Lesch-Nyhan disease (LND) is a rare neurological condition characterized by severe action dystonia, baseline hypotonia, gout, and self-mutilating behavior. The disease inheritance is X-linked, and the disease phenotype results from a deficiency of the purine salvage enzyme hypoxanthine-guanine phosphoribosyltransferase. Dystonia management is often the focus of clinicians treating children with LND; however, the hallmark self-mutilating behavior seen in LND is severely disabling and results in a dramatically reduced quality of life. The neuroanatomical and pathophysiological mechanisms responsible for self-mutilation in LND are unknown. Currently, there is no specific treatment for the LND-associated self-mutilation, and children often require edentulation as well as physical restraints.

Chronic pallidal stimulation has emerged as a treatment for children with generalized dystonia, including those with LND. As expected, pallidal stimulation results in improved dystonia symptoms, consistent with reports of treated adults with generalized dystonia. Interestingly, chronic pallidal stimulation also has the unexpected benefit of reducing self-mutilation behaviors, and this effect has been reproduced in several case reports. The mechanism underlying improvement in self-injurious behavior is unknown. Specifically, it is not known whether the improvement reflects the modulation of basal ganglia circuitry or is a nonspecific epiphenomenon of pallidal stimulation.

In this paper, we describe a boy with LND who underwent chronic pallidal stimulation for generalized dystonia. After significant improvement in both dystonia and self-mutilation following the initiation of deep brain stimulation (DBS) therapy, his right globus pallidus internus (GPI) electrode fractured, and he again exhibited self-injurious behavior but only on the left side of his body. To our knowledge, lateralization of the stimulation effect on self-mutilation has not been previously reported.
Case Report

Presentation. This 15-year-old boy with LND was referred to the neurosurgery clinic at the University of Iowa for consideration of pallidal DBS to treat generalized dystonia. The patient was suspected of having a motor abnormality (later interpreted as dystonia) as early as 6 months of age. He was not given a formal diagnosis of LND until the age of 3 years when self-mutilation behavior began. He never exhibited aggressive behavior toward others, but he did undergo dental extractions 1 month after diagnosis for frequently biting his hands. Self-mutilation most frequently involved the eyes, but sometimes also the mouth or nose. He required constant physical restraints to prevent self-injury. He also required a wheelchair given the severity of his generalized dystonia, which was refractory to treatment with diazepam and intrathecal baclofen therapy. He had been hospitalized with rhabdomyolysis of unknown etiology, which may have been caused by the dystonia. This event contributed to his eventual referral for DBS placement.

On examination, the boy was able to communicate effectively with relatives. Because of his severe dysarthria, only his mother and primary caretaker could interpret what he was saying. His face was symmetric. He exhibited generalized dystonia that included the hands, legs, neck, and perioral region. Because of the self-mutilating behavior, he required wrist restraints and mitts. Despite his dystonia and these precautions, he was still able to perform self-injuring behaviors, which were nearly constant and required early edentulation. Brain MRI demonstrated a normal macroscopic brain structure. Given the severity of the patient’s dystonic symptoms despite maximal medical measures, we decided to proceed with bilateral GPi DBS in accordance with his family’s wishes.

Operation. The patient was taken to the operating theater where he was positioned and placed under general endotracheal anesthesia using propofol. A CRW stereotactic frame was placed. Stereotactic targeting was performed using merged preoperative MR and CT volumetric imaging (Medtronic StealthStation S7 Surgical Navigation System). The stereotactic coordinates targeted for the GPi were ±20 mm lateral, 2 mm anterior, and 4 mm deep to the midcommissural point. Using these indirect coordinates, we performed microelectrode recordings (StimPilot, Medtronic) bilaterally to define borders of the GPi. Single microelectrode tracts were used. Microelectrodes recorded 10- to 20-Hz firing rates, consistent with the GPi. Photic bursts were captured deep to the inferior border of the GPi. Based on these recordings, the optimal targets for implantation were 2 mm anterior to the original indirect targets bilaterally. The leads were secured and subsequently connected to extensions and a dual-channel implantable pulse generator (IPG; Activa PC, Medtronic) in a single-stage operation. The patient tolerated the procedure well without complication and was discharged home after 2 days.

Postoperative Course. Stimulation commenced 1 month following implantation. With settings of the left lead at case positive, contact 3–, amplitude 0.5 V, pulse width 60 μsec, and frequency 120 Hz and the right lead at case positive, contact 7–, amplitude 0.5 V, pulse width 60 μsec, and frequency 120 Hz, the boy’s dystonia symptoms demonstrated moderate improvement over the course of several weeks. Dystonia improved to the point that the boy could play video games. The self-mutilating behavior became so rare that the patient no longer required restraints and could go for up to 90 minutes without any evidence of self-mutilation. The family reported that this was by far the best control of self-mutilation that the patient had ever experienced.

Several months later, the patient fell out of bed while sleeping. He was not evaluated immediately following this event. After the fall, his dystonia symptoms increased on the left side of the body, and the self-mutilating behavior from the left side also returned to the point that his left wrist had to be restrained. The patient would use his left arm to mutilate both the left and right sides of his body. Plain radiographs revealed fracture of the right lead just proximal to the extension and lead junction (Fig. 1). It was also apparent that both lead junctions had been pulled down from the original parietal scalp location into the neck. Volumetric CT scanning demonstrated, in addition to the fracturing, that the right lead had been pulled back approximately 4 mm from its original location (Fig. 2). There was no evidence of injury to adjacent subcortical structures; therefore, the decision was made to take the patient back to the operating room to replace both GPi leads.

