Regression of ventriculomegaly following medical management of a patient with Hurler syndrome

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Hurler syndrome is the most severe form of mucopolysaccharidosis (MPS) Type 1. Progressive neurocognitive decline in this condition can be accompanied by macrocephaly, ventriculomegaly, and/or periventricular signal changes on MRI, which often leads to a neurosurgical referral. In this case, the authors describe a 2-year-old boy with ventriculomegaly and periventricular T2 signal changes, both of which decreased following medical management of Hurler syndrome. The authors discuss the possible mechanisms for this finding and the implications for neurosurgical treatment of this condition.

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A ventriculoperitoneal shunt has often been used to treat individuals with communicating hydrocephalus, typically before hematopoietic stem cell transplant (HSCT).1

In this report, we describe a unique case of ventriculomegaly regression following medical management of MPS Type 1. We explore the possible mechanisms related to the findings in our case and discuss the implications for treatment.

Case Report

History and Examination

This 3-year-old boy initially presented to British Columbia Children’s Hospital at 20 months of age with macrocephaly, coarse facial features, developmental regression, corneal clouding, obstructive sleep apnea, skeletal contractures, and an umbilical hernia. He was born following an uncomplicated pregnancy via cesarean section at 42 weeks due to macrocephaly. His parents are nonconsanguineous, and there was no prenatal teratogen exposure. Clubfoot was diagnosed at birth and was treated with casting. Results of a neonatal hearing screen were found to be nonsatisfactory. At 3 months of age, bilateral inguinal hernias were repaired, and at 11 months of age, bilateral tympanostomy tubes were inserted for multiple serious otitis media. Review of developmental milestones found
that the patient was sitting unsupported at 7–8 months and was walking by 15 months. At 20 months, the patient's gait appeared unstable, and frequent falls and trips were reported. Expressive language skills regressed from 1 to 2 words at 1 year of age to no words at the time of initial assessment. Receptive language skills were also impaired, and sensorineural hearing loss was suspected. At 20 months of age, the patient’s head circumference was measured to be 54.5 cm, which corresponds to greater than 2 standard deviations above the mean. Frontal bossing was also noted. No papilledema was found on funduscopic examination. A prominent metopic suture line suggested metopic synostosis. Splenomegaly and a systolic heart murmur were also noted.

A CT head scan showed low attenuation in the periventricular white matter with prominent lateral and third ventricles. This was followed by an MRI scan that showed T2 signal hyperintensity in the periventricular and deep white matter as well as evidence of ventriculomegaly (Fig. 1 left). Given the clinical findings, imaging results, urine mucopolysaccharides of 91 mg/mmol creatinine (reference level < 22 mg/mmol creatinine) and α-1-iduronidase activity of 8.1 pmol/punch/hr on blood spot enzyme testing (reference level ≥ 16.8), the diagnosis of Hurler syndrome was confirmed.

Treatment

Enzyme replacement therapy (ERT) with laronidase (Aldurazyme) was started immediately. At 25 months of age, this patient received an allogenic umbilical cord HSCT from an unrelated donor.

Posttreatment Course

Repeat MRI was performed 1 year later at 32 months of age. Findings included a decrease in T2 signal hyperintensity in the periventricular and deep white matter. In addition, ventriculomegaly had improved (Fig. 1 right). Head circumference was 55 cm, keeping him at greater than 2 standard deviations about the mean. Clinically, improvements in developmental motor milestones were seen. He was able to walk with a normal gait pattern, climb stairs unassisted, and feed himself. Progress in speech and language development was also noted. Although he was still nonverbal, he displayed the ability to make more sounds and showed more expression.

Discussion

Hurler syndrome is the most severe form of MPS and is often associated with progressive neurocognitive decline.5,9,15 In this case, ventricular enlargement and periventricular signal change were noted on the initial MR image; however, given that there were no signs to suggest increased intracranial pressure, no surgical CSF diversion was initially completed.

HSCT is currently the gold standard treatment for Hurler syndrome in individuals diagnosed by 2.5 years of age.5 ERT can be started prior to grafting to optimize HSCT success, as was done in our case.4 On the follow-up MRI, white matter changes were noted, as well as a decrease in ventricular enlargement. Wang et al.14 reported on 3 patients with MPS Type 1, where white matter changes improved; one of these patients experienced some post-treatment decrease in ventricular size. That study did not present radiographic documentation of the pretreatment ventriculomegaly or the posttreatment changes that were stated to have occurred in one case within their series.

The reasons for treatment-related improvement in ventriculomegaly are not entirely clear. Meningeal deposition of GAGs has been thought to affect CSF resorption in the arachnoid granulations and may lead to ventriculomegaly and hydrocephalus.1,2,11 HSCT may help decrease GAG storage, improve CSF flow, and decrease ventricular size.14 In addition, cerebral atrophy as a consequence of MPS affecting the brain parenchyma may contribute to the development of ventriculomegaly.2,6,8 Following HSCT, reversal of periventricular changes may have additional effects on ventricular size.4,7,12

A limitation to this case is that only one follow-up MRI study was obtained, 1 year after starting ERT and 7 months after HSCT. Takahashi et al. demonstrated a transient increase in ventricular size in a Hurler patient post-HSCT with no overall net change in ventricular size.13 Unfortunately, we are unable to comment on how early ventricular size improvement occurred and if there were any transient changes.

Our case contributes to the current understanding of Hurler’s syndrome, with radiological improvement in ventriculomegaly as well as improvement in periventricular T2 signal changes. The clinical and radiographic circumstances of Hurler’s syndrome patients at the time of neurosurgical referral (such as macrocephaly, ventriculomegaly, or periventricular T2 signal change) might lead many to contemplate surgical CSF diversion. However, the more prudent course of action may well be to await the improvements associated with medical management of the underlying MPS.

References


![Fig. 1. T2/FLAIR MR images obtained at 20 months of age before starting ERT and before HSCT (left) and at 32 months of age after 12 months of ERT/7 months post-HSCT (right). Signal hyperintensity in the periventricular and deep white matter as well as ventriculomegaly decreased significantly following treatment.](image-url)
Ventriculomegaly decrease following treatment for Hurler syndrome


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Disclosures
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