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Bicuspid aortic valve: a synergistic factor for aortic dilation and dissection in Marfan syndrome?

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ABSTRACT

Patients with either Marfan syndrome or bicuspid aortic valve are at increased risk for aortic dilation and dissection, but occurrence of both conditions has barely been reported. Whether bicuspid aortic valve adversely impacts the cardiovascular outcome in Marfan syndrome patients is unknown. The objective was to investigate the prevalence of bicuspid aortic valve and to define whether its combined presence would adversely impact cardiovascular outcome in patients with Marfan syndrome. We performed a retrospective review on a Marfan syndrome database from a single center. Comparisons between patients with or without bicuspid aortic valve were performed by χ^2 or Student t test as appropriate. Bicuspid aortic valve was found in 4 of 89 Marfan syndrome patients (two males; mean age 21.5 ± 13 years) for 4.5% prevalence; in contrast, 1.5% prevalence was found in 200 control subjects (p = 0.1). Each patient with bicuspid aortic valve is separately discussed. Presence of bicuspid aortic valve shows trends for association with aortic dilation (Odds ratio [OR] 4.2; 95% Confidence interval [95%CI] 0.2-81), and aortic dissection (OR 5.5; 95%CI 0.7-42), while negative association with the Walker-Murdoch sign (OR 0.07; 95%CI 0.006-0.73) was found. Prevalence of bicuspid aortic valve in patients with Marfan syndrome patients is 4.5%. While it is intriguing and even intuitive that the concurrence of both conditions would lead to more aggressive aortic disease, a true synergistic role for aortic wall weakening cannot be supported.

Key words. Marfan syndrome. Bicuspid aortic valve. Aortic dissection.

Válvula aórtica bicúspide: ¿un factor sinérgico para dilatación y disección aórtica en el síndrome de Marfan?

RESUMEN

Los pacientes con síndrome de Marfan o con válvula aórtica bicúspide tienen incrementado el riesgo de dilatación y disección aórtica, aunque la ocurrencia de ambas condiciones apenas ha sido reportada. No se sabe si la presencia de válvula aórtica bicúspide impacta de manera adversa el desenlace cardiovascular en pacientes con síndrome de Marfan. Nuestro objetivo fue investigar la prevalencia de válvula aórtica bicúspide y definir si su presencia impacta de manera adversa el desenlace cardiovascular en pacientes con síndrome de Marfan. Realizamos un estudio retrospectivo en nuestra base de datos de síndrome de Marfan. Las comparaciones entre pacientes con o sin válvula aórtica bicúspide fueron realizadas con prueba de χ^2 o t de Student, según correspondiera. Se encontró válvula aórtica bicúspide en cuatro de 89 pacientes con síndrome de Marfan (dos hombres, promedio de edad 21.5 ± 13 años), para una prevalencia de 4.5%; en contraste, en 200 individuos sin el síndrome la prevalencia fue de sólo 1.5% (p = 0.1). Cada paciente con síndrome de Marfan y válvula aórtica bicúspide es discutido de manera individual. La presencia de válvula aórtica bicúspide mostró tendencias de asociación con dilatación aórtica (razón de momios [RM] 4.2; IC95% 0.2-81), y con disección aórtica (RM 5.5; IC95% 0.7-42), mientras que se encontró asociación negativa con el signo de Walker-Murdoch (RM 0.07; IC95% 0.006-0.73). La prevalencia de válvula aórtica bicúspide en pacientes con síndrome de Marfan es de 4.5%. Si bien es interesante y aun intuitivo que la concurrencia de ambas condiciones pudiera condicionar una enfermedad aórtica más agresiva, un papel sinérgico para el debilitamiento de la pared aórtica no puede ser sustentado.

