Abstract

Marfan’s syndrome (MFS) is an autosomal dominant connective tissue disorder where ophthalmic problems are often the presenting symptom in childhood. Diagnosis is based on established criteria outlined by expert opinion in 1996, known as the Ghent criteria. These criteria have recently been revised, and place more weight on two cardinal features of MFS: ophthalmological and cardiovascular pathology. Ophthalmologists thus have a prominent role to play in both diagnosis and lifelong care for MFS patients. This article aims to outline the presentations of ocular pathology and diagnostic challenges for aspiring ophthalmologists who will be key members of the multi-disciplinary team in future. In light of the revised Ghent classification, ophthalmology trainees must have a low threshold for investigation of a suspected MFS patient with a working knowledge of the diagnostic criteria. This will allow prompt correction of the sight threatening complications of MFS and early initiation of long-term monitoring of the life-threatening cardiovascular complications.

Keywords: marfan’s, ghent nosology, ectopic lentis, marfanoid habitus, pathological myopia

Introduction

Marfan’s syndrome (MFS) is a connective tissue disorder with autosomal dominant inheritance first described in 1891 by AntoineBernard de Marfan. It is characterised by cardiovascular, musculoskeletal and ocular complications relating to a mutation in the fibrillin gene on chromosome 15 and 21 (FBN1). The protein that this gene encodes is an integral component of elastin, a structural protein. MFS has a prevalence of approximately 5 per 100,000. Those affected often have the classical marfanoid features of tall stature, scoliosis, chest wall deformities, acetabular protrusion, arachnodactyly and a resultant association with pneumothoraces (Figure 1). The cardiovascular complications include valvular insufficiency, aortic aneurysms and dissection, aortic root dilatation and mitral valve prolapse. Dural ectasia, a weakening of the dural sac connective tissue, is the main CNS-related manifestation of MFS, causing headaches, back pain and other neurological symptoms. Ophthalmologists are familiar with MFS as it can seriously affect vision, through the characteristic supero-temporal bilateral lens subluxation, as well as its associations with cataract, myopia, retinal detachments and early onset glaucoma.
MFS in the media

MFS has attracted media attention in recent years with physicians and historians postulating the presence of the disease in celebrities past and present who demonstrate the characteristic morphological features. Perhaps the most well-known of these is the swimmer Michael Phelps, whose dominance in his sport must, in part, be attributed to his tall stature, and wide arm span, both features of MFS. He assures us in his autobiography that this is not the case, but in doing so he has unintentionally raised the profile of this rare condition.

Moreover, since 1954 a debate has raged since paper published in the Journal of the American Medical Association suggested that Abraham Lincoln may well have suffered from this condition. Lincoln, was famously almost 6 ft 4 tall by the age of 17, which was particularly unusual in the 19th century. He was also described as having a ‘strange shaped chest’ ‘spider-like legs’ and ‘loose joints’ by friends and physicians alike, which seemed to fit the morphological description of MFS. It was also suggested that Lincoln’s facial features were commonly blurred in photographs because he suffered from aortic regurgitation, causing the characteristic ‘nodding dog’ or De Musset’s sign. The debate was re-ignited with the discovery of the causative genetic defect in 1991 and lead to a number of attempts to retrieve his DNA from clothing and bone fragments, all to no avail. More recently it has been decided that there is not enough conclusive evidence to support the retrospective diagnosis of MFS in Abraham Lincoln, but the speculation has nonetheless brought the disease into the public eye.

Diagnosis

Whilst there is a known associated genetic mutation, the diagnosis of MFS remains clinical despite the fact that the condition is notoriously phenotypically heterogeneous. Molecular approaches and identification of the FBN1 gene can aid in the diagnosis of MFS in pre-symptomatic individuals and prenatally. However, currently the genetic testing reveals only a high correlation rather than causality, and there is association with the FBN1 gene and several other similar disorders such as familial ectopia lentis, familial aortic aneurysm and congenital contractural arachnodactyly. With this level of overlap between disorders, the testing provides less than 90% sensitivity, a low level of specificity and is a costly process. Hence, diagnosis has been shown to be most successful through history, examination and investigation with a slit lamp and echocardiogram. MFS diagnostic criteria was first classified as the Berlin criteria in 1988, followed by the Ghent classification in 1996. The classifications have been revised to reduce risk of over-diagnosis using a set of major and minor criteria, and in 2010 a revised Ghent classification system was adopted. The ocular

