Eastern Journal of Medicine 16 (2011)248-252

Original Article

Retrospective analysis of cardiac manifestations of our patients with marfan syndrome

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Abstract. Marfan syndrome (MS) is an autosomal dominant connective tissue disorder affecting mainly cardiovascular system, eyes and skeleton. However, the most serious complication in patients with MS is progressive aortic root dilatation, aortic dissection or regurgitation. We have reviewed all patients with MS in our hospital over a six year period to determine the symptoms, clinical aspects, treatment modalities and long term follow-up. The medical records of all patients with MS in Yuzuncu Yil University Department of Cardiology from January 2004 to May 2010 were reviewed. MS was defined by Ghent criteria. Individuals without a family history of MS require major criteria in at least two different organ systems and involvement of a third organ. Individuals carrying an FBN1 mutation known to cause MS or cases with a positive family history require one major criterion and involvement of an additional organ to diagnosis of MS. Eleven patients have diagnosis of MS according to Ghent criteria. Patients with mean age of 37.5 years. In our patient group wasn't a presence woman. Main complaint of patients was dispnea. Primary findings in physical examination were apical systolo-diastolic murmur, mediastinal enlargement at chest X-ray. Aortic root dilatation, aortic regurgitation was seen echocardiographically. Mean follow-up time was 3.8 years. During follow-up six patients died. Main cause of die was aortic complication. Early detection and close monitoring of the MS are very important for prevent complications. MS patients should be followed closely especially in terms of cardiovascular complications.

Key words: Marfan syndrome, cardiac manifestation

1. Introduction

Marfan syndrome (MS) is an autosomal dominant connective tissue disorder affecting mainly cardiovascular system, eyes and skeleton (1). The estimated prevalence of MS is one in 5–10,000 (2). About 25% of cases have no family history and their syndrome is the result of sporadic mutation (3,4). Clinical spectrum of the MS, ranging from mild musculoskeletal or ocular manifestations to severe neonatal presentation (2).

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Received: 05.11.2010
Accepted: 24.05.2011

In the past three decades there has been significantly advancement in the diagnosis and treatment of MS. Marfan syndrome mortality from aortic complications has decreased (from 70% to 48% in nowadays and life expectancy has increased (5,6).

The diagnosis of Marfan syndrome more consistent and of more prognostic value, the Berlin Nosology of Heritable Disorders of Connective Tissue was published in 1988 (7). Under the headings cardiovascular, skeletal, ocular, pulmonary, skin and nervous system it lists four major manifestations-aortic dissection, ectopia lentis, dilatation of the ascending aorta, and dural ectasia-and a host of minor manifestations including arrhythmia and endocarditis. The Berlin nosology has been replaced by the Ghent criteria (8) that include the same major cardiovascular manifestations.

Table 1. Ghent criteria to diagnosis of Marfan Syndrome

Major criterion	Minor criterion
Skeletal System Pectus carinatum Pectus excavatum requiring surgery Reduced upper to lower segment ratio or arm span to height ratio > 1.05 Positive wrist and thumb signs Scoliosis of > 20° or spondylolisthesis Reduced extension of the elbows (< 170°) Medial displacement of the medial malleolus causing pes planus Protrusio acetabulae of any degree (on X-ray)	Pectus excavatum of moderate severity Joint hypermobility Highly arched palate with dental crowding Facial appearance (dolicocephaly, malar hypoplasia, enophthalmos, retrognathia, down-slanting palpebral fissures) *For the skeletal system to be involved, at least two of the components comprising the major criterion, or one component comprising the major criterion plus two of the minor criteria must be present.*
Ocular System Ectopia lentis	Abnormally flat cornea (as measured by keratometry) Increased axial length of globe (as measured by ultrasound) Hypoplastic iris or hypoplastic ciliary muscle causing a decreased miosis *For the ocular system to be involved, at least two of the minor criteria must be present.*
Cardiovascular System Dilatation of the ascending aorta with or without aortic regurgitation and involving at least the sinuses of Valsalva, or Dissection of the ascending aorta	Mitral valve prolapse with or without mitral valve regurgitation Dilatation of main pulmonary artery, in absence of valvular or peripheral pulmonic stenosis or any other obvious cause, under the age of 40 years Calcification of the mitral annulus below the age of 40 years, or Dilatation or dissection of the descending thoracic or abdominal aorta below the ageof 50 years *For the cardiovascular system to be involved, a major criterion or only one of the minor criteria must be present*
Pulmonary System None	Spontaneous pneumothorax, or Apical blebs (ascertained by chest radiography) *For the pulmonary system to be involved, one of the minor criteria must be present.*
Skin and Integument Lumbosacral dural ectasia by computed tomography or magnetic resonance imaging	Striae atrophicae (stretch marks) not associated with marked weight changes, pregnancy or repetitive stress, or Recurrent or incisional herniae *For the skin and integument to be involved, the major criterion or one of the minor criteria must be present.*
Family History 1.Having a parent, child, or sibling who meets the diagnostic criteria MS 2. Presence of a mutation in FBN1 known to cause the Marfan syndrome, or Presence of a haplotype around FBN1, inherited by descent, known to be associated with unequivocally diagnosed Marfan syndrome in the family	None *For the family history to be contributory, one of the major criteria must be present*

