The Neurosurgical Manifestations of Marfan Syndrome

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Background

Antoine-Bernard Marfan first described the skeletal manifestations of Marfan's syndrome (MFS) in 1896. Since then, a variety of associated clinical manifestations have been identified and numerous diagnostic criterions for MFS proposed. Following the identification of *FBN1* as a causal gene for MFS, more stringent diagnostic criteria were put forth, referred to as the 'Ghent nosology' [1]. This employed a set of 'major' and 'minor' manifestations of MFS in numerous tissues. It has been criticised as difficult to use in children, that it includes non-specific physical manifestations and has poorly validated diagnostic thresholds. To address these issues a 'revised Ghent nosology' was proposed [2] based on clinical characteristics of large published patient cohorts and expert opinion. These systems include systemic features relevant to neurosurgical practice, most notably the identification of dural ectasia (DE). This chapter focuses on the diagnosis and management of this condition and discusses some of the other possible spinal and cerebro-vascular sequelae of MFS relevant to neurosurgical practice.

Dural Ectasia (DE)

Definition and Pathophysiology

Dural ectasia has been defined as: "enlargement of the neural canal anywhere along the spinal column, but nearly always in the lower lumbar and sacral regions; thinning of the cortex of the pedicles and laminae of the vertebrae; widening of the

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neural foramina; or an anterior meningocele." A more recent definition of DE is widening of the dural sac or spinal nerve root sleeves, usually associated with bony erosions of the posterior vertebral body [3]. In MFS, it is typically identified in the lumbosacral spine and associated with the thinning of adjacent osseous structures. DE is one of the 'major' criteria in the Ghent nosology and has an incidence ranging from 63 to 92 % in Ghent positive patients [4, 5].

DE is considered a sign of potential MFS however is not specific to the syndrome. DE has been observed in scoliosis, neurofibromatosis [6], ankylosing spondylitis [7, 8] and Ehlers-Danlos syndrome [9] as well as following trauma. It has been suggested that DE may be more a sign of inherited connective tissue disorders than MFS alone, as DE has been found in persons with mutations in *TGFBR1* and *TGFBR2* genes, some of these individuals fulfilling the Ghent criteria, and some not [10–12]. It is proposed that defective fibrillin results in abnormally weak connective tissues causing incompetence of the dural sac. This theory is supported by the fact that the ectasia mostly occurs in the caudal portions of the spinal column, where the cerebrospinal fluid pressure is highest with the patient in the upright position [4, 13]. Animal studies of dural ectasia have shown increased levels of TGF-b in the dura [14] correlating with the current understanding of MFS as a fibrillin-1 deficiency resulting in an increased expression of TGF-b [15].

Clinical Presentation

In the majority of cases, DE is asymptomatic and may only be identified incidentally on imaging studies or as part of clinical surveillance. The range of commonest reported symptoms in patients with radiologically confirmed DE, based on previous studies, are summarised in Table 19.1.

The prevalence of moderate to severe back pain in patients with MFS is common [17], reportedly in as many as 53 % of patients in the largest series [18] however DE may be present without any significant back pain [16]. The amount of pain may correlate with the intradural volume (i.e. severity of ectasia). Interestingly, this is not the case in MFS patients with associated spinal dysraphism. This may be because the enlarged bony canal in dysraphia allows more room for the DE to expand without eroding vertebral structures [16]. The pathophysiology of DE pain is not fully understood. Theories include: direct pressure on the periosteum, erosion

Table 19.1 Frequency of symptoms in MFS patients with radiologically confirmed dural ectasia [16]

Symptom	Incidence (previous studies)	%
Back pain	20/63	31.7
Headache	5/16	31.3
Radiculopathic leg pain	8/30	26.7
Neurologic deficit	3/36	8.33
Gait abnormality	1/19	5.3
Abdominal pain	1/20	5.0
Sphincter disturbance	3/20	15.0

of structural lumbosacral elements, nerve root traction and sacral bone thinning resulting in microfractures [17, 19–22]. Symptoms associated with anterior meningoceles associated with MFS include abdominal discomfort, constipation and incontinence and are discussed later in this chapter [16, 22–24].

