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ORIGINAL PAPER

Outcomes from 18 years of cervical spine surgery in MPS IVA: a single centre's experience

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Abstract

Purpose This study examines the long-term outcomes of paediatric Morquio (MPS IVA) patients undergoing cervical spine surgery and evaluates the factors that impacting this.

Methods A retrospective review was performed on all MPS IVA patients undergoing cervical spine surgery, since the introduction of standardised neuroradiological screening. The impact of preoperative neurological status, growth, genotype and radiological status on outcome is assessed, whilst long-term surgical, radiological and neurological outcomes are documented.

Results Twenty-six of the eighty-two MPS IVA patients (31%) reviewed underwent cervical spine surgery at a median age of 6.1 years (range, 1.45 to 15.24). Preoperatively, cord signal change was seen in 11 patients with 5 being myelopathic; however, 6 clinically manifesting patients had no overt cord signal change. Postoperatively, none of the 14 preoperatively clinically asymptomatic patients followed long term progressed neurologically during a median follow-up of 77.5 months (range = 18–161). Of the ten preoperatively clinically symptomatic patients who were followed up for the same duration, seven continued to deteriorate, two initially improved and one remained stable. Radiological follow-up performed for a median duration of 7 years (range = 0.5–16) has shown a degree of stenosis at the level immediately caudal to the termination of the graft in 76% of patients, though only one has become clinically symptomatic and required revision.

Conclusions Once clinically elicitable neurological signs become evident in patients with MPS IVA, they tend to progress despite surgical intervention. Referring clinicians should also not be falsely reassured by the lack of T2 spinal cord signal change but should consider surgical intervention in the face of new clinical symptomology or radiological signs of progressive canal stenosis or instability.

Keywords Morquio syndrome · Dysostosis multiplex · Cervical spine · Magnetic resonance imaging · Myelopathy

Background

MPS IVA (Morquio's syndrome, OMIM No. 253000), an autosomal recessive lysosomal storage disease, is caused by a deficiency in activity of the enzyme *N*-acetylgalactosamine-6-sulfate sulfatase encoded by the GALNS gene on chromosome 16 [1]. At a cellular level, the resultant accumulation of the partially

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degraded glycosaminoglycans (GAGs) Keratan [2] and possibly to a lesser extent, chondroitin sulphate [3], drive the ensuing pathogenic cascades [4]. In keeping with the intrinsic structural importance of Keratan sulphate to cartilage and the extracellular matrix [5], one of the chief causes of morbidity and mortality in MPS IVA is the resultant skeletal dysplasia [6, 7], with the degree of the growth restriction reflecting the severity of the disease [8]. The aspect of the skeletal dysplasia that traditionally requires the greatest degree of medical intervention is the cervical spine [6, 9]. Here, a combination of atlantoaxial instability, caused by ligamentous laxity [10] sometimes combined with the presence of os odontoideum, as well as the presence of compressive spinal stenosis as a result of ligamental thickening and excessive GAG accumulation occurs [11, 12]. Whilst C1–2 is the site most susceptible to these changes, the subaxial spine can also be affected and if unrecognised can lead to progressive spinal cord compression, myelopathy and ultimately paralysis [13–15]. Whilst previously this led to recommendations for prophylactic cervical spine fusion [16], currently combined clinical and radiological monitoring is used to identify cervical spine instability prior to irreversible myelopathy occurring [11, 17]. In our centre, the radiological monitoring consists of six monthly to yearly MRI combined with plain film extension and flexion cervical spine X-rays, with CT being reserved for preoperative planning. Indications for operative intervention are the presence of cervical spine instability evidenced on plain film flexion extension studies and/or increasing cervical cord stenosis without overt signal change or presence of signal intensity on T2 without advancing stenosis which may indicate instability. The final surgical indication is progressive clinically elicitable neurological signs in patients with radiological changes even if these of themselves appear to be non-progressive. Historically, surgical stabilisation has been provided by posterior occipito-cervical fixation and fusion using both instrumentation and bone graft [16], although a small minority also require decompression [18]. This template is used in our centre, thus after induction of the general anaesthesia, neurophysiology probes are positioned and once satisfactory SSEPs and MEPs are obtained, the halo-thoracic vest is applied using inline manual head stabilisation. On turning prone, satisfactory cranio-cervical junction and C spine position is confirmed with an image intensifier, with alignment corrected by repositioning of the halo vest bars if required. The suboccipital skin area is prepped and draped including a suitable skull donor site, whilst ensuring no interference between the posterior aspect of the vest and the operative site. A midline occipitocervical incision is made and a combination of blunt and bipolar dissection exposes the occipital bone, foramen magnum and spinous processes of C2. It is normally necessary to minimally expose spinous process of C3. A high-speed drill is employed for the laminectomy and subsequent preparation of pairs of burr holes in the occipital bone either side of the midline. Titanium cable wires are passed using the soft solid wire headers under the occipital bone whereas at C2 a small aneurysm hook is used to pass a sublamina silk thread, which in turn is used to pass the titanium cable wires whose solid header had been removed. When required, a foramen magnum decompression is performed using a high-speed drill combined with upcut rongeours until the dura is satisfactory decompressed, which typically entails laminectomy of C1 in most cases. This may be particularly challenging given the short neck and C1 invagination into the foramen magnum. Particular attention is made to removal of all GAG deposits. Next, a rectangular graft of skull bone is obtained through a posterior parietal paramedian incision, with the wound closed in the standard fashion. The graft is then prepped into two rectangles, a small gutter is drilled at both extremes, which serves as a bed for the sublaminar wire. A small hole drilled under the gutter allows passage of the sublaminar wires so that the bone graft can be stabilised against the occiput posteriorly and the lamina of C2 caudally (Fig. 1). The wires are tightened to 30–40 lb. tension and crimped in place. Additional commercially available bone graft material is employed to supplement the bone grafts, before standard wound closure.

