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Mucopolysaccharidosis Type IVA: Evidence of Primary and Secondary Central Nervous System Involvement

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Mucopolysaccharidosis type IVA is a rare lysosomal storage disease caused by a deficiency of *N*-acetylgalactosamine 6-sulfatase. Studies usually focus on skeletal abnormalities and their consequences. This study explores the neurological manifestations in a cohort of mucopolysaccharidosis type IVA patients, with a detailed focus on brain and spinal magnetic resonance imaging (MRI) findings. We performed a cross-sectional study involving nine patients with a biochemical confirmation of mucopolysaccharidosis type IVA. The protocol consists of a comprehensive clinical examination and brain and spinal cord MRI analysis for all subjects. The mean age was 16.4 years (±5.7) and the mean onset of symptoms was 11.5 months (±6.3). Overall, cognition was spared in all but one patient and motor weakness was a constant finding in all patients. Deep sensation impairment was found in six patients. The brain MRIs showed non-specific white matter changes in two patients. Other abnormalities such as clival hypoplasia, basilar invagination, and arachnoid cists appeared in seven of the nine patients. Eight patients presented spinal cord compression, and in three of them, two spinal levels were compromised. Odontoid hypoplasia and degenerative features in the neuroaxis were present in all patients. Our experience with mucopolysaccharidosis type IVA patients supports the evidence of central nervous system involvement. We emphasize the importance of regular clinical assessments with complete MRI studies, as an attempt to detect the early signs of spinal cord compression. This evaluation may be especially important before surgical interventions, as occult lesions may become symptomatic and promote postoperative unfavorable outcomes.

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INTRODUCTION

Mucopolysaccharidosis type IVA (MPS IVA, MIM #253000) or Morquio A syndrome is a lysosomal storage disease characterized by skeletal dysplasia and short stature. This disorder is caused by a deficiency of *N*-acetylgalactosamine 6-sulfatase encoded by the *GALNS* gene at 16q24.3 [Baker et al., 1993; Davison et al., 2013]. Heterogeneity in clinical manifestations has been described [Nelson and Thomas, 1988], but some degree of spondylo-epiphyso-metaphyseal involvement was often observed. The incidence of MPS IVA is about 1 in 640,000 live births in Western Australia [Nelson et al., 2003], to 1 in 300,000 in British Columbia [Lowry et al., 1990] and 1 in 76,000 in Northern Ireland [Nelson, 1997].

Due to the rarity of this syndrome, researches analyzing patients with MPS IVA usually had a small number of subjects, and the studies focused exclusively on the atlanto-axial involvement leading to neurological impairments. As this involvement has life-threatening potential, it raised recommendations for surveillance yearly [Solanki et al., 2013] or in alternate years [Giugliani et al., 2007] with magnetic resonance imaging (MRI). However, MRI is not easily performed on MPS IVA patients because of the difficulties in sedation and orotracheal intubation [Sam et al., 2011]. Detection of early neurological signs in follow up appointments is extremely

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important to prioritize patients who may need urgent complementary investigation and surgical approaches.

Earlier researches showed that cognitive functions were usually spared in MPS IVA, and in other types of mucopolysaccharidosis cognitive functions were compromised. However, more recent studies have shown intellectual involvement in MPS IVA patients raising the hypothesis that intelligence may not be entirely preserved [Davison et al., 2013].

The purpose of this study is to describe the neurological manifestations in a cohort of MPS IVA patients, with a detailed focused on brain and spinal MRI findings. We also intend to evaluate whether neurological signs and image abnormalities are helpful in planning the strategies for follow up management of MPS IVA patients.

METHODS

A cross-sectional study was conducted between May 2011 and October 2012 in two genetic services of Universidade de São Paulo, Brazil. Inclusion criteria comprised biochemical confirmation of MPS IVA (low levels of the *N*-acetylgalactosamine-6-sulfatase enzyme and an increase in the urinary excretion of keratan sulphate) and willingness of patients and/or their guardians to participate in the study. Exclusion criteria included any contraindication to perform MRI studies. A total of nine patients were selected.

Written consent was obtained from all patients or guardians before enrolment. The study was approved by the Institution's Ethics Committee (CAPPesq 0556/09).

