Marfan's syndrome: a review

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Marfan's syndrome is an inherited disorder of connective tissue, in which the most pronounced abnormalities occur in the musculoskeletal, cardiovascular and ocular systems. Aortic dilatation and dissection are the major causes of morbidity and mortality. Recent advances in surgical techniques and earlier intervention have reduced postoperative mortality and morbidity.

Antoine Marfan, a French paediatrician, described a 5-month-old girl with long and slender extremities and congenital contractures (Marfan, 1896). As noted by Missri and Swett (1982), it is not clear if this patient did, in fact, have what we now call Marfan's syndrome. Achard (1902), who also noted the familial incidence, introduced the term arachnodactyly. Borger (1914) described ocular abnormalities and Ormond and Williams (1924) made the association between lens displacement and arachnodactyly. Baer et al (1943) described aortic dissection and dilatation.

DIAGNOSIS

Marfan's syndrome is a disorder of connective tissue resulting from defective metabolism of fibrillin. Even though Kainulainen et al (1990) localized the gene responsible to chromosome 15, chromosome analysis is not currently practical for diagnostic purposes and the diagnosis is based mainly on clinical history and examination. Other connective tissue disorders have similar features, and diagnostic criteria for Marfan's syndrome have been put forward in an attempt to achieve some consistency in the diagnosis.

The diagnostic criteria are somewhat cumbersome and are likely to change with improvements in our understanding of the genetic defect. As reported by De Paepe et al (1996), it is recommended that there are major criteria in at least two different systems and involvement of a third organ system to make the diagnosis. This is outlined briefly below and clinicians interested in the precise recommendations for diagnosis will need to read their entire publication. Involvement of a system is defined as any of the minor criteria for skin, pulmonary and cardiovascular systems. For the ocular system, at least two minor criteria must be present and for the skeletal system, two major or one major and two minor should be present.

CLINICAL EXAMINATION

Many of the features given in *Tables 1* and *2* can be determined from a standard clinical examination. However, assessment of the cardiovascular, ocular and central nervous system requires specialist involvement. Lens dislocation can be missed and for a definitive diagnosis a slit lamp examination by an ophthalmologist is required. The clinical examination of the skeletal system is important. The facial features characteristic of Marfan's syndrome are the result of overgrowth of the long bones in the face, and this is also

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TABLE 1.
Major diagnostic criteria

Skeletal (four or more)	Pectus carinatum
	Pectus excavatum (severe)
	Reduced upper/lower segment ratio or arm span to height ratio >1.05
	Scoliosis (>20°)
	Pes planus
	Reduced elbow extension (<170°)
	Protrusio acetabulum (on X-ray)
	Wrist and thumb signs (see text)
Central nervous system	Lumbosacral ductal ectasia (computed tomography or magnetic resonance imaging)
Cardiovascular system (one or more)	Dilatation of the ascending aorta
	Dissection of the ascending aorta
Ocular	Ectopia lentis
Family history	First degree relative
	Presence of mutation in FBN1
	Haplotype around FBN1

FBN1= fibrillin-1-gene

responsible for the high arched palate. Careful measurement of the height and arm span is important and an arm span to height ratio greater than 1:1.05 is significant.

Hyperflexibility of the wrist is detected by trying to oppose the thumb to the forearm (*Figure 1*). Steinberg (1966) described the thumb protruding beyond the ulnar border of the clenched hand, which is the result of a combination of hyperflexibility and long bone overgrowth (*Figure 2*). If the distal phalanges of the first and fifth digits of the hand overlap and wrap around the opposite wrist, the Walker and Murdoch (1970) wrist sign is positive. The metacarpal index is a radiographical measurement where the length to width ratio of the metacarpal is measured (significant if greater than 1:8.0), and is not routinely performed.

DIFFERENTIAL DIAGNOSIS

There are a number of other conditions that need to be differentiated from Marfan's syndrome.

Homocystinuria

This is an autosomal recessive metabolic disorder associated with downward lens displacement and skeletal manifestations similar to Marfan's's syndrome. The presence of mental retardation would also suggest this diagnosis. Elevation of both methionine and homocystine in body fluids are the diagnostic laboratory finding. The diagnosis may be established by assay of the enzyme in liver biopsy specimens, cultured fibroblasts, or phytohaemagglutinin-stimulated lymphocytes.

