Anaesthesia for *Marfan's Syndrome*

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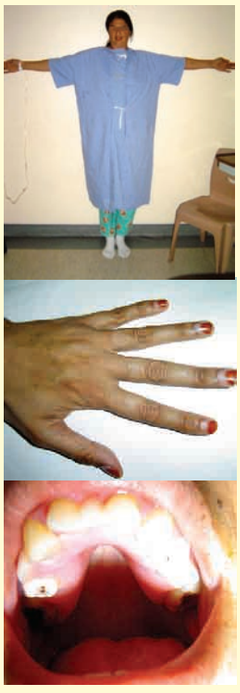


CASE REPORT
A 35 year-old female with Marfan's Syndrome, presented for medical termination of pregnancy at 8 weeks' gestation. She had no family history of Marfan's. Despite having undergone dental work for teeth overcrowding, her first medical presentation was with severe aortic regurgitation and cardiac failure in 2003. At that time she underwent urgent aortic valve and aortic root replacement. She has been followed up bi-annually, relatively uneventfully, at cardiac clinic. She is well controlled on furosemide and a beta-blocker, Carvedilol. She had no symptoms of congestive cardiac failure (CCF) and was graded as NYHA class 2. She is also taking warfarin and haematinics.

Although she is in regular contact with the health care system, she claims to have little knowledge regarding her diagnosis in terms of prognosis, natural history and lifestyle issues. The patient informed cardiologists of her plans to fall pregnant, but appeared not to have been advised against this. Only on referral to cardiology, once already pregnant, was she sternly advised to terminate the pregnancy in order to avoid potentially catastrophic cardiovascular consequences associated with pregnancy in patients with Marfan's syndrome.

On examination she is a tall, thin lady with a "wingspan" greater than her height. She has long spidery fingers, dental overcrowding and a high-arched palate. Skeletal anomalies included kyphoscoliosis, pectus carinatum, hypermobility of her joints and pes planus. She had a sternotomy scar, regular pulse, mechanical second heart sound, a soft systolic murmur but no evidence of cardiac failure. Her chest was clear. She had no striae or hernias. ECG showed no significant abnormalities.

Warfarin was changed to heparin prior to the termination. Heparin was stopped 6 hours prior to surgery. No premedication was ordered. She was carefully positioned to reduce the risk of joint trauma or dislocation. She received an intravenous induction with propofol/fentanyl and maintenance with isoflurane, while breathing spontaneously via a face mask. The procedure was uneventful. While she remained in hospital for re-warfarinizing, she complained of a visual field disturbance. This was diagnosed as retinal detachment. She subsequently underwent uneventful surgical correction of the retinal detachment prior to discharge.

Introduction

Marfan's Syndrome (MFS) was first described in Paris in 1896 by a French paediatrician, Antoine Marfan. The first to use the term Marfan's syndrome was Henriculus Weve in Utrecht, Nederland in 1931. Recently it has been argued that in fact the 5 year old girl described by Marfan may have had Beals syndrome (contractural arachnodactyly), a syndrome that has a very similar phenotype but the defect is in fibrillin-2 gene.

MFS is a multisystem disorder with a prevalence of 1/3000-1/5000, occurring in all racial groups. It is an autosomal dominant condition, with variable expression. The pathology is related to mutations of the fibrillin-1 gene (FBN-1). Two gene loci have been identified – the majority have abnormalities at 15q21, others at 3p24.1.[1-3] 25% of cases represent a new mutation.

