Spinal cord compression in young children with type VI mucopolysaccharidosis

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1. Introduction

Mucopolysaccharidoses (MPS) comprise a group of genetic lysosomal storage disorders that result from the deficiency of one or more of the enzymes required for glycosaminoglycan (GAG) catabolism [1]. Since GAGs are mainly found in connective tissue, the skeletal system, heart valves, and other areas with stroma, these are the primary sites of pathology in MPS. There are eleven MPS subtypes, classified according to which enzyme is deficient [2].

Maroteaux–Lamy syndrome (MPS VI) was first characterized by Maroteaux and Lamy in 1963 [3] and is caused by the accumulation of dermatan sulfate due to the deficiency of the enzyme galactosamine-4-sulfate sulfatase (arylsulfatase B). Clinical features of MPS VI are similar to the features of other MPS disorders: skeletal dysostosis, coarse facies, corneal opacification, visceromegaly, upper airway obstruction, and valvular heart disease. Intellectual development is preserved in this disease [1,3].

Previously, treatments for the MPS disorders were mainly supportive therapies. Bone marrow transplantation is a relatively successful therapeutic option for certain MPS subtypes. However, the advent of intravenous enzyme replacement therapy (ERT) has improved the care of many MPS patients [4] and changed several aspects of the clinical history of the disease [4–6]. Previous human clinical trials have demonstrated that ERT for MPS VI with recombinant human N-acetylgalactosamine 4-sulfatase (rhASB; galsulfase; Naglazyme®) had a significant impact on physical endurance and reduced urinary GAGs; although serious adverse events were reported, most were mild to moderate during infusions, including urticaria and brochospasm.

Cervical myelopathy is a well-known long term complication in MPS patients [13,14] which is usually caused by diffuse thickening of the dura and of extradural soft tissues in the cervical region, especially the posterior longitudinal ligament, and by posterior indentation by the arch of the atlas [15]. Atlantoaxial instability is another important cause of cervical spinal cord compression (SCC) in MPS patients (especially MPS IV).

Here we report on six MPS VI patients that displayed signs of spinal cord compression as an early and unexpected complication for their age (all were 7 years old or younger). Five of them were on ERT and responding positively to the recombinant enzyme (fewer episodes of upper airway infections, decrease in visceromegaly).
2. Case reports

2.1. Patient 1

Patient 1, an 11 year old male and the third child of a non-consanguineous couple, was diagnosed with MPS VI in early infancy due to a positive family history (affected older sister). At 6 years of age the patient presented with symptomatic cervical spinal cord compression, with very narrow cord and signs of myelomalacia (Fig. 1A). Prior to that, he had a ventriculoperitoneal shunt for intracranial hypertension. He has been reported in literature previously [13] because he was the first MPS VI patient to receive intrathecal (IT) ERT with galsulfase (Naglazyme®) as an experimental treatment for SCC as his family refused surgery due to the risks involved. During the course of IT therapy, he showed improvement in sensitivity and in his neurogenic bladder condition, but his gait progressively worsened and he gradually stopped walking [13]. He started regular weekly intravenous (IV) ERT after four intrathecal infusions, at age 7 years and 8 months. Over a period of 2 months he became extremely hypotonic and developed severe SCC symptoms with oxygen desaturation. A new MRI revealed no significant changes when compared to baseline (Fig. 1B). Lifesaving spinal decompression laminectomy and neck fixation surgery was performed at age 8 years. Two months after the surgery, muscle tonus and strength improved while hyperreflexia decreased. Follow-up MRI, however, revealed myelomalacia (Fig. 1C).

2.2. Patient 2

Patient 2, a 3 year old female born to a non-consanguineous couple, was diagnosed at 6 months old due to a positive family history (affected older brother, patient 4). IV ERT was started at 10 months old; brain/spinal cord MRIs were not performed at that time, however, neurological physical examination showed normal findings. After 2 months on ERT, she began presenting with hypotonia and repeat neurological examination revealed pyramidal signs. Six months after commencing ERT, she underwent a brain and spinal cord MRI which showed craniovertebral junction stenosis with SCC on the bulbo-spinal transition (Fig. 2A). Motor evoked potentials (MEP), not available from baseline, were also abnormal. Laminectomy and posterior fixation were performed when the patient was 20 months old. Motor development was normal after the surgical procedure; neurological evaluation showed recovery with normal muscular tonus and reflexes and she is still under evaluation for neurogenic bladder but with progressive improvement. A follow-up MRI 8 months after the procedure showed wider spinal canal diameters, though the areas of myelomalacia did not show any improvement (Fig. 2B).
2.3. Patient 3

Patient 3, a 6 year old female, the second child of a consanguineous couple, started on IV ERT at 35 months old. Her baseline brain/spinal cord MRI showed craniovertebral junction stenosis and her clinical neurological examination was normal (Fig. 3A). After 2 years on weekly IV ERT, she began to complain of lower limb pain. Clinical neurological evaluation did not identify any abnormalities; MRI showed cervical spinal cord compression (Fig. 3B). Neurophysiological studies showed abnormal motor and somatosensory evoked potentials. Cervical laminectomy and fusion were then performed 4 months after the diagnosis of SCC. Symptoms have subsided.