TABLE 2.
Minor criteria for organ system involvement (see text)

Skeletal	Joint hypermobility
	Characteristic faces
	Pectus excavatum (moderate)
	High arched palate with crowding of teeth
Cardiovascular system	Mitral valve prolapse +/- mitral regurgitation
	Dilatation or dissection of descending aorta <50 years
	Dilatation of main pulmonary artery <40 years
	Calcification of mitral valve annulus <40 years
Ocular	Flat cornea
	Increased axial length of globe
	Reduced meiosis
Pulmonary	Apical blebs on chest X-ray
	Spontaneous pneumothorax
Skin	Striae atrophicae
	Recurrent incisional hernia

MASS phenotype

Myopia, Mitral valve prolapse, mild Aortic dilatation (less than two standard deviations above the expected diameter), Skin (striae) and Skeletal (minor criteria for Marfan's syndrome) involvement as described by Glesby and Pyeritz (1989).

Stickler's syndrome

This is a multisystem disorder which typically involves the eye (retinal detachment, myopia, and vitreoretinal degeneration), the craniofacies (midfacial hypoplasia, micrognathia and cleft palate), and mitral valve prolapse (Stickler et al, 1965).

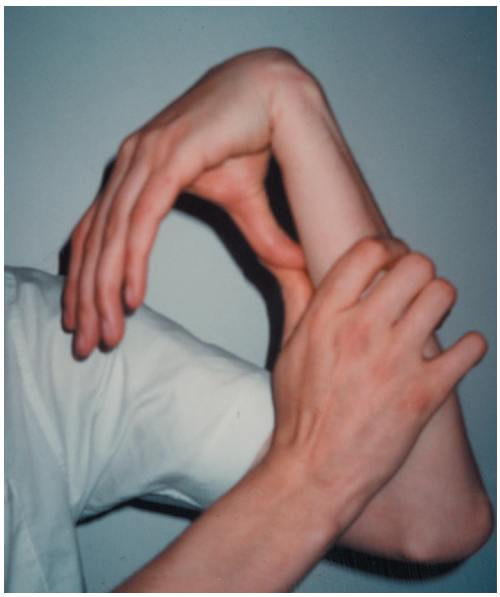

Figure 1. The wrist is flexed so that the thumb touches the forearm.

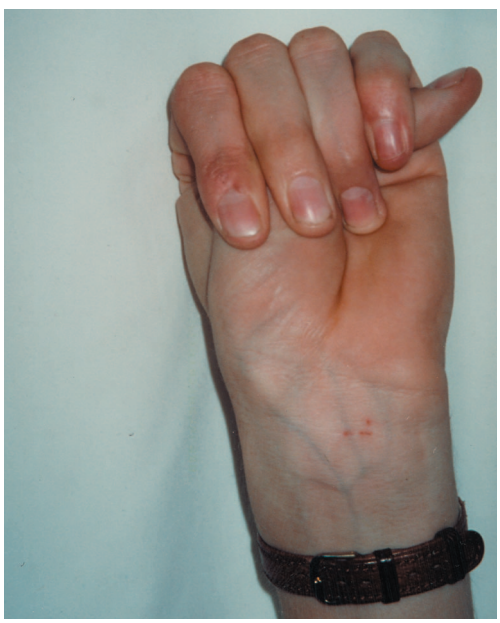

Figure 2. The thumb protrudes beyond the ulnar border of the closed hand (Steinberg's sign).

Other familial conditions

A number of other familial conditions (e.g. congenital contractural arachnodactyly or Beals' syndrome, familial thoracic aortic aneurysm, familial aortic dissection and familial mitral valve prolapse) may have some overlap with Marfan's syndrome, but are not currently diagnosed as such as they do not reach the diagnostic criteria.

CARDIAC COMPLICATIONS

Cardiac involvement is the major cause of morbidity and mortality in patients with Marfan's syndrome. The main cardiac complication is dilatation of the aorta and dissection is the main cause of premature death. The diagnosis of aortic root dilatation is made on cross section echocardiography with careful measurement of the aortic sinus and the sinotubular junction. This measurement is compared to the normal data provided by Roman et al (1989). As Roman et al (1993) have shown, aortic dilatation may either be fusiform or sacular and there is evidence that fusiform dilatation is more likely to dissect.

It is difficult to find an accurate incidence of aortic root dilatation and other cardiovascular abnormalities (mitral valve prolapse, aortic regurgitation) as most reports have significant selection bias. *Table 3* outlines some of the main studies and one can see that with the advent of echocardiography (in the mid-1980s), the detection of aortic root dilatation has increased. The main risk factors for aortic dissection are the maximum aortic diameter, the rate of increase in the aortic diameter and familial tendency to dissect. Sporadic cases also tend to do worse in terms of risk of aortic dissection. Any patient that is diagnosed or suspected of having Marfan's syndrome should have echocardiographical assessment. If the aorta is dilated it needs to be followed up regularly. The frequency of follow-up will depend on the actual size and the change from any previous measurements. Even though major aortic complications are relatively rare in childhood they are well recognized.

