Commentary

Intrathecal enzyme replacement therapy to treat spinal cord compression in mucopolysaccharidosis: Overview and rationale

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Spinal cord compression has been described in mucopolysaccharidosis I, II, IV, VI, and VII. The spinal cord compression in the mucopolysaccharidoses is believed to originate from narrowing of the vertebral canal due to bony abnormalities, and thickening of the meninges and spinal ligaments due to glycosaminoglycan infiltration [12]. The current standard of care involves surgical decompression. However, the surgery is extensive, MPS patients are high-risk surgical and anesthesia candidates, and the problem may recur after surgery. Neurosurgical treatment of spinal cord compression involves a multi-level decompressive laminectomy and opening of the thickened dura [12]. Many patients also require a suboccipital craniectomy. Some patients require instrumentation and fusion because they have ligamentous or spinal instability. Overall, the surgical repair can be more extensive than that required for spondylotic degeneration and myelopathy in normal elderly individuals.

Mucopolysaccharidosis patients are risky surgical candidates due to their airway, lung, and cardiac disease. Mucopolysaccharides accumulate in the oropharynx, tongue, epiglottis, aryepiglottic folds, and tracheal wall. This can distort the anatomy and make intubation extremely difficult [21]. There have been multiple reports of emergent tracheotomies performed in the course of surgery because of airway obstruction caused by significant upper airway storage [7,17]. In addition, these abnormalities tend to worsen over time, making subsequent surgeries even more risky [7,16]. Intubation is also made more difficult by immobility of the neck, shortened neck, and cervical spine instability [21]. There is additional anesthesia risk due to obstructive and restrictive lung disease, restriction of temporomandibular joint range of motion, and cardiac disease. Intraoperative complications have been attributed to stroke, pulmonary edema, and coronary artery disease [2].

There is evidence that spinal cord compression can recur even after decompression surgery. In 1987, Tama-ki et al. published a case of a 36-year-old man with Maroteaux-Lamy syndrome who underwent C1–C3

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transcervical anteromedial fenestration for compression due to thickened dura [20]. He had temporary improvement, but returned with myelopathy one year later and was found to have much more severe concentric narrowing of the entire cervical region. He underwent a second surgery consisting of a C1–C7 laminectomy and duraplasty. Longer lifespan due to current therapies for systemic disease may increase the chance of recurrence in treated individuals.

Hematopoietic stem cell transplantation (HSCT) has been shown to be successful in treating many clinical symptoms of MPS I, but it is only available to the most severely affected patients given its high morbidity and mortality. In addition, many of the skeletal manifestations of the disease are probably not reversed nor prevented by HSCT. In 2000, Kachur et al. reported on an MPS I patient who received a bone marrow transplant at age two, but then presented at eight years of age with a cervical myelopathy [12]. This patient underwent a suboccipital craniectomy, C1–C5 laminectomy and duraplasty. She was found to have ligamentous and dural thickening, and an extradural mass comprising storage material and fibrosis.

Intrathecal or intracerebroventricular enzyme replacement therapy has been studied in animals as a potential therapy for mucopolysaccharidosis types I, II and IIIA, globoid cell leukodystrophy (Krabbe disease), late-infantile neuronal ceroid lipofuscinosis, and Niemann-Pick type A [4,6,8,13,14,18]. Distribution via cerebrospinal fluid appears to be widespread in all cases. Reduction in stored material, improved histopathology, longer lifespan and neurobehavioral improvement have been observed with intrathecal or intracerebroventricular enzyme replacement therapy in animal models [4,6,9,10,14].

