Marfan syndrome: diagnosis and management

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ABSTRACT The diagnosis of Marfan syndrome requires a multidisciplinary assessment including clinical genetics, cardiology, ophthalmology, and radiology. It is caused by mutation in the fibrillin 1 gene on chromosome 15. Gene testing remains problematic, as current techniques fail to find a mutation in 10–30% of cases, while a small number of non-Marfan patients (often with MASS – **m**itral valve prolapse, mild non-progressive **a**ortic dilatation, **s**kin and **s**keletal features – phenotype) do have mutations. The diagnosis remains clinical and is based on the Ghent criteria. Beta-blockers or angiotensin-converting enzyme inhibitors slow the rate of aortic dilatation. Prophylactic aortic root surgery should be considered when the aortic root exceeds 5·5 cm at the sinus of Valsalva. Marfan patients require regular follow-up including aortic root measurement, usually by transthoracic echocardiography. Lens dislocation is not universal in Marfan, but expert ophthalmology assessment, especially in childhood, is advisable. Arthralgia and other skeletal symptoms are common, and associated with joint hypermobility. Respiratory complications include recurrent pneumothorax and sleep apnoea. Patients should be advised to avoid contact sports and scuba diving. There is an increased risk of aortic dissection in pregnancy, particularly when the aortic root diameter exceeds 4 cm. Younger patients should be assessed in the neonatal period, pre-school, at age 10, and at age 18 if they have some Marfan features, but fail to meet the Ghent criteria by one system, or if they have a family history of Marfan syndrome.

KEYWORDS Aneurysm, ectopia lentis, fibrillin, genetics, Marfan

LIST OF ABBREVIATIONS Magnetic resonance imaging (MRI), mendelian inheritance in man (MIM)

DECLARATION OF INTERESTS No conflict of interests declared.

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INTRODUCTION

Marfan syndrome is a variable, autosomal dominant, connective tissue disorder, affecting mainly the cardiovascular system, eyes, and skeleton, with an incidence of 1 in 9,800. Progressive aortic dilatation associated with aortic valve incompetence is the key life-threatening feature, although mitral valve prolapse and incompetence, lens dislocation and myopia, and the arthritic sequellae of chronic joint laxity can cause significant disability. The diagnosis is often considered in a young person with a tall, thin body habitus with long limbs, arachnodactyly, pectus deformities, and perhaps scoliosis (see Figure 1). A high-arched palate with dental crowding, skin striae distensae, recurrent hernias, or recurrent pneumothorax may increase suspicion. Family history may be helpful, but is negative in around 26% of cases, because of new mutation. The Marfan syndrome gene, fibrillin 1 on chromosome 15, was discovered in 1994, but molecular testing is expensive and often unhelpful, as between 10 and 30% of patients have no mutation detectable by current methods. In addition, fibrillin mutations are sometimes found in patients who do not have Marfan syndrome, but have Marfan-like disorders with a good prognosis, such as MASS

phenotype (**m**itral valve prolapse, mild non-progressive **a**ortic dilatation, **s**kin and **s**keletal features) or isolated ectopia lentis. To help make the diagnosis of Marfan syndrome more consistent, and of prognostic value, the clinical features were codified into the Ghent diagnostic nosology. This helps identify which patients are at risk of cardiovascular complications, and might benefit from regular follow-up and prophylactic medical and surgical treatment. Equally, others can be reassured that they do not have Marfan syndrome, and avoid the financial stigmatisation and lifestyle restrictions that often accompany the diagnosis.