MEDICAL TREATMENT

A study by Shore et al (1994) on adolescent and adult patients with Marfan's syndrome randomized 32 patients to treatment with β-blockers and 38 to being untreated controls. After an average follow up of about 9 years, clinical end points (aortic regurgitation, aortic dissection, cardiovascular surgery, congestive heart failure or death) were reached in five of the treatment group and nine of the control group. The survival curve for the treatment group was significantly better and the mean slope of the aortic root dimensions was also less than the treated group. Based mainly on the results of this study many centres routinely prescribe β-blockers for children and adults with aortic root dilatation.

SURGICAL TREATMENT

In Marfan's syndrome both the aortic and mitral valves are at risk. Both valves may develop regurgitation either primarily as a result of the connective tissue problem or as a result of dilation or dissection of the aorta. The aortic root may require operation either electively or because of life-threatening sequelae related to aortic dissection.

Current recommendations for replacement or repair of the ascending aorta are based on the size of the aorta, rate of growth of the aorta and familial tendency to dissection. In patients with a positive family history of premature rupture of

TABLE 3.
Prevalence of cardiac involvement in patients with Marfan syndrome from literature review and population studies

Author	Year	No	Age	Data	Finding
Rados	1942	204	5 weeks–61 years	Literature review	32% Cardiac abnormalities
Goyette and Palmer	1953	34	?	Autopsy	30–60% Cardiovascular system lesions
McKusick	1955	105	?	Clinical/autopsy	44% Cardiovascular system lesions
Phornphutkul et al	1974	36	1 day–15 years	Clinical	61% Cardiac abnormalities
Brown et al	1974	35	3–61 years	Clinical	54% Abnormal cardiac
				Echo	60% Aorta root dilation
Sisk et al	1983	15	<4 years	Clin/Echo	69% Aorta root dilation
Geva et al	1987	25	0–16 years	Clin/Echo	80% Aorta root dilatation and aortic regurgitation
el Habbal	1992	186	<1–20 years	Clin/Echo	80% Aorta root dilatation and ascending aorta
Gillinov et al	1997	26	8 months–17 years	Echo	81% Aorta root dilatation

the ascending aorta, surgery is usually considered if the measured:expected aortic diameter is over 1.3 (this would correspond to a measured aortic diameter of 4.3 cm in an average adult with a surface area of 2 m^2). In patients with a negative family history of dissection, surgery is recommended if the ratio is over 1.5 (this would correspond to an aortic diameter of 4.8–5 cm in an average adult with a surface area of 2 m^2).

The surgical options are to replace the ascending aorta with a composite graft, incorporating a mechanical valve (*Figures 3a* and *b*), or undertaking a valve-sparing operation (*Figure 4*). The native aortic valve can be preserved in selected patients. A dacron tube graft is used to replace the dilated aorta and the native valve is resuspended as shown in *Figure 4*. The advantage of this operation is that anticoagulation may be avoided. However, the long-term results of this operation are not yet known and it is possible that aortic regurgitation may develop and aortic valve replacement is required eventually.

INHERITANCE

Marfan's syndrome is inherited as a Mendelian autosomal dominant trait. Aoyama et al (1993) reported that children might not be affected in the same way as parents (variable penetrance and expressivity). The mutation of the fibrillin-1 gene (FBN1) is located on the long arm of chromosome 15. However, DNA diagnosis of Marfan's syndrome is not routinely available for clinical practice because FBN1 is a large glycoprotein that has a repetitive domain structure. A total of 137 FBN1 mutations have been characterized in individuals with Marfan's syndrome by Dietz et al (1995), which are distributed throughout the FBN1 gene. All but 25 of the 137 reported mutations are unique to an affected individual or family.

Milewicz (1998) identified the major problems preventing the molecular diagnosis of Marfan's syndrome. FBN1 mutations are now known to cause not only Marfan's syndrome, but also a spectrum of phenotypically-related conditions. The mutational screen needs to be done for every family or isolated case (almost all mutations are unique), and the entire gene needs to be either screened for mutations or sequenced (which would be prohibitively expensive).

PREGNANCY

A number of cardiovascular problems, as described by Elkayam et al (1995), have been described during pregnancy and the risk of having affected offspring also needs to be explained to patients of childbearing age. The risk of aortic dissection significantly increases with pregnancy. There have been a number of reports of fatal dissections during or shortly after delivery. When these studies are reviewed it appears that if the aortic root is less than 4 cm before pregnancy, the risk of a complication is very low. However, if the aortic root dimension is greater than 4 cm, and in particular if it is greater than 4.5 cm, there is a significant risk of further dilatation and even more serious complications. Vaginal delivery is permissible in patients with Marfan's syndrome with no aortic dilatation.

