# A 23-year-old woman with Marfan syndrome and spine deformity (RCD code: I-2A.1)

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## Abstract

Marfan syndrome is one of the most common heritable connective tissue disorders that is caused by various mutations of the Fibrillin-1 (FBN1) gene. The cardinal features of Marfan syndrome are aortic root dilatation and ectopia lentis, but the abnormalities may also concern other cardiovascular problems as well as musculoskeletal and central nervous systems, eyes, lungs and skin. Due to the high prevalence of disease the diagnosis and treatment may be often complicated. We present a 23-year-old female with Marfan syndrome and severe thoracic scoliosis, after the procedures of insertion of corrective rods in the past, who came to medical attention due to enlargement of the bulb of the aorta over 4-year period observation. The patient was treated conservatively and until present she remains uneventful. We discuss the common presentation, diagnostic tools, and treatment options for patients with Marfan syndrome based on most recent literature and guidelines. JRCD 2013; 1 (3): 36–42

**Key words:** fibrillin mutation, aortic root dilatation, skeletal deformity

## Background

Marfan syndrome is one of the most common inherited disorders of the connective tissue, transmitted as an autosomal dominant trait, with the prevalence of 2 to 3 per 10 000 population [1]. It is characterized by clinical variability and pleiotropic manifestations – from isolated features to severe neonatal presentation. It involves abnormalities of the cardiovascular, musculoskeletal, and central nervous systems, eyes, lungs, and skin. [2]

Typical characteristics of Marfan syndrome are associated with various mutations of the fibrillin-1 (FBN1) gene [2]. However, there are also cases of Marfan syndrome, where no mutation in FBN1 is identified (10%) [1]. In some of these patients, mutation in the gene for transforming growth factor-β receptor may be responsible [2].

FBN1 gene is located on chromosome 15q-21.1, and it encodes extracellular matrix protein called fibrillin. It is a major component of elastic and nonelastic connective tissues [2]. Mutation of the FBN1 gene leads to widespread fragmentation of usually thin, elastic fibers, causing abnormalities in the formation of collagen, and, consequently, weakening the connective tissue [2]. Other frequent histologic features include cystic medial necrosis, fibrosis, and loss of the smooth muscle cells [3]. All of the above characteristics are not specific for Marfan syndrome; however, they are more commonly found in microscopic examinations in patients operated for ascending aortic aneurysms who have Marfan syndrome than in those with ascending aortic aneurysms and without Marfan syndrome [3].

The cardinal features of Marfan syndrome are aortic root dilatation and ectopia lentis [4]. The various other systemic features support the diagnosis. In 1996, the stringent criteria for the diagnosis of Marfan syndrome (Ghent nosology) were proposed [5]. They were based on the recognition of both "major" and "minor" clinical manifestations involving the skeletal, cardiovascular, and ocular systems, and the dura [5]. The major criteria included ectopia lentis, aortic root dilatation involving the sinuses of Valsalva or aortic dissection, and lumbosacral dural ectasia (found in computed tomography [CT] or magnetic resonance imaging [MRI]), family or genetic history, and 4 of 8 typical skeletal manifestations. However, the criteria had their limitations. The validation of these criteria was insufficient; moreover, they could not be applied to children and required expensive and specialized evaluation [4]. As a result, in 2010, the revised Ghent nosology was introduced (Table 1), underlining the importance of aortic root aneurysm/dissection and

ectopia lentis as the cardinal clinical features of Marfan syndrome and of testing for mutations in FBN1 and other relevant genes [4].

## Multisystemic abnormalities

### Cardiovascular system

Aortic root dilatation is found on echocardiography in 60% to 80% of the patients with Marfan syndrome [1], and it is often accompanied by aortic regurgitation [1]. In most cases, dilatation affects the root of the aorta, but it may be found in any part of the thoracic or abdominal aorta. It may also include the carotid and intracranial arteries.

Aortic root aneurysm or dissection is the key diagnostic criterion in the new nosology; therefore, it is essential to evaluate it properly. Aortic root aneurysm is as enlargement of the aortic root at the level of the sinuses of Valsalva. The measurements should be done parallel to the plane of the aortic valve and perpendicular to the axis of blood flow. The largest correctly measured root diameter was obtained from at least 3 transthoracic images. Because the normal range for aortic diameter varies depending on the body size and age, the measurement should be corrected and interpreted as a Z-score [4,6]. Z-scores are based on the assumption of the linear relationship between the body surface area and aortic root size [6]. However, there are reports which suggest that dilatation is identified in all patients who have an aortic root diameter of 40 mm or more [7].

