

Marfan syndrome: clinical diagnosis and management

Marfan syndrome is a multisystem connective tissue disorder usually associated with mutation in fibrillin, and occasionally with mutation in TGFBR1 or 2. The clinical diagnosis is made using the Ghent nosology, which will unequivocally diagnose or exclude Marfan syndrome in 86% of cases. Use of a care pathway can help implementation of the nosology in the clinic. The penetrance of some features is age dependent, so the nosology must be used with caution in children. Molecular testing may be helpful in this context. The nosology cannot be used in families with isolated aortic dissection, or with related conditions such as Loeys–Dietz syndrome, although it may help identify families for further diagnostic evaluation because they do not fulfill the nosology, despite a history of aneurysm. Prophylactic medical (eg β -blockade) and surgical intervention is important in reducing the cardiovascular complications of Marfan syndrome. Musculoskeletal symptoms are common, although the pathophysiology is less clear – for example, the correlation between dural ectasia and back pain is uncertain. Symptoms in other systems require specialist review such as ophthalmology assessment of refractive errors and ectopia lentis. Pregnancy is a time of increased cardiovascular risk for women with Marfan syndrome, particularly if the aortic root exceeds 4 cm at the start of pregnancy. High-intensity static exercise should be discouraged although low-moderate intensity dynamic exercise may be beneficial. The diagnosis and management of Marfan syndrome requires a multidisciplinary team approach, in view of its multisystem effects and phenotypic variability.

In brief

- Variable autosomal dominant disorder, characteristically with cardiovascular, eye and skeletal features.
- The minimal birth incidence is 1 in 9800
- 27% of cases arise from new mutation
- Mutation in fibrillin-1 on chromosome 15 is detected in 66–91% of cases
- Some cases may be due to mutation in TGFBR1 or TGFBR2
- TGFBR1 or TGFBR2 are also associated with Loeys-Dietz syndrome, and TGFBR2 with familial thoracic aortic aneurysm
- The clinical diagnosis in adults should be made using the Ghent criteria
- The Ghent criteria are unreliable in children
- Prophylactic medical treatment to protect the aorta with regular follow-up helps prevent or delay serious complications
- Prophylactic aortic surgery should be considered when the aortic root at the Sinus of Valsalva exceeds 5 cm

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Introduction

Marfan syndrome (MIM 154700) is a variable, autosomal-dominant disorder of connective tissue whose cardinal features affect the cardiovascular system, eyes and skeleton (Figure 1). The minimal birth incidence is around 1 in 9800.¹ Progressive aortic dilatation, usually maximal at the sinus of Valsalva, associated with aortic valve incompetence leads to aortic dissection or rupture and is the principal cause of mortality, but mitral valve prolapse with incompetence may be significant, and lens dislocation, myopia and arthritis associated with chronic joint laxity can cause substantial morbidity. The diagnosis is