Figure 1 | Marfanoid appearance. Features include tall, slender stature, arachnodactyly, pectus deformation, arm span>height. Glasses suggest myopia and there is evidence of facial features of MFS Reproduced courtesy BMJ.
features of MFS have always been played an important role in the accurate diagnosis of the disease. There is variation in the development of the pathognomic features of MFS over time, and the ocular pathology tends to be among the earlier features to develop. In particular, myopia is often the first thing noticed by the patient, hence ophthalmologists have a key early role in the diagnosis and subsequent management of MFS patients. Ectopia lentis makes up one of the major features of the diagnostic criteria, whilst in the past increased axial length of the globe – causing myopia, and a hypoplastic iris or ciliary muscle – have made up minor criteria. The Ghent classification was revised by a multi-national panel in 2010, and the outcomes have subsequently placed more emphasis on the cardiovascular and ocular manifestations of MFS, of which aortic root aneurysm and ectopia lentis are the cardinal clinical features (Table 1). In the absence of any family history, the presence of these two manifestations is sufficient for the diagnosis of MFS.

Ophthalmological Problems

The extent of ocular pathology relates to a deficiency in the structure and function of FBN1-containing microfibrils, which are present in the cornea, scleral stroma, zonular fibres, iris and ciliary body, Bruch’s membrane, choroid and vitreous. FBN1 is a force-bearing structural protein that provides elasticity and tensile strength and is crucial to maintaining structural integrity. MFS is the most frequent cause of heritable ectopia lentis, occurring in 75% of patients. Myopia occurs in 28% of MFS patients and retinal detachment in approximately 5-11%. Ectopia lentis is a displacement or malpositioning of the lens. Classically, the direction of lens dislocation occurs in a bilateral, symmetrical, and superior temporal pattern (Figure 3). It is considered to be dislocated when it lies outside of the lens patellar fossa, floating freely in either the vitreous, the anterior chamber (AC) or directly apposed to the retina. Lens dislocation occurs due to a dysfunction of the zonular fibres of the lens and hence why it tends to be bilateral, symmetrical and non-progressive. The patient may present clinically if there is significant dislocation with a either new onset of monocular or binocular diplopia. Mild subluxation can be monitored where no visual disturbance is evident. Severe dislocation requires surgical intervention in order to avoid amblyopia, with lensectomy and correction with contact lenses or replacement of an intra-ocular lens. The indications for lensectomy include lens-induced uveitis, glaucoma, visual impairment and refractive error not suitable for optical correction. There is a higher risk of complications in MFS due to the weak connective tissues, causing ocular instability. Lens-induced inflammation, glaucoma and post-operative retention of lenticular material may contribute to ocular

<table>
<thead>
<tr>
<th>Table 1</th>
<th>The Revised Ghent criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>In Absence of Family History:</td>
<td></td>
</tr>
<tr>
<td>• Aortic root dilatation/dissection + Ectopia Lentis = MFS</td>
<td></td>
</tr>
<tr>
<td>• Aortic root dilatation/dissection + FBN-1 mutation = MFS</td>
<td></td>
</tr>
<tr>
<td>• Aortic root dilatation/dissection + *Systemic score &gt;7 = MFS</td>
<td></td>
</tr>
<tr>
<td>In Presence of Family History:</td>
<td></td>
</tr>
<tr>
<td>• Ectopia Lentis + Family History = MFS</td>
<td></td>
</tr>
<tr>
<td>• Systemic score &gt;7 + Family History of Marfan’s = MFS</td>
<td></td>
</tr>
<tr>
<td>• Aortic root dilatation/dissection + Family History = MFS</td>
<td></td>
</tr>
</tbody>
</table>

