Clinical Presentation and Echocardiographic Findings of Thai Patients with Marfan Syndrome

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Objective: *Marfan syndrome is an inherited disorder with systemic connective tissue involvement. The condition is clinically diverse and extremely pleiotropic. Though several articles had been published, no data from Thai individuals has ever been reported. Here we presented clinical manifestations and echocardiographic findings of Thai patients with Marfan syndrome.*
Material and Method: *Clinical and echocardiographic data were collected from series of Thai index cases with diagnosis of Marfan syndrome at Siriraj Hospital between 1995 and 2009. Demographic data, clinical presentations, and echocardiographic data were reviewed and analyzed.*
Results: *Fifty individuals and thirty echocardiograms were identified. Thirty eight individuals (76%) fulfilled clinical criteria for definite Marfan syndrome and twelve individuals (24%) were incomplete Marfan syndrome. The majority of those individuals had significant organ involvement including dilatation of ascending aorta (78%), ectopia lentis (54%), and skeletal involvement (96%).*
Conclusions: *In summary, this is the first report of clinical manifestation and echocardiographic findings of Thai patients with Marfan syndrome*

Keywords: *Aortic dilatation, Aortic regurgitation, Ectopia lentis, Lens, Subluxation*

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Marfan syndrome (MFS) (MIM 154700) is an autosomal dominant disorder of fibrous connective tissue with various organ involvements mainly in cardiovascular, ocular and skeletal system. The incidence is estimated to be 1 in 10,000. The MFS gene locus was mapped to chromosome 15q21.1. Subsequently, germline mutations in the fibrillin-1 gene (FBN1) were reported to be responsible for the susceptibility to MFS. The cardinal manifestation of MFS appears in 3 main systems. However, the disease shows striking pleitropism and variable clinical expressivity[1]. Widely accepted criteria for clinical diagnosis of MFS have been established but some of the features are age dependent. The condition is also not common in general practice and physician may not be familiar with the disease presentation. As the result, many MFS patients are overlooked during both childhood and early adulthood. Progressive cardiovascular abnormality is the principle cause of death among individuals with MFS. Prophylactic medical and surgical intervention is important in reducing cardiovascular morbidity and mortality[2]. Therefore, the ability to make diagnosis and initiate proper management is crucial in treating and preventing complication of this condition. There have been several articles of clinical manifestation of MFS but mostly from Western populations. Moreover, no clinical description of Thai patients with MFS has ever been reported. In this study, we report the clinical manifestation and echocardiographic parameters of Thai individuals with Marfan syndrome.

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Material and Method

Clinical evaluation

The research protocol was approved by the Siriraj Institutional Review Board. The study was con-

ducted according to the Declaration of Helsinki principles. Patients and their families were referred or consulted to Division of Medical Genetics for evaluation of MFS clinical diagnosis and counseling between 1995 and 2009. All patients were evaluated at Siriraj Hospital. Detailed physical examination, particularly in the ocular, cardiovascular and skeletal systems, was performed by geneticists, cardiologists and ophthalmologists, who were experienced of MFS, as standard of care. Diagnosis of MFS was made based upon Ghent's clinical criteria[3]. At least 2 systems with major criteria plus one additional system involvement, either major or minor, are required for diagnosis of 'definite MFS'. Incomplete MFS is defined when only 2 organ systems are involved with at least one being the major criterion. Clinical phenotypes of at least one organ system involvement but do not fulfill those definitions are considered 'possible MFS'.

Echocardiography

Each patient underwent transthoracic echocardiography to evaluate the cardiovascular anatomy and function at the echocardiographic laboratory of Siriraj Hospital. The measurement was performed on 3-5 consecutive cardiac cycles and the average value was used for the statistical analysis. Two-dimensional, M-mode and Doppler echocardiography were performed using standard technique. The left ventricular (LV) end-systolic and end-diastolic dimensions were measured using M-mode tracing. The LV ejection fraction was determined using the Modified Simpson's rule (biplane) and Teicholtz's method. Significant pulmonary hypertension was defined as estimated right ventricular systolic pressure more than 50 mmHg. Size of aortic root was measured at aortic valve, sinus, sinotubular and tubular level. LV systolic dysfunction was defined as LV ejection fraction less than 40%.

Results

Clinical findings

A total of fifty families were included in the study. In order to represent true clinical presentation without ascertainment bias from expanded early diagnosis among family members, only clinical data from probands were collected and analyzed. There were 25 males and 25 females with mean age at diagnosis of 30 years (range 16-51 years). Of those fifty probands, 38 individuals (76%) fulfilled clinical criteria for definite MFS and 12 individuals (24%) were defined as incomplete MFS. Subluxation of lens (ectopia lentis) was the presenting symptom and sign in 18 individuals (36%). Fifteen individuals (30%) were presented with symptoms and signs of aortic valve regurgitation. Among seven individuals initially evaluated for skeletal problems, four were presented with scoliosis while the remaining (one individual each) had pectus deformity, flat feet and joint laxity as their chief complaints. Aortic dissection and mitral valve prolapse were the first manifestation in 2 individuals. One individual had pneumothorax as the initial presentation.