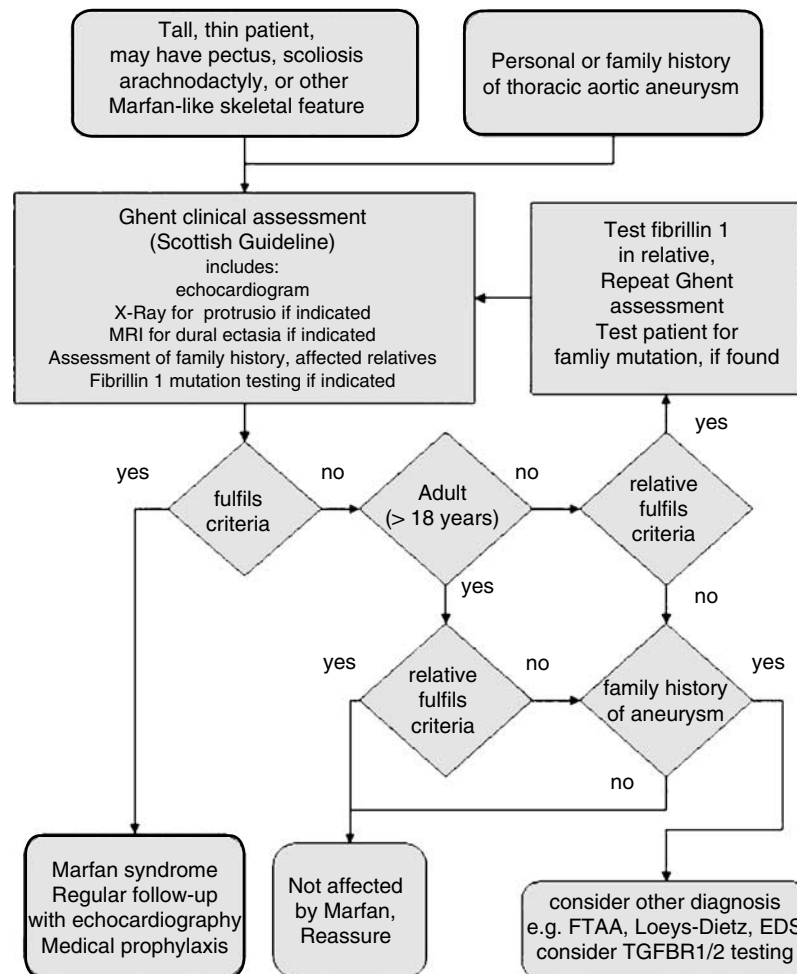


Figure 1 Algorithm for using the Ghent nosology in the diagnosis of Marfan syndrome and related disorders. Relative in this diagram means first degree relative. Consider TGFBR1 and 2 testing in Marfan syndrome if no ocular features.

commonly considered in a young person with a tall, thin body habitus, long limbs, arachnodactyly, pectus deformities and sometimes scoliosis (Figures 2 and 3). Other findings in the clinic such as a high arched palate with dental crowding, skin striae distensae, recurrent hernia or recurrent pneumothorax may increase suspicion. Family history may be helpful, but around 27% of cases arise from new mutation.¹ In 1991, fibrillin-1 gene mutation on chromosome 15 was identified as a cause of Marfan syndrome,² but molecular testing is not as diagnostically useful as was originally hoped. Fibrillin-1 mutation causes some Marfan-like disorders with a better prognosis (eg MASS phenotype, MIM 604308, mitral valve prolapse, mild non-progressive aortic dilatation, skin and skeletal features, or isolated ectopia lentis, MIM 129600),³ and between 9 and 34% of *bona fide* Marfan patients have no identifiable fibrillin-1 mutations using current testing techniques.^{4,5} Recently, mutations in the transforming

growth factor β -receptor 2 (TGFBR2) gene on chromosome 3 and in the TGFBR1 gene on chromosome 9 were found in some families with apparent Marfan syndrome.^{6–8} These ‘Marfan syndrome type 2’ (MIM 154705)⁹ families seem less likely to have ectopia lentis. TGFBR2 mutations at the R460 codon have also been described in families with the chromosome 3-linked form of familial thoracic ascending aortic aneurysm^{10,11} (FTAA3, MIM 608967), and TGFBR1 and 2 mutations are found in Loeys–Dietz syndromes type 1 and 2.^{12,13}

To make the diagnosis of Marfan syndrome more consistent and of more prognostic value, the Berlin diagnostic criteria of 1988 were revised and the clinical features codified as the Ghent nosology in 1996.¹⁴ Using this, nosology should help identify which patients with a Marfan-like build are at risk of cardiovascular complications, needing regular follow-up with prophylactic medical and surgical treatment, and which can be reassured that



Figure 2 Boy aged 12 years 3 months with tall stature, joint hypermobility, a high arched palate with dental crowding, arachnodactyly and pes plenus. As he has no other clinical signs (particularly no eye signs), the diagnosis using the Ghent criteria can only be assured following echocardiography (showing a dilated aortic root), and with knowledge of his positive family history.

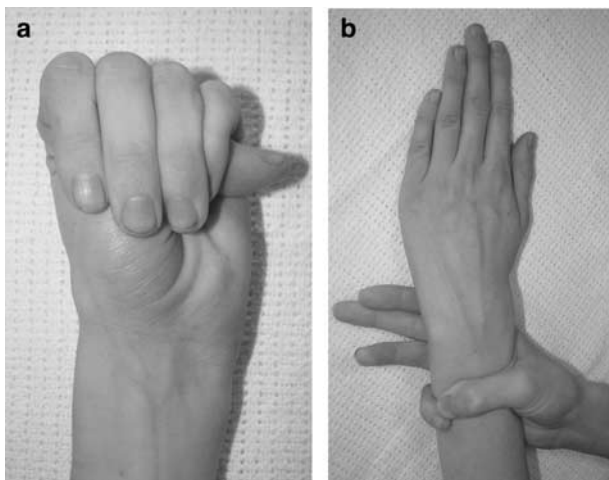


Figure 3 Arachnodactyly (a) positive thumb sign: entire thumb nail protrudes beyond ulnar border of hand. (b) Positive wrist sign: thumb and fifth finger overlap when encircling the wrist.