*Systemic Score

<table>
<thead>
<tr>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wrist and Thumb sign</td>
</tr>
<tr>
<td>Pectus carinatum</td>
</tr>
<tr>
<td>Hindfoot deformity</td>
</tr>
<tr>
<td>Pneumothorax</td>
</tr>
<tr>
<td>Protrusio acetabula</td>
</tr>
<tr>
<td>Dural Ectasia</td>
</tr>
<tr>
<td>Reduced upper segment to lower segment ratio AND no severe scoliosis</td>
</tr>
<tr>
<td>Scoliosis or thoracolumbar kyphosis</td>
</tr>
<tr>
<td>Reduced elbow extension</td>
</tr>
<tr>
<td>Facial features (3/5) (dolichocephaly, enophthalmos, downslanting palpebral fissures, malar hypoplasia, retrognathia</td>
</tr>
<tr>
<td>Skin striae</td>
</tr>
<tr>
<td>Myopia &gt;3 diopters</td>
</tr>
</tbody>
</table>
hypertension, inflammation and corneal oedema. The technique for lensectomy is also modified in the MFS eye where fewer zonular fibres or complete dislocation may require that the intact capsule be excised. Lack of capsular support necessitates either an anterior chamber lens or iris-clip lens. Modern lenses have fewer complications than a sutured lens into the ciliary sulcus which carries a higher risk of endophthalmitis and rupture.

Another alternative is to leave the eye aphakic and use contact lenses instead. MFS is also associated with a flattened cornea and increased axial length and therefore myopia. Elongation of the globe is known as posterior staphyloma and results from scleral thinning. Myopia is found in 38-44% of patients as opposed to ectopia lentis which is found in 50-80%. It can be treated using spectacles or contact lens correction, however this cannot reverse or arrest the progression completely. The use of laser-assisted in-situ keratomileusis (LASIK) as a treatment alternative is also contraindicated as the cornea may continue to change shape throughout the patient’s life. Myopia is a minor criterion for the Ghent nosology, and its incidence is even higher with ectopia lentis and retinal detachment in MFS patients. The most serious complication of MFS is retinal detachment, which is most frequent in the presence of ectopia lentis. This can occur bilaterally and tends to occur in younger male patients. It is a particular diagnostic challenge as the small pupils and lens abnormalities make visualization with a slit-lamp more difficult. It is thought that the longer Marfanoid eye is associated with earlier liquefaction and detachment of the vitreous, and the dislocated lens can exert traction which leads to retinal tears. Glaucma is also a known ocular manifestation of MFS, most commonly open-angle glaucoma. Other types include chronic angle-closure, phacolytic and neovascular glaucoma. In phacolytic glaucoma, a posterior dislocation can cause shear stress on the vitreous with resultant vitreous traction and leakage of lens protein into the vitreous causing inflammation. It is thought that the mechanism behind angle closure can be either due to pupillary block via an ectopic lens or vitreous brought forward by dislocation. Chronic angle closure may be precipitated by the formation of peripheral synchiae and attachment to adjacent tissues of the lens. There have been isolated case reports where chronic anterior lens subluxation has been misdiagnosed as primary angle-closure glaucoma; patients are treated with conventional medical therapy and laser iridotomy/iridoplasty in the first instance, but the dislocated lens is left undiagnosed resulting in a chronically recurring raised IOPs, with predictable effects on the optic nerve. In extremely rare cases anterior lens dislocation has resulted in acute angle-closure glaucoma secondary to a pupillary block.

Figure 2 | The wrist and thumb sign. This is where top of the thumb covers the little finger when wrapped around the wrist of the other hand. Image reproduced courtesy of National Marfan Founda-

Figure 3 | Ectopia lentis bisecting the pupil in MFS on slit lamp examination. Image reproduced courtesy of EyeRounds.org.
small number of case reports have suggested that these patients should be treated with laser iridotomy followed by surgical lens extraction. Indeed, in true anterior lens dislocation the use of miotics has been shown to exacerbate the pupillary block by allowing further forward movement of the lens. Correctly diagnosing a dislocated lens as the cause of angle-closure glaucoma is therefore of paramount importance in these patients. Glaucoma secondary to lens subluxation has also been described in similar inherited conditions including homocysteinuria and Weill-Marchesani syndrome. Some advocate the use of prophylactic iridotomies in these patients, something which may be worth considering in high-risk MFS patients.