Fibrillin is an important component of microfibrils, and is essential for the integrity of both elastic and non-elastic connective tissue. Abnormal fibrillin alters the elasticity and tensile strength of connective tissue, particularly in areas where fibrillin is abundant such as the proximal aorta, zonule of the lens in the eye; in long bones and the skin.[1]

Some of the clinical manifestations of MFS cannot be explained by mechanical properties alone. Recent studies suggest that dysregulation of transforming growth factor beta (TGFbeta) signalling in lung, mitral valve and aortic tissues has been implicated in a subset of patients with MFS.[3, 4]

Although discovery of the gene loci may allow for laboratory diagnosis in the future, diagnosis is still largely based on clinical features. The diagnostic criteria used by Ghent include a family history and involvement of at least two organ systems; or three organ systems if a mutation is suspected. [5, 6]

Clinical manifestations

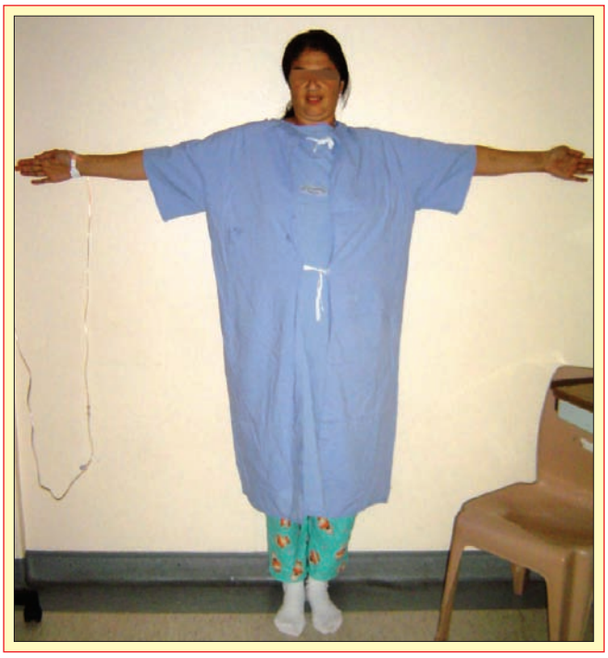
The skeletal, cardiovascular and pulmonary systems are the major systems involved.[5-7] These are of particular relevance to the anaesthesiologist.

Skeletal abnormalities

Skeletal abnormalities resulting from disproportionate length of the long bones are pathognemonic of Marfan's syndrome. Patients are tall and thin with an arm span greater than their height (Figure 1). Arachnodactyly (long thin spidery fingers) (Fig 2) and high-arched palate with secondary dental overcrowding (Fig 3) are also common findings.

When growth is asymmetric, kyphoscoliosis results. Sternal abnormalities (pectus excavatum or carinatum) are thought to be due to excessive rib growth. In addition joints are hypermobile

Figure 1: Individuals with Marfan's syndrome are typically tall and thin; their arm length ("wingspan") is greater than their height. The plastic stool is 75cm high for reference.



and can sublux or dislocate easily. Pes planus (flat-feet) with medial rotation of the medial malleoli on standing is another common problem.

Dural ectasia i.e. a widening or ballooning of the dural sac surrounding the spinal cord, has been described[8] This ectasia, usually at the lumbosacral level, causes an enlargement in the spinal canal and an increased volume of CSF at that site. This may affect the dose required for spinal anaesthesia to achieve an adequate level of blockade.[8]

Cardiovascular manifestations

Cardiovascular manifestations are the main cause of morbidity and mortality in MFS.[4] Weakened arterial media results in aortic dilatation and aneurysm formation. Dilatation of aortic ring progresses to aortic valve regurgitation. Aortic dissection is also common and usually involves the aortic arch proximal to the innominate artery. Pulmonary dilatation is less common but is seen in severely affected individuals.

Dilatation is slowed by beta-blocker therapy, by decreasing aortic wall stress. However the likelihood of rupture increases greatly once the aortic root width exceeds 4-5cm. At this point surgical correction becomes the treatment of choice. Redundant mitral chordae causing mitral valve prolapse and mitral regurgitation may compound the cardiac compromise.

Pulmonary manifestations

Pulmonary manifestations[5-7] may have extrinsic or intrinsic causes. Extrinsic causes secondary to pectus excavatum, (less commonly pectus carinatum), and kyphoscoliosis interfere with pulmonary mechanics. A restrictive pattern may be evident on lung function tests.

Intrinsic lung disease is related to the loss of elasticity of the lung. Bronchogenic cysts and emphysema can develop, progressing to a honeycomb multicystic lung. Loss of elastic tissue in the small airways increases the closing volume. Pulmonary blebs, typically in the apex, can rupture causing a spontaneous pneumothorax. Pharyngeal laxity and high arch palate may contribute to obstructive sleep apnoea.