The immediate operative and postoperative course are complicated not only by the potential cervical instability, but also from potentially significant cardiorespiratory problems. This is particularly true from the respiratory perspective [19]

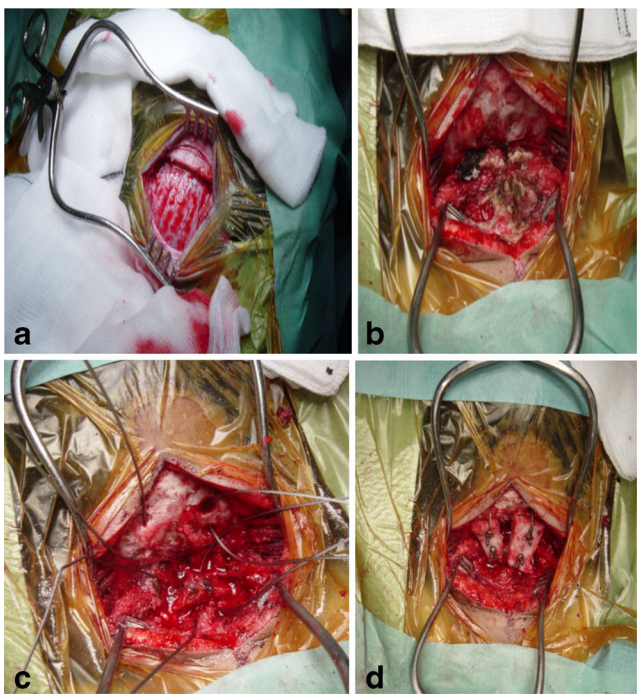

Fig. 1 Intraoperative images to illustrate procedure; **a** Square of full thickness skull graft taken from parietal region. **b** Exposure of cervical spine. **c** Decompression of spinal canal and passage of cable wires. **d** Fusion using skull grafts

whereby intrinsic structural changes in the upper and lower airways [20], with tracheal deviation a particular problem [21], as well as a variable degree of restrictive lung disease [6]. Despite the frequency of cervical instability in MPS IVA, estimated to be at least 20% even at diagnosis [6], the reports on the long-term surgical outcomes are limited to two large-case series [16, 18]. We report the radiological and clinical experience of a single tertiary paediatric centre in the pre- and postoperative periods in all MPS IVA patients undergoing cervical spine surgery, since MRI imaging was introduced as part of routine monitoring.

Methods

A retrospective case note review of all patient with MPS IVA who underwent cervical spine surgery since 1999, the time of institutional routine MRI was introduced. Patients operated on prior to this were excluded, although the majority have previously been reported by Hughes et al. [22].

A single radiologist reviewed all the available spinal imaging, looking where available at baseline (earliest postdiagnosis), preoperative and latest postoperative MRI scans and X-rays, specifically noting cord and canal diameter, odontoid dysplasia and cord signal change. This was performed on the sagittal image with cross reference to transverse images where appropriate using a picture archive and communication system (PACS) system. Both the T1 and T2 sequences were used to facilitate accurate measurements, cord signal changes were assessed with T2 sequences. The patient's genotypes, clinical status, pre- and perioperative complications and the long-term surgical outcomes were documented. All statistics were done on Graphpad Prism 6.0e, non-parametric comparisons were made using Wilcoxon matched-pairs signed-rank test or Mann-Whitney test as appropriate, whilst contingency analysis was performed using Fisher's exact testing.