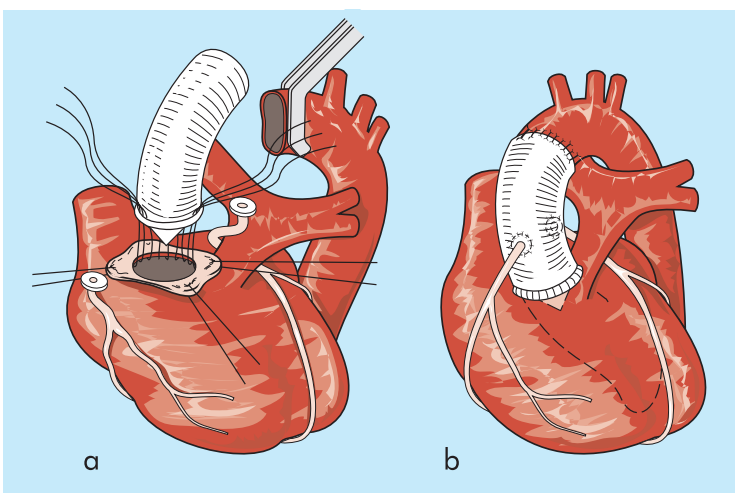

Figure 3. Replacement of the ascending aorta with a composite graft. a. The dacron tube graft with the prosthetic valve is sewn into position at the aortic annulus. b. The coronary arteries are re-implanted into the dacron tube.

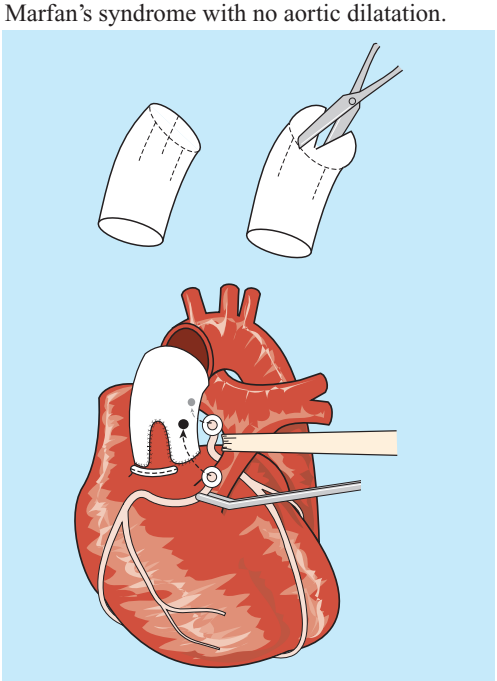

Figure 4. Aortic root replacement using a valve sparing technique. The dacron tube is cut to join it to the native aorta at the sinotubular junction. The native valve is preserved and the coronary arteries re-implanted.

In patients with mild aortic dilatation active pushing should be minimized, and therefore the second stage expedited. Antibiotic prophylaxis is usually recommended for the delivery. In patients with significant aortic root dilatation (as defined above), delivery may be hazardous and therefore caesarean section under general anaesthesia is usually preferred in an attempt to minimize the surges in blood pressure. It must be emphasized that the management of each individual case will need careful planning with close liaison between the cardiologist, obstetrician and obstetric anaesthetist.

EXERCISE

Most physical activities involve both dynamic and static demands, although one may predominate. Braverman (1998) reported that strenuous physical activities and contact/collision sports are dangerous for those with Marfan's syndrome because of the risk of aortic dissection. Isometric exercise such as gymnastics and weightlifting should be avoided. Activities that risk rapid changes in atmospheric pressure like flying in unpressurized aircraft and scuba diving should also be avoided.

THE FUTURE

There will undoubtedly be advances in the molecular diagnosis of Marfan's syndrome in future. At present it seems that each kindred has a unique mutation and gene tracking is not available for clinical use. The rather cumbersome diagnostic criteria will probably need to be revised in future years in line with advances in the understanding of genetic defects. Follow-up of patients who have had conservative surgery on the aortic valve at the time of root replacement will help clarify whether or not this is a feasible long-term strategy. At the moment there remain a number of unanswered questions with regard to Marfan's syndrome. The difficulty of precise diagnosis makes it hard to give an accurate population prevalence figure. It is still not possible to completely predict those patients who will dissect. Managing these patients in dedicated clinics offers the best chance of providing answers to these and other questions. HM

Conflict of interest: none.

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KEY POINTS

- Marfan's syndrome is inherited as an autosomal dominant trait with variable penetrance.
- The major cause of premature death is dissection of the aorta.
- Careful monitoring of the aortic root by cross-sectional echo is important particularly in patients with a positive family history of aortic dissection.
- Cardiac assessment is particularly important before undertaking pregnancy as the risk if dissection is increased.
- Aortic root replacement is required in certain patients and some cases can be carried out with preservation of the native aortic valve.