they are unaffected, avoiding the financial stigmatisation and lifestyle restrictions that may accompany the diagnosis. To further this aim, an integrated care pathway for clinical diagnosis and Scottish clinical guideline for management of Marfan patients was devised by a consensus group in 1999¹⁵ using SIGN methodology.¹⁶

Implementing the Ghent nosology using the Scottish pathway

In the Ghent nosology, clinical features are assessed within seven body 'systems', to determine whether that system provides a major criterion, or only system involvement (Table 1). A diagnosis of Marfan syndrome requires a major criterion in two systems and involvement of a third. The cardiovascular, ocular and skeletal systems can provide major criteria, or system involvement, the pulmonary system and skin/integument can provide only system involvement, the dura and family/genetic history provide only major criteria. The cardiovascular assessment requires measurement of the aortic diameter at the Sinuses of Valsalva, usually by transthoracic echocardiography (Figure 4), and comparison with normal values based on age and body surface area, calculated from height and weight.^{14,17} Other imaging techniques such as transoesophageal echocardiography or MRI scanning may be helpful in some cases. Assessment of the skeletal system should include pelvic X-ray to detect protrusion acetabulae,¹⁸ if a positive finding would provide system involvement, or change skeletal system involvement to a major criterion, such that a positive Marfan diagnosis could then be made in conjunction with other system findings. Similarly, lumbar MRI scan for dural ectasia, or genetic testing by linkage or mutation screening should be undertaken where a positive finding would make the diagnosis of Marfan syndrome. Ocular evaluation for myopia and lens subluxation requires ophthalmology assessment. The original nosology suggests measurement of axial globe length by ultrasound and keratometry, but these are not required in the Scottish pathway.¹⁵ Diagnosis in an index case and in a relative were originally described separately, as family/genetic history was assumed not to apply to an index case. The Scottish pathway allows the detection of a mutation known to cause Marfan syndrome (discovered in another family or known to affect fibrillin-1 function) to count as a major criterion in an index case, so that the same criteria may be applied to both index cases and relatives, as is implicit in the original nosology.

Because many Marfan features (echocardiographic findings,¹⁹ ectopia lentis, scoliosis, upper–lower segment ratio, protrusio acetabulae) are age dependent in their occurrence,^{20,21} younger patients with a family history of Marfan syndrome who do not fulfill the diagnostic criteria and younger Marfan-like patients with no family history who fail to meet the diagnostic criteria by one system should be offered repeat evaluations periodically (eg at least at ages 5, 10 and 15 years) until age 18.

The differential diagnosis of a tall, young person with Marfan-like skeletal features includes homocystinuria (MIM 236300), Beals syndrome (MIM 121050), Marshall–Stickler syndrome (MIM 108300, 604841, 184840), Ehlers–Danlos syndrome (MIM 130050) and MASS phenotype (MIM 604308). Where there is a family history of aortic

Table 1 Ghent diagnostic nosology

System	Major criterion	Involvement
Skeletal	At least 4 of the following features: <ul style="list-style-type: none"> ● Pectus carinatum ● Pectus excavatum requiring surgery ● ULSR <0.86 or span:height >1.05 ● Wrist and thumb signs ● Scoliosis >20° or spondylolisthesis ● Reduced elbow extension (<170°) ● Pes planus ● Protrusio acetabulae 	2 of the major features, or 1 major feature and 2 of the following: <ul style="list-style-type: none"> ● 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

Abbreviations: ULSR, Upper:lower segment ratio.

Having one of the features listed constitutes a major criterion or system involvement for all systems except the skeletal system, where more than one feature is needed.