Results

In total, 26 out of 82 patients under review during this period have undergone cervical spine surgery, 1 patient (patient 12) was listed and admitted for surgery but could not be intubated at the time of anaesthesia despite extensive preoperative work up. As described above, all patients underwent autologous bone graft from calvarial donor site and wire fixation, whilst seven also underwent decompression. Eight of the patients had been commenced on enzyme replacement therapy prior to surgery and an additional four have been commenced since. Four patients were referred for revision having undergone a primary fixation in another centre (patients 7, 8, 16 and 24); the initial local preoperative imaging being available for 3. Patients 8 and 16 were referred due to failure of graft fusion at initial operation with subsequent clinical neurological progression, whilst patients 7 and 24 had radiological signs of worsening stenosis. The genotype was available in 19/26 of the patients and as expected the majority (78%) were missense point mutations [23] with the common Caucasian severe I113F variant [24] being the most prevalent variant. All the patients' latest available heights were below the 3rd centile when compared with their age equivalent unaffected population, suggestive of severe, i.e. classical Morquio. However, when plotted on disease-specific growth charts [8], 20% fell between the 50th and 75th centiles, 30% between the 25th and 50th but 50% fell below the 25%. The median age of diagnosis was 32 months (range = 16 to 96 months) and of first cervical surgical intervention being 6 years 1 month (range 1 year 5 months to 15 years 3 months), see Table 1. There was no statistical difference in age at surgery ($p = 0.96$) between those who received prior ERT (median age = 5.6 range = 4.4 to 15.2 years) compared with those that did not (median age = 7.18 range = 1.4 to 15.3 years). There is a statistically weak but significant correlation between age at diagnosis and age of initial surgical intervention ($p = < 0.0001$, $r^2 = 0.2$). In 19 of the 24 patients for whom the preoperative radiology was available, the site of maximal narrowing was C1–2, with C2–3 being the site of maximal stenosis in the rest of the cohort. Of the 24 patients where preoperative imaging was available all patients had a degree of cervical spine subluxation. Eleven showed signal changes, though only four showed restriction CSF suggestive of localised soft tissue compression. Of the 11 patients prior to surgery, of these, 5 patients had developed clinically elicitable signs of myelopathy on review. However, there were six patients with clinically definable neurology, ranging from increasing gross hyperreflexia in two to definable weakness in four others that had no obvious T2 signal change at the time of surgery (Table 2). In itself, signal change on T2 was not predicative of outcome with 6 out of the 11 patients with preoperative T2 changes having no residual neurological sequelae, one having minimal parathesia, 1 an improvement in power and 3 progressing. No patient had alteration in bowel or bladder function prior to surgery. Of note, although all patients had radiological evidence of lumbar kyphosis, there were no signs of multilevel cord compression and although one patient did go on to lumbar surgery, 6 years had elapsed since their cervical spine surgery; the indication being radiological bony progression and discomfort rather than for myelopathy.

Although 13 patients had some degree of valvular dysplasia, with mitral dysplasia in 13 and additional aortic dysplasias in 3, no patient had clinically significant cardiac dysfunction at time of surgery. Except for patient 12, all the patients were successfully endoscopically intubated and successfully extubated without need for tracheostomy. Patient 11 did have an episode of apnoea and bradycardia on intubation, but