Figure 2: Long thin spidery fingers (arachnodactyly) are a typical feature of MFS. Cultural staining of the finger nails is noted.

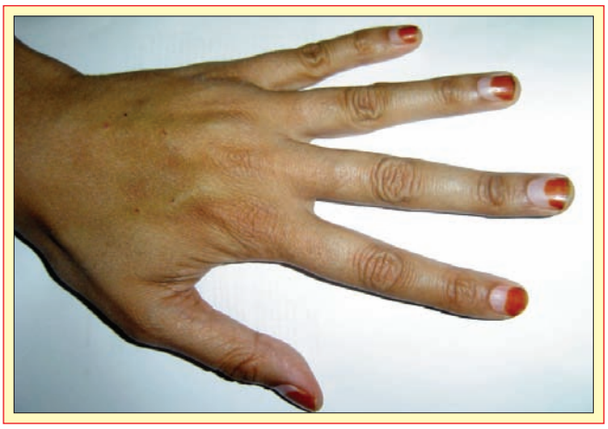
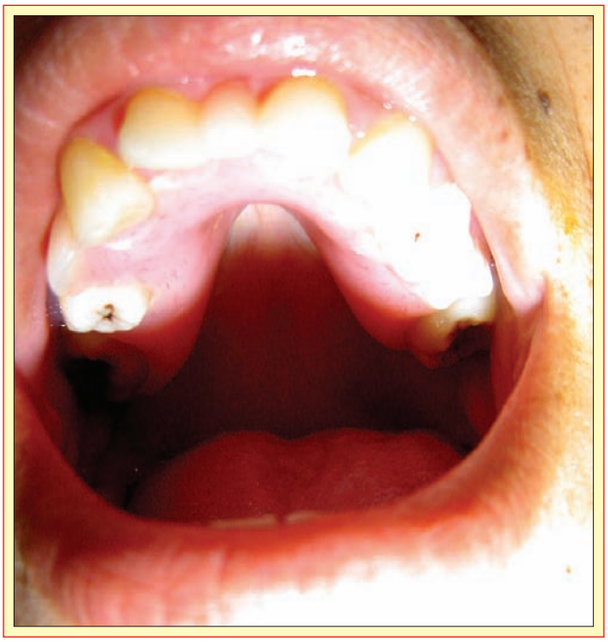


Figure 3: High-arched palate with secondary dental overcrowding may require orthodontic treatment. This patient has had teeth removed - a central crown is in place to improve the cosmetic appearance.



Eye manifestations

Eye manifestations[9] result from weakened ligaments of the lens. The lens may sublux or dislocate. The globe may be elongated and this contributes to myopia or glaucoma, which are common problems in these patients. MFS patients are also at increased risk of retinal detachment.

Other manifestations

Other manifestations[5, 6] involve connective tissue of the skin. MFS sufferers may develop striae and abnormal scarring. Poorly developed peripheral musculature and defects in the abdominal wall may present as recurrent hernias at any site.

MFS patients presenting in the neonatal period are severely affected and are usually the result of a *de novo* mutation.[10] Affected neonates are long, have arachnodactyly, contractures and cardiac disease. Mitral insufficiency is the more common primary manifestation. Tricuspid regurgitation and other vascular findings may also be present.

Pregnancy-related issues
Prior to falling pregnant, patients should be counselled regarding the risk of inheritance as well as the increased risk for complicated pregnancy, including potentially catastrophic events.[1, 11-13] The risk of inheritance in offspring is 50%.

In addition, embryopathy needs to be considered. Foetal exposure to warfarin during the first eight weeks of pregnancy may cause abnormal development of the facial structures (nasal hypoplasia), hypoplastic digits, stippled epiphyses, and mental retardation. Mid-trimester exposure may result in optic atrophy, faulty brain growth, and developmental retardation. Third-trimester exposure may produce foetal anticoagulation.[14] Anti-hypertensives, including beta-blockers, may also affect foetal growth.[15]

Parturients are at significant risk of aortic dissection even in the absence of any cardiovascular abnormality prior to conception.[1, 11-13] This risk increases with advancing gestational age and continues up to 6 weeks post partum.