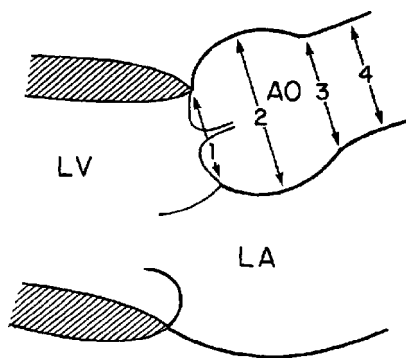


Figure 4 Diagram of the aortic root as seen at echocardiography. The aortic diameter should be measured at the aortic annulus (1), the sinuses of Valsalva (2), the supra-aortic ridge (3), and the proximal ascending aorta (4). In Marfan syndrome, dilatation usually starts at the sinuses of Valsalva, so this measurement is critical in monitoring the early evolution of the condition. Diameters must be related to normal values for age and body surface area. LV, left ventricle; LA, left atrium; Ao, aorta. After Roman *et al.*¹⁷

aneurysm, familial thoracic aortic aneurysm (FTAA) should be considered (MIM 607086, other features of Marfan syndrome may or may not be present). Additional clinical findings may suggest other disorders – bicuspid aortic valve and FTAA type 1 (MIM 607086), craniosynostosis, intellectual impairment and Shprintzen–Goldberg syndrome

(MIM 182212), arterial tortuosity or widespread aneurysms, hypertelorism, bifid uvula/cleft palate, craniosynostosis and Loey’s–Dietz syndrome type 1¹² (MIM 609192), arterial tortuosity or widespread aneurysms, visceral rupture, joint hypermobility, thin skin, and Loey’s–Dietz syndrome type 2¹³ or intellectual impairment, velopharyngeal insufficiency and Lujan–Fryns syndrome (MIM 309520). The initial evaluation of patients with possible Marfan syndrome requires a multi-disciplinary approach including clinical genetics, cardiology, ophthalmology and radiology.

Evaluating the use of the Ghent criteria

Assessment of a patient using the Ghent nosology requires evaluation of 30 clinical features. Interpreting the outcome can be complex, yet this nosology is the ‘gold standard’ for clinical diagnosis. The Scottish care pathway and clinical guideline were devised to make use of the nosology more practical in the clinic. Between 1999 and 2006, 232 individuals were evaluated for possible Marfan syndrome in Aberdeen using the integrated care pathway. They comprised 95 probands and 137 at risk relatives (Table 2). In 20%, Marfan syndrome could be unequivocally diagnosed using the Ghent criteria (24% of probands, 18% of

relatives), and in 66% (63% of probands, 67% of relatives) it could be unequivocally excluded. Ten patients from five families had FTAA, on the basis of a personal or family history or aortic root dilatation or dissection in the absence of other Marfan syndrome features. Five families had isolated ectopia lentis. One case of neonatal Marfan syndrome did not fulfill the criteria, although she had recurrent pneumothorax, aortic root dilatation and joint laxity. Fourteen patients from one family did not fulfill the Ghent criteria, but were thought to have Marfan syndrome, as they had a connective tissue disorder causing various features of Marfan syndrome in different individuals, including aortic dilatation and dissection, ectopia lentis and skeletal findings, segregating with fibrillin-1-linked DNA markers in the family. A definitely pathogenic fibrillin-1 mutation has not yet been detected, and no single individual fulfills the criteria independently. The three relatives whose Ghent assessment was 'uncertain' were all children, and will be re-assessed at follow-up. In children whose family diagnosis is Marfan syndrome (excluding the neonatal case), 7 were unequivocally affected, 17 were unequivocally unaffected and 3 were uncertain. Thus, the Ghent criteria did not establish Marfan status in 11% of children with a family history of Marfan syndrome, in keeping with the age-dependent penetrance of many Marfan features. This audit showed that the Ghent criteria were useful in diagnosing or excluding Marfan syndrome in 87% of probands and 85%

of relatives. An equivocal outcome of the Ghent assessment in a proband should prompt consideration of an alternative diagnosis and further individual and family investigation. Confirming reported family history is vital, as the criteria will be misleading in families where other conditions have predisposed to arterial rupture (eg Loeys–Dietz syndrome, FTAA). Children must be kept under review, as the criteria will not reliably exclude Marfan syndrome in those under 18 (Table 3). Although the criteria are very useful in classical Marfan syndrome, the rapidly emerging information about disease phenotypes associated with fibrillin-1, TGFBR2 and TGFBR1 mutations may require some revision to include disorders such as Loeys–Dietz syndrome and FTAA. This would allow their more general use to guide molecular investigation of families and identify individuals at risk of aneurysmal disease.