Headache is reported in approximately 30 % of MFS patients with DE. In the majority of cases, patients report an improvement when they are in the supine position. A direct association between the volume of ectasia and presence of headache has not been found; however, there may be an association between headache and persistent CSF leak from DE, which is considered later in the context of intracranial hypotension.

It is rare to identify neurological deficits in patients with MFS-associated DE [4, 22]. However neurological deficits have been observed in DE associated with ankylosing spondylitis [25, 26]. There are also reports of radiculopathic dysfunction (pain and weakness) due to DE and scoliosis associated with MFS in adults [27]. Less common presentations of DE in MFS include sepsis [28], where enteric flora (e.g. E.coli) may enter into the central nervous system via recto-thecal fistulas and vertebral/meningeal anomalies.

Natural History

The natural history of dural ectasia in MFS is relatively unknown [14, 29]. In one study, dural ectasia was noted in 40 % of children with MFS at a median age of 12.6 years [30]. A 10 year follow up study of patients with MFS-associated DE, (age range 40–60 years old), did not identify any significant change in imaging features, supporting the concept that dural ectasia size peaks during adolescence or early adulthood and then plateaus [5]. The same study did not identify a significant increase in Oswestry Disability Index (ODI) scores, dural volume or any progression of any associated spondylolisthesis [5].

Diagnosis

A number of methods of how to best assess DE in MFS have been reported using conventional radiographs, CT, and MR imaging [9, 29, 31, 32], yet no gold standard for DE diagnosis has emerged. A number of radiologic features of DE have been defined (Figs. 19.1 and 19.2), including:

- Anterior sacral meningocele: herniation of a dural sac via a defect in the anterior sacral surface [33] or through a widened foramen.
- Lateral herniation of the dura along the nerve root sleeves [29] (widened root sleeve throughout the neuroforamen).
- Dural sac ratios (DSR) >0.48 at L5 and >0.57 at S1. DSR is the ratio between the dural sac diameter (DSD) measured on the midline sagittal image and the vertebral body diameter (VBD) at the same level [32].