CLINICAL DIAGNOSIS OF MARFAN SYNDROME

The Ghent diagnostic nosology was devised in 1996, as a revision of the earlier Berlin criteria of 1988. In this nosology, clinical features are assessed as part of seven body 'systems', to determine whether that system provides a major criterion, or simply system involvement (see Table 1). A diagnosis of Marfan syndrome requires a major criterion in two systems and involvement of a third. The cardiovascular assessment requires measurement of the aortic diameter at the sinuses of Valsalva, usually by transthoracic echocardiography (see Figure 2), and
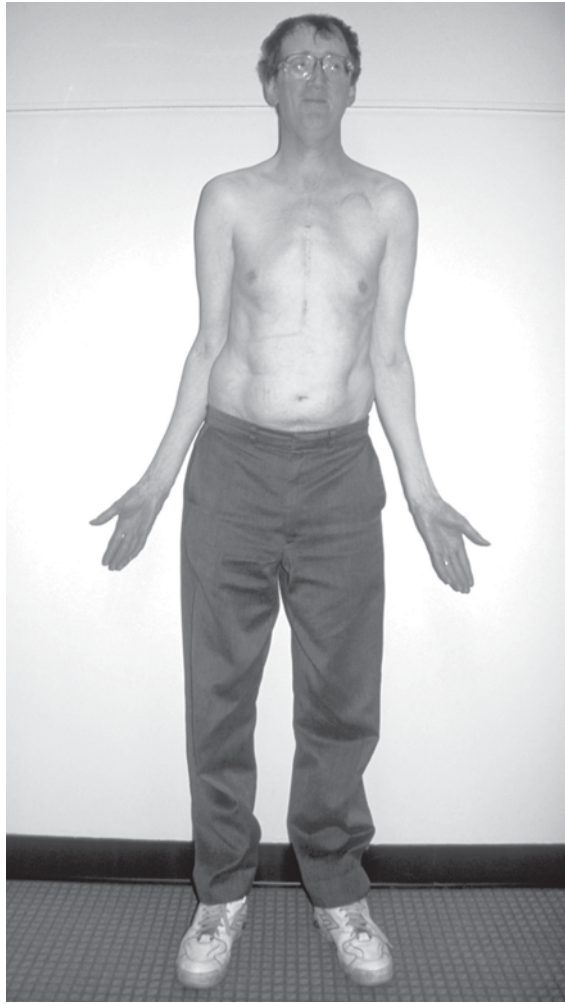
FIGURE 1 Patient with Marfan syndrome.

comparison with normal values based on body surface area, calculated from height and weight. Assessment of the skeletal system may include a pelvic X-ray to look for protrusio acetabulae, if a positive finding would provide a major criterion in this system or involvement of this system, such that a positive diagnosis of Marfan syndrome could then be made in conjunction with findings in the other systems. Similarly, lumbar MRI scan for dural ectasia should be undertaken where a positive finding would make the diagnosis of Marfan syndrome. Ocular evaluation for myopia and lens subluxation requires ophthalmology assessment.

Many Marfan features (echocardiographic findings, ectopia lentis, scoliosis, upper-lower segment ratio, protrusio acetabulae) are age-dependent in occurrence, and so younger patients with a family history of Marfan syndrome who do not fulfil the diagnostic criteria, and younger Marfan-like patients with no family history who fail to meet the diagnostic criteria by only one system, should be offered further periodic evaluations until the age of 18. Younger patients with a positive family history can be offered genetic testing, if the causative mutation can be detected in a clinically definitely affected relative.

The differential diagnosis includes conditions such as homocystinuria (MIM 236200), Beals syndrome (MIM 121050), Marshall–Stickler syndrome (MIM 108300, 604841, 184840), Ehlers–Danlos syndrome (MIM 130050), familial ascending aortic aneurysm (MIM 132900), and MASS phenotype (MIM 604308). (For MIM, see www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=OMIM.) The initial evaluation of patients with a possible diagnosis of Marfan syndrome thus requires a multidisciplinary approach involving clinical genetics, cardiology, ophthalmology, and radiology, and should be undertaken by teams with expertise in this area.