Table 1 Age at diagnosis and degree of growth restriction and age of operation

Patient	Age at diagnosis (months)	Latest height (cm) and age when taken	Height centile	Age at operation (years and months)
1	N/A	N/A		1 year 5 months
2	25	105 (7 years 7 months)	50–75th	4 years 4 months
3	36	110 (16 years 4 months)	25th	8 years 11 months
4		100.1 (13 years 5 months)	10–25th	10 years 5 months
5	96	86.8 (9 years 2 months)	3rd	8 years 10 months
6	29	96 (7 years 8 months)	10–25th	2 years 11 months
7a	38	N/A		3 years 2 months
7b				5 years
8a	N/A	107 (14 years 4 months)	25–50th	8 years 9 months
8b				9 years 3 months
9	34	95.9 (10 years 7 months)	10th	9 years 4 months
10	36	N/A		5 years 7 months
11	33	102 (12 years 3 months)	25th	4 years 5 months
12	16	N/A		7 years 10 months
13	71	99.6 (8 years 11 months)	25th	15 years 3 months
14	16			5 years 9 months
15	16	N/A		5 years 4 months
16a	N/A	99 (23 years)	< 3rd	3 years 6 months
16b				12 years 9 months
16c				15 years 4 months
17	N/A			7 years 4 months
18	43	101 (7 years 2 months)	50–75th	4 years 2 months
19	30	93.2 (13 years 8 months)	3rd–10th	5 years 1 month
20	28	91.6 (7 years 1 month)	25th	6 years 5 months
21	54	100.4 (13 years 9 months)	50–75th	12 years 4 months
22	N/A	99.8 (10 years 4 months)	50–75th	8 years 10 months
23	44	101 (10 years 10 months)	75th	4 years
24	N/A	95.2 (14 years 3 months)	25–50th	3 years
25	N/A	95.7 (6 years 7 months)	50–75th	9 years 11 months
26	N/A	90 (15 years 4 months)	10th	6 years 7 months
27	N/A	85 (4 years 5 months)	10th	2 years 11 months

NB: Patient 12 had no operation due to airway instability. If patients had more than one operation, then listed operation is listed alphabetically

otherwise intraoperative and immediate postoperative anaesthetic complications were minimal. Significant neurological deterioration occurred peri/postoperatively in two patients (patients 13 and 22). In the former complete irreversible quadriplegic paralysis developed on reversal of anaesthesia, whilst the latter, who preoperatively displayed significant upper and lower limb weakness, developed complete paralysis at 48 h postop. Despite acute investigation with MRI, no obvious surgically correctable cause, i.e. misalignment, haematoma or signs of external compression was discovered in patient 9, indeed only minimal cord signal changes were seen. In patient 22, MRI changes were in keeping with an acute ischaemic event, thought to have occurred during an episode of upper airway obstruction caused by localised laryngeal oedema on day 2 postoperatively (Table 3).

The overall median follow-ups was 84 months (range = 7–191 months); this excludes two presurgically asymptomatic patients who after halo removal were exclusively followed up by their original referring centres. In the remaining 14 preoperatively clinically asymptomatic patients, no neurological progression has been subsequently detected (median duration of follow-up = 77.5 months, range = 18–161 months). In the ten patients who were preoperatively clinically symptomatic, two suffered neurological deterioration in the perioperative period, whilst of the other eight, five continued to deteriorate, two improved although one subsequently declined further and one remained stable (median duration of follow-up = 117.5 months, range = 7–191 months). There was no significant difference in the follow-up times of the preoperatively asymptomatic and symptomatic groups (p =

Table 2 Preoperative and postoperative radiological and neurological assessments

Patient	Spinal levels where cord narrowest preop	Spinal levels where pathological cord changes present preop	Pathological changes present in spinal cord at point of cord narrowing	Clinical neurology preop	Cervical spinal levels where cord narrowest postop	Spinal levels where pathological cord changes present postop	Pathological changes present in spinal cord	Clinical neurology postop
1	N/A	N/A	N/A	None	N/A	N/A	N/A	None
2	C1–2	C1–2 C4–5	CN, SC, CF (C1–2) rCSF (C4–5)	None	C6–7	C4	rCSF	None
3	C1–2	C1–2	CN	None	C6–7	C7	CN	None
4	C1–2	C1–2	CN, SC, CF, rCSF	None	C3–4	C4	CN	None
5	C2–3	C1–2	CN, CF	None	C1–2	C1	CN	None
6	C1–2	C-2	CN	None	C6–7	C7	CN	None
7a	C1–2	C1–2	CN	None	C1–2	C1	CN	None
7b	C1–2	C1–2	CN, SC, rCSF	None	C2–3	C2	CN, SC	None
8a	C1–2	C1–2	CN	Limb weakness and hyperreflexia	C1–2	C1–2	CN	Progressive limb weakness and hyperreflexia
8b	C1–2	C1–4 C2–3	CN, SC, CF (C1–4) rCSF, SS (C2–3)	Progressive limb weakness and hyperreflexia	C1	C1–3	CN, CF	Increased power in limbs
9	C2–3	C1–2	CN, SC	None	N/A	N/A	N/A	None
10	C1–2	C1–2	CN	Hyperreflexia	N/A	N/A	N/A	None
11	C1–2	C1–2	CN	None	C1–2	C2	CN, rCSF, CF	None
12	C2–3	C1–2	CN, SC	Deteriorating power in lower limbs	N/A	N/A	N/A	N/A
13	C1–2	C1–2	CN	Hyperreflexia in upper limbs	C7	C7	CN	Complete loss of neurological function in upper and lower limbs on reversal of anaesthetic
14	C1–2	C1–2 (SS)	CN	None	N/A	N/A	N/A	None
15	C1–2	C1–2 (SS)	CN	None	N/A	N/A	N/A	None
16a	C2–3	C2–3 (SS, SC)	CN, SC	None	C2–3	C2–3	CN, SC	Progressive limb weakness
16b	C2–3	C2–3 (SS, SC)	CN, SC	Progressive limb weakness	C2–3	C2–3	CN, SC	Significant myelopathy
16c	C2–3	C2–3 (SS, SC)	CN, SC	Significant myelopathy	C2–3	C2–3	CN, SC, significant stenosis of the spinal canal	Further progression of limb weakness and myelopathy