Palabras clave. *Síndrome de Marfan. Válvula aórtica bicúspide. Dilatación aórtica, Disección aórtica.*

INTRODUCTION

Marfan syndrome (MFS) is a genetic disorder in which aortic root dilation represents a main life-threatening complication leading to aortic regurgitation, dissection, and rupture.[1] Similarly, patients with bicuspid aortic valve (BAV) malformations are at increased risk for aortic dilation, aneurysm formation, and dissection.[2] While in MFS a genetic background is well established –mutations in the *FBN1* gene–,[3] in BAV (the most common congenital heart malformation) heritable defects in valvulogenesis have been suggested.[4]

MFS and BAV share a number of characteristics, such as defective production of extracellular matrix proteins,[5] increased aortic tissue expression of matrix metalloproteinases,[6] as well as extracellular matrix degeneration leading to cystic medial necrosis in absence of significant inflammatory response in the aortic wall aneurysms.[5] These molecular and histopathological similarities suggest a common pathogenetic pathway leading to aortic wall tissue damage, abnormal vessel distensibility, and ultimately aortic dilation and dissection. Thus, even when could be reasonable to speculate that simultaneous occurrence of both conditions increases the risk for development of aortic aneurysms and dissection, the presence of BAV in MFS has barely been reported,[7,8] and cardiovascular outcome for patients with coexistence of both conditions is unknown.

We performed a retrospective review on a MFS cohort from a single center to investigate the prevalence of BAV and to define whether its combined presence would adversely impact cardiovascular outcome in patients with MFS.

PATIENTS AND METHODS

Patients fulfilling the Ghent criteria for the clinical diagnosis of MFS,[9] who also completed their cardiovascular, musculoskeletal, and ocular assessments (including anthropometry, arachnodactyly, joint hypermobility, electrocardiogram, echocardiogram, chest x-ray, fundoscopy, slit lamp examination, and visual acuity) were selected for analysis. Presence of BAV required confirmation by transthoracic or transesophageal echocardiography (number of cusps observed in real-time motion, irregularity of folding of cusp margins, and location of commissural insertions). All data were obtained from medical chart review. For comparisons, we retrospectively review echocardiograms performed by every reason from 200 non-selected, consecutive patients with no clinical data of MFS.

For statistical analysis, continuous variables were compared using the Student t test, while χ^2 tests were used for categorical variables. Odds ratios (OR) and 95% confidence intervals (95% CI) were calculated. Multivariate analyses were planned to include all variables reaching statistical significance. A $p < 0.05$ value was considered significant. Statistics were performed using GraphPad Prism 4.0 software (GraphPad Inc, San Diego, CA, USA).

RESULTS

Our whole cohort is composed of 117 patients with MFS of Mexican/mestizo ethnicity; of these, 89 (76%) patients were eligible for inclusion. At least one transthoracic echocardiogram was available in all included patients. The presence of BAV was clinically suspected in four patients (age range, 21.5 ± 13 years; two males) and confirmed by echocardio-

Table 1. Demographics and selected clinical features of MFS.

	MFS/BAV n = 4	MFS alone n = 85	OR (95% CI)	p
Male (%)	2 (50)	45 (53)	-	ns
Age, years (mean ± SD)	21.5 ± 13	24.9 ± 13	-	ns
Aortic dilation (%)	4 (100)	58 (68)	4.2 (0.21-81.4)	ns
Aortic aneurysm (%)	2 (50)	19 (22)	3.4 (0.45-26.3)	ns
Aortic dissection (%)	2 (50)	13 (15)	5.5 (0.71-42.9)	ns
Joint hypermobility (%)	2 (50)	63 (74)	0.34 (0.04-2.6)	ns
Steinberg's sign (%)	2 (50)	72 (85)	0.18 (0.02-1.39)	ns
Walker-Murdoch's sign (%)	1 (25)	70 (82)	0.07 (0.006-0.73)	0.005
Ectopia lentis (%)	1 (25)	50 (59)	0.23 (0.02-2.3)	ns
MFS family history (%)	4 (100)	49 (58)	-	ns

graphy and cardiac magnetic resonance imaging (MRI), while in the remaining 85 patients (age range, 24.9 ± 13 years; 45 males) this was ruled-out by physical examination and echocardiogram. Although differences in demographics between MFS with or without BAV were not found (Table 1), the combined presence of BAV and MFS tended to be associated with a higher risk for aortic dissection (OR 5.5; 95% CI 0.7-42; p = 0.07). Unexpectedly, a negative association between BAV and the Walker-Murdoch sign (a hallmark of arachnodactyly) was found (OR 0.07; 95% CI 0.006–0.7; p = 0.005). Because of the small size of the BAV group and the lack of other associations, multivariate analyses were not performed.