Neurologic Assessment

An experienced pediatric neurologist completed full neurological examinations adapted to the age of the patient. Occipital frontal head circumference (OFC) was measured in all patients, and the Denver Developmental Scale was applied for patients under 6 years old [Frankenburg and Dodds, 1967]. The neurologist observed attitude, behavior and speech. The Medical Research Council (MRC) scale was used as follows to evaluate muscle strength and power: grade 5-normal contraction against full resistance placed by examiner; grade 4-reduced muscle strength and power with some ability to move joints against resistance; grade 3-reduced muscle strength and power and joints mobility only against gravity; grade 2-muscles mobility only without resistance of gravity; grade 1-trace of movements or fasciculations seen or felt; and grade 0-absence of any muscle contraction. Deep tendon reflexes were graded as absent, diminished, normal, brisk, or hyperactive. Sensory examinations consisted on evaluation of both superficial and deep sensations. Superficial sensations were tested through reports of skin pain and temperature variation (spinothalamic tract neurons integrity or damage); and skin touch and pressure (medial lemniscus pathway integrity or damage). The deep sensations examinations consisted of vibration tests using a tuning fork and joint position assessments (both tests were essential for the evaluation of the spinal cord posterior columns). Other parameters of neurological examinations focusing on cranial nerves, coordination, balance and gait, muscles tone, involuntary movements were tested using the guide "De Jong's-The Neurologic Examination" [Campbell, 2005].

MRI Assessment

The protocol included brain and spine images for all subjects, from a 1.5T MR scanner. The brain MRIs included axial AC-PC bicomissural axis oriented T1-weighted, T2-weighted and fluid attenuated inversion recovery (FLAIR) images. Coronal and sagittal T1-weighted images (WI) were reformated from the volumetric fast acquisition. Cervical and thoracic spinal MRI studies comprised sagittal T1 WI and T2 WI and axial T2 WI. Three patients (2, 3, and 5) had lumbar studies also included. One patient (5) had a volumetric CT scan study of the spine, reformatted in the sagittal axis.

RESULTS

Clinical Findings

We analyzed nine patients with MPS VIA; there was a male predominance (seven ♂: two ♀). The mean age was 16.4 years (±5.7, ranging from 5 to 26 years) with mean of symptoms' onset at 11.5 months (±6.3, ranging from 3 to 24 months). Seven patients (7/9) reported the first symptoms related to MPS IVA between 6 to 18 months. The majority of patients (7/9) had parental consanguinity, as expected for autosomal recessive inheritance (see Table I).

One patient (Patient 5) had undergone a C1–C2 vertebrae fixation 1 month prior to the MRI assessment. His neurological examination performed before surgery showed no cognition impairment, MRC scale grade 3 in the upper limbs and grade 2 in the lower limbs, global hyperactive deep tendon reflexes, and no involvement of sensorial systems. Unfortunately, Patient 5 had an acute spinal ischemia in the immediate postoperative period. The spinal ischemia occurred at T2 level and the neurological examination described in Table I refers to a later stage as he was being assessed throughout the clinical study protocol.

Cognition, attitude, and speech corresponded to the patients' ages for all but the youngest participant patient (Patient 1, who was 5 years old). The Denver Scale was applied to this patient. His social contact, language, fine, and gross motor skills were delayed.

Other findings resulted from neurological examinations. Motor weakness was present in all patients. Pyramidal signs such as hyperactive deep tendon reflexes were found in four patients (4/9). Abnormalities in superficial sensitivity were seen in two patients (2/9), while deep sensation impairment was found in six patients (6/9). Hearing loss was observed in five patients; however, the physical examination with the tuning fork revealed a conductive mechanism responsible for the loss of hearing. Therefore, this finding was not considered a primary neurological manifestation.

Neuroimaging Findings

Brain MRI. The most common brain MRI finding was the "J"-shapped sella in seven patients (7/9). The ventricular system and perivascular spaces were spared in all patients, while nonspecific white matter changes (Fig. 1A and B) were seen in two patients

TABLE I. Demographic Data and Neurological Findings in Mucopolysaccharidosis Type IVA Patients