Diagnosis, follow-up plan and treatment strategy for MS require a multidisciplinary team. The team should include cardiologist, ophthalmologist, orthopedic surgeon and geneticist. In order to decrease aortic dissection or rupture once a clinical diagnosis of MS is established, it is crucial to place the patient on routine plan of aortic dilatation monitoring (9).

We have reviewed all patients with MS in our hospital over a six year period to determine the symptoms, clinical aspects, treatment modalities and long term follow-up.

2. Method

The study was approved by the Yuzuncu Yil University Faculty of Medicine Ethics Committee in accordance with the Declaration of Helsinki. The medical records of all patients with MS of our department from January 2004 to May 2010 were reviewed.

Marfan syndrome was defined by clinical and Ghent criteria (8). Ghent criteria was wrote Table 1. Individuals without a family history of MS require major criteria in at least two different organ systems and involvement of a third organ. Individuals carrying an FBN1 mutation known to cause MS or cases with a positive family history require one major criterion and involvement of an additional organ to diagnosis of MS (10). Adaptation of referance 8.

3. Results

Eleven patients have diagnosis of MS according to Ghent criteria. Patients with mean age of 37.5 years. All of patients were man and hadn't family history. Main complaint of patients was dispnoea. Primary findings in physical examination were apical systolo-diastolic murmur, mediastinal enlargement at chest X-ray. Aortic root dilatation, aortic regurgitation was seen echocardiographically. Mean follow-up time was 3.8 years. During follow-up six patients died. Main cause of die was aortic complication. Characteristics of patients with MS were summarized Table 2.

Table 2. Characteristics of our patients with Marfan syndrome

	Year	Symptom	Laboratory Results	Treatment	Follow-up	Outcome
1	18	None	Aortic root 3.9 cm and bicuspid aorta mild aortic regurgitation	Beta blocker	4.4 year, no complication	Survival
2	46	Dispnoea	Aortic root 4.4 cm, mild aortic regurgitation	Beta blocker	2.9 year, no complication	Survival
3	42	Palpitation	Aortic root 5.4 cm	Beta blocker and advised surgery	3.4 year, Denied surgery	Death
4	33	Palpitation	Aortic root 4.1 cm, mild aortic and mitral regurgitation	Beta blocker	4.7 year, no complication	Survival
5	51	Dispnoea Palpitation	Aortic root 7.9 cm, (figure 1), severe aortic and moderate mitral regurgitation	Aortic root surgery	Patient died after surgery	Death
6	27	None	Aortic root 3.8 cm	Beta blocker	5.2 year, no complication	Survival
7	24	None	Mitral valve prolapse, aortic root 3.6 cm	Beta blocker	3.9 year, no complication	Survival
8	45	Dispnoea	Aortic root 4.9 cm,	Beta blocker and Aortic root surgery	2.5 year, Denied surgery	Death
9	54	Dispnoea Palpitation	Aortic root 6.3 cm, severe aortic and mitral regurgitation	Aortic root surgery and mitral valve replacement	Patient died because of left ventricular failure	Death
10	44	Dispnoea	Aortic root 4.4 cm and sinus valsalva rupture	Aortic root surgery	3.6 year, Patient died three year after surgery	Death
11	29	Cardiac arrest	Spontaneous pneumotorax	Pleural tube	Aortic dissection developed during intensive care unit	Death

(Age: year, Follow-up: year, Laboratory results: Echocardiography and chest X-ray)

