Marfan Syndrome

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Marfan syndrome was first described in 1896 by Antonine-Bernard Marfan, Professor of Pediatrics in Paris. It is a relatively common inherited connective tissue disorder with an incidence of 1 in 10,000 individuals. The condition is inherited in an autosomal dominant pattern, with an equal distribution in males and females.

Case

The following case is meant to serve as a prompt to guide the discussion on the clinical aspects of Marfan Syndrome.

An 18 year old man develops sudden chest pain while playing basketball. He is noted to be quite tall at 6'5" and has long fingers and toes. Does he have Marfan syndrome? What are the diagnostic criteria? If he has Marfan syndrome, what are 3 possible causes of his chest pain? It would be relevant to note whether the patient wears contact lenses as individuals with Marfan syndrome are often near- or far-sighted and/or have other eye abnormalities.

Clinical Presentation

Most patients who have Marfan syndrome are usually diagnosed incidentally. Typically, patients with Marfan syndrome present with tall stature, lens dislocation (ectopia lentis), aortic root dilatation and a positive family history. Less common presentations include:

- Dominant ectopia lentis with variable skeletal and negligible cardiac involvement
- Mitral valve prolapse without skeletal features
- Dominant aortic aneurysm without skeletal and ocular features
- Presentation at birth, rapid aortic dilatation, deformities (such as pectus deformities, where the breastbone protrudes inward or outward), and death
- Sudden death

Pathogenesis

The genetic basis for Marfan syndrome is a mutation in the gene encoding fibrillin-1 (FBN-1) found on chromosome 15. Fibrillin is a glycoprotein that is an integral part of microfibrils found in the connective tissue of the body. Microfibrils function as the main component of elastic fibres, anchoring fibres between the dermis and epidermis, as well as in the lens of the eye. Classically, it was thought that the ubiquitous features of Marfan syndrome could be attributed to weak or deformed connective tissue. However, recent research suggests that a defect in the fibrillin-1 structure reduces its ability to bind to the cytokine TGF-B, which results in increased expression of TGF-B. In mouse models, increased TGF-B signaling was associated with myxomatous mitral valve leaflets and aortic dilatation, both features of Marfan syndrome. Furthermore, by administering an antibody that binds TGF-B, it was shown that these common features could be prevented. Thus, it is now thought that it is the over-expression of the cytokine TGF-B, due to the inability of the defective fibrillin-1 that would in normal circumstances bind TGF-B, that results in the features of Marfan syndrome.
Marfan syndrome has diverse manifestations that can affect many organ systems such as the skeletal, ocular, cardiovascular systems and can also involve the skin, lungs and muscle tissue - an example of pleiotropy.

**Clinical Diagnosis**

The diagnosis of Marfan syndrome (MFS) is usually based on clinical features and family history. The features of Marfan syndrome may overlap with other connective tissue disorders and the presentation of Marfan syndrome varies widely, even among family members. Nonetheless, the development of a set of guidelines, known as the Ghent criteria, has brought clarity to the issue.

- If an individual has a first-degree relative affected by Marfan syndrome, a diagnosis of Marfan syndrome requires major involvement in one organ system (skeletal, cardiovascular, or ocular) and minor involvement of a second organ system.
- In the absence of a family history for Marfan syndrome (or ambiguous family history), a diagnosis of Marfan syndrome requires major criteria in two different organ systems and minor involvement of a third.

Please refer to Table 1 attached at the end of the article for more details on the clinical features that would constitute major or minor involvements in different organ systems.

As a simplified guideline, for a patient suspected of having Marfan syndrome some investigations that are helpful in making a clinical diagnosis include:

- Examination by an ophthalmologist to look for lens dislocation or subluxation; often patients with Marfan syndrome are near-sighted (myopia) and at increased risk for developing cataracts and glaucoma
- Referral to a cardiologist for an echocardiogram to assess if there are any cardiovascular abnormalities such as mitral valve prolapse, aortic root dilatation or aortic dissection
- Physical exam to assess skeletal features: ratio of arm span-to-height ratio which is considered significant if it is greater than 1.05, or wrist and thumb signs. (A positive wrist sign is present if the thumb and fifth finger overlap when encircling the opposite wrist. A positive thumb sign is present if the entire thumbnail protrudes beyond ulnar border of hand when the thumb is adducted across the palm.)