Because of the abnormal structure of the aortic wall, aortic dissection is a common problem, especially in untreated patients with Marfan syndrome. It is usually due to an intimal tear in the proximal ascending aorta. In most cases, it starts above the coronary arteries and extends the entire length of the aorta (type I dissection in the DeBakey classification or type A in the Dailey scheme). Ten percent of the dissections are type III (DeBakey classification) or type B (Dailey scheme), beginning distally to the left subclavian artery. Clearly, the wider the aortic root diameter, the bigger the risk of dissection, but dissection may occasionally occur even in patients with mild aortic dilation [1].

Mitral valve prolapse, caused by elongated leaflets, is another characteristic cardiac problem in patients with Marfan syndrome, although nonspecific [8]. Mitral valve prolapse in patients with Marfan syndrome may be accompanied by mitral regurgitation. The worsening of mitral regurgitation may occur due to spontaneous rupture of the chordae tendineae or as a result of infective endocarditis. In some of these cases, tricuspid valve prolapse may also occur.

### Skeletomuscular system

Most patients with Marfan syndrome are tall (but not necessarily) because of excessive linear growth of long bones. They have disproportionately long extremities compared with the length of the trunk. Consequently, the ratio of the upper to the lower segments (US/LS) is decreased and the ratio of the arm span to height is increased (greater than 1.05). The lower segment is measured from the top of the symphysis pubis to the floor in the standing position, and the upper segment is the height minus the lower segment [4]. Because the measurements may vary with age and ethnicity, a reduced US/LS ratio is <0.85 for white adults and <0.78

**Table 1.** Systemic scoring presented in the revised Ghent nosology includes [4]

| Feature | Scoring |
|---|---|
| Wrist **AND** thumb sign | 3 points |
| Wrist **OR** thumb sign | 1 point |
| Pectus carinatum deformity | 2 points |
| Pectus excavatum **OR** chest asymmetry | 1 point |
| Hindfoot deformity | 2 points |
| Plain pes planus | 1 point |
| Pneumothorax | 2 points |
| Dural ectasia | 2 points |
| Protrusio acetabuli | 2 points |
| Reduced upper segment/lower segment ratio **AND** increased arm span/height **AND** no severe scoliosis | 1 point |
| Scoliosis or thoracolumbar kyphosis | 1 point |
| Reduced elbow extension (≤170 degrees with full extension) | 1 point |
| Facial features at least 3 of the following 5 features:<br>■ dolichocephaly (reduced cephalic index or head width/length ratio)<br>■ enophthalmos<br>■ downslanting palpebral fissures<br>■ malar hypoplasia<br>■ retrognathia | 1 point |
| Skin stria | 1 point |
| Mitral valve prolapse | 1 point |

A systemic score ≥7 indicates systemic involvement.

for black adults. A typical feature is arachnodactyly with positive thumb and/or wrist signs. Generalized joint hypermobility may also occur, but there are some individuals with Marfan syndrome who have reduced joint mobility of the elbow and digits, for example, reduced elbow extension (≤170 degrees with full extension) [4]. Chest deformity may be present: pectus carinatum (thought to be more specific for Marfan syndrome), pectus excavatum, or chest asymmetry [4]. Hindfoot valgus is the result of the abduction of the forefoot and lowering of the midfoot. In some patients, only flat foot without hindfoot valgus is present. Acetabular protrusion is diagnosed by plain radiography, computed tomography (CT), magnetic resonance imaging (MRI) [9]. It is the deformity of the hip joint, in which the femoral head is displaced and the medial wall of the acetabulum invades the pelvic cavity. It causes hip joint stiffness, limited range of motion, and pelvic tilt resulting in hyperlordosis of the spine. The criteria involve loss of the normal oval shape of the pelvic inlet at the level of the acetabulum.

### Visual problems

Ectopia lentis is a displacement or malposition of the lens caused by dysfunction or disruption of the supporting zonular fibers. It is recognized in 60% of the patients with Marfan syndrome.

