The Cardiac Society of Australia and New Zealand

Guidelines for the diagnosis and management of Marfan Syndrome

1. Clinical Characteristics

1.1   Definition and prevalence

Marfan syndrome (MFS) is an autosomal dominant connective tissue disorder involving the cardiovascular, skeletal and ocular systems, the integument, lungs and dura. Cardinal manifestations include aortic aneurysm and dissection, ocular lens dislocation and long bone overgrowth. In 90-93% of cases, MFS is caused by mutations in *FBN1*. Mutations in a second gene, *TGFBR2*, have been shown to cause MFS, designated MFS2. Current early estimates quote this gene as responsible for up to 10% of all MFS cases. The prevalence of MFS is at least 1/5,000 and 25% of cases are sporadic. Penetrance is extremely high. Isolated cases with no family history are often more severely affected. Several examples of "homozygous" MFS have been reported. Gonadal mosaicism is rare (probably <1%). Compound heterozygosity at the *FBN1* locus is very rare.

1.2   Clinical presentation

MFS demonstrates both intra- and inter-familial variability. Each child of an affected parent has a 50% chance of inheriting a disease-causing gene mutation, with males and females equally at risk. Clinically affected individuals often present with tall stature and dolichostenomelia (decreased upper:lower segment ratio; arm span: height ratio >1.05), but may present with lens dislocation, aortic dilatation or with skeletal manifestations such as pectus deformities and/or scoliosis. MFS is usually associated with normal intelligence, unless due to deletion of *FBN1* and additional neighbouring genes.

1.3   Clinical diagnosis

The diagnosis of MFS is based on recently revised Ghent criteria (Loeys BL et al. The revised Ghent nosology for the Marfan syndrome. J Med Genet 2010;47:476-485), which places more weight on the cardiovascular manifestations and in which aortic root aneurysm and ectopia lentis are the cardinal clinical features. In the absence of any family history, the presence of these two manifestations is sufficient for the unequivocal diagnosis of MFS. In the absence of either of these two, the presence of a bonafide *FBN1* mutation or a combination of "systemic manifestations" is required. For the latter, a new scoring system has been designed, that guides diagnosis when aortic disease is present, but ectopia lentis is not. In this revised nosology, *FBN1* testing, although not mandatory, has greater weight in the diagnostic assessment. Special considerations are given to the diagnosis of MFS in children and alternative diagnoses in adults. The new guidelines are predicted to delay a definitive diagnosis of MFS in some individuals, but will decrease the risk of premature diagnosis or misdiagnosis.

Diagnostic dilemmas arise because of inter- and intra-familial variability. Many features of MFS (e.g. mitral valve prolapse, scoliosis) are also common in the general population, or may occur in other connective tissue disorders. Many manifestations are age-dependent. The clinical criteria in the revised Ghent nosology cannot always be applied to children, particularly those with sporadically occurring disease. Known associations with early death include new mutation, family history of dissection at <5cm (aortic root diameter), male sex, and emergency surgery where the death rate is five times higher than in elective surgery. Pregnancy bears a 1% risk of fatal complication; this risk increases with increasing aortic root diameter.

The diagnosis of MFS is largely clinical and pragmatic, based on what can be done to define the phenotype in any given case. Investigations listed may not be practical for every patient. Wherever possible, clinical examination should include:

1) AP x-ray of spine for scoliosis of >20° or spondylolisthesis.
2) AP x-ray of pelvis for protrusioacetabulae.
3) Lumbosacral MRI or CT for duralectasia. MRI is not appropriate for anyone with an indwelling defibrillator. Prevalence figures for duralectasia range from 65-92%. Whilst usually asymptomatic, it may cause nerve root compression, intracranial hypotension headaches and may mimic an acute abdominal emergency. Determination of duralectasia has been shown to establish a diagnosis of MFS under the Ghent criteria in 25% of patients.
4) Ophthalmology examination including slit lamp. Optometry is inadequate.
5) Cardiology evaluation. The abdominal aorta may be involved, although the usual site of dilatation is the thoracic aorta.
6) Accurate height and weight measurements to allow calculation of body surface area.
7) Use of appropriate nomograms for plotting aortic root dimension. There is unresolved controversy about this; several different nomograms have been published. Whilst it is unclear which of these is the most appropriate to use in the paediatric and adult MFS populations, the Ghent nosology recommends the use of the nomograms established by Roman et al. (Am J Cardiol 1998;64:507-512).
8) Urine metabolic screen or fasting plasma amino acids (in absence of supplemental pyridoxine) to exclude homocystinuria for the first person in the family being evaluated for MFS.
9) Chromosome karyotype to exclude Klinefelter syndrome in any individual with predominant skeletal features.
10) Screening of first-degree relatives with echocardiogram +/- ophthalmological examination.

Family history: A detailed family history and a high level of clinical suspicion are essential.

Family screening: See (9) above.