Molecular pathology of Marfan syndrome and related disorders

Classical Marfan syndrome is associated with mutation in fibrillin-1, an important component of the elastic microfibril. Fibrillin-1 is a 350 kD glycoprotein, synthesized as a 375 kD precursor that is processed and secreted into the extracellular matrix (ECM). It polymerises to form microfibrils and helps to stabilise latent transforming growth factor β -binding proteins (LTBPs) in the ECM. LTBPs hold transforming growth factor- β (TGF β) in an inactive state.⁹

Table 2 Application of Ghent criteria to Aberdeen Marfan clinic

Ghent outcome	Diagnosis	Probands	%	Relatives	%	Total	%
Ghent positive	Marfan	23	24	24	18	47	20
Ghent negative	FTAA	5	5	5	4	10	4
Ghent negative	EL	5	5	0	0	5	2
Ghent negative	Neonatal Marfan	1	1.5	0	0	1	1
Ghent negative	Marfan	1	1.5	13	9	14	6
Ghent negative	Uncertain	0	0	3	2	3	1
Ghent negative	Not affected	60	63	92	67	152	66
Total		95	100	137	100	232	100

Abbreviations: EL: isolated ectopia lentis; FTAA, familial thoracic aortic aneurysm.

Table 3 Key issues in the assessment of Marfan syndrome

- Diagnosis or exclusion of Marfan syndrome in an individual should be based on the Ghent diagnostic nosology.
- The initial assessment should include a personal history, detailed family history and clinical examination including ophthalmology examination and transthoracic echocardiogram.
- The aortic diameter at the Sinus of Valsalva should be related to normal values based on age and body surface area.
- The development of scoliosis and protrusio acetabulae is age dependent, commonly occurring following periods of rapid growth. X-ray for these features, depending on age, if a positive finding would make the diagnosis of Marfan syndrome.
- A pelvic MRI scan to detect dural ectasia is indicated if a positive finding would make the diagnosis of Marfan syndrome.
- The Ghent nosology cannot exclude Marfan syndrome in children, because of the age-dependent penetrance of many features.
- Younger patients with a positive family history but unsuccessful DNA testing and insufficient clinical features to fulfill the diagnostic criteria, and younger patients with no family history who miss fulfilling the diagnostic criteria by one system only should be offered further clinical evaluations at least until age 18, or until a diagnosis can be made.
- Family history of aortic aneurysm may represent a disorder such as familial thoracic aortic aneurysm, where the use of the Ghent nosology to assess risk in relatives is inappropriate.

A failure of the interaction between fibrillin-1 and LTBP5 may result in excess TGF β signalling.²² Most fibrillin-1 mutations are missense, suggesting a dominant-negative effect on microfibrillar assembly. Ectopia lentis tends to be associated with missense mutations causing cysteine substitutions within the epidermal growth factor – like domains of the protein, but nonsense and frameshift mutations are seen in other cases, suggesting that while cysteine residues are important to the function of the suspensory ligament of the eye, either abnormal fibrillin or reduced amounts of fibrillin (haploinsufficiency) may cause other aspects of the Marfan phenotype. Marked variability in severity has been documented – different mutations in the same codon can cause either severe neonatal Marfan syndrome, or classical adult Marfan syndrome. Similarly, mutations in the central region of the gene (exons 24–32), sometimes called the ‘neonatal region’, may be associated with phenotypes ranging from severe neonatal Marfan syndrome to isolated ectopia lentis.^{3,4,9} Although it was thought that abnormalities of microfibril structure might play an architectural role in causing the Marfan phenotype, it is now clear that the role of fibrillin-1 in regulation of TGF β signalling may be more pertinent. The discovery of TGFBR1 and TGFBR2 mutations in some cases supports this, as does evidence from mouse models.^{9,23} TGFBR1 or 2 mutation in humans are also associated with loss of elastin fibres and fibre disarray. Although the TGFBR1 and 2 mutations described so far are loss of function mutations, increased TGF β signalling was found in patient tissues and Marfan mouse models, and TGF β blockade by neutralising antibodies or angiotensin II type 1 (AT1) receptor blockers rescues the model phenotypes.^{9,12,24} The pathogenetic process must involve a complex disruption of TGF β signalling yet to be elucidated.

