Chiari 1 Malformation and Holocord Syringomyelia in Hunter Syndrome

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Abstract Compressive cervical myelopathy is a well-known life-threatening complication in mucopolysaccharidosis (MPS) patients. Glycosaminoglycan accumulation in the growing cartilage results in dens dysplasia, atlanto-axial instability, and subsequent periodontoid fibrocartilaginous tissue deposition with upper cervical stenosis.

Chiari malformation type 1 (CM1) is a congenital downward cerebellar tonsil ectopia determined by clivus and posterior cranial fossa underdevelopment, possibly leading to progressive spinal cord cavitation (syringomyelia) and severe neurological impairment.

We present a boy affected with Hunter syndrome (MPS II) and cerebellar tonsil ectopia who developed a holocord syringomyelia at the age of 6 years. The child underwent atlanto-occipital decompressive surgery with rapid clinical and neuroimaging improvement.

Sharing a primary mesenchymal involvement of the cervical-occipital region, the coexistence of CM1 in MPS might be not unexpected and complicate further the disease course. In these patients, strict monitoring and prompt

treatment might be of foremost importance for preventing major neurological complications.

Introduction

Hunter syndrome (Mucopolysaccharidosis type II; MPS-II; OMIM#309900) is a rare X-linked recessive lysosomal storage disorder (1/170,000 live male births) (Martin et al. 2008) caused by iduronate-2-sulphatase (IDS; EC3.1.6.13) deficiency. The resulting lysosomal accumulation of upstream metabolites affects a variety of organ systems, including visceral organs, skeleton, connective tissue, and the central nervous system. At birth, MPS-II patients appear phenotypically normal, but they gradually develop morphologic changes, recurrent respiratory infections, joint stiffness, and organomegaly (Young et al. 1982; Finn et al. 2008). About 10 % of MPS-II patients present with severe upper spinal canal stenosis causing spinal cord compression (Manara et al. 2011). Though less frequent than in other MPS forms, such as Morquio disease, severe myelopathy requiring decompressive surgery may also occur (Ballenger et al. 1980; O'Brien et al. 1997; Kaendler et al. 1990; Vinchon et al. 1995). As the clinical manifestation of spinal cord involvement might fairly overlap with signs and symptoms of concomitant multisystem involvement, myelopathy diagnosis and monitoring are mainly based on MRI evaluation of the cranio-cervical region.

Chiari malformation type 1 (CM1) is a congenital downward ectopia of cerebellar tonsils (more than 6 mm below the foramen magnum in the pediatric population). CM1 is an uncommon condition (about 1 % in the pediatric population) (Aitken et al. 2009) due to underdevelopment of mesenchymal structures forming the clivus and posterior cranial fossa bones (Milhorat et al. 2010). The abnormal position of

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the cerebellar tonsils disrupts the normal CSF flow dynamics (Shah et al. 2011) at the cranio-cervical junction and may result in spinal cord damage. The latter presents usually with a progressive cavitation (syringomyelia) that might involve the entire length of the cord and/or the medulla oblongata. Typically, syringomyelia appears in adulthood (Masson and Colombani 2005); children might be affected and present with insidious onset and slow progression (Singhal et al. 2011). Signs and symptoms of CM1 (e.g., headache, neck pain, or lower brainstem dysfunction) (Wu et al. 1999; Greenlee et al. 2002) and syringomyelia (e.g., scoliosis, motor or dissociate sensory impairment) (Isu et al. 1990; Attenello et al. 2008) also overlap or might be difficult to ascertain in MPS patients.

Here, we describe a child affected with MPS type II and CM1, who developed a holocord syringomyelia and underwent suboccipital craniectomy and laminectomy with duroplasty to decompress the foramen magnum.

Clinical Description

Second-born from unrelated parents, during the first year of life the child presented with recurrent infections of the upper respiratory tract. Concomitantly, he showed psychomotor delay and altered sleep–wake rhythm. Mild organomegaly was also noted. A metabolic storage disease was suspected and biochemical and genetic tests were performed after obtaining parents' informed consent. Analysis of urinary glycosaminoglycans (GAG) revealed a high urinary GAG/creatinine ratio of 92.2 mcg GAG/24 h (normal values 1.59–30.3). L-Iduronate-2-sulfatase activity of leukocytes was 1.2 nmol/mg/h (control: 28 nmol/mg/hr). The patient was diagnosed with MPS type II at the age of 18 months. Genetic investigation revealed a c.589-592 del CCTG of the IDS gene.