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Patient 9
Age (y/o)	5	12	15	17	17	18	19	19	26
Gender	Male	Male	Female	Male	Male	Male	Male	Male	Female
Parental consanguinity	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes
Age of first symptoms (months)	24	7	3	12	18	12	11	6	11
OFC (cm)	49 (normal)	55.5 (normal)	55 (normal)	55.5 (normal)	56 (normal)	56 (normal)	58 (normal)	56 (normal)	54 (normal)
Denver scale L/M/PS/FM (y/o)	3/2/3.5/3.5	NA	NA	NA	NA	NA	NA	NA	NA
Cognitive evaluation	Delayed	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal
MRC upper limbs	4	4	3	3	3	3	3	4	4
MRC lower limbs	4	4	3	3	0[a]	2	4	3	4
Deep tendon reflexes	Nomal and symmetric	Globally diminished	Globally hyperactive	Globally hyperactive	Hyperactive in upper limbs and absent in lower limbs[a]	Globally hyperactive	Nomal and symmetric	Globally diminished	Globally diminished
Superfical sensibility	Normal	Normal	Hypoestesia under C3 level	Normal	Normal	Hypoestesia under C3 level	Normal	Normal	Normal
Deep sensitivity	Normal	Distal impairment	Distal impairment	Normal	Distal impairment	Distal impairment	Normal	Distal impairment	Distal impairment
Other findings	Convergent non paralytic strabismus	Conductive hearing loss	None	Conductive hearing loss	Conductive hearing loss	Conductive hearing loss	None	None	Conductive hearing loss

OFC, Occipital frontal circumference; L, language; M, motor; PS, personal-social; FM, fine motor; MRC, Medical Research Council; C, cervical vertebra.
[a]Neurological examination after acute spinal ischemia at immediate postoperative.

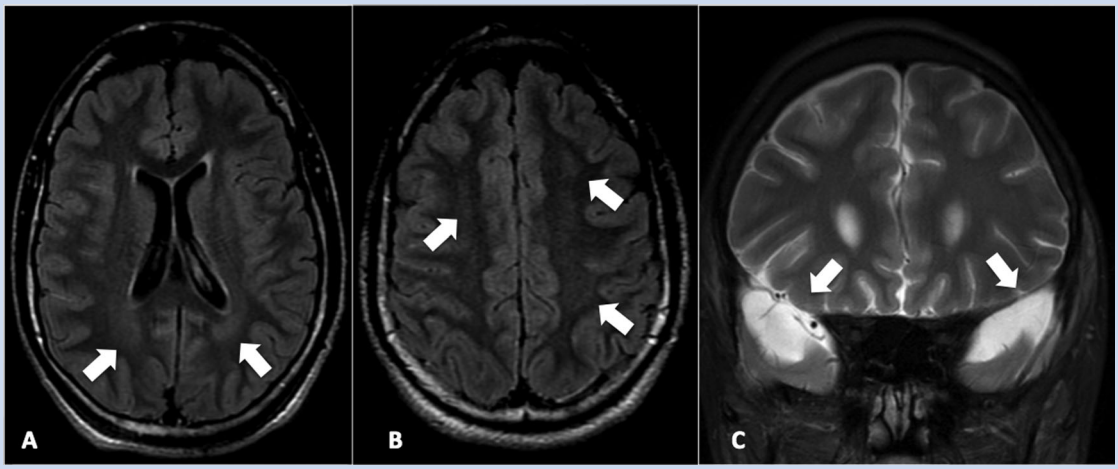

FIG. 1. Patient 5—Axial FLAIR with mild nonspecific periventricular (A) and focal subcortical (B) hyperintensities. Patient 6—Coronal T2 WI with bilateral temporal pole arachnoid cysts (C).

(2/9). In addition, there were other findings such as clival abnormalities (4/9), basilar invagination (1/9), enlargement of subarachnoid spaces (2/9), and arachnoid cists (1/9) in our sample (Fig. 1C; Table II).

Spinal MRI. Eight patients (8/9) had spinal cord compression, and in 7 of them (7/8) the compression was localized in the cervical levels (Fig. 2). Spinal cord T2 WI hyperintensties indicated myelopathy in six of seven patients with cervical compression (Fig. 3). All patients with myelopathy had atlantoaxial subluxation (6/6), while two patients also had constitutional cervical spinal stenosis in association with atlantoaxial subluxation (2/6). Four patients had compression in the thoracic levels. In three of them (3/4) the thoracic compression was associated with cervical compression, while in one patient we found a normal atlantoaxial joint and thoracic stenosis causing spinal compression (see Table III).

We found different degrees of odontoid hypoplasia with soft tissue mass around it in all patients (Fig. 2). The mean mass size had ± 13.2 (± 4.3) $\times$ 14.1 (± 4.7) mm, in craniocaudal $\times$ anteroposterior diameters respectively. The tissue had a homogeneous (5/9) or heterogeneous (4/9) appearance, with T2 WI hypo-intensity, and T1 WI iso or hypointensity signal. Three patients with severe odontoid hypoplasia had normal atlantoaxial joints with no signs of subluxation; for this reason, we cannot say that odontoid hypoplasia was associated with atlantoaxial subluxation in all patients. Epidural lipomatosis was responsible for thoracic spinal compression in two patients (2/9). Discal protrusions, particularly in the thoracic levels, were seen in all but one patient. All nine patients presented at least one degenerative feature like as anterior or posterior vertebrae indentations, vertebrae body flatness, and/or spondylolisthesis.