A common symptom of Marfan syndrome is myopia greater than 3 diopters, which is due to increased axis globe length. There is also an increased risk of retinal detachment, glaucoma, and early cataract formation [2].

### Other findings

Dural ectasia follows the enlargement of the spinal canal usually in the lumbosacral part of the spine [10]. It is a nonspecific feature of Marfan syndrome and is commonly observed in patients with Loeys–Dietz syndrome and in the vascular form of Ehlers–Danlos syndrome.

Skin stria are characteristic for Marfan syndrome after exclusion of other causes of stria such as weight changes or pregnancy. They are also usually found in an uncommon location such as the mid back, lumbar region, upper arm, axillary region, or thighs [4].

The differential diagnosis of Marfan syndrome includes evaluation of the characteristic features that may be present in other conditions. Marfan syndrome should be differentiated with regards to cardiac and aortic problems with Loeys–Dietz syndrome, mitral valve prolapse syndrome, MASS phenotype, familial thoracic aortic aneurysm syndrome, Ehlers–Danlos syndrome; with regards to ocular problems with Ectopia lentis syndrome; and with regards to skeletal problems with Shprintzen–Goldberg syndrome, and Ehlers–Danlos syndrome.

### Diagnostic criteria

In the absence of family history of Marfan syndrome, the presence of one of any of the following criteria is diagnostic for Marfan syndrome:
- Aortic dilatation (aortic diameter Z ≥2 or aortic root dissection) and ectopia lentis
- Aortic dilatation (aortic diameter Z ≥2 or aortic root dissection) and a causal *FBN1* mutation
- Aortic dilatation (aortic diameter Z ≥2 or aortic root dissection) and a systemic score ≥7 ( Table 1)
- Ectopia lentis and a causal *FBN1* mutation that has been identified in an individual with an aortic aneurysm

In the presence of family history of Marfan syndrome, the presence of one of any of the following criteria is diagnostic for Marfan syndrome:
- Ectopia lentis
- Systemic score ≥7 points (Table 1)
- Aortic dilatation (aortic diameter Z ≥2 above 20-years old, Z≥3 below 20-years old, or aortic root dissection)

## Case presentation

A 23-year-old white woman (height, 169 cm; weight, 48 kg) with the familial history of Marfan syndrome (mother and sister after aortic aneurysm operation) presented for a routine check-up in May 2012. In 2007, at the age of 18 years, she was referred to a cardiac clinic by a pediatrician to continue observation and treatment. In 2000 and 2003, corrective rods were inserted because of severe thoracic scoliosis.

On a physical examination (May 2012) performed according to the revised Ghent nosology [4], she received 10 points: arachno-



**Figure 1.** Physical examination. Abnormalities in the skeletomuscular system. Arachnodactyly in a patient with Marfan syndrome
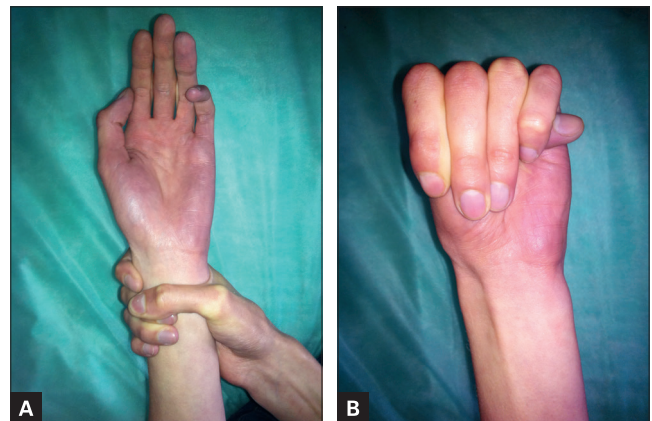


**Figure 2.** Physical examination. Abnormalities in the skeletomuscular system. A. A positive wrist sign: the top of the thumb covers the entire fingernail of the fifth finger when wrapped around the contralateral wrist. B. A positive thumb sign indicates that the entire distal phalanx protrudes beyond the ulnar border of the clenched fist with or without the assistance of the patient or examiner to achieve maximum adduction

dactyly (fig. 1) with present wrist and thumb sign (fig. 2), severe chest deformity due to thoracic scoliosis (fig. 3, 4), facial features (dolichocephaly, enophthalmos, downslanting palpebral fissures), hindfoot deformity, and plain foot.