Each individual patient with MFS/BAV is briefly presented:

- **Case No. 1**. A 39-year-old female with pes planus and chest wall deformities since childhood presented with a 15-year history of intermittent dyspnea on exertion, palpitations, and syncope. At age 36 years, bilateral ectopia lentis was diagnosed, and the patient was referred to our institution for additional evaluation. On clinical examination, highly arched palate, dental crowding, arachnodactyly, Walker-Murdoch and Steinberg signs, dolichostenomelia, pectus excavatum, and valgus deviation of hind feet were found. A decrescendo diastolic aortic murmur and an ejection click in the apex were also present. Transthoracic echocardiogram revealed BAV with severe regurgitation, mitral and tricuspid valve prolapse, and moderate pulmonary hypertension. Aortic root dilation (79.5 mm) involving the sinuses of Valsalva was further demonstrated by cardiovascular MRI. Despite the requirement of surgical management, patient refused the latter, and therapy with propranolol, digoxin, and aspirin was then initiated. For the ensuing 2 years, the patient remained clinically stable, until she suddenly developed thoracic pain and paresthesia in the upper and lower extremities. Computed tomography (CT) imaging revealed aortic dissection extending from aortic annulus to renal arteries. Due to the high surgical risk, the patient again refused surgical treatment, and medical management including atenolol, captopril, and bumetanide was initiated. Three years later, the patient remains asymptomatic in cardiovascular functional class II on close medical follow-up. Interestingly, her 10 year-old offspring also presents MFS, although there is no clinical or imaging evidence of BAV.
- **Case No. 2.** A previously healthy, 25-year-old female suddenly developed dyspnea and acute chest pain during the second trimester of pregnancy. Family history was remarkable for positive MFS (father and three first cousins). Physical examination disclosed dolichostenomelia, highly arched palate, dental crowding, and pectus excavatum. Echocardiography and MRI demonstrated BAV with severe regurgitation and aortic root dilation (55 mm) with dissection extending from aortic annulus to iliac arteries. A surgical stepwise approach was used. First, an endovascular stent was placed in the descending aorta. After successful delivery, surgical replacement of aortic valve and ascending aorta by composite graft according to the Bentall and deBono procedure was performed. Valve histology showed advanced myxomatous changes, while aortic wall exhibited areas of cystic medial necrosis in absence of inflammatory infiltrates. At 2 years of follow-up, the patient remains asymptomatic on metoprolol and anticoagulant therapy.
- **Case No. 3.** An asymptomatic 15-year-old male was referred to our institution because of an incidental finding of cardiac murmurs during a routine physical evaluation. As relevant medical history, relatives by maternal lineage have died due to sudden cardiovascular events, although a diagnosis of MFS was never established. On initial examination, highly arched palate, dental crowding, joint hypermobility, protrusio acetabuli, and planovalgus foot deformity were found. Echocardiogram and MRI showed BAV with aneurysmatic aortic root dilation (62 mm) and severe regurgitation. The patient underwent successfully Bentall and deBono surgery with aortic valve replacement. Advanced myxomatous changes were found on valve histology, while aortic wall showed cystic medial necrosis. Three years later, patient remains asymptomatic on beta-blocker and anticoagulant therapy.
- **Case No. 4.** An asymptomatic 7-year-old male was referred for evaluation because of MFS; his family history was remarkable for MFS (mother). On examination, highly arched palate, dolichostenomelia, Steinberg sign, joint hypermobility, pectus carinatum, as well as plurifocal, diastolic murmurs were found. On 3-D echocardiography, BAV with aortic dilation (25 mm) and severe regurgitation, as well as mitral and pulmonary valve prolapses were recorded. The patient was placed on propranolol therapy and close cardiovascular follow-up.

DISCUSSION

This retrospective study demonstrates a 4.5% prevalence of BAV in patients with MFS of Mexican/mestizo ethnicity. These patients tend to present aortic root dilation and dissection with more frequency and severity than those with MFS alone.