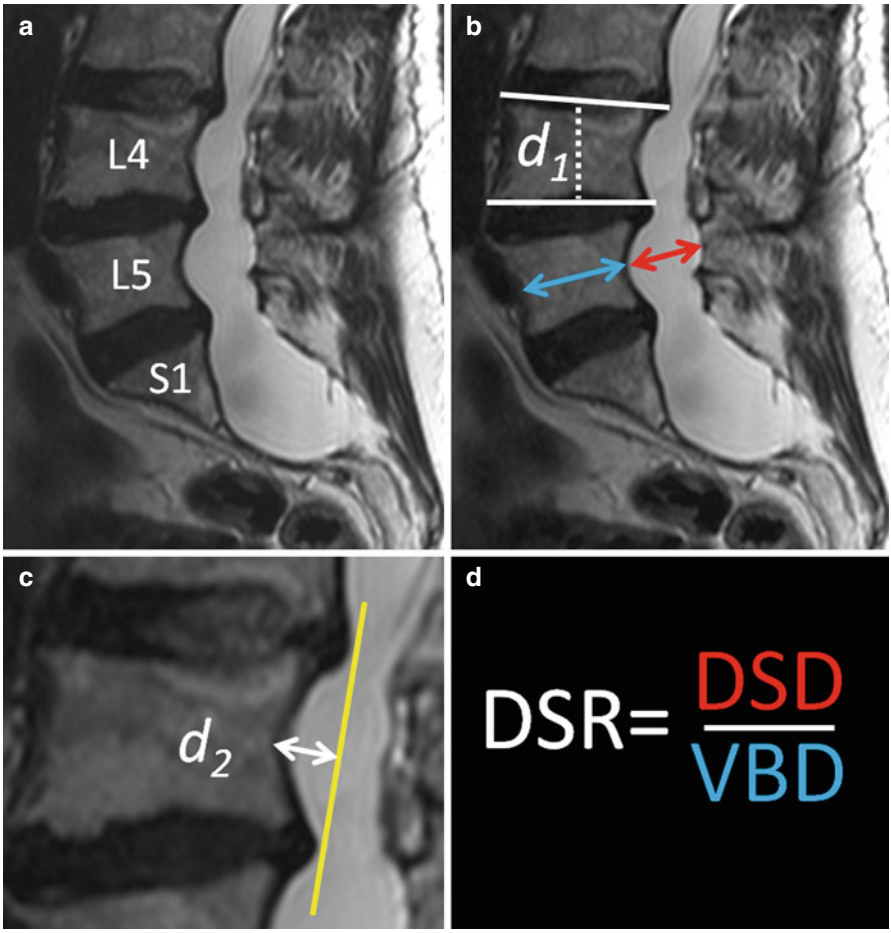

Fig. 19.1 Quantitative radiological assessment of DE. (**a**) Sagittal T2-weighted MRI acquired from a patient with DE, centred on L4, L5 and S1. (**b**) *White lines* drawn through the plane of the superior and inferior endplates of the vertebral body of L4. The perpendicular distance between them (d_1) is a measurement of the vertebral body height and the mid-point of this line ($d_1/2$) is nominated at the level at which to measure corresponding axial metrics such as dural sac diameter (DSD, *red arrow*) and vertebral body diameter (VBD) and to assess for scalloping. Dural sac ratio can be determined at each level using equation D. (**c**) Assessment of scalloping. Posterior vertebral margin drawn for L4 (*yellow line*). The distance in mm (d_2) between this line and the posterior margin of the vertebral body through the plane of the mid-point of the body is measured. A value of d_2 greater than 2 mm suggests scalloping

- Scalloping of the vertebra (posterior vertebral margin halfway between the superior and inferior endplates was greater than 2 mm anterior to a line drawn from the upper to lower posterior margin of the vertebral body [34].
- Perineural or Tarlov cysts (cystic dilation containing spinal fluid along the nerve root) [35].