A CT scan performed in 2008 showed widened aortic bulb at the level of coronary sinuses (40 mm) and normal width at the level of the sinotubular junction (32 mm), ascending aorta (26 mm), and descending aorta (18 mm). Follow-up cardiovascular CT performed in January 2012 showed enlargement of the aortic bulb (48 mm) and mild enlargement at the level of the sinotubular junction (35 mm), ascending aorta (27 mm) (fig. 5). At that time, she remained under observation.

Echocardiography (June 2012) revealed enlarged left ventricle (67×43 mm) and left atrium (43×53×55 mm) with the ejection fraction of 63%; the width of the aortic annulus was 29 mm, aortic
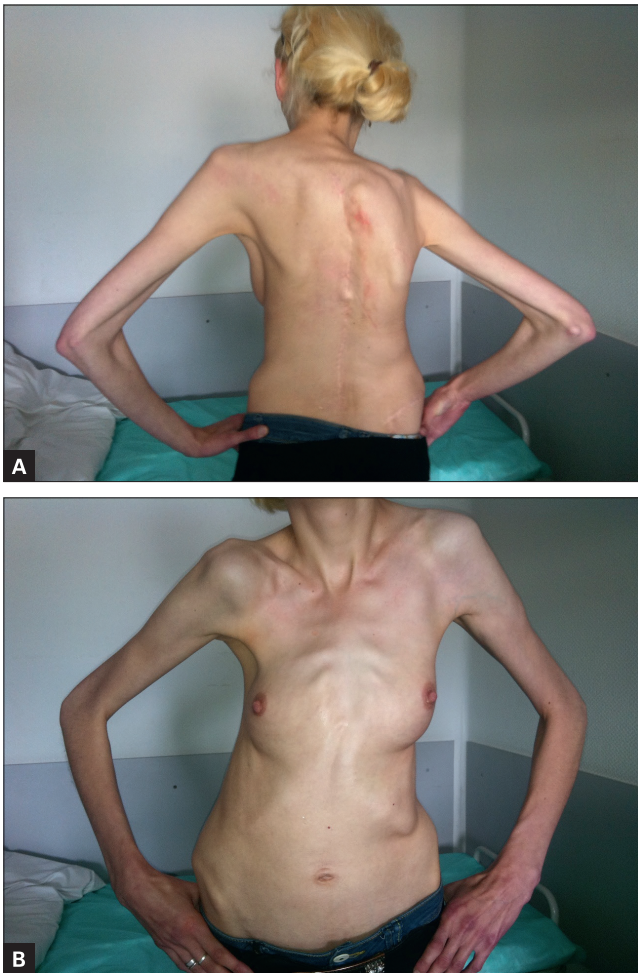
**A**



**B**

**Figure 3.** Physical examination. Abnormalities in the skeletomuscular system. Patient with Marfan syndrome. Severe scoliosis and chest deformity



**Figure 4.** Chest X-ray. Patient after implantation of corrective rods (red arrows)

ac surgery department in good general condition. She is currently symptom-free.

## Discussion

The 2010 American College of Cardiology / American Heart Association / American Association for Thoracic Surgery guidelines for thoracic aortic disease recommend to perform transthoracic echocardiography in patients with Marfan syndrome at the time of diagnosis and 6 months later to determine the aortic root and ascending aortic diameters and their rate of enlargement [11]. If the aortic diameter is stable over time and is less than 45 mm, annual echocardiography should be performed. A more frequent examination is necessary if the aortic diameter is 45 mm or more or grows significantly. At that time, surgery may be indicated [4].

During echocardiography, the assessment of the aortic root should include the measurements at the level of the ring, sinus, sinotubular junction, and distal ascending aorta. The evaluation of the left ventricular function, aortic valve, and aortic regurgitation, or mitral valve and/or tricuspid valve prolapse and regurgitation should be performed.