CARDIOVASCULAR MANAGEMENT

Aortic root dilatation is the most common cause of morbidity and mortality. Aortic valve incompetence usually occurs in the context of a dilated aortic root, and risk of aortic dissection is associated with an aortic diameter at the sinus of Valsalva exceeding 5·5 cm, a rate of dilatation exceeding 5% or 2 mm per year, and a family history of aortic dissection. Myocardial infarction may occur if an aortic root dissection occludes the coronary ostia.

Elastic fibre degeneration in the aorta is associated with reduced distensibility in response to the pulse pressure wave. This abnormal aortic compliance (increased stiffness) can be detected at any age by echocardiography or gated MRI scanning, although it is less marked in children. The pulse wave velocity is increased. Early studies in turkeys prone to aortic dissection showed improved survival with beta-blockade, and trials in Marfan patients show a reduced rate of aortic dilatation and fewer aortic complications with propranolol, atenolol, or metoprolol therapy. Some patients respond better than others, with responders showing improved aortic distensibility, reduced pulse wave velocity, smaller aortic diameters, and they tend to be younger. Poor response may be associated with more extensive elastic fibre degeneration, either due to a more severe fibrillin mutation, or later stage disease, with a more dilated aorta. Beta-blocker therapy should therefore be considered in all patients with Marfan syndrome, including children. For those who cannot tolerate beta-blockers, alternatives such as calcium blockers or angiotensin-converting enzyme inhibitors should be considered. Angiotensin-converting enzyme inhibitors reduce vascular smooth muscle cell apoptosis *in vitro*, and such apoptosis has been implicated in the cystic medial degeneration seen in the Marfan aorta. This theoretical benefit may be in addition to any haemodynamic effects. Enalapril has been shown to improve aortic distensibility and reduce the rate of aortic dilatation in one trial in children and adolescents.

If medical treatment fails, and the aortic root dilates to 5·5 cm or more, then prophylactic surgery should be considered. Other factors such as the rate of aortic growth, and family history of dissection should be taken

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System	Major criterion	Involvement
Skeletal	At least four of the following features: • pectus carinatum • pectus excavatum requiring surgery • ULSR (Upper to Lower Segment Ratio)[1] <0·86 or span:height >1·05 • Wrist and thumb signs • Scoliosis >20° or spondylolisthesis • Reduced elbow extension (<170°) • Pes plenus • Protrusio acetabulae	Two of the major features, or one major feature and two of the following: • pectus excavatum • joint hypermobility • high palate with dental crowding • characteristic face
Ocular	Lens dislocation (ectopia lentis).	Flat cornea. Increased axial length of globe (causing myopia). Hypoplastic iris or ciliary muscle (causing decreased miosis).
Cardiovascular	Dilatation of the aortic root. Dissection of the ascending aorta.	Mitral valve prolapse. Dilatation of the pulmonary artery, below age 40. Calcified mitral annulus, below age 40. Other dilatation or dissection of the aorta.
Pulmonary	None.	Spontaneous pneumothorax. Apical blebs.
Skin/Integument	None.	Striae atrophicae. Recurrent or incisional hernia.
Dura	Lumbosacral dural ectasia.	None.
Genetic findings	Parent, child, or sibling meets these criteria independently. Fibrillin 1 mutation known to cause Marfan syndrome. Inheritance of DNA marker haplotype linked to Marfan syndrome in the family.	None.

TABLE 1 Ghent diagnostic nosology. [1]The lower segment is measured from the symphysis pubis to the floor, and the upper segment calculated by subtracting the lower segment from height.

into account. Many studies show better survival rates for prophylactic compared with emergency aortic surgery, and improved longevity for Marfan patients who undergo prophylactic surgery compared with their untreated relatives. Alternative procedures include the Bentall composite graft repair, in which both the aortic root and the aortic valve are replaced, and valve conserving techniques which can involve re-implantation of the native aortic valve in a Dacron® tube. The Bentall procedure has a low mortality in experienced hands but requires lifelong anticoagulation post-operatively, whereas valve conserving techniques may avoid the need for anticoagulation. Some argue that there may be an increased need for re-operation following a valve conserving procedure, as subsequent degeneration of the aortic valve leaflets may require aortic valve replacement at a future date.

