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Association between Psychiatric Disorders and Marfan's Syndrome in a Large Sardinian Family with a High Prevalence of Cardiac Abnormalities

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Summary

Background: Marfan's syndrome is an inherited disorder of connective tissue associated with characteristic abnormalities of the skeletal, ocular, and cardiovascular systems. Marked clinical variability and age dependency of all manifestations of Marfan's syndrome may render the unequivocal diagnosis difficult in mildly affected, young subjects.

Hypothesis: The study and care of a 32-year-old woman with evidence of Manfan's syndrome, several cardiac abnormalities, and paranoid schizophrenia led to an investigation of her consenting relatives to verify the penetrance of Marfan's syndrome and the degree of comorbidity between the disease and psychiatric disorders.

Methods: The patient and 12 subjects belonging to three generations of her family underwent cardiovascular, skeletal, ophthalmologic, and psychiatric examinations. Two-dimensional and Doppler echocardiography were performed.

Results: One female index patient and six of her first-degree relatives were found to be affected by Marfan's syndrome. All seven patients were found to have mitral valve prolapse associated with other cardiac abnormalities. Four of these patients were affected by the following psychiatric disorders: generalized anxiety disorder, major depressive disorder, paranoid schizophrenia (two cases). Six more relatives without Marfan's syndrome showed mitral valve prolapse in association with other echocardiographic features. Two of these were found to be affected by a major depressive disorder.

Conclusions: The present data support the hypothesis that a psychiatric condition, associated with a significantly high frequency of cardiac involvement, may be part of the phenotype of Marfan's syndrome.

Key words: connective tissue disease, cardiovascular findings, neuropsychiatric symptoms, schizophrenia

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Introduction

Marfan's syndrome is an inherited disorder of connective tissue associated with characteristic abnormalities of the skeletal, ocular, and cardiovascular systems.[1] The gene of fib-

TABLE I Clinical and echocardiographic features of patients with the Marfan's syndrome

Patient	Age/sex	Echo/Doppler					Eye	Skeletal	Skin and integument
		AAD (mm)	MVP	MR	TVP	Other			
I.1[a]	77/M	+ (47)	AL	+	–	PAV/LAE	–	A	IH
II.2[c]	41/F	+ (45.5)	AL/PL	+	LL/SL	MML	My	HAP	SD
II.5	34/F	–	AL	–	–	MML	–	PE/S/HAP	–
II.6[c]	32/F	+ (44)	AL/PL	+	LL/SL	MML/ AS/LAE	EL	PE/S/A	–
II.7[b]	27/F	+ (42)	AL	+	–	MML	–	PE/S	
III.3	14/F	–	AL/PL	+	–	MML/HS	My	S/HAP	–
III.4	12/F	–	AL/PL	+	LL/SL	MML	–	S/HAP	–

Association with psychiatric disorders:
[a] Generalized anxiety disorder.
[b] Major depressive disorder.
[c] Paranoid schizophrenia.
Ordinal numbers: generations (first, second, third). Cardinal numbers: patients (see family pedigree). II.6: the proband.
Abbreviations: A = arachnodactyly, AAD = ascending aorta dilatation, AL = anterior leaflet, AS = atrial septal aneurysm, EL = ectopia lentis, F = female, HAP = high-arched palate, HS = hypertrophy septum primum, IH: inguinal hernia, LAE = left atrium enlargement, LL = lateral leaflet, M = male, MML = myxomatous mitral leaflets, MR = mitral regurgitation (moderate to severe), MVP = mitral valve prolapse, My = myopia, PAV = prosthetic aortic valve, PE = pectus excavatum, PL = posterior leaflet, S = scoliosis, SD = striae distensae, SL = septal leaflet, TVP = tricuspid valve prolapse, + = present, – = absent.

rillin, a major glycoprotein component of the elastin-containing microfibrils found in the extracellular matrix, is the site of mutations causing the classic Marfan's syndrome in the majority of patients.[1] Marked clinical variability and age dependency of all manifestations of Marfan's syndrome may render the unequivocal diagnosis difficult in mildly affected, young subjects.

The study and care of a 32-year-old woman with evidence of Marfan's syndrome, several cardiac abnormalities, and paranoid schizophrenia led us to extend the investigation to her consenting relatives in order to verify the penetrance of Marfan's syndrome and the degree of comorbidity between the disease and psychiatric disorders.

Materials and Methods

On the basis of findings observed in the female index patient, we studied a further 12 subjects belonging to three generations of her family (three males and nine females, age 12 to 77 years). The study was approved by the Ethical Committee for Medical Research of our University, and all subjects gave informed consent for their participation. A complete family history was obtained. Each person underwent cardiovascular, skeletal, ophthalmologic, and psychiatric examinations. Two-dimensional and Doppler echocardiography was performed using an Acuson 128XP/S ultrasound system with a 2.5–3.5 MHz transducer. The presence of mitral or tricuspid valve prolapse and of ascending aorta dilatation was determined in accordance with previously published criteria.[2,3] In the index patient (II.6 in Table I) the diagnosis of Marfan's syndrome had been made on the basis of characteristic abnormalities in the skeleton (arachnodactyly, pectus excavatum, and scoliosis) and the cardiovascular system (ascending aorta dilatation, mitral valve prolapse with mitral regurgitation, myxomatous mitral leaflets, tricuspid valve prolapse, atrial septal aneurysm, and left atrium enlargement) and on identification of one major criterion (bilateral ectopia lentis with superior displacement);[4] in the other family members, because of the presence of one affected primary relative, the diagnosis of Marfan's syndrome was made on the basis of typical manifestations of the disease in the skeleton and in one of the other organ systems, according to the Berlin nosology of heritable disorders of connective tissue[4] (Table I).

