Intraventricular baclofen as treatment for Lesch-Nyhan dystonia: A case report and review of 3 cases in literature

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Abstract
Lesch-Nyhan (LN) disorder is a genetic condition caused by mutation of HPR1 and deficiency of the corresponding hypoxanthine-guanine phosphoribosyltransferase (HPR1) enzyme. HPR1 mutation results in elevated uric acid levels in the body and progressive physiological and cognitive impairment. There is no cure for LN, and treatments are experimental and targeted towards motor symptoms. It is imperative to investigate alternative therapies with a more comprehensive perspective. We present an 11-year-old boy with confirmed LN. He presented with severe spasticity, dystonia, and self-mutilating behaviour, which were poorly controlled, even with six different medications. He received some benefit from botulinum toxin injections and alcoholic nerve blocks but the improvement was temporary and inadequate. Intrathecal baclofen (ITB) was thus considered by his pediatric physiatrist. He underwent placement of a pump for the long-term administration of ITB. We report the effects of ITB on both motor and behavioural symptoms of LN, and compare the efficacy between spinal-intrathecal and intraventricular baclofen (IVB). We also review three other cases in the literature.

Introduction
Lesch-Nyhan is a X-linked recessive disorder that has no cure. It presents with several symptoms which can be grouped into motor and cognitive impairments. Motor impairments generally include spasticity, dystonia, ballism, uncontrollable self-mutilation, choreoathetosis, and opisthotons (Sturt et al., 2016). Many children have a simultaneous diagnosis of cerebral palsy due to the similarities in movement presentation. Ambulation is rare and becomes increasingly difficult with age. Cognitive impairments vary between individuals but many develop compulsive violent tendencies such as self-mutilation, aggression, and coprolalia (see Image 1).

Recent studies hypothesise an underlying cause of irregular neurotransmitter homeostasis and transport, specifically in dopamine, norepinephrine, and serotonin (Jankovic et al., 1988). Dysfunction of purine degradation is also studied since HPR1 deficiency allows for increased xanthine levels, a predecessor for uric acid production.

Case Report
The patient was a full-term 11 year old boy referred for spasticity and dystonia in May of 2017. He presented with self-mutilating behaviour (e.g. lip biting, finger biting) and was producing crystals in his diaper, which were identified as uric acid crystals. A genetic evaluation revealed a HPR1 mutation on his X chromosome and consequently a diagnosis of Lesch-Nyhan disorder. He was subsequently placed on six medications, including gabapentin, clonazepam, sinemet, and oral baclofen for his motor dysfunction. His spasticity and dystonia did not adequately improve with any medical treatment. ITB was suggested by his physiatrist as a next logical step.

A baclofen test dose (100mcg) showed a decrease in the patient’s spasticity and dystonia with subjective clinical assessment. The surgical team proceeded with a placement of an intrathecal baclofen pump (Medtronic Synchromed 2, 40mL, 2000ug/mL) under fluoroscopic guidance, with the catheter tip placed at C1-C2 and the pump set to deliver 150 mcg per day (see Image 2). There were no intraoperative complications and his baclofen dosage was increased to 200 mcg / day over the next 48 hours. He was discharged to Children’s Specialized Hospital for rehab on POD3. Two weeks after surgery, there was considerable improvement in his motor and behavioural symptoms, with a decrease in destructive behavior, clearer speech, and decreased tone. His Ashworth scale was 1.5 for his upper extremities and 2.5 for his lower extremities, which was an improvement from his baseline of 5/5 for all extremities preoperatively.

In May of 2019, the patient returned for a re-evaluation of his baclofen pump, which had progressively been adjusted to deliver 1,483mcg/day due to progressive dystonia. He had severe opisthotons and dystonia, which his family reported had been occurring since December of 2018. It was determined that the patient had a growth spurt causing the catheter tip to descend to C7 as confirmed by an x-ray (see Image 3). A surgery to replace the catheter was scheduled.

The original surgical plan was to replace the intrathecal catheter and position the tip back at C1-C2. However, the catheter could not be threaded above T1-T2, possibly as a result of intradural adhesions from prior surgery. After multiple attempts, the surgical team decided to discuss alternatives with the family, which included 1) cervical laminectomy with direct placement of catheter or 2) intraventricular baclofen (IVB). Intraoperative consent was given for placement of an intraventricular catheter. The catheter was placed with endoscopic assistance, with the tip positioned through the foramen of Monro into the third ventricle (see Image 4). The old baclofen pump was replaced with a new one and the ITB dose decreased to 200 mcg/day. There were no intraoperative complications, and the baclofen dosage was increased to 275 mcg in response to observation. He was discharged POD3 with improved tone, appetite, and mood.

His incision healed well and his IVB was lowered from 275 to 260mcg/day since his extremities were initially too loose, but was then reverted to 275mcg/day after an increase in dystonia and self-reported discomfort. As of March 2020, the patient is now receiving 120 mcg/day and has been able to discontinue many of his medications. Overall, the patient demonstrated a notable improvement of his symptoms, which was quantified through the UDRS scale for dystonia and interviews to measure episodes of self-mutilation and sleep awakenings. He continued his discharge medications and followed up with his physiatrist for further monitoring.

Conclusion
The management of spasticity, dystonia and opisthotons has improved the quality of life for LN patients. The surprising result is that ITB and IVB also alleviated other symptoms such as self-mutilation, coprolalia, and aggression. Whether this result is a direct effect of the medication itself or a secondary effect of better motor control is unknown.

References

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