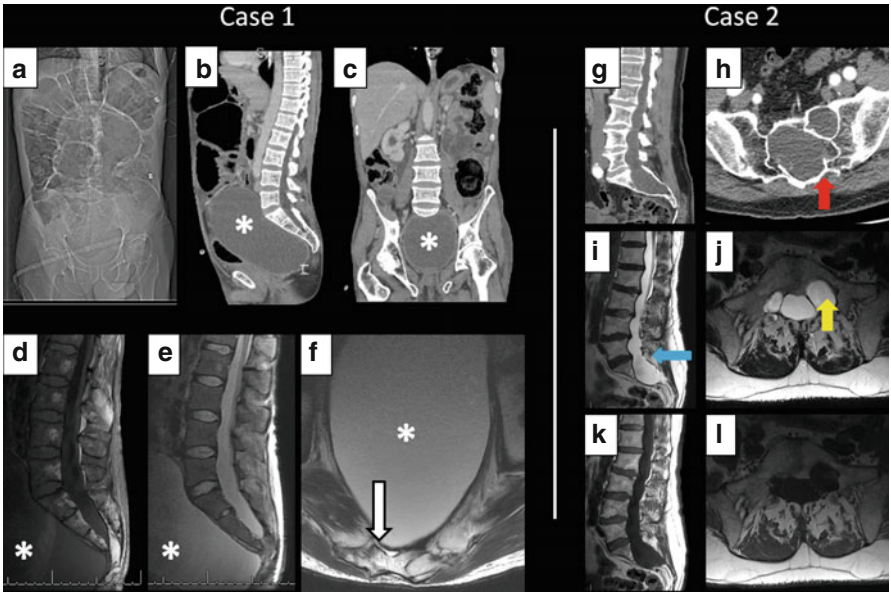

Fig. 19.2 Case 1. A 45 year old 'Marfanoid' man presents with a painful, distended abdomen. Plain radiographs (**a**) confirm acute large bowel obstruction. He proceeded to CT scanning (**b** sagittal reconstructed & **c** coronal reconstructed) which identifies a large cystic mass within the pelvis, thinned sacral bone and a possible defect in the anterior sacrum. This is further characterised by MRI (**d** sagittal T1-weighted, **e** sagittal T2-weighted, **f** axial T2-weighted through the level S3) which confirms a diagnosis of anterior meningocele (*), filling via an antero-lateral ectactic defect at S3 (*white arrow* on **f**). He was managed conservatively and went on to make a full recovery. Case 2. A 36 year old Ghent positive MFS patient presents to clinic with chronic back pain with no radiculopathy, neurological deficit or reported headaches. Sagittal reconstructed CT (**g**) and axial images (**h**) identify a widened lumbosacral canal (S1 > L5), thinning of the sacral laminae (*red arrow*) and enlarged sacral foraminae. Subsequent MR imaging (**i** sagittal T2-weighted, **j** axial T2-weighted, **k** sagittal T1-weighted, **l** axial T1-weighted) confirms the diagnosis of dural ectasia (*blue arrow*) with nerve root enlargement (*yellow arrow*) with early signs of lateral meningocele. As a result the body of the sacrum is severely thinned due to remodelling around the expanded theca. Some disc and facet degeneration is also observed as well as 'scalloping' of the posterior vertebral bodies at other levels. She was successfully treated with oral analgesia and a course of physiotherapy

CT and conventional radiographs are best suited to identify the osseous changes associated with DE. MRI allows direct visualisation of soft tissues of the spine [16, 17, 29]. Sagittal images best identify the antero-posterior (AP) spinal canal and vertebral body diameters, whereas additional information may be obtained from axial and coronal images. The latter are of particular importance to characterise lateral or anterior meningoceles. It has been proposed that quantitative signs of DE (e.g. DSR & DSD) have major advantages over qualitative assessments (e.g. presence of Tarlov cysts and vertebral scalloping) as definitive diagnostic 'cut-off' values can be applied and tested more uniformly than qualitative signs [32, 36].

The role of vertebral body scalloping as a diagnostic marker of DE is controversial. Habermann et al. found no differences in scalloping between patients with MFS and controls [36]. Ahn et al. [29] found scalloping at S1 a useful minor criterion for DE however another study found significantly higher scalloping at S1 level in Ghent-positive patients than in others [34].

Lundby et al. [34] investigated imaging criteria to characterise DE in patients with MFS. They studied 105 subjects divided into three groups: (i) those already fulfilling the Ghent criteria for MFS, independent of a diagnosis of DE (group 1, n = 73), (ii) those fulfilling the Ghent criteria dependent on a diagnosis of DE (group 2, n = 14) and (iii) those suspected of having MFS, but not fulfilling the criteria (group 3, n = 18). 91 % of all Ghent-positive patients (group 1) had DE on the basis of lateral or anterior meningoceles, the latter were only found in Ghent-positive patients. Lateral meningoceles were present in 37 % of group 1 patients and 14 % in group 2 patients. The sensitivity of this finding in diagnosing MFS was 37 % and the specificity, 100 %. Herniation of the nerve root sleeve was frequently present in Ghent-positive patients. They were most commonly found at levels S1 and S2. A larger DSD at S1 than L4 was found in a high proportion of Ghent-positive patients and could be assessed with high inter-observer agreement, agreeing with previous studies [29, 36].