Every patient should undergo imaging of the entire aorta preferably with CT angiography (CTA) or magnetic resonance angiography (MRA) [1]. It was reported that evaluation of aortic elasticity of the thoracic descending aorta MRA, was an independent predictor for progressive descending aortic dilation [12]. MRA should be performed at baseline and, if the size of the aorta beyond the root is normal, it should be repeated every 5 years. If an aneurysm develops, MRA imaging should be repeated at least once a year [1]. CTA or MRA imaging should also be performed if transthoracic echocardiography do not allow precise visualization and measurement of

bulb – 46 mm, sinotubular junction – 41 mm, and ascending aorta – 44 mm (fig. 6). The aortic valve was bicuspid, tricommissural with thick platelets and mild aortic regurgitation towards anterior mitral platelet (fig. 7); the mitral valve were also platelets thick. There was a prolapse of both platelets with moderate mitral regurgitation (fig. 8).

The patients' history and images were presented at the 5th meeting of the Center for Rare Cardiovascular Diseases at the John Paul II Hospital in Krakow. The experts agreed that severe chest deformity was not contraindication for an urgent operation of the aorta, preferably the Bentall procedure.

The patient underwent a surgery in January 2013. It was performed with the use of a cardiopulmonary bypass, hypothermia, and crystalline cardioplegia. During the procedure, the aortic aneurysm (50 mm) and the bicuspid tricommissural aortic valve were observed. They were removed and replaced with the prosthesis of the aortic root and valve (ST. Jude Medical 25 A Masters). Mitral valve was also replaced during the procedure (ST. Jude Medical 33 M Masters). The postoperative course and wound healing were without complications. The patient was discharged from the cardi-
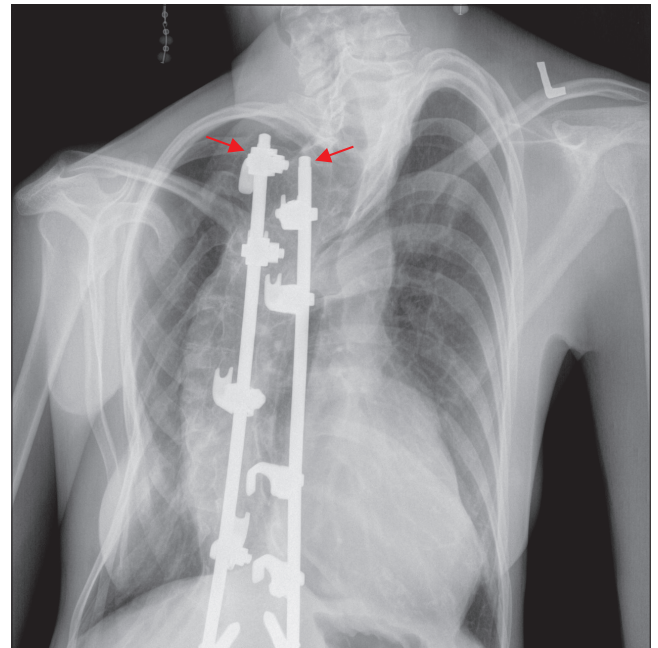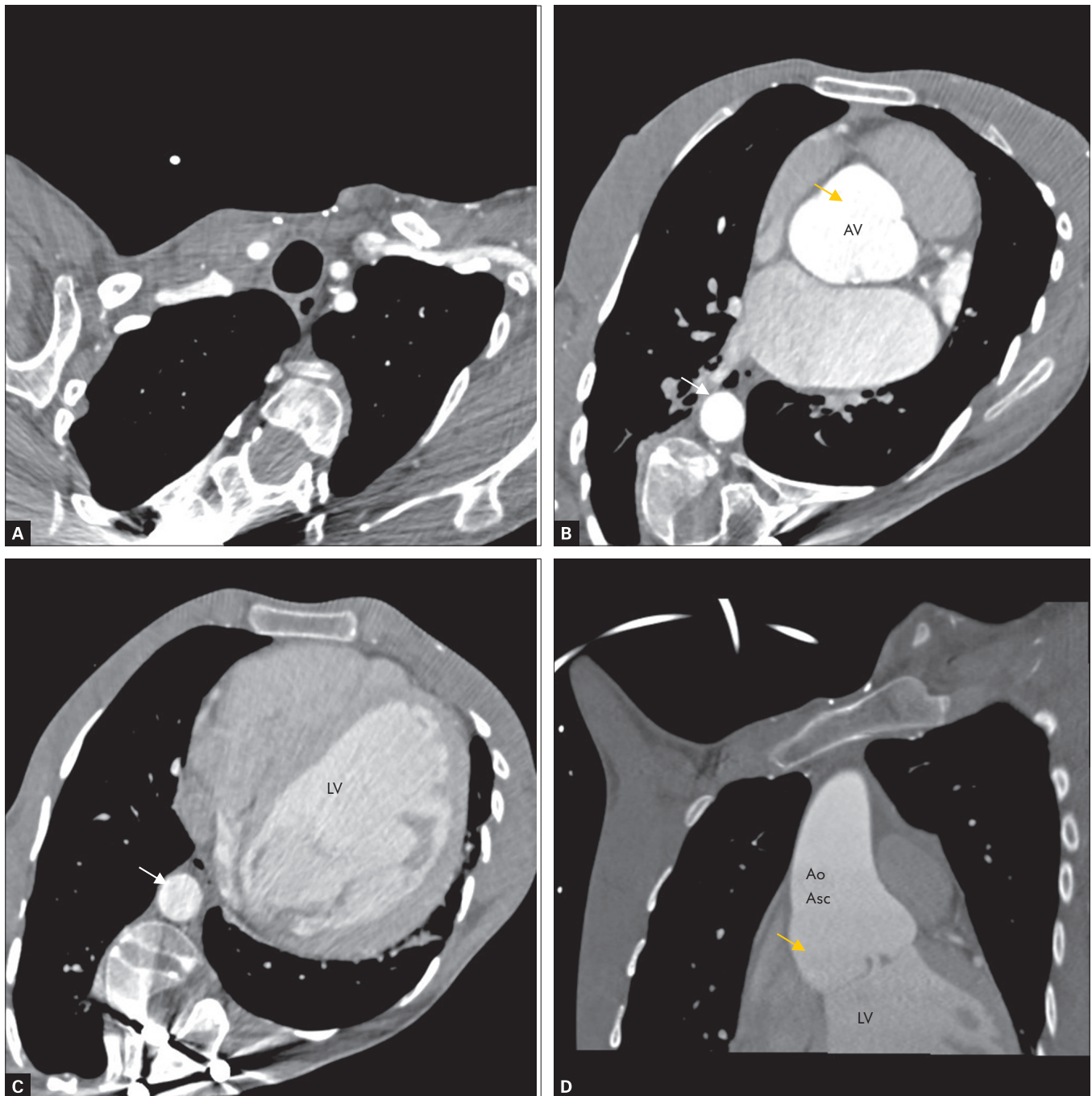
**Figure 5.** Computed tomography. A. Severe chest deformity due to thoracic kyphoscoliosis. B–D. Enlargement of the aortic root (yellow arrow). Descending aorta (white arrow). LV – left ventricle, Ao Asc – ascending aorta, AV – aortic valve