**Differential Diagnosis**

The differential diagnosis for MFS includes homocystinuria, congenital contractual arachnodactyly, mild aortic root dilatation-skeletal-skin (MASS) syndrome, Ehlers-Danlos syndrome, Stickler syndrome, congenital bicuspid aortic valve disease, aortic coarctation, Loeys-Dietz syndrome, and familial thoracic aortic aneurysm with aortopathy. The most similar differential is homocystinuria as the two diseases share a similar phenotype. Features that overlap between Marfan syndrome and homocystinuria include ectopic lentis, severe myopia, mitral valve prolapse, and skeletal abnormalities, such as body habitus, chest deformities, and spine deformities. Patients with homocystinuria are at an increased risk for thromboembolic events, but many patients with this condition are responsive to pyridoxine. Thus, it is important to screen for homocystinuria with measurement of urinary amino acids, as there are implications for management.

**Management**

Overall, the prognosis for Marfan syndrome is relatively favorable. Activity restrictions, medications, monitoring, and elective surgical interventions were associated with an improved life span for MFS patients from 41 years in 1993 to 61 years in 1996.
Aortic disease is the most significant source of morbidity and mortality for patients with MFS. Untreated MFS can be associated with an aortic dissection spanning the entire length of the aorta. Aortic dissection occurs earlier among patients with MFS compared to the other cases of aortic dissection. Assessment for aortic root dilatation and regurgitation can be performed by thoracic echocardiography; however, if that yields incomplete or insufficient information, transesophageal echocardiography can be used. Routine measurements can be performed annually as long as the aortic root diameter increases proportional to increases in body surface area. If

Table 1. Ghent Criteria for Diagnosis of Marfan Syndrome*

<table>
<thead>
<tr>
<th>System</th>
<th>Major</th>
<th>Minor</th>
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</thead>
<tbody>
<tr>
<td>Family/genetic history</td>
<td>• Having a first-degree relative who meets these diagnostic criteria</td>
<td>• None</td>
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<td></td>
<td>• Presence of a mutation in FBN1 known to cause Marfan syndrome</td>
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<tr>
<td>Skeletal</td>
<td>• Presence of at least 4 of the following manifestations:</td>
<td>• Pectus excavatum of moderate severity</td>
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<td></td>
<td>• Pectus carinatum</td>
<td>• Joint hypermobility</td>
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<td></td>
<td>• Pectus excavatum requiring surgery</td>
<td>• Highly arched palate with crowding of teeth</td>
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<tr>
<td></td>
<td>• Reduced upper-to-lower segment ratio or arm span-to-height ratio &gt; 1.05</td>
<td>• Facial appearance (dolichocephaly, malar hypoplasia, enophthalmos, down-slanting palpebral fissures)</td>
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<tr>
<td></td>
<td>• Wrist and thumb signs</td>
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<td></td>
<td>• Scoliosis &gt; 20 degrees or spondylolisthesis</td>
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<td></td>
<td>• Reduced extension at elbows (&lt;170 degrees)</td>
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<td></td>
<td>• Medial displacement of medial malleolus causing pes planus</td>
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<td></td>
<td>• Protrusio acetubulare of any degree</td>
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<tr>
<td>Ocular</td>
<td>• Ectopia lentis (dislocated lens)</td>
<td>• Abnormally flat cornea</td>
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<td></td>
<td></td>
<td>• Increased axial length of globe</td>
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<td>Cardiovascular</td>
<td>• Dilatation of ascending aorta with or without aortic regurgitation and involving at least the sinuses of Valsalva or dissection of ascending aorta</td>
<td>• Mitral valve prolapse with or without mitral valve regurgitation</td>
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<td>• Dilatation of the main pulmonary artery, in the absence of valvular or peripheral pulmonic stenosis or any other obvious cause in patients &lt; 40 years</td>
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<td></td>
<td>• Calcification of mitral annulus in patients &lt;40 years</td>
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<td></td>
<td>• Dilatation or dissection of the descending thoracic or abdominal aorta in patients &lt; 50 years</td>
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<tr>
<td>Pulmonary</td>
<td>• None</td>
<td>• Spontaneous pneumothorax</td>
</tr>
<tr>
<td>Skin and integument</td>
<td>• None</td>
<td>• Apical blebs</td>
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<tr>
<td>Dura</td>
<td>• Lumbosacral dural ectasia (by CT or MRI)</td>
<td>• Stretch marks not associated with weight changes, repetitive stress</td>
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<td></td>
<td></td>
<td>• Recurrent incisional hernias</td>
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<td></td>
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<td>• None</td>
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* Adapted from Rangasetty UC, Karnath BM. (2006)1
the increase is disproportional, or if the aortic root diameter is greater than 45 mm, biannual measurements should be performed.

