CLINICAL MANIFESTATIONS OF MARFAN SYNDROME IN A MIDDLE EAST COUNTRY: A CASE SERIES

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Abstract

Marfan syndrome is a genetic disorder characterized by cardiac, ocular, and skeletal manifestations. While cardiac disease, notably aortic dilation and dissection, determines life expectancy of the patients, other manifestations can help in early diagnosis which is essential for erly therapy and prevention of catastrophic events. Therefore, information about the relative frequency of each manifestation can be helpful. In different geographical regions, there may exist different mutations with different phenotypes.

In this study we interrogated manifestations of Marfan syndrome in a cohort of 23 Iranian patients. Positive wrist and thumb signs, hind foot valgus, down-slanting palpebras, and enophthalmos were the most frequent manifestations in this cohort. Ectopia lentis, aortic root dilation, and pes planus were less frequently seen than in western reports.

Awareness of the frequent manifestations of Marfan syndrome is crucial in early diagnosis of the patients which may significantly increase their life spans.

Keywords: aortic root dilation, aortic dissection, ectopia lentis, wrist sign, thumb sign

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Introduction

Marfan syndrome (MFS) is a genetic disorder with cardiac, ocular, and skeletal involvements. Mutations in FBN 1 gene cause this disease. However, incomplete penetrance of the gene, diversity of mutations and incomplete knowledge about all wild mutations make the diagnosis difficult and unreliable based only on genetic analysis. Therefore, complex criteria were created to diagnose this syndrome. The revised Ghent criteria were presented in 2010 and are one of the most reliable methods for diagnosis (1). Early detection of the syndrome and use of drugs to prevent aortic dilation can increase life expectancy (1). Therefore, clinical suspicion based on the skeletal and facial manifestations is very important especially in children.

Except rare cases with the diagnosis of neonatal MFS (2), prevalence of manifestations is age dependant (1). Up to the 20 years of age, the prevalence often increases with increasing age (3).

In this study, we examine patients referred to two university hospitals with the diagnosis of MFS based on revised Ghent criteria (1). Most features used in these criteria were interrogated in our patients, with addition of some other features. The aim was to show the relative importance of each feature in the diagnosis of MFS. An additional aim was whether the distribution of manifestations is different from that in western countries or not.

Methods

All patients with the diagnosis of MFS who were visited in the Marfan syndrome clinic of Rasoul Aram Hospital, or pediatric cardiology clinic of Children's Medical Center from April 2015 to March 2016 were included in this study. The patients who are not willing to participate in the study (or their parents in case of children) were excluded. Informed consent was obtained from the patients or their parents. Thorough skeletal and ophthalmic examinations, and echocardiography were performed for all patients. Skeletal and facial examinations were done by the coauthors. Echocardiography for children was done by one of the coauthors, while that for adult patients was done by adult cardiologists. Ophthalmologic examination was performed by ophthalmologists.

In echocardiography, we measured aortic root diameter at the sinuses of Valsalva in end-diastole from leading edge to leading edge. Z values were calculated using the values presented by Roman et al (4). Z values more than 2 were considered abnormal (1).

Family history of MFS and possible genetic testing were interrogated. Data were expressed as mean ± standard deviation and range.

Results

A total of 23 patients were enrolled in this study. Mean age of the patients was 19.9±12.2 years (range 3-46). Ten patients were under 18 years of age. There was a predominance of male patients (16 versus 7). Mean height was 157±31 cm (range 100-198). Mean weight was 47±24.5 kg (range 15-97). Familial history of MFS was positive in 12 patients. In two patients, genetic testing found mutation in FBN 1 gene. Both mutations were new and previously have not been reported.

Cardiac involvement: Mean aortic root diameter was 3.3±1.1 cm (range 2.2-7.5). Z score of aortic root diameter was ≥2 in 12 patients (52%). Valvar diseases included mitral valve prolapse in 13, mitral regurgitation in 9, aortic regurgitation in 5, and tricuspid valve prolapse in 5 patients.

Ocular involvement: Ectopia lentis (EL) was found in 12 patients (52%). No patient had normopia or hyperopia. Myopia more than +3 diopter was seen in 11 patients (48%). Mean M diopter in the right eye was 6.5±6.8 and in the left eye 6.4±6.8 (range in both eyes 0.25-19).