the proximal aorta [4]. CTA should preferably be used for exclusion of coronary artery disease before surgery since catheter manipulation may carry a risk of dissection of the weakened aortic wall [1].

## Medical treatment

Medical therapy includes β-blockers that decrease myocardial contractility and pulse pressure. They may improve the elastic properties of the aorta and reduce the rate of aortic dilation [1,13].

It is important to maintain systolic blood pressure at the level of 120 mm Hg. If the aortic dissection occurs, a rigorous antihyper-

tensive medical treatment should be introduced, aiming at reducing the systolic blood pressure to 110 mm Hg. The data suggest usefulness of β-blockers and angiotensin receptor blockers or angiotensin-converting-enzyme inhibitors [1].

The angiotensin receptor blocker, losartan, because of antagonism to transforming growth factor-β, is also reported to reduce the rate of aortic dilatation. However, its potential usefulness should be supported by presently ongoing clinical trial [13]. Medical treatment should be continued after surgery.
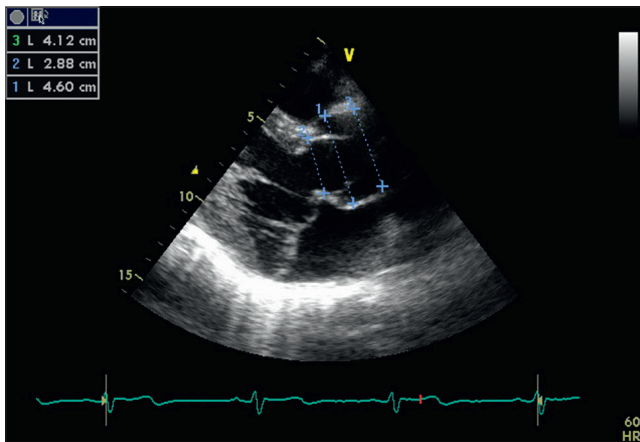
**Figure 6.** Transthoracic echocardiography. Parasternal long-axis view. Width of the aortic annulus – 2,88 cm, aortic bulb – 4,6 cm and sinotubular junction – 4,12cm. LV – left ventricle, LA – left atrium
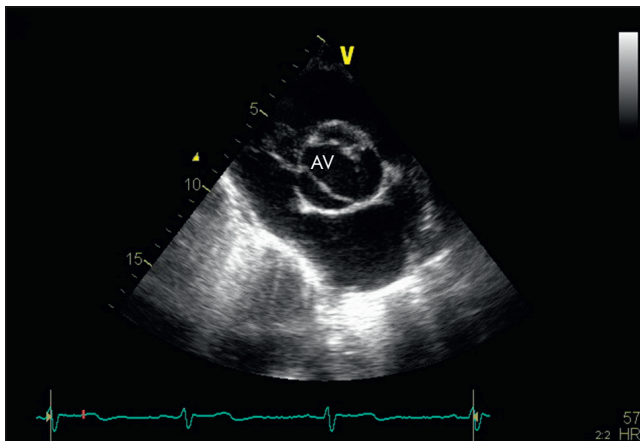


**Figure 7.** Transthoracic echocardiography. Parasternal short-axis view. Bicuspid tricommissural aortic valve. AV – aortic valve



**Figure 8.** Transthoracic echocardiography. A. Parasternal long-axis view. view. The prolapse of both leaflets of the mitral valve (arrow). B. Apical 3-chamber view. LA – left atrium

## Surgical treatment

Since the operation of the replacement of the aortic valve and ascending aorta has become a low-risk and a very durable procedure, patients with Marfan syndrome and aortic root aneurysms are recommended to undergo elective operation. Regular diagnostic imaging and early planning of the operation may prevent critical dilatation or the life-threatening outcomes of aortic dissection and emergency repair [14]. The valve may be replaced with the artificial one or with the homogenic aortic graft [15]. Aortic homograft implantation does not require postoperative anticoagulation [15].

The 2010 European Society of Cardiology (ESC) guidelines [1] recommend elective operation for patients with Marfan syndrome if the diameter of the aorta (root [IC] or any other part [IIaC]) is 50 mm or more to avoid acute dissection or rupture. If the diameter is between 46 and 50 mm, the indications for repair include family history of aortic dissection, progression of dilatation (>2 mm/year), severe aortic regurgitation, or desire of pregnancy.
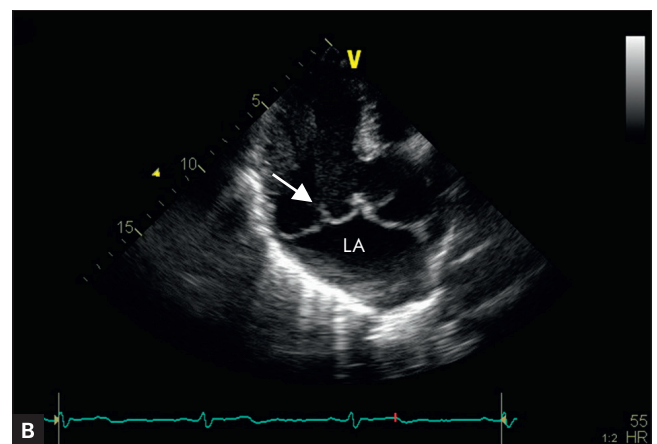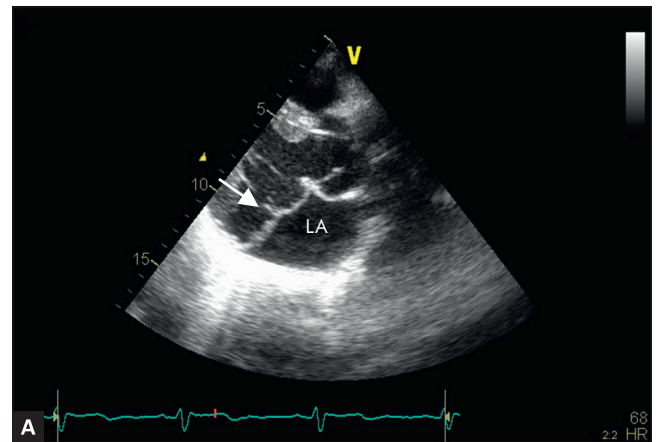
## Conclusion