There is a canine model of mucopolysaccharidosis type I, which has a null mutation in the IDUA gene [19]. We have published results on 19 MPS I dogs treated with intrathecal recombinant human alpha-L-iduronidase (formulated as laronidase, BioMarin Pharmaceutical Inc., Novato, CA). Thirteen of these MPS I dogs received ~1 mg and six received 0.46 mg intrathecal recombinant human alpha-L-iduronidase administered into the cisterna magna in 3–4 weekly, monthly, or quarterly (every three month) repeated injections [5, 13]. At 48 hours following the final dose, cervical, thoracic, and lumbar meninges (dura and arachnoid) were assayed for iduronidase activity and glycosaminoglycan storage levels. Iduronidase activity levels in the spinal meninges were very high, with the mean enzyme activity ranging from 33- to 435-fold the normal level (15.4 units/mg) in all three regions (Fig. 1). In the
cervical meninges, enzyme activity ranged from 465 to 20,700 units/mg protein (30- to over 1300-fold normal); in thoracic meninges, 558 to 9973 units/mg (36- to over 600-fold normal); in lumbar meninges, 95.4 to 5820 units/mg (6- to over 300-fold normal).

As previously reported, dogs treated with intrathecal recombinant alpha-L-iduronidase showed reduction in glycosaminoglycan storage in the cervical, thoracic, and lumbar spinal meninges by 57–70%, from the untreated level of $35.9 \pm 3.03 \mu g/mg$ ($n = 2$) to means of roughly $9–16 \mu g/mg$ ($n = 19$) [5]. Normal total glycosaminoglycan content in the spinal meninges was $4.78 \pm 0.82$ ($n = 4$). There was no difference between the 1 mg and 0.46 mg dose in glycosaminoglycan storage reduction. Mean glycosaminoglycan storage in the cervical meninges was reduced to a greater extent than thoracic or lumbar, and overlapped with the normal range (Fig. 2). Six of the 19 dogs were evaluated three months after the final intrathecal laronidase dose. Glycosaminoglycan storage was equally low in these animals as at 48 hours [5]. Histopathology showed storage reduction in the meninges.

An immune response occurs to intrathecal enzyme administration in animals. Mice with mucopolysaccharidosis IIIA treated with intrathecal sulfamidase showed no cellular immune response (meningitis), but all mice developed antibodies in serum [10]. Mice treated with intraventricular tripeptidyl peptidase-I for late-infantile neuronal ceroid lipofuscinosis had no apparent side effects, but also developed antibodies to therapy [4]. In our dogs with mucopolysaccharidosis type I, intrathecal enzyme therapy resulted in a lymphocytic and plasmocytic infiltrate in the meninges, accompanied by anti-iduronidase antibodies in serum and cerebrospinal fluid [5,13]. There was no clinical evidence of meningitis in the animals, however. Induction of immune tolerance, or even partial immune suppression, may reduce the cellular and humoral response, though less frequent intrathecal injections may also be a factor [5].

Preliminary clinical trials to determine the safety of this approach in patients with mucopolysaccharidosis type I are underway (NCT 00215527 and NCT 00786968). The goal is to study patients with symptomatic spinal cord compression who are not in urgent need of surgical intervention and whose compression is not mainly due to extradural factors (such as spinal disk intrusion). The initial pilot study is four months’ duration, with a one-year extension for subjects with measurable gains from therapy. Subjects receive intrathecal laronidase injections of 1.74 mg diluted in Elliotts B artificial spinal fluid (total volume 9 mL) via lumbar spinal tap. Evaluations include serial neurologic examinations, six-minute walk test, modified Japanese or-
Clinical effects of intrathecal enzyme replacement therapy for spinal cord compression in mucopolysaccharidosis may be difficult to assess. Thickening of extradural ligaments is a major contributor to cervical cord compression; this is not expected to respond to intrathecal enzyme replacement therapy, and cannot reliably be differentiated from dural thickening on spinal imaging. Other extradural factors also contribute to cord compression, and can be the primary cause. Damage to the spinal cord is typically irreversible, making the measurement of success difficult. Long-standing glycosaminoglycan storage can lead to tissue damage and fibrosis, which may not respond to therapy. Prevention of damage may be a more achievable goal, but this is very hard to assess clinically, as it would require very long-term, controlled studies.

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Conflicts of interest

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