Botulinum toxin as a novel treatment for self-mutilation in Lesch–Nyhan syndrome

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Lesch–Nyhan syndrome (LNS) is an X-linked recessive disorder resulting from a deficiency of the metabolic enzyme hypozanthine–guanine phosphoribosyltransferase (HPRT). This syndrome presents with abnormal metabolic and neurological manifestations including hyperuricemia, mental retardation*, spastic cerebral palsy (CP), dystonia, and self-mutilation. The mechanism behind the severe self-mutilating behavior exhibited by patients with LNS is unknown and remains one of the greatest obstacles in providing care to these patients. This report describes a 10-year-old male child with confirmed LNS who was treated for self-mutilation of his hands, tongue, and lips with repeated botulinum toxin A (BTX-A) injections into the bilateral masseters. Our findings suggest that treatment with BTX-A affects both the central and peripheral nervous systems, resulting in reduced self-abusive behavior in this patient.

Lesch–Nyhan syndrome (LNS) was first described in 1964 as a familial disorder of uric acid metabolism and central nervous system (CNS) function (Lesch and Nyhan 1964). LNS is a rare X-linked recessive disorder resulting from a mutation on the gene encoding for the enzyme hypozanthine–guanine phosphoribosyltransferase (HPRT) located between Xq26 and Xq27 (Pai et al. 1980, Gerard and Kohn 1999). The syndrome is caused by a complete or partial lack of activity of HPRT. Patients are found to have high urinary concentrations of uric acid and increased serum uric acid levels due to the HPRT deficiency. Furthermore, this disorder may be associated with deficits in dopaminergic activity in the basal ganglia (Visser et al. 2000). LNS is characterized by delays in motor development and variable degrees of mental retardation manifesting within the first year of life. Patients typically are unable to sit independently and remain non-ambulatory throughout life. Motor activity is dominated by severe dystonia and behavioral manifestations including severe self-mutilation are characteristic (Schroeder et al. 2001). Treatments aimed at reducing levels of uric acid have not been effective in reducing the neurological symptoms, including the self-mutilation.

Biting is a specific behavior observed in LNS, most often causing damage to the patient’s fingers, lips, and occasionally the toes (Robey et al. 2003). In fact, this pathological behavior...
can be so severe that it results in partial amputations of the fingers and destruction of the tongue and surrounding mouth tissue. Patients may also show aggression toward family members and other individuals, but are limited in their actions by their motor impairment. Nyhan (1997) reported that children with LNS feel pain and remorse as a result of their self-mutilating behavior; however, they are unable to control their actions. Unfortunately, self-mutilating behavior is poorly responsive to behavioral modifications or medication, often requiring surgical intervention and removal of the primary teeth. Bite guards are incompletely effective in minimizing the traumatic effects of biting; dental extraction has its own complications, including progressive dental decay. Despite its limitation, dental extraction has been the only effective method for preventing the effects of self-mutilation when all other treatment options have failed (Lee et al. 2002).

This report describes the case of a child diagnosed with LNS who was treated with botulinum toxin A (BTX-A) injected into the bilateral masseters. BTX-A temporarily prevents presynaptic release of acetylcholine, causing motor end-plate dysfunction and muscle weakness. Treatment resulted in a reduction of self-mutilating behavior and healing of the patient’s sites of injury. This case suggests a biological mechanism of action of BTX-A on the peripheral and CNS, resulting in a disruption of this behavioral pathway. Parental consent for publication of the case notes was obtained.