Among organ system involvement of MFS, thirty-nine individuals (78%) had dilatation of ascending aorta. Of those patients, seven also had aortic dissection. Ectopia lentis was identified in 27 individuals (54%). Forty-eight individuals (96%) had skeletal involvement but only 16 of them (32%) fulfilled major criteria, which required patients to have at least 4 out of 7 skeletal findings. It is of interest that MFS is a heritable condition; however, only 25 probands had family history of MFS.

Echocardiographic findings

Due to limitation in data archiving within period of the study span across cohort, thirty echocardiographic videotape records were available for review. The mean LV ejection fraction of affected individuals was $65.8 \pm 9.7\%$. None of them had LV systolic dysfunction. The LV end-systolic and end-diastolic dimensions were 33.8 ± 8.9 and 53.1 ± 9.5 mm, respectively. Mitral valve prolapse was detected in 4 patients and one patient associated with significant mitral regurgitation. Aortic regurgitation was identified in 13 patients and the degree was determined severe in 4 patients. Significant pulmonary hypertension was identified in 2 patients; one with severe mitral regurgitation and the other with severe aortic regurgitation. The size of the aortic root was shown in Table 3.

Discussion

In this study, we reported for the first time the clinical presentation and echocardiographic findings from Thai patients with MFS. We found that mean age of diagnosis was higher than western individuals with MFS[4]. The reason for late diagnosis was likely due to lack of medical attention among affected individuals as well as medical personnel who were not familiar with the condition. Our data also showed that all patients are symptomatic and most of them had already manifested significant major organ involvement and fulfilled Ghent's clinical criteria for definite MFS at time of diagnosis. Since only individuals who got first seen in adult period were included, the late diagnosis could also be

caused by ascertainment bias as childhood MFS was identified and treated early. Another possible reason for late diagnosis is that some affected individuals may have less severe clinical phenotype or those organ dysfunctions may present later on.

Table 1. Clinical presentation of 50 patients with MFS

Clinical Characteristics		
Age at diagnosis	30 years (16-51 years)	
Presenting signs/symptoms		
Ophthalmological system	19	(38%)
Ectopia lentis	18	(36%)
Severe myopia	1	(2%)
Cardiovascular system	19	(38%)
Aortic valve regurgitation	15	(30%)
Aortic dissection	2	(4%)
Mitral valve prolapse	2	(4%)
Skeletal system	7	(14%)
Scoliosis	4	(8%)
Pectus deformity	1	(2%)
Pes planus	1	(2%)
Joint laxity	1	(2%)
Other complaints	2	(4%)
Pneumothorax/Dyspnea	2	(4%)
Undetermined/Unknown	3	(6%)

Table 2. Organ system involvement in patients with MFS

Number of individuals with organ system involvement		
Cardiovascular system	41	(82%)
Ophthalmological system	36	(72%)
Skeletal system	48	(96%)
Others	11	(22%)
Cutaneous striae	8	(16%)
Pneumothorax	1	(2%)
Hernia	1	(2%)
Hip dislocation	1	(2%)
Presence of involved 'major' organ		
Aortic root dilatation at Sinus of Valsava	39	(78%)
With Aortic dissection	7	(14%)
Ectopia lentis	27	(54%)
At least 4 in 7 skeletal findings	16	(32%)
Family history	25	(50%)

Table 3. Aortic root diameter

Level	Size of Aortic root (cm) (Mean $\pm$ SD)
Aortic valve	2.5 ± 0.5
Aortic sinus	4.1 ± 1.1
Sinotubular junction	3.3 ± 1.1
Tubular part	3.5 ± 1.4

Clinical manifestations of MFS are various among affected individuals. Ectopia lentis was the most common presentation and the main reason for referral in our report. Patients may complain with sudden or gradual decrease in visual acuity, eye pain or headache due to secondary glaucoma. Subluxation of lens tends to be bilateral and usually develops asymptomatically during childhood.

Cardiovascular involvement remains the most common morbidity and mortality among patients with MFS[5]. The major cardiovascular manifestations of MFS are aortic dilation, which may involve the proximal and distal aorta, aortic regurgitation, aortic dissection, mitral valve prolapse, and mitral regurgitation. Though 38% of individuals presented with mitral or aortic valve disease including dissection of ascending aorta, aortic root dilatation was seen in 78% of cases. Therefore, detailed cardiovascular examination including echocardiographic investigation is crucial in diagnosis and follow-up affected individuals with MFS. Two-dimensional and Doppler echocardiography is an integral part of the evaluation of patients with MFS. Serial echocardiography should be performed in patients with MFS to measure the diameter of aortic root and aorta as the risk of aortic dissection, which is the most serious manifestation of MFS, increases as the aorta enlarges. Also, the findings from echocardiography can detect the presence of aortic dissection and evaluate the severity of aortic and mitral regurgitation that commonly complicate MFS.