DISCUSSION

We evaluated nine Brazilian patients with MPS IVA and we demonstrated that the central nervous system was not completely spared. One patient demonstrated cognitive delay, two asymptomatic patients presented nonspecific white matter MRI changes, and in two others we found enlargements of subarachnoid spaces without clinical correlation. Although these are minor findings, we propose the question about whether their incidence is higher than it is in a healthy population. Unfortunately, only larger examinations of samples or methanalysis studies would reveal a clearer picture. The evidence of central nervous system involvement was also supported by another recent study showing scores below average in 3/8 children, a number of behavioural problems highlighted, and subtle neuroimaging abnormalities in over half of the patients studied [Davison et al., 2013].

Some thypotheses have reasoned the biochemical mechanisms of central nervous system involvement in MPS IVA. Keratan sulphate accumulation might activate secondary cascades and interfere with other biochemical pathways; for instance, evidence of calcium signaling abnormalities and mitochondrial dysfunction in other lysosomal storage disorders and neurodegenerative diseases have been described [Vicencio et al., 2010; Vitner et al., 2010; Davison et al., 2013].

Two other neuropathologycal studies showed abnormalities with swollen neurons containing PAS-positive globular inclusions in the cerebral cortex, Ammon's horn, basal ganglia and thalamic nuclei in MPS IV patients [Gilles and Deuel, 1971; Koto et al., 1978].

Although brain involvement in MPS IVA seems to be present, there can be no doubt that the spinal cord lesions secondary to atlantoaxial subluxation are a major cause of morbidity and mortality among these patients. All patients of the present study presented tetraparesis, six of them showed posterior column signs and two had spinothalamic signs. The usual course of the disease begins with slow progressive spastic tetraparesis, with mild posterior column signs (identified through deep sensation tests), and spinothalamic findings (pain and temperature tests) [Hughes et al., 1997]. Our results which showed signs of spinal cord compression in all patients are contrasted with another case series

TABLE II. Brain MRI Findings in Mucopolysaccharidosis Type IVA Patients

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Patient 9
Sella turcica shape	"J"	Normal	"J"	"J"	Normal	"J"	"J"	"J"	"J"
Ventricular system	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal
Brain white matter	Normal	Normal	Normal	Mild right semi-oval center T2WI/FLAIR hyperintensity	Mild nonspecific periventricular and focal subcortical T2WI/FLAIR hyperintensities	Normal	Normal	Normal	Normal
Perivascular spaces	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal
Other findings	None	Heterogeneous clivus	Mild enlargement of subarachnoid spaces	Clival hypoplasia	Heterogeneous clivus	Basilar invagination and bilateral temporal pole arachnoid cysts	Mild enlargement of subarachnoid spaces	None	Clival hypoplasia

FIG. 2. Sagittal T2 WI from patients 7 (A) and 6 (B) show different degrees of: spine curve abnormalities, "J" shapped sella (black *), spine stenosis with spinal cord compression hyperintensity, due to anterior displacement of C1 posterior arch/atlantoaxial subluxation (white arrow), hypoplasia of odontoid process with soft tissue mass (white *), vertebral bodies flatness with diffuse anterior and posterior indentations.

from United Kingdom, in which five from 11 patients were totally asymptomatic [Hughes et al., 1997].

Subluxation is by no means the sole cause of spinal cord compression, as several neuroaxis abnormalities may contribute to the neurological deficits in MPS IVA patients. In the past, the degree of odontoid dysplasia was thought to be well correlated with the clinical severity of patients [Nelson and Thomas, 1988]. Not only odontoid dysplasias, but also anterior extradural soft tissues were reported responsible for the severity of spinal cord compression [Stevens et al., 1991]. Indeed, we observed odontoid dysplasia in all patients from our sample; however the thickening of the connective tissues surrounding the bony spinal canal, epidural lipomatosis, and degenerative features in vertebral bodies also contributed to compression. Therefore, we believe that a combination of abnormalities leads to spinal cord compression.