2.4. Patient 4

Patient 4, a 6 year old male, is the older brother of patient 2. He began ERT when he was 3 years and 9 months old. His baseline neurological evaluation before beginning IV ERT was normal. Cervical stenosis was observed on his first brain/spinal cord MRI, performed 6 months after commencing ERT. An MRI 1 year later (after 18 months on ERT) revealed mild to moderate spinal canal narrowing at the craniocervical junction with mild spinal cord compression, without signal changes (Fig. 4). Neurophysiological studies were abnormal. The patient is under evaluation for laminectomy and has recently begun to complain of lower limb pain.

2.5. Patient 5

Patient 5, an 8 year old male born to a non-consanguineous couple, started on IV ERT at 5 years old. His baseline MRI studies showed cervical stenosis at the craniovertebral junction, but his clinical neurological exam was normal. Complaints of lower limb pain began after 2.5 years on ERT. At that time, brain and spinal cord MRI showed canal stenosis at the craniovertebral junction as previously observed, with posterior longitudinal ligament thickening and anterior subluxation of C1. The spinal cord was compressed, but still presented normal signal (Fig. 5). Neurophysiological studies at the time of the MRI were abnormal. This patient is presently under evaluation for neurosurgical intervention.

2.6. Patient 6

Patient 6, a 4 year old female born to non-consanguineous parents, presented with seizures and intracranial hypertension and had a ventriculoperitoneal shunt placed before being diagnosed with MPS VI. Upon diagnosis of MPS VI, before the introduction of ERT, a brain and spinal cord MRI was performed and showed cervical SCC (Fig. 6). Neurological examination disclosed pyramidal signs (bilateral Babinski sign and hyperreflexia in lower limbs) and motor evoked potentials were abnormal. Based on the experience with the previous cases described here, it was decided not to start the patient on IV ERT until the spinal surgery is scheduled.

3. Discussion

Neurological complications are a burden for MPS VI patients and are not rare in such population [14–17]. Hydrocephalus, cervical

![Fig. 3. Patient 3 — T2-weighted MRI of the craniocervical junction in the sagittal plane. A (age 2 years and 1 months, baseline, before ERT introduction) — Narrow spinal canal at the craniocervical junction with probable spinal cord compression. The spinal cord does not show significant signal changes. B (age 6 years; exam performed after 3 years on ERT) — Marked spinal canal narrowing at the craniocervical junction with severe spinal cord compression already with spinal cord volume loss. The posterior longitudinal ligament is thickened and C1 is hypoplastic.](image)

![Fig. 4. Patient 4 (age 5 years and 4 months): T2-weighted MRI of the craniocervical junction in the sagittal plane. Mild to moderate spinal canal narrowing at the craniocervical junction with mild spinal cord compression. The posterior longitudinal ligament is thickened. The spinal cord still has normal volume and does not show significant signal changes.](image)

![Fig. 5. Patient 5 (age 7 years and 5 months), whose baseline MRI showed stenosis at the craniocervical junction. Exam performed after 2 years and 5 months on ERT. A — T1-weighted image in the sagittal plane. Caliper shows marked thickening of the posterior longitudinal and atlanto-odontoidal ligaments. There is also hypoplasia and anterior subluxation of C1. B — T2-weighted MRI of the atlantoaxial junction in the axial (transverse) plane. Caliper shows narrowing of the anteroposterior diameter of the spinal canal. Moderate to severe spinal canal narrowing with spinal cord compression. The spinal cord still has normal signal.](image)
myelopathy, and compressive sensory-motor neuropathies are common manifestations of neurological symptoms that may need neurosurgical interventions [18,19].

Spinal cord compression is one of the major clinical complications of MPS VI [20,21]. Storage of GAGs in the dura mater and supporting ligaments, kyphoscoliosis, and cervical bony stenosis are thought to be the main causes of myelopathy in MPS VI patients [22,23].

MRI is the method of choice to detect spinal cord compression and intramedullary signal abnormalities. Nevertheless, MRI studies are not able to provide information on the functional involvement of the cervical cord. SCC assessment is best achieved with somatosensory evoked potential (SEP) and MEP studies. MEPs are obtained using magnetic brain stimulation and calculating central motor conduction time to access the function of central motor pathways to upper and lower limbs. Ulnar and posterior tibial nerve SEPs demonstrate the function of posterior columns of the spinal cord and medial leminisci [24–27]. MEPs recording from the thenar and the tibialis anterior muscle appear especially sensitive for detecting myelopathy secondary to cervical spondylodiscitis. There is some evidence to suggest that MEPs may be more sensitive than SEPs [28].