Oosterhof et al. [32] reported that DSR could be used to identify MFS with 95 % sensitivity and 98 % specificity. Their method has been discussed and tested in later studies, but similar results have not been reproduced [37, 38]. Weigang et al. [39] detected DE in 94 % of patients with MFS and in 44 % without MFS when they followed the methods and cut-off values of Oosterhof et al. [32]. Habermann et al. [36] found a difference in DSR between patients with MFS and controls at L5 and S1 only. At S1, they calculated a diagnostic sensitivity of this metric of only 56 % and a specificity of 65 %. Lundby et al's study applied the DSR cut-off values from Oosterhof et al. to a group of normal controls and found DE 'diagnostic' levels in 12 % at S1 and 19 % at L5, suggesting that these cut-off values are too low. In practice, the radiological diagnosis of DE is formed by a qualitative appreciation of a range of imaging features and the variation of opinion on the clinical utility of spinal measurements, mean these techniques are suited more to the stratification of disease in clinical trials at this stage.

Spondylolisthesis is found in 6 % of patients with Marfan syndrome [18], usually as a high-grade slip. It is not known if dural ectasia leads to the progression or development of spondylolisthesis/spondylolysis over time [18]. It has been postulated that this slip may be due to the underlying connective tissue disorder affecting ligament and disc properties [5].

Management of DE

Several previous reports present posterior laminectomy as a technique to relieve back pain secondary to dural ectasia [21, 40, 41]. Owing to the risk of peri- and post-operative cerebrospinal fluid (CSF) leak plus the lack of long-term data on

spinal stability, DE, in the majority of cases, should be managed non-operatively. This may especially the case in DE associated with MFS owing to potential anaesthetic risks associated with the cardiovascular features of the syndrome. Dural ectasia results in erosion of the osseous structures of the lumbosacral spine [42, 43]. Mean pedicle widths and lamina thickness in the lumbosacral spine are significantly less than in normal controls [42]. The combination of thin pedicles, thin laminae, and weak dural connective tissue in MFS can make operative fixation of the Marfan spine perilous with a conservative estimate of dural tear rate of 8 % and a 8 % rate of adjacent segment lamina fracture reported [44].

Surgery for anterior sacral meningocele (Fig. 19.2, case 1) is not indicated for stable and asymptomatic lesions [45]. The presence of escalating pelvic discomfort, neurologic deficits, altered bowel habit and urinary frequency may lead the surgeon to consider operating. The two classical approaches are either posteriorly via sacral laminectomy or anteriorly via an open transperitoneal approach. A more recent case series proposed employing a laparoscopic transperitoneal drainage of the cyst [46]. We propose that the management of these lesions is complex and that surgery is reserved for selected cases requiring allied general and neurological surgical input.

Intracranial Hypotension

Spontaneous intracranial hypotension (SIH) is an important cause of new-onset headache, which are typically orthostatic in character and relieved by recumbency. SIH may be caused by a spinal cerebrospinal fluid (CSF) leak, the exact cause of which usually remains unknown however a combination of an underlying weakness of the spinal meninges and a trivial precipitating event is generally suspected. The underlying pathological substrate may range from small dural rents and tears to complex fragile meningeal diverticula or absence of the dura normally enveloping the spinal nerve roots.

Auditory and visual vestibular symptoms often accompany SIH [47]. Intracranial subdural haematoma with accompanying signs and symptoms of meningeal irritation is a recognised complication. The presumed aetiology of haematoma is rupture of the bridging veins between the cortical surface of the brain and the dura when the brain descends as CSF volume decreases. These changes are mirrored radiologically on MRI scan as a ‘sinking brain’, with herniation of the cerebellar tonsils through the foramen magnum. There is often accompanying enhancement of the dura evident on gadolinium-enhanced T1-weighted MR images. The mechanism of pain production in SIH is unclear [47]. It has been hypothesised that it is not low CSF pressure, rather displacement of pain sensitive structures in the cranial vault that cause headache when the patient is upright.