1.4   Differential Diagnosis

MFS is the most common syndromic presentation of ascending aortic aneurysm, but vascular Ehlers-Danlos syndrome and Loeys-Dietz syndrome (LDS) also have ascending aortic aneurysms, with the risk of aortic dissection and rupture. Familial segregation of the risk for ascending aortic aneurysm may occur in the absence of associated systemic findings of a connective tissue abnormality in patients with familial thoracic aortic aneurysm and dissection (FTAAD) or bicuspid aortic valve with ascending aortic aneurysm (BAV/AscAA). LDS features that overlap with MFS, include arachnodactyly, pectus deformity, scoliosis, duralectasia, and aortic root aneurysm. Cardiovascular involvement can include congenital heart malformations, but most importantly, patients show widespread and aggressive vascular disease with arterial tortuosity and a strong predisposition for aneurysms and dissections throughout the arterial tree. Mutations that cause LDS occur in either of the two genes that encode the TGF-β receptor (*TGFBR1* and *TGFBR2*). The phenotype designated LDS-II may mimic the vascular sub-type of Ehlers-Danlos syndrome (*COL3A1* gene), and is associated with mutations in the *TGFBR* genes. Mutations in *TGFBR2* have been reported in patients described as having MFS or FTAAD (thoracic aortic aneurysms (prominently of the ascending aorta) in the absence of systemic vascular disease or features of a connective tissue disorder). There are no apparent differences between the mutations that cause LDS and those described as causing MFS or FTAAD. Many of the identical mutations described as causing MFS or FTAAD have been found in families with LDS-I or LDS-II.

2. Molecular Genetics

2.1   MFS genes

FBN1: DNA diagnostic services for *FBN1* testing for MFS and related clinical entities (*TGFBR1*, *TGFBR2*) are available. Prenatal diagnosis is available where a familial mutation is known, but cannot predict disease severity. For women with MFS in whom a pregnancy is contraindicated, pre-implantation genetic diagnosis and surrogacy may be possible.

2.2   Genetic screening

Mutation screening of *FBN1* should yield a result in up to 97% of MFS patients who meet the Ghent criteria, and is much lower in those who do not meet the criteria. Only 1-2% of cases are thought to be due to large deletions; these would not be identified by DHPLC. In the absence of a *FBN1* mutation in a "Ghent positive" case, *TGFBR2* screening may be appropriate.

3. Management

3.1   Affected individuals

These are best discussed on a case by case basis with an expert in the relevant field.

Cardiac: Serial echocardiographic surveillance is indicated for all affected individuals. Frequency should be tailored to each individual by their cardiologist. Based on current evidence, the use of ß-blockers remains first-line treatment (except where contra-indicated eg asthmatics) in aortic dilatation in MFS even in young children if a diagnosis of MFS is clear, or if there is a known *FBN1* mutation in a young child without clinical features of MFS but where there are other affected first degree relatives with a known mutation and aortic root dilatation. There is no published scientific or longitudinal data to prove that prophylactic ß-blockade prior to the development of aortic enlargement is necessarily of benefit. When β-blockade is ineffective or contraindicated, verapamil or ACE inhibitors would constitute appropriate second-line treatment based on the currently available human data. Preliminary evidence suggests that angiotensin converting enzyme (ACE) inhibitors (eg perindopril) may be useful in MFS. TGFβ antagonism by the angiotensin II type 1 receptor blocker, losartan, was shown to prevent aortic aneurysm and partially reverse impaired alveolar septation in a mouse model of MFS. Large multi-centre prospective clinical trials comparing β-blockers with losartan in adult MFS are in progress (USA). A small number of children with severe aortic dilatation have been treated with losartan, either alone or in addition to β-blockers, with up to four years of follow-up. These data demonstrate a significant reduction in aortic root growth. The NHLBI-sponsored Pediatric Heart Network is currently conducting a study in children and young adults with MFS. MFS mouse models have shown that the matrix metalloproteinase inhibitor, doxycycline, improved aortic wall architecture and delayed aortic dissection. It is possible that doxycycline and losartan will show synergistic effects.

Prophylactic aortic root replacement in MFS carries a risk of death of 1-2%. Symptomatic aneurysms have a much worse prognosis than asymptomatic ones, and should be resected regardless of size. There is an operative mortality of up to 20% for acute ascending aortic dissection in MFS. MFS patients who suffer aortic dissection have a significantly reduced long-term survival, reported at 50-70% at 10 years. This underscores the importance of prophylactic aortic surgery before aortic dissection occurs in MFS. Recent guidelines have suggested that prophylactic aortic surgery be performed in adults with MFS when the aortic root diameter exceeds 5cm. Aortic surgery should also be considered in MFS when the aortic root exceeds 4.5cm and there is a family history of aortic dissection, when there is rapid aortic growth (>5-10mm per year), and when significant aortic insufficiency is present. After surgical resection of an aortic aneurysm, initially yearly evaluation with CT or MRI is recommended to evaluate for aortic graft pseudo-aneurysm, coronary artery aneurysms (rare, but may occur some years after Bentall procedure) and coexistent aneurysms in other aortic segments. The interval between scan could be gradually increased in stable patients as clinically indicated, interval echocardiography to image the aortic root could be considered in patients with adequate echocardiographic windows.