A 4.5% prevalence of BAV is much higher than that reported in the general population. In this study, we evaluate echocardiograms performed by every reason from 200 consecutive patients with no clinical data of MFS; BAV was found in only 3 patients (age range, 38 ± 17.5 years; two males) for 1.5% prevalence ($p = 0.1$, *vs.* MFS patients). Interestingly, two of these patients underwent aortic valve replacement due to severe aortic valve regurgitation and congestive heart failure. Additionally, bacterial endocarditis was found in one of these cases; however, none of them had aneurysmal dilation or aortic dissection. Similarly, on reviewing 24,265 echocardiograms performed for any reason, Movahed et al. found a 0.6% prevalence of BAV, while this figure was 0.5% for teenage athletes.[10] Although to our knowledge there are no studies assessing BAV prevalence in MFS, in a report from an Italian MFS cohort of 227 patients, Porciani, *et al*. found four of these with BAV.[8] Indeed, this 1.7% prevalence of BAV in Italian MFS patients is lower than the 4.5% prevalence found in Mexican/mestizo patients. This may be related to differences in genetic background. Faivre et al. studied 1,013 probands with MFS and demonstrated that the underlying genotype (type of mutation and its location) strongly influences phenotype and organic involvement.[11] Whether mutations conferring high cardiovascular risk are more prevalent in Mexican/mestizo ethnicity remains unknown; however, we have previously found a higher prevalence of interatrial septal aneurysm and pulmonary valve prolapse in our cohort than that reported for other ethnicities.[12]

There was no evidence whether the concurrence of BAV exerts an influence on the frequency and severity of aortic involvement in patients with MFS. In the study by Porciani, *et al*.,[8] a cross-sectional design was used and the outcome of patients with MFS and BAV was not outlined; moreover, there was no additional information on this subset of patients. In a single-case report, Gershoni-Baruch, *et al*. informed on a patient of Jewish descent with concurrence of MFS and BAV in whom premature aging and primary hypogonadism were also present; during their clinical course, non-dissecting aortic ectasia was detected, but the patient died suddenly from pulmonary embolism.[7]

In the present study, in addition to the fact that all patients with MFS and BAV developed aortic dilation, in one half of these aortic dissection was also present. Moreover, three patients required surgical treatment, although only two underwent the latter. Despite the lack of significance, trends for association between BAV and aortic dilation, aneurysm, and dissection were found. These could suggest the possibility of synergistic effects between BAV and MFS for aortic wall damage. Aortic wall integrity is largely dependent on adequate arrangement of extracellular matrix proteins, and its disruption is associated with aortic dissections.[13] In MFS, mutant monomers of fibrillin-1 are misincorporated into microfibril, resulting in defective matrix proteins, and several mutations have been associated with aortic dilation.[11] Although the etiology of BAV remains unknown, it may arise from developmental defects of neural crest cells, which in turn results in premature vascular smooth muscle cell (VSMC) apoptosis.[4] In aneurysm tissue from patients with BAV, Nataamadja, *et al*. showed intracellular accumulation and reduction of extracellular distribution of fibrillin, fibronectin, and tenascin to a similar degree as that found in patients with MFS.[5] Additionally, up-regulation of matrix metalloproteinase-2 has been demonstrated into aortic tissue from both patients with MFS and those with BAV.[5] Deficiencies in extracellular matrix protein arrangement, increased aortic tissue matrix disruption, along with premature VSMC apoptosis appear to be synergistic factors resulting in aortic wall weakening, and might contribute to its dilation, dissection, and spontaneous rupture.

Unexpectedly, musculoskeletal and ocular involvement tends to be less prevalent in patients with BAV. The Walker-Murdoch sign was present in 82% of patients with MFS, while this was only observed in 25% of patients with MFS also with BAV (OR 0.07; 95% CI, 0.006-0.73). The retrospective study design did not allow us to determine whether BAV and arachnodactyly are segregated in an exclusionary manner, but a strong negative association cannot be denied.

The present study has some limitations. First, because our study cohort derives from a single cardiologic referral center, a selection bias cannot be excluded. Second, the number of patients with MFS and BAV was low, rendering it difficult to state reliably that the incidence of BAV is different from that of the general population. Finally, other methodological design as a cohort study conducted in a large population is required to either confirm or discard the observations found herein.

In conclusion, the prevalence of BAV in patients of Mexican/mestizo ethnicity with MFS is 4.5%, in comparison with only 1.5% in controls. While it is intriguing and even intuitive that the concurrence of both conditions would lead to more aggressive aortic disease, a true synergistic role for aortic wall weakening cannot be supported.

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