Retrospective studies suggest connective tissue disorders are present in 16–36 % of patients presenting with spontaneous spinal CSF leaks [48–50]. In some cases a heritable connective-tissue disorder is suspected on the basis of physical examination alone, e.g., isolated joint hyper-mobility in up to two-thirds of patients with SIH [51]. Isolated skeletal features of MFS (i.e. absence of the major ocular or cardiovascular

manifestations) are found in 10–20 % of patients with SIH [48, 51]. These patients do not typically harbour mutations in *FBN1* gene [52], however, abnormalities of fibrillin-1 containing microfibrils have been demonstrated in these patients. Studies have failed to show a direct relationship between SIH and MFS using clinical examination techniques (e.g. joint hypemorbility scores) [53, 54] or gene studies alone [52]. A small study of 18 patients with spontaneous intracranial hypotension found that seven (38 %) did have subtle signs of connective tissue disorders with three of the patients having some of the minor skeletal features of MFS [51].

Conservative management of SIH may include bed rest, hydration, analgesia, a high-salt diet and caffeine in the first instance [55]. Refractory cases may require epidural venous blood patching [56] and a period of flat bed rest, even in the context of SIH and intracranial subdural collections [57]. A report exists of Chiari malformation secondary to the CSF leak in MFS [58]. In this case, primary surgical decompression of the foramen magnum did not relieve the patient's symptoms however a subsequent recovery was noted following blood patching. In most cases of MFS associated SIH, the suspected site of CSF leak is lumbo-sacral ectatic dura however there exists a report of a leak via a CSF fistula located in the clivus [59], presumably caused by a failure in bone development. This patient was successfully treated by trans-sphenoidal approach to perform a graft repair covering the fistulous defect.

Other Spinal Manifestations of MFS

Atlanto-Axial Subluxation

There is an increased prevalence of focal kyphosis in the cervical spine and atlanto-axial translation (on flexion and extension) reported in patients with MFS [60]. The Marfan population also has an increased rate of basilar impression, possibly explained by an associated general increase in odontoid height when compared to age-matched controls. In light of these features, it is possible that MFS patients are at increased risk of cervical spine injuries, particularly when muscle tone is attenuated by muscle relaxants peri-operatively. Several authors recommend that MFS patients avoid sports at risk of high-impact loading of the cervical spine. However, the rarity of actual neurologic injuries in MFS means that pre-operative radiographs for all patients with MFS undergoing general anaesthesia is not necessary or recommended. Our experience (Fig. 19.3) and those of small case series however have reported incidence of rotational atlanto-axial subluxation following minor trauma and neck manipulation during intubation for general anaesthesia [61]. This may be due to ligamentous laxity coupled with dysmorphic cervical spine anatomy. Of particular concern, the combination of atlanto-axial hypermobility and increased odontoid height may predispose MFS to life-threatening cervicomedullary compression. The typical cause of sudden death in MFS is cardiac arrhythmias, especially in the presence of ventricular dilation [62], there exists however reports of sudden death in patients with MFS with a normal cardiovascular system on post mortem examination however abnormal anterior axis height and cervical stenosis suggesting cervical subluxation as the likely cause [63].