Aspects of clinical management in Marfan syndrome

Although clinical management of many genetic disorders is not backed by extensive trials and case series,¹⁵ there are a large number of published studies of Marfan syndrome. Some of these studies will now be reviewed, based on work carried out by the Scottish Marfan Guideline Group, to

provide a flavour of the evidence and dilemmas that influence Marfan management today.

Cardiovascular system in Marfan syndrome

Cardiovascular complications of Marfan syndrome include mitral valve prolapse and regurgitation, left ventricular dilatation and cardiac failure, pulmonary artery dilatation, but aortic root dilatation is the most common cause of morbidity and mortality (Table 4). Aortic valve incompetence usually arises in the context of a dilated aortic root, and the risk of aortic dissection increases when the diameter at the sinus of Valsalva exceeds 5 cm,^{17,25} when the aortic dilatation is more extensive, when the rate of dilatation exceeds 1.5 mm per year, and where there is a family history of aortic dissection.^{19,25–27} Myocardial infarction may occur if an aortic root dissection occludes the coronary ostia. Marfan syndrome mortality from aortic complications has decreased (70% in 1972, 48% in 1995) and life expectancy has increased (mean age at death 32 \pm 16 years in 1972 versus 45 \pm 17 years in 1998)¹ associated with increased medical and surgical intervention.

The Marfan aorta is characterised by elastic fibre fragmentation and disarray, paucity of smooth muscle cells, and deposition of collagen and mucopolysaccharide between the cells of the media. These appearances are sometimes described as ‘cystic medial degeneration’ although there are no true cysts present. Mucopolysaccharide deposition in the valves may cause valve leaflet thickening. Elastic fibre degeneration in the aorta is associated with reduced distensibility in response to the pulse pressure wave. This abnormal aortic compliance can be detected at any age by echocardiography²⁸ or gated MRI scanning,²⁹ although it is less marked in children. Reduction of the systolic ejection impulse by β -blockers might be expected to reduce the risk of aortic dissection in Marfan syndrome.¹⁹ Studies in turkeys prone to aortic dissection showed improved survival with propranolol and two trials in Marfan patients (a randomised trial of propranolol therapy and a retrospective historically controlled trial of propranolol or atenolol therapy) demonstrated a reduced rate of aortic dilatation and fewer aortic complications in

Table 4 Key issues in cardiovascular management

- β -Blocker therapy should be considered at any age if the aorta is dilated, but prophylactic treatment may be more effective in those with an aortic diameter of less than 4 cm.
- Risk factors for aortic dissection include aortic diameter greater than 5 cm, aortic dilatation extending beyond the sinus of Valsalva, rapid rate of dilatation (> 5% per year, or 1.5 mm/year in adults), and family history of aortic dissection.
- At least annual evaluation should be offered, comprising clinical history, examination and echocardiography. In children, serial echocardiography at 6–12 month intervals is recommended, the frequency depending on the aortic diameter (in relation to body surface area) and the rate of increase.
- Prophylactic aortic root surgery should be considered when the aortic diameter at the Sinus of Valsalva exceeds 5 cm.
- In pregnancy, there is an increased risk of aortic dissection if the aortic diameter exceeds 4 cm. Frequent cardiovascular monitoring throughout pregnancy and into the puerperium is advised.