Table 2 (continued)

Patient	Spinal levels where cord narrowest preop	Spinal levels where pathological cord changes present preop	Pathological changes present in spinal cord at point of cord narrowing	Clinical neurology preop	Cervical spinal levels where cord narrowest postop	Spinal levels where pathological cord changes present postop	Pathological changes present in spinal cord	Clinical neurology postop
17	C1–2	C1–2 (SS, SC)	CN, SC	None	N/A	N/A	N/A	None
18	C1–2	C1–2 (SS)	CN	Significant loss of power in right upper limb with hyperreflexia	N/A	N/A	N/A	Initial improvement in neurological symptoms but gradual deterioration postop followed
19	C1–3	C-3	CN, SC	Paraesthesia in upper limbs	C3–4	C3–4	CN, SC	Mild paraesthesia
20	C1	C1	CN	Reduced power in lower limbs	C1–4	C1–4	CN, SC	None
21	C1–2	C1–2	CN, SC	Lower limb hyperreflexia and clonus in upper limbs	N/A	N/A	N/A	None
22	C1–2	C1–2	CN	Progressing loss of power in upper and lower limbs	N/A	N/A	N/A	Permanent loss of neurological function in upper and lower limbs 48 h postop
23	C1–2	C1	CN, SC	None	N/A	None	None	None
24	N/A	N/A	N/A	None	N/A	N/A	N/A	N/A
25	C1–2	C1–2	CN	None	N/A	N/A	N/A	N/A
26	C1–2	C1–2	CN	Loss of power in upper limbs	Generalised narrowing throughout cord	Generalised narrowing throughout cord	CN, significant stenosis	Progressive deterioration in upper limb function
27	N/A	N/A	N/A	None	C2–3	C2-C3	CN	None

CN, cord narrowing; SC, signal, CF, cord flattening; rCSF, restricted of normal CSF surrounding cord

Table 3 Operative and postoperative complications

Patient	Length of anaesthetic (h)	Endoscopic intubation necessary	Intra-operative complications	Postoperative complications	Length of halo (weeks)	Length of follow-up	Failure of fusion	Graft reabsorption	Evidence of progressive stenosis below level of decompression
1	2.75	Yes	None	None	16	18	No	No	No
2	N/A	Yes	None	Parietal pin loosening—new pin had to be inserted to rectify	12	46	No	No	Yes
3	N/A	Yes	None	None	13	90	No	No	Yes
4	N/A	Yes	None	None	17	46	Yes	No	Yes
5	3.5	Yes	None	Postoperative bleeding from pin site	16	63	No	No	No
6	N/A	Yes	None	None	13	84	No	No	No
7a	N/A	Yes	None	None	15	N/A	No	Yes	Yes
7b	N/A		None				No	No	N/A
8a	N/A	Yes	None	Graft inappropriately fused causing further spinal cord stenosis—revision necessary	N/A		Yes	No	N/A
8b	N/A		None	None	15	60	No	No	N/A
9	1.5	Yes	None	Pain from pin sites	12	78	No	No	Yes
10	3.5	Yes—difficult intubation kit required	None	N/A	N/A	7	No	No	Yes
11	2	Yes	Period of apnoea and bradycardia intra-operatively; given dexamethasone	None	13	88	No	No	N/A
12	N/A	Yes—surgery cancelled due to severe tracheal stenosis	None	None	N/A	N/A	No	No	N/A
13	2.5	Yes	None	Severe—permanent failure to regain neurological activity in upper and lower limbs	N/A	161	No	No	Yes
14	N/A	N/A	None	Fluid leak 1 week postoperatively from pin site	16	35	No	No	Yes
15	N/A	Yes	None	None	15	113	No	No	No
16a	N/A	Yes	None	None	N/A		Yes	No	Yes
16b	N/A		None	Significant myelopathy	N/A		Yes	No	Yes
16c	N/A		None	None	38	110	No	No	Yes