As Marfan patients survive longer, re-operation for new aneurysms developing elsewhere in the arterial tree are becoming common: in one series, 70% developed second aneurysms requiring surgery. Continuation of long-term medical prophylaxis after surgery is therefore strongly recommended. Other cardiac valves may also be affected by Marfan syndrome: mitral valve replacement may be required in up to 10% of those requiring aortic root surgery.

With modern management, life expectancy for those with Marfan syndrome has increased (mean age at death 32 ± 16 years in 1972 v s 45 ± 17 years in 1998), although there is still scope for improvement.

OCULAR MANAGEMENT

Ocular features of Marfan syndrome include bilateral ectopia lentis (40·7%), myopia (28%), and retinal detachment (0·78%). Lens dislocation into the anterior chamber may occur. Subluxation usually develops in early childhood, but may first present in the second decade. Myopia is associated with an increased length of the globe and an increased risk of retinal detachment. Early detection and correction of refractive errors is vital to prevent amblyopia, as correction after the age of 12 years is unlikely to restore visual acuity. Anisotropia (unequal refraction between the two eyes) and the possibility of anterior chamber abnormalities are further important considerations for management. Ophthalmology assessment is important, and regular orthoptic review is recommended, particularly in childhood.

SKELETAL MANAGEMENT

Skeletal abnormalities generally develop and may progress during childhood. Scoliosis affects around 60% of Marfan
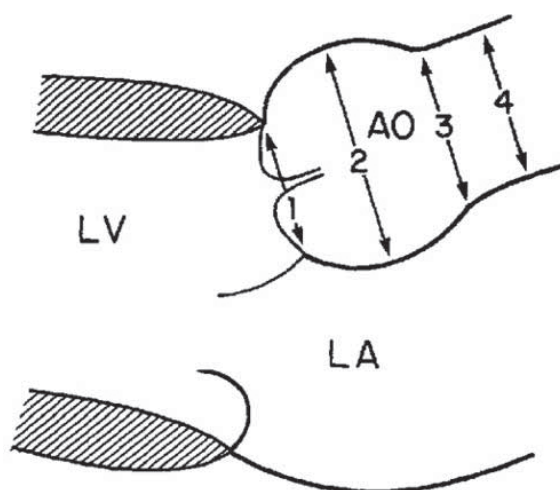
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FIGURE 2 Diagram of aortic root. The aortic diameter can be measured at: 1, the aortic annulus; 2, the sinuses of Valsalva; 3, the supra-aortic ridge; or 4, the ascending aorta. (Published with permission, Roman *et al.*[7].)

patients and there may be rapid progression during growth spurts, leading to marked deformity, pain, and restricted ventilatory deficit. In adults, back pain (associated with scoliosis) is three times more frequent than in the general population. Occasionally, scoliosis may progress in adult life, especially if the angle of curvature is >40°.

Bone mineral density may be reduced in Marfan patients, particularly older males, but there is no correlation with clinical features or risk of fracture. Routine prescription of bone mineral replacement therapy is not recommended.

The use of oestrogens in pre-puberty to prevent excessive height in girls with Marfan syndrome has been advocated. There is almost no published evidence concerning this treatment, but reports suggest it is less effective than in girls who are tall for other reasons. Such treatment should only be considered in exceptional circumstances.

Joint laxity affects 85% of children and 56% of adults with Marfan syndrome, and is associated with arthralgia, myalgia, and an increased risk of ligamentous injury. Although there have been no trials to investigate the effectiveness of sports limitation to avoid joint damage, common sense suggests that activities likely to stress the joints should be avoided. Contact sports are not advised, to protect the aorta and the lens of the eye, and scuba diving should be avoided because of the increased risk of pneumothorax.

