). The median and range of aortic sinus diameters were 3.0 cm (2.2–3.7 cm) in MVPS, 2.8 cm (2.1–3.6 cm) in MASS, and 4.1 cm (2.5–7.4 cm) in MFS ($P < .001$). The median and range of aortic sinus Z-scores were −.47 (−4.11–1.02) in MVPS, −.97 (−4.22–3.14) in MASS, and 3.6 (−.377–10.46) in MFS ($P < .001$).

spectrum of Marfan-like syndromes [40]. We applied modern diagnostic criteria and excluded individuals carrying mutations in *FBN1*, *TGFBR1* and *TGFBR2* in MVPS and MASS, because these mutations are associated with a high risk for aortic aneurysm and dissection, or their carriers may develop outright MFS or LDS [14]. Moreover, we accepted MVPS and MASS only with aortic Z-scores <2. Finally, as the MFS phenotype may emerge with age we only considered individuals as having MVPS and MASS with confirmation of the diagnosis at an age >20 years. These rigid diagnostic policies may explain the distinct long-term prognosis of MVPS and MASS as compared with MFS.

Our study identified Marfan-like skeletal features, skin striae, and primary spontaneous pneumothorax in MVPS. The literature confirmed

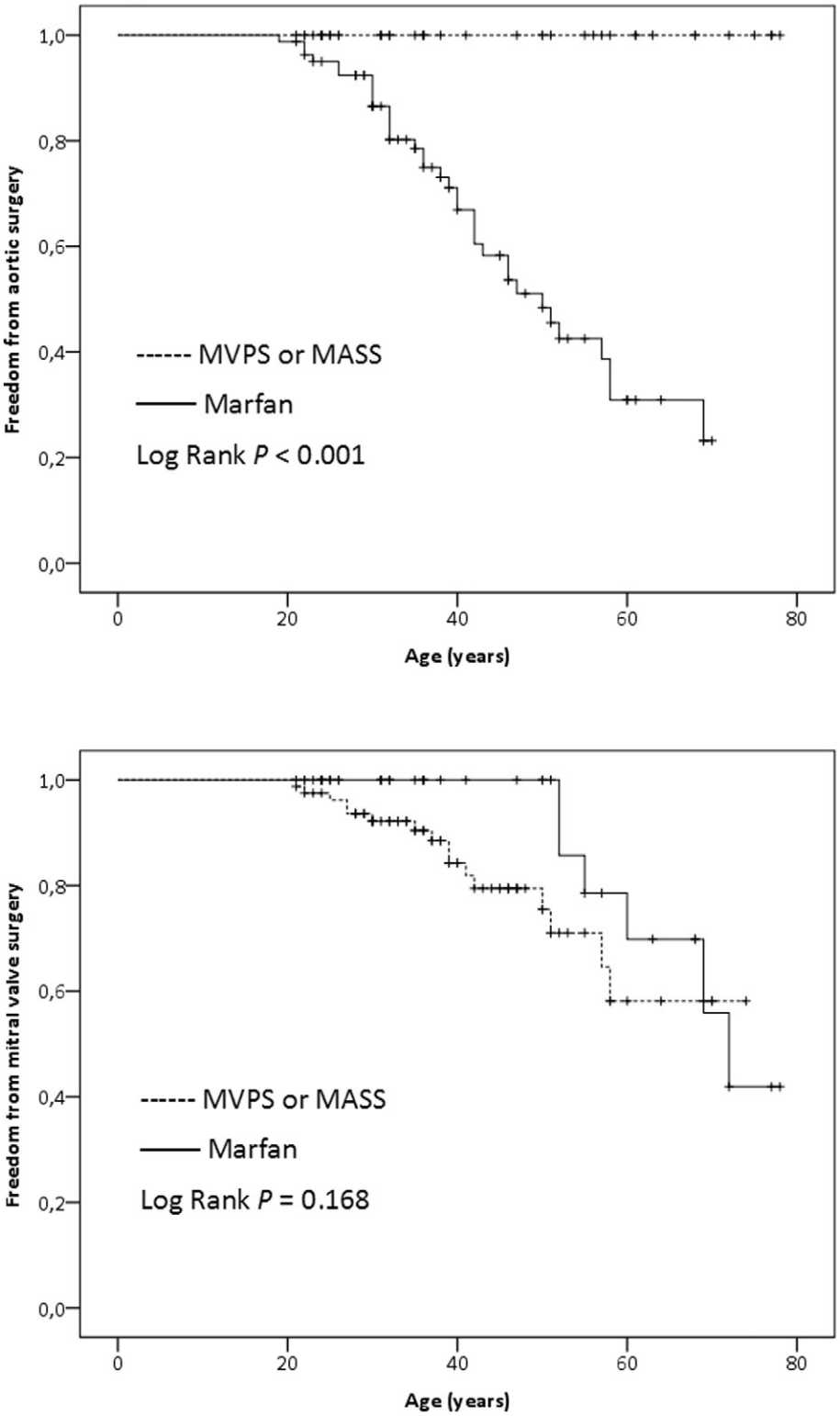

Fig. 3. Kaplan–Meier curve analysis comparing the cumulative probability for clinical events in individuals with mitral valve prolapse syndrome (MVPS) or MASS phenotype (MASS) versus individuals with Marfan syndrome (MFS) according to age. The upper panel analyses the cumulative probability for aortic root surgery, and the lower panel analyses the cumulative probability for mitral valve surgery.