As in the original surgery, a stereotactic frame was placed with the patient under general anesthesia. Final targets were determined using microelectrode recordings (Alpha Omega). The new left lead was ultimately positioned in the same location as the original lead position. The new right lead was positioned 2 mm posterior and 2 mm deep to the original indirect microelectrode recording–based implantation. The patient tolerated the procedure well without any complication. He was discharged from the hospital after his DBS generator was programmed. Over the course of weeks, his left dystonia improved, although he continued to have moderate dystonia in all extremities that was slightly worse on the left side. His self-injurious behavior improved but not to the same level it had after the first DBS operation. However, it did improve significantly to the point that he no longer required wrist restraints.

![Fig. 1. Lateral radiographs demonstrating fracture of the right DBS lead.](image-url)
Discussion

The self-mutilating behavior characteristic of classic LND significantly impacts quality of life for children with the disease. Traditional medical therapy has focused on the motor symptoms of LND, but effective treatments for self-mutilation are virtually nonexistent. Characteristically, self-mutilation begins with the development of teeth, at which point individuals begin to bite both their lips and their fingers destructively.\(^5\) This results in tissue loss around the lips and partial amputation of fingers, which in many cases is managed with a combination of edentulation and wrist restraints. Given the morbidity of self-mutilation in children with LND, its successful treatment is a very important goal.

Although the genetic and biochemical bases for LND are known, the neural substrates underlying LND-associated self-mutilation are poorly understood. Neuroimaging studies show loss of volume in the basal ganglia,\(^4\) and indeed basal ganglia dysfunction is implicated in the motor symptoms manifest in LND.\(^3\) Specifically, neurochemical research suggests a role for basal ganglia dopaminergic systems in the pathophysiology of LND.\(^4\)\(^,\)\(^14\) Recently, Schretlen et al. compared regional brain volumes of children with classic LND to those of children with variant LND (that is, without the self-injurious behavior) and reported a decreased size of the posterior cingulate, ventral striatum, and orbitofrontal cortex, although these results were not statistically significant.\(^2\) Connections between the ventral striatum and orbitofrontal cortex may play an important role in the reward mechanism and related self-injurious behavior.\(^10\)\(^,\)\(^13\)

More evidence of a role for the ventral striatum in LND-associated self-mutilation comes from case reports of chronic pallidal stimulation improving self-mutilation behavior in children with LND. In 2003, Taira et al. documented the first case of GPi stimulation improving self-mutilation behavior in a patient with LND.\(^1\) Since then, other instances of pallidal stimulation leading to improvement in self-mutilation behaviors have emerged in the literature.\(^2\)\(^,\)\(^3\)\(^,\)\(^8\) Two reports describe implantation of a single pallidal electrode on each side,\(^3\)\(^,\)\(^11\) and two reports describe implantation of two electrodes per globus pallidus to stimulate the sensorimotor GPi and limbic GPi separately.\(^2\)\(^,\)\(^8\) Both stimulation schemes appear to have the same efficacy for the motor symptoms and self-mutilation behaviors of LND.

The report by Cif et al. is of particular interest and demonstrates that stimulation of the sensorimotor GPi and limbic GPi had distinct effects in their LND patient.\(^2\) These authors describe a 16-year-old boy with LND who underwent placement of bilateral sensorimotor and limbic GPi electrodes. Stimulation was initiated at both electrode sites with improvement in motor symptoms and self-mutilation behaviors. When stimulation of the limbic GPi was selectively discontinued, self-mutilation behaviors recurred, but motor symptoms remained stable. When sensorimotor GPi stimulation was selectively discontinued, motor symptoms worsened and self-mutilation behaviors remained stable. These results suggest that the motor symptoms and self-mutilation behaviors of LND are mediated by distinct neural circuits in the ventral striatum, lending further support to the hypothesis that the ventral striatum plays a crucial role in LND-associated self-mutilation behavior. Ultimately, the clinical relevance of selective sensorimotor and limbic GPi stimulation is uncertain because central GPi stimulation appears to have similar clinical efficacy for the motor symptoms and self-mutilation behaviors of LND without the increased risk of placing two additional electrodes.

The reports of GPi stimulation in patients with LND, specifically the report of Cif et al., suggest that the pathogenic locus of self-mutilating behavior is dysfunction of the GPi limbic circuit. Whether this effect is lateralized is unknown. Our patient underwent central GPi stimulation and when the right lead fractured, motor symptoms and self-mutilation behaviors developed on the left side only. This finding suggests that not only is the circuitry responsible for self-mutilation localized to the limbic GPi, but the circuitry is also lateralized.

Conclusions

We report the case of a 15-year-old boy with LND who underwent the placement of bilateral GPi electrodes,
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resulting in improvement in the motor and self-mutilation symptoms. When his right lead fractured, he developed motor and self-mutilation symptoms only on the left side of the body. This finding supports the idea that the self-mutilation behaviors of LND are localized to the circuitry of the limbic GPi and that they are lateralized.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

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References


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