The European Society of Cardiology has published recommendations for the treatment of patients with MFS.8 The standard of care involves beta blockers which can delay the progression to aortic dissection. Beta blockers decrease myocardial contractility and pulse pressure and may also improve the elastic properties of the aorta, particularly in patients with an aortic root diameter <40 mm.9,10 In a randomized trial, treatment with propranolol was associated with delayed progression of aortic dilatation, and higher survival at approximately five years. Longer term survival differences between propranolol and placebo were less clear.11 No randomized trials have been done to establish the efficacy of beta blockers in children.12 However, many clinicians would give beta blockers to all children with MFS. In the future, therapy directed at the renin-angiotensin-aldosterone system may prove beneficial, but the role of these drugs in MFS has not yet been established.13,14

Patients with MFS may participate in low to moderate intensity, non-competitive exercise such as bowling, golf, stationary bike, or modest hiking. Strongly discouraged activities include: weight lifting, ice hockey, rock climbing and surfing.15 The choice of permissible activities requires individual assessment. For children to comply with these activity restrictions, there must be coordination between parents, school officials, and physical educators.

Elective surgical repair for an aortic dilatation is associated with reduced mortality compared to urgent or emergent repairs. For adults and children, surgical repair should be considered at an aortic root diameter of ≥50 mm.16 Uncertainties exist regarding the root diameter for performing elective surgery. The 2006 American College of Cardiology/American Heart Association (ACC/AHA) guidelines recommend elective surgery for an aortic root diameter ≥50 mm, while European Society of Cardiology (ESC) recommends surgery for an aortic root diameter of ≥45 mm.17 In addition to the absolute size of the aortic root diameter, other considerations are a family history of aortic dissection or a rapid increase in aortic size (i.e., ≥5 mm per year).18 Some suggest using aortic root dimensions relative to body surface area. This factor is particularly important for children. For children, the only clear indications for surgical intervention are: an aortic root diameter of ≥45 mm (“giant aneurysm”), rapid enlargement of >10 mm/year, or progressive aortic insufficiency. Other cut-offs for aortic root diameter are less clear.

A few options exist regarding the surgical technique and the choice depends on patient factors. One approach involves total replacement of the aortic root.19 Alternatively, for patients with structurally normal valves the native aortic valve may be retained using remodeling and reimplantation techniques.20,21 In this latter option, life-long anti-coagulation is not required; however, repeat operations may be necessary. Antibiotic prophylaxis should be individualized. As other sites throughout the aorta maybe involved, follow-up radiography using MRI or CT angiography is required indefinitely.22

Ocular and muskeloskeletal problems also require attention. Eyeglasses can correct myopia, while artificial lens insertion should only be undertaken when growth of the eye is complete. Further, photocoagulation can correct retinal tears and detachment. If intervention with physical therapy and bracing fails, scoliosis may require surgical stabilization of the spine. Orthotics can correct flat foot, which is associated with muscle cramps and leg fatigue.

Answers to Case

Diagnosis would be made based on Ghent criteria. Possible causes of chest pain are: muscle/ligament strain, aortic root dissection, and pneumothorax.

Glossary

pectus carinatum: deformity of the chest characterized by protrusion of ribs and sternum
pectus excavatum: deformity in which several ribs and the sternum grow abnormally, producing a concave appearance in anterior chest wall
protusio acetabulare: protrusion of the acetabulum (socket that receives femoral head to make the hip joint)
pes planus: flat foot
dolichocephaly: elongated skull
enophthalmos: recession of eyeball within the orbit
sinuses of Valsalva: also known as aortic sinus; the space between each semilunar valve and the wall of the aorta

References