In addition, there are obstetric or neonatal complications in up to 40% of all completed pregnancies. Prematurity is common, mainly due to premature rupture of membranes and cervical incompetence.[1, 11]

Anaesthetic considerations
Patients may present for elective orthopaedic, cardiovascular or ocular surgery, or emergency surgery for aortic dissection or urgent valve replacement. The risk of perioperative morbidity and mortality, including unexplained death, is high.[14] Careful preoperative evaluation and investigation is essential.[16, 17] Cardiovascular functional status needs to be assessed, including ECG, cardiac catheterization, MRI and echocardiography as indicated to assess the size of the aortic root and valvular function. Cardiac surgical intervention may need to be considered prior to incidental major elective surgery, depending on the cardiovascular status of the patient. Control of blood pressure is vitally important to minimize shear forces and wall stress in the aorta to decrease the risk of aortic rupture or dissection.[18] Beta-blockers should therefore be continued perioperatively. Pulmonary function tests, with or without arterial blood gas should be considered if thoracic skeletal abnormalities are severe. This is particularly important when the contribution of cardiac or pulmonary function on effort tolerance is in dispute, and difficult to assess.

In patients with valve replacements, antibiotic prophylaxis and conversion from warfarin to heparin anticoagulation should be carried out timeously.

Intraoperatively, careful positioning of the patient is important to prevent damage to lax joints. Monitoring will vary according to functional status. Utmost care must be taken when placing arterial lines, endotracheal tubes and probes to prevent damage to weakened tissues. Control of the airway may be difficult, secondary to facial abnormalities (malar hypoplasia and retrognathia); however difficult intubation per se has not been described. Forceful use of the laryngoscope may cause dislocation or subluxation of the temporo-mandibular joint. Ventilatory pressures must be kept as low as possible to prevent barotrauma and to reduce the risk of pneumothorax. Tracheomalacia has been reported as a potential complication.[19]

Regional anaesthesia is not contraindicated but may be technically difficult. Coagulation status will need to be addressed in those on anticoagulants. Lax ligaments, connective tissue of lower tensile strength and kyphoscoliosis all contribute to the difficulty, while dural ectasia may alter the dose of local anaesthetic required for spinal anaesthesia.[8] Dural ectasia was thought to be responsible for the failure to attain an expected level of blockade in two reported cases.[8]

Anaesthesia in pregnancy
There is a general lack of consensus about the optimal anaesthetic and obstetric management during labour and pregnancy.[1, 16-17] Timing of delivery is a balance between risk and benefit to both mother and fetus. Pregnancy should be allowed to continue as long as possible to allow for fetal maturity. Serial echocardiography antenatally to evaluate root size and valve function are essential to prevent unnecessary risk to the mother.[1, 4]

The mode of delivery depends on the mother's cardiovascular status.[11-14] Normal vaginal delivery is possible if no cardiovascular abnormalities are present. If aortic root width is greater than 40mm or other cardiovascular abnormalities exist, then caesarean section is the preferred method of delivery.[12]

Successful general and regional anaesthesia have been described for both normal vaginal delivery and caesarean section. Evaluation of cardiovascular status and a multidisciplinary approach are key in this decision.[1, 11] Aggressive control of hypertension is important to keep delivery as haemodynamic stable as possible.

Conclusion
Geneticists continue to unravel the secrets of MFS. Research on TGFbeta signalling and the potential treatment role of TGFbeta antagonists may lead to exciting new treatments, but the results of clinical trials are awaited.[3, 4]

For anaesthesiologists, perioperative morbidity and mortality is high in patients with MFS, especially MFS parturients. Anaesthetic management includes careful investigation of the organ systems involved. A multidisciplinary approach is key. While no one technique is superior, prevention of hypertension remains the single most important factor in minimizing cardiovascular complications. **SAJAA**

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