Table 3 (continued)

Patient	Length of anaesthetic (h)	Endoscopic intubation necessary	Intra-operative complications	Postoperative complications	Length of halo (weeks)	Length of follow-up	Failure of fusion	Graft reabsorption	Evidence of progressive stenosis below level of decompression
17	2.5	Yes	None	None	N/A	45	No	No	Yes
18	4	Yes	None	None	16	191	No	No	Yes
19	N/A	Yes	None	Mild paraesthesia in upper limbs	16	99	No	No	Yes
20	3.5	Yes	None	None	16	159	No	Yes	Yes
21	2.25	Yes	None	None	12	12	No	No	Yes
22	3	Yes	None	Respiratory difficulty developed 2 days later resulting in permanent loss of function in upper and lower limbs	N/A	124	No	No	N/A
23	N/A	Yes	None	None	11	77	No	No	No
24	N/A	Yes	None	None	N/A	N/A	N/A	N/A	N/A
25	2.5	Yes	None	Temporary, mild tongue swelling	16	94	No	No	Yes
26	2	Yes	None	None	26	158	No	No	Yes
27	N/A	Yes	None	None	N/A	161	No	No	Yes

0.14). Of the six patients who continued to decline, none showed radiological signs of compression distal to the cervical spine. In the two patients who improved immediately postoperatively, the power on the Medical Research Council scale in the patients' upper limbs increased from 4 to 4+ and 4 to 5, respectively. However, overall, the preservation of preoperative neurological function was significantly worse in those who were clinically symptomatic present prior to surgery ($p = 0.0001$).

All patients were immobilised with halo vest orthosis postoperatively for several months with postop radiological follow-up except patient 4 where a plaster cast orthosis was necessitated by the degree of skull osteopenia present. Three patients developed head fixation-pin-related complications which required revision. The median duration of halo vest requirement was 15 ½ weeks (range, 11–38 weeks). Fusion of the occipitocervical graft occurred in all patients except patient 4, who was also the only patient to display radiological signs of graft reabsorption, which was first seen at 13 months postop. All patients showed an improved cord diameter postoperatively and resolution of cord signal change if previously present (Fig. 2); there was no obvious relationship between postoperative CSF space and neurological progression. Only one patient (patient 16) operated on at our centre has required further surgical revision. This patient was initially referred for revision of stenosis developing at adjacent levels below the initial graft performed prior to their initial referral to our centre. The same patient subsequently required further revision for increasing clinical and radiological significant stenosis occurring inferior to the revised graft. Serial radiological follow-up either MRI or X-ray in 21 patients, where imaging was available, has shown evidence of some degree of stenosis at the level immediately caudal to the termination of the graft in 16 (median duration of follow-up = 92 months, range = 7–191), no stenosis in 5 (median duration of follow up = 77 months, range = 18 to 113); there was no significant difference in follow-up time $p = 0.52$. Excepting patient 16, none of the other patients have shown MRI or neurological symptoms suggestive of compression by the graft.

Discussion

To the best of the authors' knowledge, this is the largest documented case series of paediatrically diagnosed Morquio patients undergoing cervical spine surgery and with a median of 7 years, the series with the longest follow-up. Whilst caution must always be taken when extrapolating from retrospective data, the findings support previous opinions [16, 18], that intervention prior to the development of clinical symptoms is crucially important for long-term neurological preservation. Certainly, in this cohort, all preoperatively asymptomatic patients remained clinically unaffected at end of follow-up. In contrast in eight of ten patients with preoperative myelopathy, surgical intervention failed to halt neurological progression, indeed in two the surgery acutely exacerbated the decline. This is the first case series where definitive neurological progression has been documented despite apparent operative success. Whilst good primary fusion of the graft was the typical outcome, the majority (76%) developed a radiological detectable degree of narrowing of the spinal canal inferior to the graft, though this only became clinically significant in one patient during subsequent follow-up. The weakness of this series is its retrospective nature and that it covers a period