RESPIRATORY SYSTEM

Pectus excavatum occurs in approximately two-thirds of patients with Marfan syndrome, and, when severe, can be associated with a restrictive ventilatory defect. It can cause difficulty with cardiac surgical procedures but correction is most often requested for cosmetic reasons. Patients with Marfan syndrome are more likely to have delayed wound healing following repair of pectus excavatum. Surgical correction in children should be avoided where possible, as recurrence is common in this age group.

Spontaneous pneumothorax occurs in 4–11% of patients and may be associated with apical bullae. Recurrence is common, and there should be a low threshold for surgical intervention. Activities such as scuba diving should be avoided. Mechanical ventilation can exacerbate respiratory difficulties in Marfan neonates because of susceptibility to pneumothorax, bullae, and emphysema.

Adult patients with Marfan syndrome have an increased tendency to upper airway collapse during sleep, causing obstructive sleep apnoea. This is associated with abnormalities of craniofacial structure. It may contribute to daytime somnolence, sometimes attributed to beta-blocker therapy.

CENTRAL NERVOUS SYSTEM

Although lumbosacral dural ectasia is a major criterion for the diagnosis of Marfan syndrome, and is present in around 95% of adult patients, it is rarely symptomatic. It may reduce the effectiveness of epidural anaesthesia. Anterior sacral meningocele has been described rarely as a complication of Marfan syndrome, and may lead to diagnostic confusion when presenting as a pelvic or abdominal mass.

PREGNANCY IN MARFAN SYNDROME

The risk of aortic dissection in pregnancy is greatly increased, probably due to inhibition of collagen and elastin deposition in the aorta by oestrogen, and the hyperdynamic hypervolaemic circulatory state of pregnancy. Conditions such as gestational hypertension and pre-eclampsia may be additional risk factors. Around 11% of women with Marfan syndrome have a major aortic complication in pregnancy, and the risk is greater if the aortic root exceeds 4 cm at the start of pregnancy, or if it dilates rapidly. More frequent monitoring of aortic diameter in pregnancy is advisable. If the aortic root dilates to 5·5 cm during the pregnancy, consideration should be given to immediate aortic replacement, early delivery, or termination of pregnancy. There is no increased risk of spontaneous preterm labour, spontaneous miscarriage, or postpartum haemorrhage.

As Marfan syndrome is autosomal dominant, there is a 50% chance that the child of an affected person will inherit the disorder. Marfan patients seldom ask for prenatal diagnosis, although it is possible by molecular techniques in families who have been worked up beforehand in the genetic clinic. Ultrasound diagnosis is unreliable. Marfan patients should be offered genetic counselling before planning a family.

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It is often difficult to diagnose Marfan syndrome in a newborn baby, but offspring of Marfan patients should be assessed early in life, with gene testing where possible, so that appropriate follow-up can be organised.

KEYPOINTS

- The diagnosis of Marfan syndrome should be undertaken using the Ghent diagnostic nosology by a multidisciplinary team including clinical genetics, cardiology, ophthalmology, and radiology.
- Regular follow-up (usually at least annual) should include ultrasound measurement of the aortic root diameter at the sinus of Valsalva, related to body surface area.
- All patients should be considered for prophylactic beta-blocker or angiotensin-converting enzyme inhibitor therapy.
- Prophylactic aortic root surgery should be considered when the aortic root exceeds 5·5 cm, or grows at more than 5% or 2 mm per year.
- Aortic complications in pregnancy are more common if the aortic root exceeds 4 cm at the start of pregnancy. Frequent follow-up with monitoring of the aortic root diameter should be undertaken in pregnancy.
- Patients should avoid contact sports (to protect the aorta and the eye), and avoid scuba diving (risk of pneumothorax).

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FURTHER READING

A more detailed version of this article has appeared recently in the *European Journal of Human Genetics* (*Eur J Hum Genet* 2007; **15:**724–33).