Ocular: Annual ophthalmological examination is indicated for all affected individuals. Removal of lenses may be indicated if vision is very poor. Intraocular pressure measurement is recommended to monitor for glaucoma.

Skeletal: Orthopaedic referral may be indicated for progressive scoliosis. Bracing or spinal fusion may be necessary. In children, x-ray of the wrist may be indicated to assess final predicted height and the need for referral to an endocrinologist for hormone therapy if final height prediction is unacceptable. Surgery is possible for severe pectus deformity.

Pulmonary: Spontaneous pneumothorax should be considered in any MFS patient with sudden onset chest/pleuritic pain, associated dyspnoea or cyanosis. Rarely, emphysematous lung change may occur. Referral to a respiratory physician for evaluation of pulmonary function may be indicated. A few MFS patients develop progressive lung disease and may require lung or heart/lung transplantation.

CNS: Intracranial hypotension associated with CSF leak from dural ectasia may be severe and debilitating, requiring hospitalisation and autologous blood patch for symptomatic relief. Cerebral imaging may show an apparent Arnold Chiari-type malformation. This is actually downward tonsillar herniation secondary to low CSF pressure; neurosurgical "decompression" does not ameliorate the symptoms and should be avoided.

Pregnancy, labour and delivery: Pre-pregnancy counselling should include full discussion of the risks and benefits of pregnancy and the alternatives (childlessness, tubal ligation, adoption, surrogate pregnancy). Pregnancies are a high-risk period and should be managed through a "high risk" obstetric clinic. Dissection occurs most often in the last trimester or early post-partum period. Full assessment should be performed before pregnancy and include echocardiogram of the heart and entire aorta. Women with a maximal aortic dimension <4cm are at very low risk for a rapid change in aortic size or aortic tear during pregnancy or immediately after delivery. Outcomes for women with aortic diameters of <4cm at the time of delivery are similar for vaginal and caesarean section delivery. These women have a 1% risk of aortic dissection, endocarditis or congestive cardiac failure during pregnancy. Women with aortic dimensions >4cm are at greater risk (up to 10% risk of dissection); this risk increases proportionally to aortic size. Echocardiograms should be performed at least three-monthly during pregnancy. The overall risk associated with aortic measurement of ≥4.5cm is greater than that associated with a measurement of 4cm. The risk associated with an aortic measurement >5cm is extreme, and pregnancy is difficult to justify. The risk is lower for pregnancy following elective aortic root replacement for aortic diameters of ≥4.7cm. These women require echocardiographic monitoring of the remaining aorta every 6-8 weeks throughout pregnancy and for 6 months post-partum. Beta-blockade should be continued throughout the pregnancy. Each pregnancy should be supervised by a cardiologist and obstetrician. Epidural analgesia is recommended for labour and delivery to maintain stable blood pressure. Involuntary Valsalva manoeuvres should be avoided. If normal delivery is planned, the second stage should be expedited. Women may labour on their left side or in a semi-erect position to minimise stress on the aorta. Management of delivery in women with more significant aortic dilatation (≥4.5cm) remains controversial; caesarean section is often advised. It may be most prudent to deliver these women by caesarean section without labour using epidural anaesthesia. Epidural anaesthesia is safe for most women, but is not advised in those with moderately severe duralectasia because of the risk of spinal CSF leak.

Exercise: Physical education and activity guidelines are available through the National Marfan Foundation website: www.marfan.org/marfan/2728/Physical-Activity-Guidelines/. Competitive and collision sports may precipitate aortic dissection or rupture. Static (isometric) exercise and activities such as weight-lifting, climbing steep inclines, gymnastics and push-ups should be avoided. Dynamic (isokinetic) exercise increases heart rate and cardiac output but also decreases peripheral resistance. Patients with a dilated aortic root can participate in certain isokinetic activities but at a decreased level of intensity. High intensity, competitive sports should be avoided.

3.2   Asymptomatic family members

Annual clinical examination is indicated in asymptomatic family members +/- screening investigations, depending on the clinical context. If a familial FBN1 mutation has been identified, predictive testing in children will identify those at risk of MFS and those in whom no annual surveillance is necessary.

3.3   Genetic counselling

The diagnosis of a genetic disorder in a family and the possibility of testing for the disorder raise a number of issues. Involvement of genetics professionals (clinical geneticists and genetic counsellors) should be considered. All family members potentially at risk should receive genetic counselling, lifestyle modification advice and where appropriate, counselling with regard to carrier options.

For Further Information:
www.chw.edu.au/research/groups/hgrp/research/marfan_research_group.htm

Reference

Loeys BL et al. The revised Ghent nosology for the Marfan syndrome. J Med Genet 2010;47:476-485 http://diagnosticcriteria.net/marfan/reprints/Loeys-2010-JMedGenet-47-p476-485.pdf