MRIs are currently the gold-standard method for evaluating MPS IVA patients. No other method provides better information regarding soft tissues and spinal cords [Solanki et al., 2013]. However, the risks resulting from anesthesia are significantly higher in this population [Sam et al., 2011]. Health care providers, patients and their families should be alerted to possible complications associated with sedation for MPS IVA patients.

Spinal cord compressions in the thoracolumbar and cervicothoracic regions are usually seen due to kyphosis, scoliosis, and spinal canal stenosis. The common areas of compression appear in the thickest spinal segments located at C4–C7 (brachial expansion) and at T10–L1 (conus medullaris expansion). Additionally, we

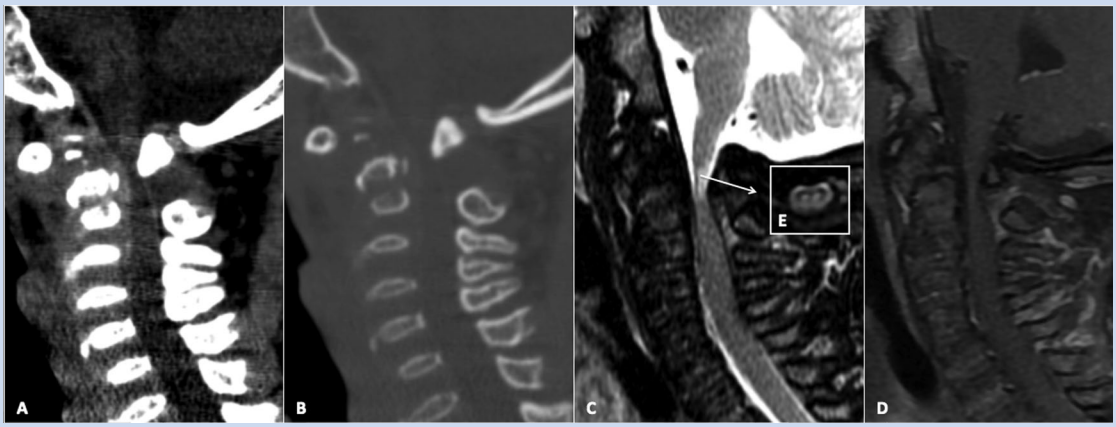

FIG. 3. Patient 5: A—Non enhance sagittal CT soft tissue window, B—Sagittal CT bone window; C—Sagittal T2 WI MRI; D—Sagittal post gadolinium T1 WI; E—Axial T2 WI MRI at C2 level. Findings: C1–C2 spine stenosis; focal myelomalacia secondary to ischemic changes of the compressed cord (C,E); anterior displacement of C1 posterior arch/atlantoaxial subluxation, odontoid hypoplasia with soft tissue mass, *os odontoideum*, vertebral bodies flatness with anterior and posterior indentations.

TABLE III. Spinal Cord MRI Abnormalities in Mucopolysaccharidosis Type IVA Patients

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5[a]	Patient 6	Patient 7	Patient 8	Patient 9
Level of spine stenosis/ degree[b]	C7–T3/mild	Absent	Craniocervical junction-C2/ moderate	Craniocervical junction-C2/ severe	C2–C3/severe	Craniocervical junction-C2/ severe	C2–C4/Mild	T3–T4/ moderate	C2/mild
Second level of spine stenosis/ degree	Absent	Absent	T1–T2/ moderate	T2–T3/mild	T2–T6/mild	Absent	Absent	Absent	Absent
Spinal cord appearance	Normal	Normal	Craniocervi-cal, C2 posterior myelopathy	Craniocervi-cal, C2 posterior myelopathy	C1–C2 central myelopathy	Craniocervi-cal, C2 posterior myelopathy	C2 mild myelopathy	Normal	Craniocervical transition - C2 posterior myelopathy
Atlantoaxial joint	Normal	Normal	Subluxation due to anterior displacement of atlas over the axis	Subluxation due to anterior displacement of atlas over the axis	Subluxation due to anterior displacement of atlas over the axis	Subluxation due to anterior displacement of atlas over the axis	Subluxation due to anterior displacement of atlas over the axis	Normal	Subluxation due to anterior displacement of atlas over the axis
Spinal canal stenosis	No	No	No	No	No	No	Cervical stenosis	Thoracic stenosis	Cervical and superior thoracic level stenosis
Intervertebral discs	Protrusion in thoracic levels	Protrusion in lumbar levels	Protrusion in cervical and thoracic levels	Protrusion in thoracic levels	Normal	Protrusion in thoracic levels	Protrusion in thoracic levels	Protrusion in thoracic levels	Protrusion in cervical and thoracic levels
Degenerative features	Cervical vertebral bodies flatness; cervical anterior and posterior vertebral bodies indentation	Cervical, thoracic and lumbar vertebral bodies flatness; cervical anterior and posterior vertebral bodies indentation; L1–L2	Cervical, thoracic and lumbar vertebral bodies flatness; diffuse anterior and posterior vertebral bodies indentation; T1–T2	Multiple levels of anterior and posterior vertebral bodies indentation	Cervical vertebral bodies flatness	Cervical anterior spondylosis	Cervical and thoracic vertebral bodies flatness	Cervical and thoracic vertebral bodies flatness; T6–T8 left lateral listhesis	Multiple levels of anterior and posterior vertebral bodies indentation; C2–C3 spondylolisth-esis.