the treatment group.^{19,30} Some patients respond better than others, responders tending to be younger and showing improved aortic distensibility, reduced pulse wave velocity, smaller pre-treatment aortic diameters (less than 4 cm in one study).^{19,26,28,30–32} Poor response may be associated with more extensive elastic fibre degeneration, either due to a more severe mutation or more advanced disease. β -Blockade should therefore be considered in all Marfan patients, including children. Some patients may not tolerate β -blockers, and alternative drugs which reduce the ejection impulse such as calcium antagonists,³³ and angiotensin converting enzyme (ACE) inhibitors have been considered. ACE inhibitors also reduce vascular smooth muscle cell apoptosis *in vitro* through an angiotensin II type 2 (AT2) receptor-dependent mechanism (apoptosis is implicated in the cystic medial degeneration seen in the Marfan aorta³⁴). This theoretical benefit may be in addition to any haemodynamic effects. Enalapril improved aortic distensibility and reduced the rate of aortic dilatation compared with β -blockers in one small clinical trial in children and adolescents.³⁵ In a mouse model, the AT1 receptor antagonist losartan reduced aortic growth rate, and prevented elastic fibre degeneration, presumably through effects on TGF β signalling as well as haemodynamic effects, although angiotensin II also stimulates Smad-2-dependent signalling in vascular smooth muscle cells and vessel wall fibrosis by an AT1 receptor-dependent but TGF β -independent mechanism.²⁴ As ACE inhibitors reduce angiotensin II production, they will act on both AT1- and AT2-dependent pathways – the benefit or otherwise of inhibiting both pathways is unknown. In another study, abnormal flow-mediated vasodilation of the brachial artery was demonstrated in Marfan patients, although agonist-mediated vasodilation was normal.³⁶ This was attributed to abnormal endothelial cell mechanotransduction associated with abnormal fibrillin. There may therefore be other molecular targets for future pharmacological intervention.

If medical treatment fails, and the aortic root dilates to 5 cm or more, then prophylactic surgery should be considered.^{14,25,37} One study suggests the threshold diameter should be 0.5 cm lower in affected women.²⁷ Other factors such as the rate of aortic growth, and family history of dissection should be taken into account. Numerous studies have shown better survival rates for prophylactic compared with emergency aortic surgery,^{25,38} and improved longevity for Marfan patients who undergo prophylactic surgery compared with their untreated relatives.³⁹ Alternative procedures include the Bentall composite graft repair, in which both the aortic root and the aortic valve are replaced, or a valve conserving technique such as re-implantation of the native aortic valve in a Dacron tube (described by David) or remodelling of the aortic root (described by Yacoub).^{40,41} The Bentall

procedure has a low mortality in experienced hands with long-term survival of around 80% at 5 years and 60% at 10 years,⁴² but requires lifelong anti-coagulation post-operatively, whereas valve conserving techniques may avoid the need for anticoagulation. Use of a valve-conserving procedure has been controversial as it is suggested that further deterioration of the aortic valve leaflets will require later valve replacement surgery. Recent case series have suggested that in expert hands, and in selected cases such as those where the aortic valve appears structurally normal (incompetence being due to annular dilatation), the long-term outcome is as good as the Bentall procedure, without the hazards of anticoagulation.^{43,44} There is certainly a case for considering this option for children, women of child-bearing age and those in whom anticoagulation may be hazardous. 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.³⁹ Continuation of long-term medical prophylaxis after surgery is therefore strongly recommended⁴² along with follow-up imaging of the descending and abdominal aorta.⁴¹ Other cardiac valves may also be involved – mitral valve surgery is required in up to 10% of those requiring aortic root surgery.³⁹

Ocular system

Ocular features of Marfan syndrome include bilateral ectopia lentis (40–56%), myopia (28%) and retinal detachment (0.78%).^{5,45} Lens dislocation into the anterior chamber may occur. Subluxation usually develops in early childhood, but may first appear in the second decade.⁴⁶ Myopia is associated with an increased length of the globe and an increased risk of retinal detachment.⁴⁷ Early detection and correction of refractive errors prevents amblyopia – correction after the age of 12 years is unlikely to restore visual acuity. Anisotropia (unequal refraction between the two eyes) and the possible anterior chamber abnormalities are further important considerations for management.⁴⁷ Ophthalmology assessment is important, and regular orthoptic review is recommended, particularly in childhood. Vitreolensotomy with laser prophylaxis to prevent retinal detachment can be effective in improving visual acuity in some patients.⁴⁸

Musculoskeletal system

Skeletal abnormalities develop and may progress during childhood. Scoliosis affects around 60% of Marfan patients and may progress rapidly during growth spurts, leading to marked deformity, pain and restricted ventilatory deficit.⁴⁹ In adults, back pain (associated with scoliosis) is three times more frequent than in the general population.⁴⁹ Occasionally scoliosis may progress in adult life especially

if the angle of curvature is $>40^\circ$. Back pain is said to be more common in patients with dural ectasia but the evidence for this is problematic. Dural ectasia is present in 69% of Marfan patients by CT scan, and 95% by MRI imaging.^{50,51} In a study of 32 patients, dural ectasia was present in 76% of those with back pain and 41% of those without.⁵² Treatment of dural ectasia to manage back pain remains speculative.⁵⁰ Similarly, bone mineral density appears to be reduced at the spine and hip in Marfan syndrome,^{53,54} but no associated increase in fracture rate has been observed.