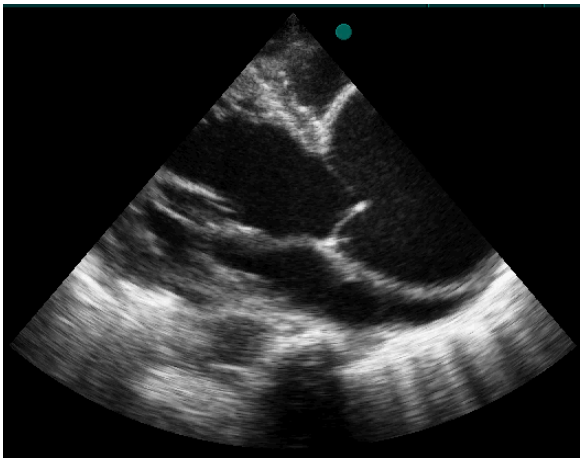

Fig. 1. Huge aortic root in patient with Marfan Syndrome.

4. Discussion

We stated that in this paper, eleven patients have diagnosis of MS according to Ghent criteria. Six patients died during follow-up because of cardiovascular complication.

Marfan syndrome is autosomal dominant connective tissue disorder, which is potentially life-threatening because of cardiovascular manifestations (11). Dilatation of the aortic root is well-known cardiovascular manifestation in MS. Before the advent of prophylactic aortic root surgery, most patients died prematurely (12,13). There is a clear association between increased diameter and the risk of dissection and rupture in this condition: the risk of rupture of a 6-cm aneurysm is 4-fold (14). The recommended aortic diameter for prophylactic surgery is 5 cm (14,15). In our study group we recommended that prophylactic surgery for three patients because of aortic dilatation (patient 3 (aortic root 5.4 cm), patient 5 (aortic root 7.9 cm), patient 8 (aortic root 4.9 cm).

The rate of acute aortic dissection is directly proportional to the maximum diameter of the aorta. Elective surgery to repair the aortic root is recommended when the maximum aortic diameter reaches 5 cm. Additional considerations include the rate of aortic growth and family history of aortic dissection less than 5 cm. In those circumstances a 4.5 cm diameter will be an indication for elective surgery (13).

Dissection involving the ascending aorta is an absolute indication for operation to replace the aortic root in MS. Aortic dissection, occurs in up to 20% of Marfan patients. In this condition, aortic valve incompetence may occur due to dilatation of the sinotubular junction with acute distraction of the valve leaflets, and/or unhinging and prolapse of the leaflets secondary to sinus wall dissection (16). One patient had aortic dissection in our group.

Published studies have shown benefit of treatment with beta blockers in MS (17,18). Beta-adrenergic receptor blockade to delay or prevent aortic aneurysm and dissection is currently regarded standard care of patients with the MS. The only randomized trial assessing the effect of beta-blockade was published in 1994 (18); using propranolol fewer patients reached a primary clinical endpoint of aortic regurgitation, aortic dissection, cardiovascular surgery, congestive heart failure and death. Furthermore, the normalized rate of aortic dilatation was lower in the propranolol group than in the control group. It is important to remember that around 10–20% of patients with MS are intolerant to beta-blockers due to chronic obstructive lung disease, depression and fatigue. For such patients, a trial of verapamil should be instituted based on the study that showed that treatment with verapamil can slow aortic growth rate (18). Because none of the patients was intolerant to beta-blockers we prescribed metoprolol for all patients appropriate dosage (mean 75±25 mg)

It is also important that aortic growth is not stopped or reversed but is slowed with beta blocker treatment. Australian study claimed that a regimen of standard betablocker with angiotensin-converting enzyme inhibitors (perindopril) reduced aortic stiffness and aortic diameter with MS (19). In the setting of aortic enlargement, even though the patient is under treatment with pharmacological agents, vigilance for further aortic enlargement with at least yearly measures of aortic dimensions is indicated. Theoretical reasons suggest considering ACE inhibitors or angiotensin II receptor blockers. Vascular muscle cell apoptosis has been implicated in the cystic medial degeneration seen in the MS aorta and both types of drug have been shown to inhibit vascular smooth muscle cell apoptosis in cultured Marfan aortic media cells (20).

In conclusion, early detection and close monitoring of the MS are very important for prevent complications. MS patients should be followed closely especially in terms of cardiovascular complications. Aortic root diameter, the rate of aortic growth and family history of aortic dissection are very important for decision of elective surgery (13).

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