The patient should undergo the operation of the aorta (the Bentall procedure) and the replacement of the mitral valve as soon as possible.

## References

1. Baumgartner H, Bonhoeffer P, De Groot NM, et al Task Force on the Management of Grown-up Congenital Heart Disease of the European Society of Cardiology (ESC); Association for European Paediatric Cardiology (AEPC). ESC Guidelines for the management of grown-up congenital heart disease (newversion 2010). Eur Heart J. 2010;31:2915–57.
2. Yuan SM, Jing H. Marfan's syndrome: an overview. Sao Paulo Med J. 2010;128:360–6.
3. Collins MJ, Dev V, Strauss BH, et al. Variation in the histopathological features of patients with ascending aortic aneurysms: a study of 111 surgically excised cases. J Clin Pathol 2008; 61:519.
4. Loeys BL, Dietz HC, Braverman AC, et al. The revised Ghent nosology for the Marfan syndrome. J Med Genet 2010; 47:476.
5. De Paepe A, Devereux RB, Dietz HC, et al. Revised diagnostic criteria for the Marfan syndrome. Am J Med Genet 1996; 62:417.
6. 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.

7. Radonic T, de Witte P, Groenink M, et al. Critical appraisal of the revised Ghent criteria for diagnosis of Marfan syndrome. Clin Genet 2011.

8. Rybczynski M, Mir TS, Sheikhzadeh S, et al. Frequency and age-related course of mitral valve dysfunction in the Marfan syndrome. Am J Cardiol 2010; 106:1048.

9. Sohn GH, Jang SY, Moon JR, et al. The usefulness of multidetector computed tomographic angiography for the diagnosis of Marfan syndrome by Ghent criteria. Int J Cardiovasc Imaging. 2011;27:679–88.

10. Lundby R, Rand-Hendriksen S, Hald JK, et al. Dural ectasia in Marfan syndrome: a case control study. AJNR Am J Neuroradiol. 2009;30:1534–40.

11. Hiratzka LF, Bakris GL, Beckman JA, et al. 2010 ACCF/AHA/AATS/ACR/ASA/SCA/SCAI/SIR/STS/SVM guidelines for the diagnosis and management of patients with Thoracic Aortic Disease: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, American Association for Thoracic Surgery, American College of Radiology, American Stroke Association, Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, Society of Interventional Radiology, Society of Thoracic Surgeons, and Society for Vascular Medicine. Circulation 2010; 121:e266–369.

12. Nollen GJ, Groenink M, Tijssen JG, van der Wall EE, Mulder BJ. Aortic stiffness and diameter predict progressive aortic dilatation in patients with Marfan syndrome. Eur Heart J 2004;25:1146–1152

13. Hartog AW, Franken R, Zwinderman AH, et al. Current and future pharmacological treatment strategies with regard to aorticdisease in Marfan syndrome. Expert Opin Pharmacother. 2012;13:647–62.

14. Song HK, Kindem M, Bavaria JE, et al. Genetically Triggered Thoracic Aortic Aneurysms and Cardiovascular Conditions Consortium. Long-term implications of emergency versus elective proximal aortic surgery in patients with Marfan syndrome in the Genetically Triggered Thoracic AorticAneurysms and Cardiovascular Conditions Consortium Registry. J Thorac Cardiovasc Surg. 2012;143:282–6.

15. P Podolec, W Tracz, M Kostkiewicz,et al. Clinical and echocardiographical study of the aortic homograft implantations in patients with Marfan syndrome. Int J Cardiol. 1997;60:41–7