At the age of 2 years and 5 months, the patient began enzyme replacement therapy (ERT) with idursulfase (Elaprase® SHIRE HGT, Lexington, MD) at a dosage of 0.5 mg/kg per week. Therapy was well tolerated and no severe adverse events were reported. The child was monitored through routine clinical assessment, laboratory analysis, and further investigations when required. His respiratory function and endurance improved while upper respiratory tract infections were significantly reduced during the following 2 years. The sleep–wake rhythm normalized, organomegaly resolved, and joint mobility improved. Cardiac examinations demonstrated mild mitral valve insufficiency before ERT introduction and did not change during follow-up while the ophthalmologic evaluation showed exophoria with normal visual acuity, eye pressure, and fundus. The child developed moderate

Fig. 1 Brain MRI at the age of 2 years, sagittal and coronal T2-w images showing the low position of the cerebellar tonsils (arrowheads) despite an enlarged cisterna magna and a posterior cranial fossa of normal size; several typical MPS features are also evident (e.g., J-shaped pituitary sella, ventricle enlargement, white matter signal abnormalities, enlarged perivascular Virchow-Robin spaces, and upper cervical stenosis due to the periodontoid cap). No signs of myelopathy were evident

mental retardation and received physical and occupational therapies both at home and at school. Sphincter control was not completely achieved. A brain MRI revealed several typical neuroradiological MPS features such as the J-shaped pituitary sella, the enlargement of perivascular (Virchow-Robin) spaces in the corpus callosum and centrum semiovale bilaterally, moderate ventricular enlargement, and enlarged cisterna magna along with ectopia of the cerebellar tonsils >6 mm below the foramen magnum, consistent with CM1. At the cranio-cervical region, the MRI showed dens hypoplasia with a periodontoid cap leading to mild stenosis of the cervical canal (score 2 according to Manara et al. 2011), while the upper cervical spinal cord was normal (Fig. 1).

A brain MRI follow-up at the age of 5 years revealed progression of cerebral atrophy while the cervical spine MRI disclosed a focal thin syringomyelia. At that time, the child complained of upper limbs numbness and no control of sphincters; no other neurological deficits were detected (Fig. 2).

A subsequent spine MRI at the age of 6 years showed a holocord syrinx, extending from the cervicomedullary junction to the conus medullaris. The neurological status was unchanged; cognitive evaluation confirmed a moderate impairment (IQ = 62 by WISH-IV and Terman-Merrill tests) (Fig. 3).

The boy underwent decompressive suboccipital craniectomy and C1 laminectomy with duroplasty. At 7-month neurological follow-up, both upper limbs numbness and bowel/bladder incontinence had disappeared. At follow-up MRI, the cerebrospinal fluid spaces at the cranio-cervical junction were well represented and the syrinx had significantly shrunk.

Fig. 2 Brain and spine MRI at the age of 6 years, midsagittal T1-w image disclosing the peg-like cerebellar tonsils (*) impinging the foramen magnum and reaching the posterior arch of C1. Holocord multiconcamerated syringomyelia is well documented also on axial T1-w and sagittal T2-w images (arrowheads). At this age, platyspondylia, intervertebral disk abnormalities, dens dysplasia, and cranio-cervical junction abnormalities were also evaluable

Fig. 3 Brain MRI at the age of 7 years, after decompressive surgery at the cranio-cervical junction. Sagittal T1-w images displaying cerebrospinal spaces around the upper cervical spinal cord and the cerebellar tonsils; the holocord syringomyelia has shrunk

Discussion

We reported on a boy affected with MPS-II-related spinal stenosis and Chiari malformation type 1, who developed holocord syringomyelia at the age of 6 and was successfully managed via surgical cranio-cervical decompression.

The cranio-cervical junction is known to be primarily involved in MPS patients. MRI examinations of this region are often featured by upper cervical spinal canal stenosis, which represents a major risk of myelopathy and even of sudden death after a minor fall (Northover et al. 1996). The accumulation of GAGs in the growing cartilage is thought to impair the ossification and maturation of the dens while ligamentous laxity seems to contribute to the

atlanto-axial instability. The latter likely induces the formation of reactive periodontoid fibrocartilaginous tissue that eventually cause spinal stenosis and spinal cord compression. Although the rate and the severity of spinal stenosis might vary according to the MPS form and is particularly important in MPS-I, IV, and VI, also MPS-II patients have been reported, who required decompressive surgery to prevent the progression of cervical myelopathy (Ballenger et al. 1980; O'Brien et al. 1997; Kaendler et al. 1990; Vinchon et al. 1995). From a clinical point of view, myelopathy usually results in progressive gait impairment, sensory deficits, and impaired sphincter control that might be overlooked due to concomitant brain, joint, and visceral involvement. In this context, MRI of the cranio-cervical region represents the main diagnostic tool for detecting and monitoring spinal stenosis and myelopathy and it is pivotal for planning the timing and the extension of surgical correction.