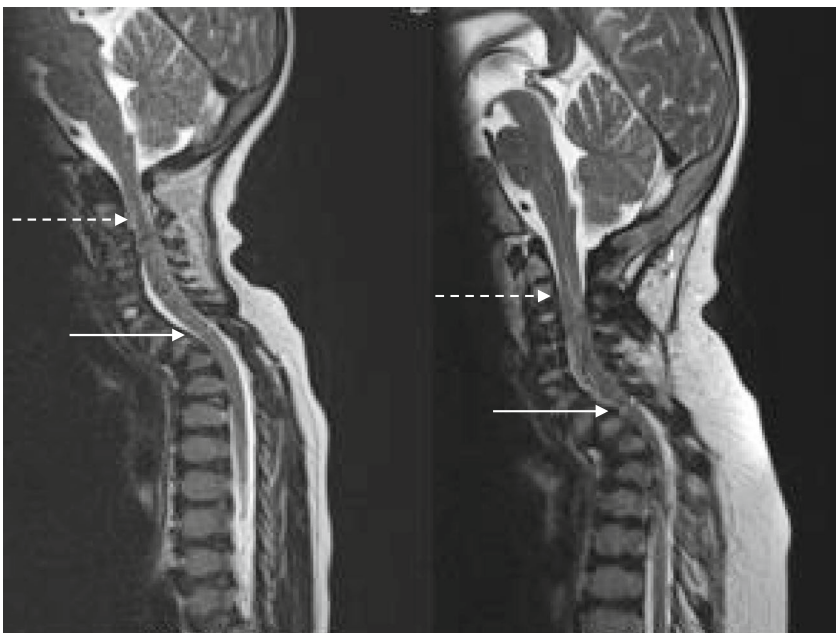

Fig. 2 The preoperative scan demonstrates significant cord narrowing at the level of C1–3 (Brocken arrows). The postoperative scan reveals the increase in cord diameter at C1–3; however, there is progressive narrowing of the cord at C6–7 (solid arrows)

where radiological, anaesthetic and surgical techniques have advanced. For example, the MRI coil strength has changed from 0.5 to 1.5 Tesla and although symptomatic patients without signal changes occurred throughout the time course, three of the patients were scanned with a 1-Tesla machine and therefore may have showed signal change on a more powerful scanner.

Whilst initial work advocated strongly for prophylactic fusion in patients after the age of 4 [13, 16], current guidance attempts to provide a more nuanced approach relying on a combination of clinical examination and radiology, particularly serial MRI imaging [11, 17]. However, this cohort highlights the inherent risks in this especially as, unlike in the previous case series [16, 18], surgical intervention did not halt neurological progression in most of the preoperatively clinically symptomatic patients. Whilst this failure to halt neurological progression has not been a feature of past case series, it would be in keeping with previous observations that clinical symptomology only manifests at an advanced stage of spinal cord compression in MPS IVA [9]. Over 50% of clinically symptomatic patients displayed no overt cord signal change in their preoperative MRI, though as with all the other patients they all did display a degree of cord narrowing. This lack of cord signal change may reflect the institutional screening policy which precludes MRI flexion and extension studies, due to the inherent dangers of manipulating a potentially unstable cervical spine under general anaesthesia. However, whilst this has been suggested as a part of regular monitoring [17], the evidence for its efficacy in skeletal dysplasias is limited to a single case series of 31 patients. That series demonstrated that in up to 30% of patients with no signal change in a neutral position, there was a demonstrable increased compression on additional extension/flexion views [25]. However, only two of these cases were MPS IVA and whilst both showed clinically significant subluxation on plain film X-rays, a previously posited indication for flexion-extension studies [11], one had minimal changes on flexion-extension. Whilst the other did show some cord compression, it is unclear if this was really the key determining factor in the decision to perform surgery. Therefore, it is still uncertain whether these additional studies or the use of other potential imaging modalities, whose strengths and weaknesses are well summarised by Solanki et al. [11] would have enabled more timely detection. Similarly, the role of electrophysiology, i.e. somatosensory-evoked potentials, in screening for compression is unclear, with conflicting results regarding their utility being found even with the same research group [26, 27]. Where electrophysiology, especially transcranial motor-evoked potential (TcMep) [28], may have impacted is intraoperatively as in patient 13, to show acute compromise. Sadly, intraoperatively neurophysiologically this was not established at that time, although the combination of SSEP and TcMep has subsequently become a standard of care in our centre. Whilst there is a paucity of data in the paediatric setting, this combined electrophysiological approach seems to offer the best protection, although there is still some ongoing debate as to whether this electrophysiology really improves operative outcome [29, 30].