Facial involvement: Among the facial changes with diagnostic value for Ghent criteria, down-

slanting palpebra in 13, enophthalmos in 13, malar hypoplasia in 12, retrognatia in 5, and dolichocephalia in 3 patients were ween. Five patients had none of the above changes. Among the other facial changes, high ached palate in 16, crowded teeth in 8, and prognathism in 4 patients were seen.

Skeletal involvement: Thumb and wrist signs were the most frequent (each in 19 patients)(1). Sixteen patients had both signs, while only one patient had neither of them. Abnormal upper body segment to the lower ratio (<1) was found in 12 patients. Increased arm span to height ratio (>1.05) was found in 6 patients. Scoliosis and kyphosis were found in 12 and 9 patients, respectively. Only 6 patients had neither of them. While 10 patients had no chest deformity, pectus carinatum and excavatum were found in 8 and 5 patients, respectively. Hind foot valgus (16), pes planus (11), striae atrophicae (10), and reduced elbow extension (4) were the other skeletal abnormalities.

Past medical history: Two patients had a history of spontaneous pneumothorax. Two patients had a history of treated inguinal hernia.

Table 1: Distribution of manifestations of Marfan syndrome in the patients. The bold manifestations have diagnostic value in the revised Ghent criteria (1). US, upper body segment; LS, lower body segment.

Manifestation		Number(Percentage)
Cardiac	**Aortic root dilation**	12(52%)
	Mitral valve prolapse	13(57%)
	Mitral regurgitation	9(39%)
	Aortic regurgitation	5(22%)
	Tricuspid valve prolapse	5(22%)
Ocular	**Ectopia lentis**	11(48%)
	Myopia > +3	11(48%)
Facial	**Downslanting palpebra**	13(57%)
	Enophthalmos	13(57%)
	Malar hypoplaia	12(52%)
	Retrognatia	5(22%)
	Dolichocephalia	3(13%)
	high ached palate	16(70%)
	Crowded teeth	8(35%)
	Prognathism	4(17%)
Skeletal	**Arm/Height>1.05**	6(26%)
	US/LS<1	12(52%)
	Thumb sign	19(83%)
	Wrist sign	19(83%)
	Scoliosis	12(52%)
	Kyphosis	9(39%)
	Reduced elbow extension	4(17%)
	Pectus excavatum	5(22%)
	Pectus carinatum	8(35%)
	Pes planus	11(48%)
	Hind foot valgus	16(70%)
	Striae atrophicae	10(44%)
History	**Familial occurence**	12(52%)
	Pneumothorax	2(9%)
	Hernia	2(9%)

Discussion:

While the diagnosis of MFS in an adult with overt skeletal manifestations, EL, and cardiac involvement is relatively easy, it is much difficult in children with generally milder skeletal and ocular manifestations in spite of cardiac disease. Late diagnosis and late administration of drugs increase the risks of aortic injury or early need of aortic root surgery (1).

Although MFS patients are generally known with their skeletal characteristics (tall stature and long arms), these characteristics were not common in our patients and hence, not sensitive for diagnosis. In contrary, manifestations like wrist and thumb signs, hind foot valgus, down-slanting palpebras, and enophthalmos were more frequent in our cohort. These manifestations need a thorough examination or high suspicion to be recognized in a child. However, they are more sensitive tools for the diagnosis.

Limited genetic analysis in 2 patients showed that there are new mutations which are responsible for MFS in our country. Obviously, there may be phenotypic difference between Iranian and western MFS patients as well. Comparison of our results with those of Stheneur et al from France (259 MFS patients) shows that positive wrist (83 versus 48%) and thumb signs (83 versus 46%) were more frequent in our patients, while pes planus (71%), EL (64%), and aortic root dilation (80%) were more commonly seen in their patients (3).

Roman et al presented phenotypic data in 183 children and 606 adults with MFS (5). Genetic study helped in the diagnosis in only 17% of the patients. Aortic root dilation was surprisingly more prevalent in their patients (90 and 88% in children and adults, respectively). The other significant difference was in the prevalence of pectus excavatum deformity (33% in children and adults). Manifestations with similar frequency in comparison to our cohort were family history of MFS, EL, pectus carinatum, spontaneous pneumothorax, scoliosis, skin striae, and mitral valve prolapsed (5).