striae and Marfan-like skeletal manifestations in MVPS, differing from MFS only in their frequency and severity [11,17]. Similarly, some studies confirmed pneumothorax in MVPS [41,42]. In MVPS we did not identify dural ectasia, and we also did not find studies to report on this association. Similarly, patients with MVPS did not exhibit myopia >3 diopters. One study reports a high prevalence of mild myopia with an average of 2 diopters in MVPS [43]. We found that all systemic features of MFS also were present in MASS, which corroborates findings from the initial description of this phenotype [11]. Systemic score points did not relate to MV-related events.

Two reasons may explain why we did not observe aortic complications in MVPS and MASS. First, we carefully excluded mutations in genes that are associated with a high risk for aneurysm, dissection or rupture of the aorta in all individuals with MVPS and MASS. Second, in agreement with the definitions, we diagnosed MVPS and MASS only in individuals with aortic sinus diameters <2 Z-scores where individuals with MVPS exhibited mean diameters of 3.1 cm (2.2–3.7 cm) and with MASS of 2.9 cm (2.1–3.6 cm) at baseline. Our patients were younger than 50 years on average at the time of final contact, and hence we were unable to exclude that aortic events may appear and evolve later in life. However, follow-up intervals and age at final contact were similar across all groups, and therefore it appears justified to conclude that the prognosis of aortic disease in MVPS and MASS is by far better than in MFS.

Posterior MVP and bileaflet MVP were less frequent in MASS than in the other syndromes. Thus, not the type of syndrome determines the progression of MV disease, but rather echocardiographic characteristics such as enlarged LV diameters, moderate MV regurgitation and MV flail leaflet. Echocardiographic characteristics are well-documented to predict progression of MV disease both in idiopathic MVP [44,45], and in MFS-related MVP [22]. Hence, clinical events in MVPS and MASS originate from MVP, where long-term prognosis does not relate to a diagnostic sub-classification as MVPS or as MASS but rather to the echocardiographic features related to MV disease.

Finally, NT-pro-BNP levels were assessed in 62 individuals (50%) of our cohort. The results indicated that myocardial dysfunction was present in MFS but not in MVPS and MASS. Interestingly, myocardial dysfunction was unrelated to moderate MV regurgitation (odds ratio = .999; 95% CI .998–1.001; $P = .476$). Myocardial dysfunction in MFS is confirmed by the literature [46,47], but we did not find previously reported data on myocardial function in MVPS and MASS.

4.1. Study limitations

We provide the first long-term experience with MVPS and MASS. However, our cohort is unlikely to reflect a sample that is representative of MVPs and MASS in the general population. Our study was retrospective, two different centers were involved, patients were selected based on completeness of clinical and molecular data, and clinical event rates were low. Therefore, we considered *P*-values as descriptive measures to indicate inhomogeneity between groups. Further, we found no mutation in *FBN1*, *TGFBR1* and *TGFBR2* in any individual with MVPS or MASS, but the etiology of these syndromes remains unknown. Due to the retrospective nature of the study, not all echocardiographic features were similarly well documented, which resulted in some missing information as delineated in Table 1. Similarly, we report long-term outcomes of MVPS and MASS but we do not provide echocardiographic follow-up data on the progression of aortic diameter or MV disease. Finally, some of the differences between groups, such as lower systemic scores, and smaller aortic root diameters in MVPS and MASS as compared with MFS were integral to the definition of groups rather than the results of our study. We should be aware that in MVPS and MASS smaller aortic diameters at baseline may result into aortic complications later in life than in MFS.

5. Conclusions

Our study provides evidence that MVPS and MASS are Marfan-like syndromes with stability of aortic dilatation but with progression of MV disease. Echocardiographic characteristics of MV predict progression of MV disease. The current nosology uses the number of systemic Marfan-like features to distinct MVPS from MASS, but the number of these features does not seem to have impact on clinical outcomes. Prospective studies with longer follow-up seem warranted to validate these findings.

Conflict of interest

The authors report no relationships that could be construed as a conflict of interest. This work is not supported by any grant.

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