A nitroprusside test performed in the proband and in other three first-degree relatives affected by Marfan's syndrome was negative for urinary homocystine.

Psychiatric evaluation for all patients was carried out at the same time of day in quiet, peaceful surroundings. The interviews were performed by trained psychiatrists and were well accepted by all patients. The diagnosis of psychiatric disorders was based on the DSM-III-R classification.[5]

Results

According to previously reported criteria, the diagnosis of overt Marfan's syndrome was made in six first-degree rela-

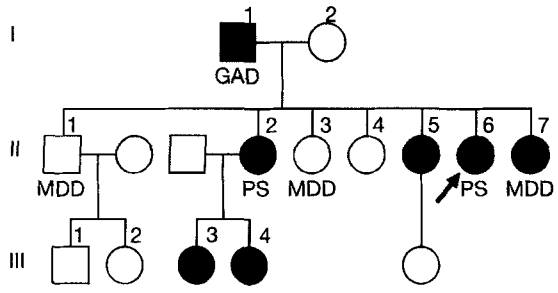

FIG. 1 Family pedigree. Squares = male family members, circles = female family members, black symbols = persons affected by Marfan's syndrome, white symbols = unaffected persons, and arrow = the proband. GAD = generalized anxiety disorder, MDD = major depressive disorder, PS = paranoid schizophrenia.

tives of the proband (her father, three sisters, 2 nieces). The family pedigree is shown in Figure 1.

The occurrence of different clinical features in all seven patients with Marfan's syndrome is summarized in Table I. Pathologic manifestations of the cardiovascular system and skeleton were documented in all subjects. Ocular manifestations occurred in three patients. All seven subjects with Marfan's syndrome were found to have mitral valve prolapse and several other cardiovascular lesions. They complained of easy fatigability, dyspnea, and palpitations. Four subjects with Marfan's syndrome were affected by the following psychiatric dis orders: generalized anxiety disorder, major depressive disorder, and paranoid schizophrenia (two cases; Table I). Three of these manifested the more severe and specific cardiac abnormalities. Furthermore, these psychiatric subjects complained of postural orthostatic phenomena, presyncope (II.2 and II.6 in Table I), and syncope (I.1).

Six other family members without overt Marfan's syndrome showed extracardiac (ocular or skeletal) and cardiac abnormalities, such as ascending aorta dilatation (three), mitral valve prolapse (five) combined with mitral regurgitation (two), myxomatous thickening of the mitral leaflets (three), and of septum primum (three). Two of these, suffering from myopia and scoliosis, ascending aorta dilatation, and mitral valve prolapse combined with mitral regurgitation, were affected by major depressive disorders (II.1 and II.3 in Fig. 1).

Discussion

Isolated cases of association between Marfan's syndrome and psychiatric disorders have been illustrated in the past.[6,7] Sirota *et al.*[7] reported five unrelated patients and three of their first-degree relatives who had both Marfan's syndrome and schizophrenia. They suggested that a schizophrenic condition may be part of the phenotype of a Marfan-like syndrome.

The present data show that Marfan's syndrome may include neuropsychiatric symptoms when associated with a considerable degree of cardiac involvement. The coexistence of cardiac and mental abnormalities was also found in family members whose phenotype did not meet diagnostic criteria for overt Marfan's syndrome, but who suffered from extracardiac findings consistent with a defect of the extracellular matrix.

Connective tissue diseases are a source of frustration for patients. The disease may cause a feeling of loss of personal efficiency due to physical disability, and possibly a shortened lifespan. In our study, this effect may have been emphasized by the coexistence of symptoms resulting from the multiple cardiac abnormalities of Marfan's syndrome. The latter may have led to mental symptoms that otherwise would have been unexpressed.

Nevertheless, the remarkable frequency of comorbidity between connective abnormalities and mental disorders among first-degree relatives of the same family might also suggest a specific susceptibility of Marfan's syndrome to psychiatric manifestations. Although we have no information of a genetic abnormality causing both diseases, and as schizophrenia and related disorders are known to be genetically hetereogeneous,[8] we can speculate that the two disorders may share a common primary etiology in selected families.

Finally, the rarity of this pathologic association in the literature compared with the high prevalence observed in the Sardinian family studied could suggest an ethnic interpretation of such specific comorbidity.

Conclusion

The present data support the hypothesis that a psychiatric condition, associated with a significantly high frequency of cardiac involvement, may be part of the phenotype of Marfan's syndrome.

While our data allow no firm conclusion and a causal relationship remains speculative at this time, the variables identified in the present study deserve more explicit attention in future studies of Marfan's syndrome and psychiatric disorders.

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