Case report

A 10-year-old male initially presented with developmental delay in infancy and was diagnosed with cerebral palsy (CP) and cognitive impairment of uncertain etiology. The prenatal course, labor and delivery, and neonatal periods were uneventful. He was diagnosed with LNS at 8 years of age after he developed a more prominent movement disorder with hyperkinetic dyskinesia, spasticity, dystonic movements, self-mutilating behavior, and impulsive behavior toward others. He began displaying severe self-mutilating behavior at 8 years of age, causing ulceration of his hands, lips, and tongue. This behavior also

![Figure 1: Tissue destruction due to self-mutilation before and after treatment with botulinum toxin A (BTX-A).](image)

(a) Before the patient initiated treatment with BTX-A, there is extensive tissue damage due to child’s severe biting of his tongue, as evident by severed tongue circled next to his head. (b,c) After child’s third series of injections with BTX-A, there is substantial healing of tissue around the child’s mouth and tongue.
resulted in severe weight loss and an inability to attend school. Studies were initially inconsistent but ultimately, hyperuricemia and increased urinary excretion of uric acid were found and metabolic studies revealed a low HPRT level of 6.7 units (reference 235–701 based on the normal population). Multiple medication trials, either as monotherapy or in combination, were attempted including, buspirone, chlorimipramine, clonazepam, clonidine, haloperidol, pimozide, and risperidone. Initially the child had a baclofen pump implanted to manage his spasticity but it had no effect on his self-mutilation. He was maintained on allopurinol at a dose of 15mg/kg/day. Behavioral modification programs and upper-limb restraints were unsuccessful in preventing self-mutilating behavior, as were dental guards, which broke due to repetitive biting.

BTX-A was administered into both masseter muscles at two sites. Each site was injected with 20 units of BTX-A for a total of 40 units per muscle group. BTX-A was reconstituted with 1cm³ of normal saline and was injected using a 27-gauge needle and a 1cm³ syringe. Injections were repeated every 3 months for a series of three visits at the time of this case report preparation. Electromyography guidance was not required.

Before BTX-A therapy this patient’s severe biting behavior resulted in ulcerative wounds around his mouth and partial loss of 2cm² of his tongue. Within days of the treatment, the biting behaviors resolved and his wounds completely healed. BTX-A was well tolerated and benefits lasted 10 weeks, at which time the behavior began to return, requiring use of restraints. As a result, injections were repeated every 12 weeks. While continuing with BTX-A therapy, the child was able to return to school. Sores on his hands, lips and tongue healed completely. The patient’s speech articulation improved, although it remains abnormal. There was no observed impact on eating or swallowing ability due to the BTX-A and the patient’s weight returned to an appropriate level for his height and age. Parents reported a decrease in observed biting behaviors. Furthermore, aggressive behavior toward others also decreased with treatment. Medications have been reduced in this patient and he continues with supportive therapy.

Discussion
Behavior modifications and multiple medications used singularly or in combination have traditionally been the first approach to managing the severe biting behaviors seen in LNS; however, both have proven to be of limited benefit (Anderson and Ernst 1994). In this condition most patients have eventually required removal of the primary teeth as the definitive intervention to prevent further self-inflicted injury. This is the first report of the use of BTX-A as a treatment for self-mutilating behavior in LNS. It would suggest that BTX-A is a safe and perhaps effective alternative therapy in reducing or eliminating further self-inflicted injury in LNS.

The mechanism of BTX-A in decreasing biting activity is not clearly defined. It is known that BTX-A inhibits the release of acetylcholine from the peripheral nerve endings, resulting in muscle weakness. However, if this were the only mode of action, a greater reduction in bite force would have occurred without a change in the frequency of the self-mutilating behavior. Our case study suggests that BTX-A may act on the CNS and may be interfering with the behavioral pathway in LNS, resulting in a reduction of self-mutilating behavior (Fig. 1). BTX-A has been reported to have an unexplained effect on the CNS, resulting in decreased behavior beyond muscle weakness. Tintner and Jankovic (2002) describe decreased biting behaviors after injection with BTX-A into the masseters in cases of bruxism and other oromandibular dystonias. Improvement in focal dystonia with BTX-A therapy has been suggested to result from a dual effect on motor and afferent pathways at the injection site (Giladi 1997). Clinical observations suggest a long-term effect that extends beyond the motor end-plate. Giladi (1997) suggests BTX-A acts on the CNS through afferent pathways coming from the injection site, resulting in a long-term ‘sensory trick’. Hallet (2002) reports that BTX-A may have an effect on intrafusal synapses influencing sensory feedback. CNS reorganization of inhibitory and excitatory intracortical circuits may originate through peripheral mechanisms. Motor denervation caused by BTX-A may alter the activity of the muscle spindle sensory afferents, and this altered input results in changes in the spinal cord and CNS (Berardelli et al. 2002).