While skeletal involvement was probably the most obvious clinical finding as it was seen in almost all patients, only one-third of cases had at least 4 in 7 clinical features which indicated major skeletal involvement. This result may be explained by the fact that many MFS do not have thin and tall body habitus and most MFS patients do not present all skeletal features. Furthermore, special imaging for protusio acetabulae, one of seven defined skeletal involvements, was not routinely performed[6].

Other minor organ involvement in our series included cutaneous features and pneumothorax were similar to other previous reports.

It had been noted that 50% of patients in our report did not have family history of MFS. Higher rate of sporadic cases, comparing to typically 25-30% seen in other series, could be from limited information from other members. Since patient's family size tends to be

large, it was not possible to obtain clinical history and detailed examination from every individual to confirm or exclude MFS. Among patients studied for this report, 24% were categorized as incomplete MFS, which requires one additional major feature to fulfill Ghent's clinical criteria. However, dural ectasia, one of the major organ involvements, produces no symptom in most individuals with MFS and it was not routinely investigated[7,8]. Interestingly, data from a large pool of adults with MFS showed that dural ectasia was the most prevalent clinical findings, followed by ectopia lentis[9]. Furthermore, a large study of MFS mutation detection recently found that the presence of at least 3 features, with at least one being major criterion, would be sufficient to achieve high mutation detection rate in FBN1[10]. Taking these results together, it is possible that most incomplete MFS with 2 organ system involvement could be definite MFS, after spinal imaging was performed.

In conclusion, we present clinical presentation and echocardiographic findings of Thai adult individuals with MFS. Careful history taking and detailed examination in major organ systems should be done to establish the diagnosis, evaluate severity and plan for life-long treatment.

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การแสดงออกทางคลินิก และลักษณะที่พบจากการตรวจคลื่นเสียงสะท้อนหัวใจ ของผู้ป่วยกลุ่มอาการมาร์แฟนในคนไทย

มานพ พิทักษ์ภากร, นิธิมา เชาวลิต

กลุ่มอาการมาร์แฟน เป็นโรคพันธุกรรมที่เกิดจากความผิดปกติของเนื้อเยื่อเกี่ยวพันตามระบบ ลักษณะทางคลินิกของผู้ป่วยกลุ่มอาการมาร์แฟนมีความหลากหลาย และสามารถแสดงออกถึงความผิดปกติในหลายอวัยวะ แม้จะมีรายงานของผู้ป่วยกลุ่มอาการมาร์แฟนในหลายการศึกษา ยังไม่มีรายงานลักษณะทางคลินิกของผู้ป่วยไทยมาก่อน ผู้วิจัยจึงนำเสนอลักษณะทางคลินิกและการตรวจด้วยคลื่นเสียงสะท้อนหัวใจของผู้ป่วยไทยที่ได้รับการวินิจฉัยกลุ่มอาการมาร์แฟน โดยรวบรวมผู้ป่วยที่ได้รับการตรวจและวินิจฉัยในโรงพยาบาลศิริราช ระหว่างปี พ.ศ. 2538 จนถึง พ.ศ. 2552 และรวบรวมข้อมูลพื้นฐาน, ลักษณะทางคลินิก และข้อมูลจากการตรวจคลื่นเสียงสะท้อนหัวใจ เพื่อทำการวิเคราะห์

***ผลการวิจัย**: คณะผู้วิจัยรวบรวมข้อมูลทางคลินิกจากผู้ป่วยจำนวนทั้งสิ้น 50 ราย และการตรวจคลื่นเสียงสะท้อนหัวใจในผู้ป่วยจำนวน 30 ราย พบว่าผู้ป่วย 38 ราย (ร้อยละ 76) มีลักษณะครบตามเกณฑ์การวินิจฉัย ผู้ป่วย 12 ราย (ร้อยละ 24) ได้รับการวินิจฉัยกลุ่มอาการมาร์แฟนชนิดไม่สมบูรณ์ ผู้ป่วยส่วนใหญ่มีการแสดงออกถึงความผิดปกติของระบบต่าง ๆ ได้แก่ ภาวะหลอดเลือดแดงใหญ่ส่วนต้นโป่งพอง (ร้อยละ 78), ภาวะแก้วตาเลื่อน (ร้อยละ 54) และความผิดปกติของระบบกระดูก (ร้อยละ 96)*

***สรุป**: คณะผู้วิจัยรายงานลักษณะทางคลินิกและการตรวจคลื่นเสียงสะท้อนหัวใจของกลุ่มอาการมาร์แฟนในคนไทยเป็นครั้งแรก*