Discussion

Visual complaints are frequently the first presentation of MFS. Usually, this complaint is related to myopia, therefore ophthalmologists or opticians are frequently the first involved. Subluxation usually develops in early childhood but may first appear in the second decade. Therefore, this places responsibility on ophthalmologists, as prompt diagnosis is essential to helping tailor patient management in order to minimise the risk to sight. For example, early detection and correction of refractive errors prevents amblyopia, whilst correction after the ages of 8-12 years is unlikely to restore visual acuity. A key part of the ophthalmic community’s role should be devoted to counselling and patient education, in terms of promoting understanding and awareness of riskier behaviours; for example, since ocular stability and strength are compromised in MFS, contact sports or activities that include jolting the body should be actively discouraged or at least mitigated. Anisotropia and anterior chamber abnormalities are further important considerations for management. Moreover, techniques such as vitreolensectomy with laser prophylaxis will remain crucial in the prevention of retinal detachment, and in some patients this can be effective in improving visual acuity.

Conclusion

With greater emphasis on the ocular complications of MFS and a renewed recognition of the role of ophthalmologists and orthoptists, it may be possible in future to identify these patients early and follow them closely, providing greater patient education and an improved long-term prognosis. MFS patients are challenging for the ophthalmic surgeon, as a result of them being young patients with thin sclera and poorly dilating pupil, making retinal examination more difficult - in particular detecting peripheral and posterior breaks in integrity. However, improved surgical techniques and an emphasis on the current recommendation of annual follow up by paediatric ophthalmologists to prevent amblyopia and to detect refractive errors will ensure that new problems are detected early and sight preservation is increased.

Acknowledgements

The authors would like to thank BMJ, EyeRounds.org and Marfan Foundation for granting permission to use the images.

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Ophthalmological Problems in MFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ectopia Lentis</td>
<td>Retinal Detachment</td>
</tr>
<tr>
<td>Glaucoma (open-angle, chronic angle closure, phacolytic and neovascular)</td>
<td>Strabismus</td>
</tr>
<tr>
<td>Myopia</td>
<td>Iridodenesis (tremulous iris)</td>
</tr>
<tr>
<td>Flattened corneal curvature</td>
<td>Early onset cataracts</td>
</tr>
<tr>
<td>Astigmatism</td>
<td></td>
</tr>
</tbody>
</table>
References


LEARNING POINTS

- MFS is a complex systemic disorder whose diagnosis remains primarily clinical.
- Much responsibility is placed on ophthalmologists as the first presentation of the disease is often associated with ocular pathology and there is potential for ongoing ophthalmological problems.
- It is imperative that ophthalmology trainees have a working knowledge of the condition, the Ghent criteria and the investigations that need to be carried out in suspected cases.
Test Yourself

1. The diagnostic criteria for Marfan’s syndrome are known as the:
   (a) Brussel’s criteria
   (b) Ghent criteria
   (c) Lincoln criteria
   (d) Quebec criteria

2. Within the diagnostic criteria are the following except:
   (a) Pneumothorax
   (b) Femur Sign
   (c) Dural Ectasia
   (d) Protrusio acetabula

3. Which of the following is the most commonly occurring ocular manifestation of Marfan’s?
   (a) Amblyopia
   (b) Myopia
   (c) Ectopia lentis
   (d) Cataracts

4. In what direction does the lens most commonly dislocate?
   (a) Anterior
   (b) Superior-temporal
   (c) Supero-nasal
   (d) Infero-nasal

MFS is a complex systemic disorder whose diagnosis remains primarily clinical. Much responsibility is placed on ophthalmologists as the first presentation of the disease is often associated with ocular pathology and there is potential for ongoing ophthalmological problems. It is imperative that ophthalmology trainees have a working knowledge of the condition, the Ghent criteria and the investigations that need to be carried out in suspected cases.