Joint hypermobility is common, affecting 85% of children under 18, and 56% of adults with many patients suffering arthralgia, myalgia or ligamentous injury.⁵⁵ A Marfan-related myopathy with abnormal muscle fibrillin was described in one family⁵⁶ causing skeletal and respiratory muscle weakness. The significance of this for musculoskeletal symptoms in the wider Marfan patient group awaits further study.

Respiratory system

Pectus excavatum occurs in approximately two-thirds of patients with Marfan's syndrome, and when severe, can be associated with a restrictive ventilatory defect.^{57,58} It can cause difficulty with cardiac surgical procedures but correction is most often requested for cosmetic reasons. Patients with Marfan's syndrome are more likely to have delayed wound healing following repair of pectus excavatum.^{59,60} Surgical correction in children should be avoided, as recurrence is common in this age group.⁶⁰

Spontaneous pneumothorax occurs in 4–11% of patients and may be associated with apical bullae.^{61,62} Recurrence is common, and there should be a low threshold for surgical intervention. 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 β -blocker therapy.⁶³

Central nervous system

Dural ectasia may reduce the effectiveness of epidural anaesthesia,⁶⁴ and has been associated with intracranial hypotension-associated headache in a few case reports.⁶⁵ 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.⁶⁶ Cerebral haemorrhage and other neurovascular disorders are uncommon in Marfan patients,⁶⁷

but intracranial aneurysms may be more common in the Loeys–Dietz syndrome.¹³

Pregnancy in Marfan syndrome

The risk of aortic dissection in pregnancy is increased, probably due to inhibition of collagen and elastin deposition in the aorta by oestrogen, and the hyperdynamic hypervolaemic circulatory state of pregnancy.⁶⁸ Conditions such as gestational hypertension and pre-eclampsia may be additional risk factors.⁶⁹ Aortic dissection occurs in around 4.5% of pregnancies in women with Marfan syndrome⁶⁹ and the risk is greater if the aortic root exceeds 4 cm at the start of pregnancy, or if it dilates rapidly.⁷⁰ More frequent monitoring of aortic diameter in pregnancy is advisable. The rate of aortic dilatation is greater in women who have been pregnant with an aortic root diameter of more than 4 cm, than in women who have remained childless, or women with children whose aortic root is less than 4 cm.⁷¹ The long-term consequences of this are uncertain, but extrapolation might suggest an increased risk of later aortic dissection/aortic root replacement. If the aortic root dilates to 5 cm during the pregnancy, consideration should be given to immediate aortic replacement, early delivery or termination of pregnancy. No increased risk of spontaneous pre-term labour, spontaneous miscarriage or postpartum haemorrhage has been observed.

As Marfan syndrome is autosomal dominant, there is a 1 in 2 (50%) chance that the child of an affected person will inherit the disorder. Marfan patients seldom ask for prenatal diagnosis, although pre-implantation genetic diagnosis would be feasible in families with prior molecular work up in the genetic clinic. Ultrasound diagnosis is unreliable. Marfan patients should be offered genetic counselling before planning a family.

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.

Marfan syndrome and sports

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. Heart rate, systolic blood pressure and cardiac output increase during both dynamic exercise (eg running) and static exercise (eg weight lifting). Peripheral vascular resistance and diastolic blood pressure tend to fall during dynamic exercise, but increase during static exercise.⁷² Marfan patients should therefore avoid high intensity static exercise, but can be encouraged to participate in lower intensity dynamic exercise.^{41,73} 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.

Conclusion

The Ghent nosology remains the most effective way of diagnosing or excluding Marfan syndrome, provided its limitations with respect to children are not forgotten. It can help to identify families with aortic dissection who do not have Marfan syndrome, but it should not be used to assess risk in such families. Despite the morbidity and mortality associated with Marfan syndrome, appropriate medical and surgical management can improve and extend the lives of many patients, and advancing research holds the promise of further improvements in the future.

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