Wozniak-Mielczarek et al from Poland found a higher rate of aortic dilation (75 and 86% in children and adults, respectively) than us (6). While mitral valve prolapse (57 and 53% in children and adults, respectively) was as frequent as in our cohort, mitral (45 and 77% in children and adults, respectively) and aortic regurgitations (26 and 37% in children and adults, respectively) were more frequent (6).

In spite of higher prevalence of aortic root dilation in the above reports, Detaint et al from France reported a prevalence of 53% in 1013 FBN 1 mutated patients at the age of 30 years, which is similar to our results (7). Mitral valve prolapse and regurgitation were seen in 43 and 24% of patients at 30 years of age, respectively. These values are lower than those in our cohort.

The difference in the prevalence of cardiac or extracardiac abnormalities among different reports may be caused by different study designs, different methods of measurement or definition of disease, or a true genotypic difference.

Limitations

This is a small cohort of MFS patients. Genetic analysis is not done in our country and blood samples should be sent abroad. The high expense of this test is not covered by insurance companies and most patients can not afford it. Hence, only 2 patients had genetic analysis in our cohort.

Conclusions

High suspicion is needed for the diagnosis of MFS, especially in children. MFS in Iran may have some genotypic and phenotypic differences with that in western countries.

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professor and a source of inspiration for his MFS patients, unfortunately passed away during aortic operation for the complications of his MFS in September, 2021. May his soul rest in peace!

Resumo

Marfan sindromo estas genetika malsano karakterizita per koraj, okulaj kaj skeletaj manifestiĝoj. Dum kormalsano, precipe aorta dilatiĝo kaj dissekcio, determinas vivdaŭron de la pacientoj, aliaj manifestiĝoj povas helpi en frua diagnozo kiu estas esenca por komenco de terapio kaj preventado de katastrofaj okazaĵoj. Tial, informoj pri la relativa ofteco de ĉiu mani- festiĝo povas helpi. En malsamaj geografiaj regionoj, povas ekzisti malsamaj mutacioj kun malsamaj fenotipoj.

En ĉi tiu studo ni pridemandis manifestiĝojn de Marfan sindromo en kohorto de 23 iranaj pacientoj. Pozitivaj pojnokaj dikfingrosignoj, malanta- ŭpieda valgo, malsupren-deklivaj palpebroj, kaj enoftalmo estis la plej oftaj manifestiĝoj en tiu kohorto. Ektopio lensa, aorta radikdilatiĝo, kaj plata piedo estis malpli ofte viditaj ol en okcidentaj raportoj.

Konscio pri la oftaj manifestiĝoj de Marfan sindromo estas esenca por frua diagnozo de la malsano kio povas multe pliigi iliajn vivdaŭrojn.

References

1. Loeys BL, Dietz HHC, Braverman AC, et al. The revised Ghent nosology for the Marfan syndrome. J Med Genet 2010;47:476-485.

2. Ghandi Y, Zanjani KS, Mazhari-Mousavi S, Parvaneh M. Neonatal Marfan syndrome: Report of two cases. Iran J Pediatr 2013;23:113-117.

3. Stheneur C, Tubach F, Jouneaux M, et al. Study of phenotype evolutionduring childhood in Marfan syndrome to improve clinical recognition. Genet Med 2014;16: 246- 250.

4. Roman MJ, Devereux RB, Kramer-Fox R, O'Loughlin J. Two-dimensional echocardiographic aortic root dimensions in normal children and adults. Am J Cardiol 1989; 64:507–512.

5. Roman MJ, Devereux RB, Preiss LR, et al. Association of age and sex with Marfan phenotype. The national heart, lung, and blood institute GenTAC (genetically triggered thoracic aortic aneurysms and cardiovascular conditions) registry. Circ Cardiovasc Genet 2017;10: 1-8.

6. Wozniak-Mielczarek, Sabiniewicz R, Drezek-Nojowicz, et al. Differences in cardiovascular manifestation of Marfan syndrome between children and adults. Ped Cardiol 2019;40:393-403.

7. Detaint D, Faivre L, Collod-Beroud G, et al. Cardiovascular manifestations in men and women carrying a FBN1 mutation. Eur Heart J 2010;31:2223-2229.