(*Continued*)

TABLE III. (*Continued*)

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5[a]	Patient 6	Patient 7	Patient 8	Patient 9
		spondylolisthesis	spondylolisthesis						
Odontoid process	Severe hypoplasia	Severe hypoplasia	Severe hypoplasia	Mild hypoplasia	Moderate hypoplasia	Mild hypoplasia	Moderate hypoplasia	Severe hypoplasia	Moderate hypoplasia
C1–C2 soft-tissue mass characteristics	Heterogeneous with T1WI and T2WI hypointensity	Homogeneous with T1WI and T2WI hypointensity	Heterogeneous with T1WI and T2WI hypointensity	Homogeneous with T1WI and T2WI hypointensity	Heterogeneous with T1WI and T2WI hypointensity	Heterogeneous with T1WI and T2WI hypointensity	Homogeneous with T1WI and T2WI hypointensity	Homogeneous with T1WI isointensity and T2WI hypointensity	Homogeneous with T1WI and T2WI hypointensity
Soft-tissue mass (height × width)	19 mm × 17 mm	15 mm × 13 mm	17 mm × 8 mm	9 mm × 12 mm	14 mm × 25 mm	11 mm × 15 mm	18 mm × 13 mm	8 mm × 13 mm	8 mm × 11 mm
C2 ossification centers	Incomplete fusion	Incomplete fusion	Incomplete fusion	Incomplete fusion	Incomplete fusion	Incomplete fusion	Incomplete fusion	Incomplete fusion	Incomplete fusion
Other relevant findings	Posterior arch defect of C1 and C2 bifid apophysis	None	Thoracic epidural lipomatosis	Os odontoideum	Epidural lipomatosis T2–T5; os odontoideum	Os odontoideum	None	None	Os odontoideum

AP, anteroposterior; R, right; L, left; C, cervical vertebra; T, thoracic vertebra; L, lumbar vertebra followed by the number of localization level in vertebral column.
[a]Pre-surgery MRI evaluated.
[b]Canal stenosis classified according to the proportion of canal reduction (mild $\leq$ 1/3, mild = 1/3 to 2/3, and severe $\geq$ 2/3).

found mild to moderate compressions involving the upper thoracic level in four patients. Also we found three patients with dual spinal compression. One of these had a spinal cord infarct at T2 after general anesthesia in the prone position, probably due to impaired cardiac output [Tong et al., 2012] or arterial compression in the narrow canal. These findings reinforce the importance of a detailed MRI evaluation encompassing all spinal levels before therapeutic interventions.

Surgical techniques such as posterior occipitocervical fusion, combined anterior transoral decompression with posterior fusion, and decompressive cervical laminectomy without posterior occipitocervical fixation/fusion have been described with variable success rates [Ashraf et al., 1991; Stevens et al., 1991; Möllmann et al., 2013]. Prospective long-term follow up studies comparing these techniques are not available yet, and the intervention decision is subjective and determined by the neurosurgeon. Recently an interesting study has proposed scoring systems for absolute and relative neurosurgical intervention indications at the craniocervical junction [Möllmann et al., 2013]. The scores developed by Möllmann and colleagues are objective and reasonable enough to indicate surgical cervical decompression. We strongly recommend the implementation of standard protocols prior to interventions in centers where MPS IVA patients are assisted.

CONCLUSIONS

Our experience with MPS IV patients supports the evidence of central nervous system involvement. In order to detect early signs of spinal cord compression, we strongly recommend routine full neurological assessments and complete MRI studies whenever patients are evaluated. This inclusive evaluation is particularly important before surgical interventions, as occult lesions may become symptomatic and promote postoperative unexpected outcomes.

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