CM1 is a congenital downward impingement of cerebellar tonsils due to discrepancy between the size of the posterior cranial fossa and the volume of the cerebellar structures. The abnormal position of the cerebellar tonsils is thought to alter the CSF flow dynamic at foramen magnum level, possibly leading to spinal cord damage (Shah et al. 2011). The latter presents usually with a progressive cavitation (syringomyelia) that might involve the entire length of the cord and/or the medulla oblongata. In 90 % of cases, syringomyelia is associated with CM1 (Fernández et al. 2009). From a clinical point of view, syringomyelia typically present in children with insidious onset and slow progression (Singhal et al. 2011). Most often, scoliosis, motor or dissociate sensory impairment are noted due to sensory tract or corticospinal tract disruption and/or anterior horn cell involvement (Isu et al. 1990; Feldstein and Choudhri 1999; Attenello et al. 2008). Also, symptoms attributable to the concomitant CM1 are often observed (e.g., headache, neck pain, or lower brainstem dysfunction) (Wu et al. 1999; Greenlee et al. 2002). All these symptoms and signs might be concealed by the multiorgan involvement in MPS, often characterized by vertebral column abnormalities (scoliosis, kyphosis), joint stiffness, brain deterioration and spinal cord dysfunction.

In the general population, CM1 is due to the underdevelopment of mesenchymal structures forming the clivus and posterior cranial fossa bones (Milhorat et al. 2010). As MPS affect connective tissues with bone growth abnormalities (dysostosis multiplex), an increased rate of CM1 should not be completely unexpected. Most interestingly, as shown in our child patient, cerebellar tonsils ectopia in MPS patients might be observed despite a normal or even increased size of the posterior cranial fossa; in these cases an enlarged cisterna magna might be evident while the cerebellar tonsils are displaced downward, suggesting

or mimicking the coexistence of a retrocerebellar arachnoid cyst. A similar brain parenchyma displacement has been observed also in some closed meningoencephaloceles, a recently described skull abnormality of MPS II patients (Manara et al. 2012), where the prolapsing parenchyma is often squeezed in a marginal portion of the cavity, suggesting a more complex structure of meningocele content. The presence of sequestered arachnoid spaces and adherences to the meningeal pouch wall might be the most likely explanations, but a direct pathologic confirmation is still lacking.

Even though cerebellar tonsils are not significantly below the foramen magnum, their impingement might contribute to odontoid cap-related upper spinal canal stenosis in altering the physiological CSF dynamic at the cranio-cervical junction in MPS patients. In a previously reported case of MPS-VI associated with (holocord) syringomyelia (Hite et al. 1997), a cerebellar tonsil impingement was evident on the provided imaging, despite preserved retrocerebellar CSF spaces. Even in this case, holocord syringomyelia appeared in early childhood, but surgery was not performed due to clinical and imaging stability. In our child, the appearance and worsening of syringomyelia was documented at the age of 5 and 6. Subsequent cranio-cervical decompression determined a rapid clinical and neuroradiologic improvement, thus suggesting that surgery might be considered in MPS patients with holocord syringomyelia.

In conclusion, this case highlights that cerebellar tonsils impingement in MPS patients does not strictly depend on the size of the posterior cranial fossa and that a low position of the tonsils should be noted even in the presence of an enlarged cisterna magna. On the other hand, cerebellar tonsils impingement in MPS patients might require a more careful monitoring as clinical symptoms might be easily overlooked or misinterpreted with MPS-related myelomalacia or with the concomitant multiorgan involvement. Finally, as the MPS-related atlanto-axial instability often induces upper spinal stenosis, the spinal cord cavitation process due to cerebellar tonsils impingement and consequent disruption of CSF dynamics might have an accelerated and more severe course predisposing to early appearance of holocord syringomyelia. The role of surgery needs to be further ascertained, as the management of MPS patients affected with syringomyelia might be clinical or benefit from prompt decompression, avoiding a severe and irreversible spinal cord damage and improve the neurological impairment.

Take-Home Messages

The coexistence of Chiari 1 malformation in mucopolysaccharidosis patients might predispose to early myelopathy and prompts for strict clinical and MR monitoring; in these cases,

Chiari 1 malformation might have a different pathogenesis than posterior cranial fossa underdevelopment.

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