It is unsurprising that both the genotypic and morphometric data indicate that in general this cohort were patients at the more severe end of the phenotypic spectrum, with the average age of operation very similar to that described by Dede et al. [18]. However, whilst height is used as a general proxy marker for severity of the disease [6, 8], it appears unsuitable for risk stratification for screening, as at least 20% of the patients were above the 50th centile on disease-specific height charts. It is also to be noted that the severity of the respiratory compromise is already well established at an early age and even with preoperative work up including chest CT, can be unpredictable as was the case in patient 12. Good airway management is particularly important given that postoperative swelling, especially of the oral mucosa and the tongue, is not an infrequent complication of cervical spine surgery in MPS IVA [31]. For although patient 25 was managed successfully with steroids, care must be taken, as given the typical tortuosity of the trachea [32] the need for urgent tracheostomy is best avoided.

Given the histological abnormalities in bone and cartilage seen in patients with MPS IVA [33, 34], it is perhaps surprising that the primary spinal fusion rate (96%) was similar to that in the recently published meta-analysis of general paediatric posterior cervical graft fusions [35]. However, in that meta-analysis, the strongest predictors of primary fusion were the use of an autologous graft and the inclusion of the occiput within the graft, both of which were fulfilled by the entire cohort. Indeed, this series would suggest MPS IVA does not of itself affect primary fusion. The only case where there was obvious disease-related interference was in patient 4 where the degree of osteopenia, a recognised feature of MPS IVA [36], prevented the use of a traditional halo for stabilisation. This experience does however reinforce the importance of full immobilisation in the postsurgical period, with halo immobilisation appearing to be a suitable means of fixation in this MPS IVA cohort, as it has in the past [16, 18]. However, alternative methods of fixation such as rigid fixation of occiput to C2/lower cervical vertebrae or the Harms technique [37] have also been successfully used in MPS IVA [38]. The use of halo fixation in our centre has been driven by the restricted size of the C2 pedicles and the desire in this complex population to minimise intraoperative surgical risk. It is to be noted that the age at interventions in this cohort are is considerably earlier than then in the groups of MPA IVA patients reported by both the Brazilian and Czech groups [38, 39] which may suggest this cohort would be prone to a smaller size vertebral pedicle, in part reflecting the age at operation but also the severity of disease. This said, in a selected patient

population with adequate bone mass, alternatives to external fixation [40] should still be considered on a case by case basis, given their safety and efficacy in MPS IVA and other skeletal dysplasias [41].

The potential for postoperative stenosis below the graft seen in this cohort, would be in keeping with the previously described abnormal movements that occur just below the graft [9] and whilst these patients have, with the exception of patient 16, not needed revision it is unclear what will happen over the patients' lifetime. Thus, despite the lack of reabsorption of the grafts, it is clear that continued radiological and clinical surveillance postoperatively is required.

Overall, the lack of a single definitive investigation does suggest that the combined clinical and radiological approach is still the best approach to screening, with this case series again demonstrating the importance of clinical neurological monitoring. However, given the range of potential orthopaedic complications, ten of this cohort have had eight plate insertion for genu valgum whilst two have had hip replacements, this can pose difficulties for examination and impact on functional assessments such as the 6-min walk test. Whilst submaximal endurance testing has been of postulated as useful for early warning of spinal disease, it has not been used in our institution. For whilst such testing is routinely performed in our institution as a guide to global function given both the multiplicity of pathogenic mechanisms impacting on these assessments and the natural intrapatient variability in childhood, they are poorly sensitive and unspecific. The difficulty in clinical monitoring is to some degree addressed in the UK by the utilisation of specialised centres where all patients are followed up regularly by clinicians familiar with both the patients and the disease. This centralisation also allows multidisciplinary review between medical, surgical and associated specialists such as physiotherapists for as complete a picture of the patient as possible. Ideally in the future, a universally accepted severity scale incorporating both elements can be validated to improve both monitoring and timing of surgical interventions. For although individual centres have published scales in the past [27], none have become universally accepted.

Conclusion

This series adds to the weight of evidence that timely surgical intervention is key to maximising good neurological outcome. Whilst radiological and clinical screening for cervical pathology in MPS IVA remain an integral part of management, this series both highlights the potential for radiological false negatives and suggests that once clinically elicitable neurology manifests surgery whilst potential stabilising is unlikely to improve established neurological symptomology.

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Compliance with ethical standards

Conflicts of interest Dr. Broomfield, Mr. Zuberi, Miss Mercer, Miss Moss and Dr. Jones have received financial support for attending symposia from Biomarin. The other authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. As this is a retrospective study, formal consent is not required.

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