It has also been reported that the sensory effect of botulinum toxin may be due to the inhibition of the release of neuromuscular neurotransmitters, such as substance P and glutamate (Purkiss et al. 2000, Aoki 2001). The dual mechanism of action may result in both an early improvement in self-abusive behavior secondary to decreased discomfort and a late response that results in a behavioral change secondary to central modification. BTX-A may also have an indirect effect on the basal ganglia as dysfunction of the basal ganglia is associated with the neurobehavioral features of LNS (Nyhan and Wong 1996, Harris et al. 1998, Visser et al. 2000). This association was also reported by Taira et al. (2003) who described the disappearance of self-mutilating behavior in a patient with LNS after bilateral chronic stimulation of the globus pallidus internus, suggesting that the neurobehavioral features of LNS are mediated in the basal ganglia pathway.

In conclusion, this case study suggests that BTX-A should be considered as a safe and effective alternative to tooth extraction and medication in patients with LNS with severe self-mutilation. Furthermore, BTX-A may serve as a preventative to the severe physical and emotional trauma that develops in the child who is unsuccessfully treated. BTX-A may be acting both directly on the peripheral nervous system and indirectly on the CNS to interfere with the behavioral pathway that causes self-mutilation in LNS. This study is limited to one individual and therefore further investigation is necessary to define the mechanism of action, safety, and therapeutic benefit of BTX-A in patients with LNS with self-mutilation.

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References

Book Review

Animal Models of Movement Disorders
Edited by M LeDoux
New York: Elsevier, 2005, pp 824, §154.95, US$249.95
ISBN 0-12-088382-1 (Hardback)

The term ‘model’ is widely used in science where it has a number of meanings. In essence, models are intellectual tools to aid in the understanding of some aspects of the natural world and to direct our investigations and theory building. Models help to identify a system that is then manipulated experimentally to explore whether the model behaves as the naturally occurring system does. There are many sorts of models: operational, descriptive, predictive, physical, mathematical, computer, and so forth. All of these and others are used in the neurosciences.

This is a big book: 66 chapters organized into 14 sections, written by 130 contributors drawn from 12 countries, though predominantly American. An unusual feature of the book is that it comes with a DVD which illustrates very effectively a range of human and animal movement disorders. Seeing the pattern of movement rather than having only a verbal description and some still figures is invaluable.

The first section of the book, which comprises eight chapters, deals with a number of basic matters: the clinical features and classification of movement disorders; an excellent introduction to animal models by the editor; two chapters on transgenic mouse models and spontaneous mutants; and two methodological chapters which discuss how to measure movement disorders in laboratory rodents. The remaining two chapters are quite different: one is devoted to a descriptive review of behaviour in the fruitfly, *Drosophila*, and the other to the use of the nematode,* Caenorhabditis elegans* to model human movement disorders. *Drosophila* is, of course, well known because of its extensive use in genetics. As models for human movement disorder, a small fly and an even smaller nematode worm may come as a surprise but their use in research on Parkinson and Huntington diseases is extensively explored in subsequent parts of the book.

The remaining 13 sections are organized around individual disease states and movement disorders: Parkinson disease (throughout the book the non-possessive forms of eponymic terms are used), dystonia, Huntington disease, tremor disorders, myoclonus, tics, paroxysmal disorders, supranuclear palsy, multiple system atrophy, ataxia, spasticity, drug-induced movement disorders, and, finally, and a little surprisingly, restless legs syndrome. The range of material used is extensive, for example, studies on Parkinson disease employ, flies, worms, mice, and monkeys.

The book is an ambitious undertaking and the editor must be congratulated on amassing so much material and so many contributors so successfully. I fancy it will be some time before an undertaking of this size and depth is attempted again. The book will surely be valuable to a range of neurobiologists and others interested in movement disorders and beyond. Its breadth of cover should stimulate some to try changing their models.

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