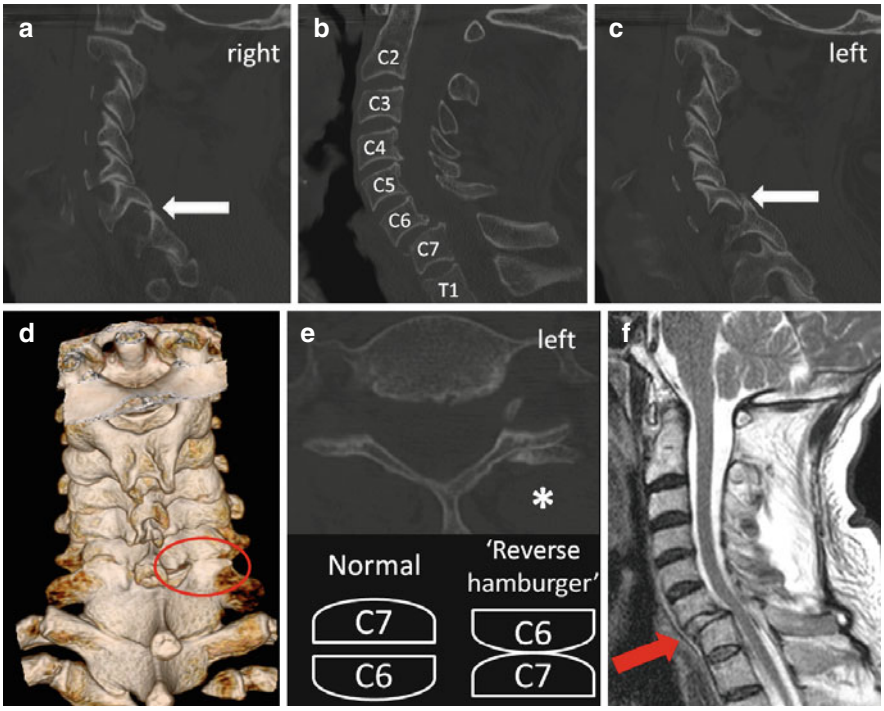

Fig. 19.3 Twenty-nine year old male with known Ghent positive MFS, who was admitted with neck following a trivial fall. No neurological deficit noted on examination. Cervical spine CT reconstructions in the sagittal plane through *right facet complexes* (**a**), *midline* (**b**) and *left facet complexes* (**c**). 3D reconstruction (**d**) showing the bilateral 'jumped' facet joints at C6/C7 (*white arrows*, *red circle* on 3D-reconstruction) which is also shown on the axial CT slice through the C6/C7 facet joint (**e**) revealing the classic 'reverse hamburger sign' in the left sided C6/7 facet (* on **e**), NB not seen on the same CT slice on the right due to angulation of the acquisition). Sagittal T2-weighted MRI shows the step deformity at C6/7 (*red arrow*), kinking of the spinal cord however no cord compression due to ruptured C6/7 intervertebral disc prior to treatment. He was successfully treated with open (operative) reduction and underwent anterior cervical discectomy and plating followed by the posterior stabilisation using lateral mass screw fixation

Spinal Scoliosis

Scoliosis, defined as curvature of the spine in the coronal plane of more than 10°, is seen in slightly more a half of individuals with MFS and can be mild to severe as well as atypically progressive [18, 64]. Close monitoring using a 'forward-bending test' at yearly intervals and management with physiotherapy is preferred to invasive and high risk surgical stabilisation of the spine [65]. Application of a spinal brace is less successful if the curves are greater than 35–40° but may have some role in prevention for smaller curves. A spinal curvature of less than 30° is associated with a good long-term prognosis with dramatic progression often seen with curvatures greater than 50°. This progression can occur well into adulthood.

Thoracic kyphosis is also common in MFS and can be postural or a result of bony over-growth and ligamentous laxity [66]. Postural education and joint stabilisation with core strengthening may be of benefit but have unproven long-term outcomes. Spinal deformities can lead to chronic back pain and, in some cases, restrictive lung disease. As with DE, the surgical management of scoliosis in these patients is complex and should be performed only by those with experience in treating patients with MFS [67].

Neurovascular Manifestations of MFS

Neurovascular Compression

The genetic defect in MFS codes for fibrillin, a glycoprotein which is a major structural component of elastic tissues within artery walls [68]. Patients with MFS may demonstrate tortuous and elongated intracranial vessels causing dissection of the internal carotid [69] or vertebral artery [70] or to intracranial giant aneurysms [71, 72]. Although these tortuous vessels can theoretically cause neurovascular compression syndromes, only two cases of hemifacial spasm [71, 73] and one case of trigeminal neuralgia [74] have been reported so far. In these case reports, digital subtraction angiography or MR angiography showed tortuous and ectatic vertebral arteries causing the neurovascular compression and all were successfully treated with microvascular decompression (MVD). MVD may in these cases be easier as patients tend to be younger and the vessels less atherosclerotic.