Neurophysiologic evaluations are also important as an objective method of monitoring post-operative and even peri-operative neurological symptoms and signs in MPS patients, and have been used in the follow-up of MPS VI patients with signs of SCC [19,29].

It is important to note that all patients with MPS VI show some degree of cervical abnormality [20]. Development of SCC can be due to dural thickening and to craniocervical canal stenosis, however, hypertrophy of the posterior longitudinal ligament is more commonly implicated in its pathology [17,19,20]. Cervical instability is another rare cause of SCC in MPS VI patients, however, it is a common complication in MPS IV [30]. It is usually present in older MPS IV patients, although there are rare reports in younger MPS patients [31]. Thickening of the posterior longitudinal ligament and canal stenosis become more prominent with age and clinical manifestations of spinal cord compression are usually seen in the adult MPS VI population. All our patients had dynamic lateral cervical spine X-ray evaluations performed. Despite measurements within the normal values, all had hypoplastic odontoids with a variation of several millimeters with movement being the largest atlanto-axial distance observed in the extension films (Fig. 7). Although cervical instability is an uncommon finding in MPS VI, some degree was present in our patients, which may point to a different mechanism of cervical involvement, possibly triggered by enhanced mobility and micro-instability after ERT.

Sometimes it is very difficult to ascertain instability in these patients because of the usually present skull bone hyperplasia or the sometimes present basilar invagination, which may obscure C1 and C2, due to overlap of the structures. Computed tomography may be performed to better define osseous anatomy. MRI scans provide optimal information on soft tissues status and best determines craniovertebral stenosis. MRI easily depicts the space available for the cord. Today it is accepted that a sagittal diameter of \(<13\) mm may be associated with neurological symptoms or signs. There can be spinal canal stenosis without cord compression on neutral cervical position, since the anteroposterior diameter of the cord is usually some millimeters narrower than the canal itself. Probable compression is present when no fluid can be discerned between the cord and the surrounding soft tissue structures; and definite cord compression is present when the cord shows indentation. The natural history of cord compression is local ischemia, edema and later neuronal death with subsequent myelomalacia, which is depicted as an abnormal high signal intensity zone in MRI T2-weighted sequences [32].

In our sample, two out of six patients had baseline SCC, diagnosed prior to the ERT (patients 1 and 6); two had stenosis on the craniovertebral junction on MRI, with normal spinal signal, and normal neurological exams (patients 3 and 5). Two patients had no baseline MRI, but normal neurological examinations (patients 2 and 298 D.D.G. Horovitz et al. / Molecular Genetics and Metabolism 104 (2011) 295–300

Fig. 6. Patient 6 (baseline exam at age 3 years): T2-weighted MRI of the craniovertebral junction in the sagittal plane. Moderate to severe spinal canal narrowing at the craniovertebral junction with spinal cord compression and volume loss. The posterior longitudinal ligament is thickened. The spinal cord displays evident areas of high signal consistent with myelomalacia.

Fig. 7. Patient 4 — Dynamic conventional X-rays of the cervical spine in the lateral projection showing instability. There is subtle retrolistesis of the odontoid in extension, and mild anterior listesis of C2 in flexion. Images were obtained at age 5 years and 4 months, after 20 months on ERT.
4. Conclusions

Since both quality of life and life expectancy have improved after ERT, the neurological complications of MPS VI will be challenging for the physicians managing the care of such patients. Neurological assessment in all MPS VI patients by MRI and neuropathological studies (prior to and during the course of ERT) are highly recommended as part of their clinical care. Neuropathological studies are particularly helpful in patients with spinal canal stenosis, not only for monitoring clinical progression, but also for establishing the best surgical timing. SCC is a common neurological complication in MPS VI patients and may cause major handicaps and life-threatening events, so surgery should be performed as soon as a myelopathy is detected. We believe that all MPS VI patients should be carefully evaluated before starting ERT and, if early signs of cervical instability or cord compression are present, early surgical intervention should be considered. Assessment of subclinical SCC with MRI, neuropathological studies, and even with urodynamic evaluation could be a strategy for baseline evaluation in those patients, as early diagnosis could avoid later complications of cervical instability that may be triggered by ERT.

We recognize the limitations of this data due to the small sample size and possibly due to a more severe spectrum of the disease in Brazil. However, a modest natural history of MPS VI is now at reality, with the introduction of ERT in clinical practice throughout the world. Close monitoring for neurological complications in this patient population with targeted data collection could contribute to the knowledge on cord compression in MPS VI and on the prevention of related complications.

References