Cerebrovascular Ischaemia

Cerebrovascular complications of MFS are rare, with an incidence of only 3.5 % in one retrospective study of 513 patients, the majority of which were a cardio-embolic ischemic stroke [75]. Reports of cervico-cephalic extension of aortic dissection associated with MFS with consequent cerebral ischemic symptoms and of extracranial arterial dissection exist in the literature [76]. Cystic medial necrosis and fibromuscular dysplasia has been identified in extracranial arterial vessels in MFS, but neither finding is considered specific for dissection [77]. Pathological analysis of intracranial arteries of three patients with MFS identified a range of findings; from normal arterial segments to combinations of intimal proliferation, medial degeneration, and fragmentation of the internal elastic lamina [78]. The physiologic stressors of hypertension, extreme physical exertion, and migraine noted before development of acute neurologic signs and symptoms may contribute to the dissection of intracranial vessels. The best approach to treat dissection remains unclear, especially in children. Recent guidelines that address both stroke and anticoagulation therapy do not recommend the use of anticoagulation for the treatment of intracranial arterial dissection [79, 80].

Intracranial Aneurysms

Intracranial aneurysms have historically been reported as a feature of MFS [78, 81]. Case series [82, 83] however have not identified an increased prevalence of intracranial aneurysm or rate of rupture in MFS and they are in fact likely to be of similar prevalence to that seen in the general population. The differential diagnosis for MFS includes multiple hereditary disorders of connective tissue (HDCT). HDCTs associated with intracranial aneurysm include pseudoxanthoma elasticum, Loeys-Dietz syndrome and Ehlers-Danlos syndrome. There was no observed increase in the prevalence of symptomatic or asymptomatic intracranial aneurysm in MFS patients compared to the general population in two large case series using post-mortem and neurosurgery audit data [82, 84, 85]. It has been proposed that the previously reported association between MFS and intracranial aneurysms came from a series of combined single-patient reports of patients. A significant proportion these patients did not, in fact, fulfil the diagnostic nosology for MFS at that time [82]. Furthermore, the autopsy series from the Mayo Clinic [78] may suffer from a sampling bias (i.e. due to its volume of neurovascular throughput). In selected cases of headache, presumed to secondary to cerebral aneurysm, alternative diagnoses such as temporo-mandibular joint dysfunction may be found [86], which affects up to 52 % of patients with MFS [87].

Migraine

The aetiology of migraine is multi-factorial, due to a combination of genetic and environmental factors. Migraine with aura has been associated with cardiac shunts, non-shunting congenital heart defects, congenital abnormalities of the aorta, pulmonary arteriovenous malformation and connective tissue disorders such as Ehlers–Danlos and MFS [88]. A questionnaire study of 457 MFS patients [89] and a multicentre study of 123 MFS patients [88] found that the lifetime prevalence of migraine with aura (but not migraine without aura), is increased in patients with MFS. This association is driven by a history of aortic root surgery and was not influenced by the presence or absence of dural ectasia [88] as previously proposed [90]. It has been postulated that the increased extracellular matrix degeneration observed in the systemic blood vessels of MFS patients results in an endothelial cell reaction, secreting vasoactive mediators (e.g. vasodilator nitric oxide and vasoconstrictor endothelin-1). Several studies have found increased levels of these mediators to be present in patients with migraine. Another possibility is the presence of micro-emboli in the affected aortic root, which can act as a trigger for spreading cortical depression. There exists one case report of a 38 year old man known to have MFS presenting with headache and neck pain and a ventral epidural mass which was found to be an engorged and thrombosed epidural venous plexus [91]. The authors postulate that MFS may have predisposed the patient to engorged veins due to a disorder of the venous connective tissue however appreciate that it may be sequelae of CSF leak resulting in a reduced CSF volume.

Conclusion

The influence of the genetic abnormality causing MFS is characterised by its multisystem involvement and variability in phenotypic expression. Whereas patients with MFS may frequently present to cardiothoracic surgeons, they are a rare entity in general neurosurgical practice and even more rarely require surgery. Despite this, the range of symptoms and signs described in the preceding sections represent the bulk of our practice. It is paramount therefore that a possible diagnosis of MFS is not overlooked, enabling referral to the relevant specialty and appreciation of the increased surgical risks associated with treating this condition.

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