

Successful Treatment of Recalcitrant Restless Legs Syndrome With Botulinum Toxin Type-A

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Study Objective: We report the effective use of injected BTX-A to treat refractory restless legs syndrome (RLS).

Methods: This is an observational case series of 3 patients meeting the essential diagnostic criteria for RLS whose symptoms were refractory to or who refused oral medication. Areas of maximal discomfort were injected as described below.

Results: Patient #1, a 58-year-old man with refractory RLS, received injections in both legs. The effect persisted for 12 weeks after injections. He temporarily stopped taking gabapentin. He experienced a mild increase in a timed run. Patient #2, a 38-year-old man with refractory RLS, received BTX-A injections in both legs and his lumbar paraspinal muscles. Three days after injection, he reported great improvement. Within 1 month, his Epworth Sleepiness Scale score had decreased from 19 to 5. He stopped oral therapy during the peak therapeutic period. There were no untoward effects. Patient #3, a 38-year-old woman had a prolonged

sleep latency due to RLS. BTX-A was administered in the legs. In 2 days, her discomfort and her subjective sleep latency improved. Both the urge to move and nocturnal restlessness resolved for 10 weeks. There were no untoward effects in all patients, and the response was repeated in successive injection cycles.

Conclusions: Intramuscular BTX-A alleviated symptoms, reduced medication use, and/or reduced daytime sleepiness with minimal, if any, untoward effects. BTX-A should be further investigated in controlled studies as a treatment of RLS.

Keywords: Restless legs syndrome, botulinum toxins, movement disorders, pain, chemodenervation

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The diurnal urge to move, characteristic of restless legs syndrome (RLS), is often associated with uncomfortable sensations. In 1 series, up to 56% of patients had pain or uncomfortable sensations.¹ Just as the movements can occur in the back and arms, so can the discomfort of RLS occur in the same anatomic areas.

Numerous pharmacologic modalities exist for the treatment of RLS. Oral medications can cause intolerable untoward effects and may have significant interactions. Unfortunately, RLS can remain refractory to treatment or even worsen with long-term use of certain agents.

Botulinum toxins mediate pain relief by reducing peripheral sensitization and subsequently, though indirectly, by reducing central nervous system sensitization. Botulinum toxin type A (BTX-A) has been successfully applied to a variety of painful conditions and movement disorders. We report the effective use of BTX-A for the treatment of recalcitrant RLS in 3 adult patients.

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METHODS

This is an observational case series. Between 2002 and 2004, we identified 3 individuals meeting the 4 essential diagnostic criteria for RLS who either were refractory to conventional treatment or who refused oral medication. These individuals had normal neurologic examinations. Informed consent was acquired for this off-label use of BTX-A. Areas of maximal discomfort were identified by the patients and injected with BTX-A as described below. Response was assessed clinically by the Epworth Sleepiness Scale (ESS) or by medication use.

Commentary Follows on Pages 279-280

Case 1

A 52-year-old man presented with a long-standing history of RLS refractory to numerous medications, excessive daytime somnolence, and disturbed sleep. At 28 years of age, the patient had noted nocturnal leg spasms with secondary daytime fatigue. A polysomnogram demonstrated periodic limb movements of sleep. The patient was treated with diazepam, which improved sleep quality and decreased daytime fatigue but had no effect on the nocturnal leg movements.

Several years later, he developed further sensory symptoms of RLS, described as a "very bothersome" urge to move his legs secondary to "deep and achy" sensations. Stretching or movement partially alleviated the symptoms that were worsened by sitting or lying down. Initially, these sensations occurred only

in the evenings. Over the following decade, they progressed to earlier times in the day, eventually occurring throughout the day. The RLS was recalcitrant to multiple medications, including phenytoin, clonazepam, acetaminophen plus oxycodone (Percocet), prochlorperazine, hydroxyzine, iron supplements, and quinine. Carbidopa-levodopa treatment was initially successful, but his condition worsened despite increasing doses. Subsequently, he incompletely responded to gabapentin (3600 mg per day) but gained 20 pounds and noted worsened daytime somnolence.

On initial evaluation in our center, he indicated that most of his dysesthesias localized to the region overlying the tibialis anterior muscles bilaterally. His neurologic examination was normal. The patient expressed considerable concern regarding the side effects that he was experiencing, and he was therefore amenable to a trial of botulinum toxin.

BTX-A (100 units per cc) was injected into each of his tibialis anterior muscles bilaterally, in divided doses of 25 units, with a total of 50 units per muscle.

The patient noted improvement within days of treatment. This effect persisted for 8 to 12 weeks after each series of injections. Three to 4 weeks after each subsequent cycle of injections, his RLS symptoms were noticeably reduced, and he reported less daytime fatigue, as measured by the ESS (Figure 1). The patient continued to respond over several injection cycles with improvement in daytime somnolence. Notably, he was able to decrease his gabapentin dosage by 50%. The patient's only untoward effect was a mild decrement in his daily timed run.

Case 2

Patient #2, a 50-year-old man with mild obesity well-controlled hypertension, hypothyroidism, and hyperlipidemia, presented to the clinic complaining of excessive daytime sleepiness, frequent nighttime awakenings, and extremity discomfort. He reported a 17-year history of a nightly need to pace and difficulty returning to sleep. His discomfort smoldered at a low level throughout the day but markedly worsened at night and while at rest. He sensed "thousands of tiny worms crawling deep" in the muscles of his calves and lateral thighs. His wife complained of his leg movements in sleep. He was undergoing involuntary medical retirement because daytime sleepiness left him unable to perform his military duties.

His symptoms began at age 33, and, by age 43, he experienced delayed sleep onset and fragmented sleep. An initial polysomnogram at the age of 42 revealed a sleep efficiency of 91%, a sleep latency of 17 minutes, and a significant number of obstructive events. No quantification of his respiratory disturbance index nor of his periodic leg movements was noted in his record. Continuous positive airway pressure (CPAP) of 9 cm H₂O was prescribed. Over the next year, his daytime sleepiness did not improve with full compliance with CPAP therapy. A second polysomnogram confirmed benefit of the CPAP at the prescribed pressure.

He underwent a series of medication trials for RLS. Carbidopa-levodopa significantly augmented his RLS symptoms. Parlodel, pergolide, ropinirole, iron, and clonazepam were ineffective. Gabapentin, pramipexole, and opiates ameliorated his discomfort. His dosage of acetaminophen-oxycodone HCl (Percocet) escalated to 5 to 6 per day and ultimately caused excessive confusion and fatigue.

At our initial consultation, he was noted to be sleeping in the

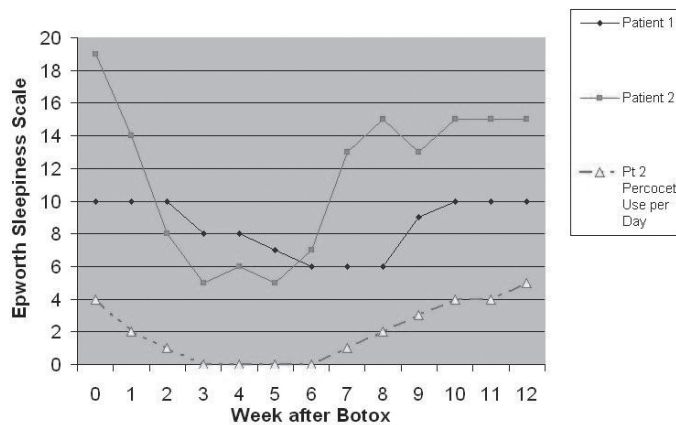


Figure 1—Responses of 2 Patients to BTXA as measured weekly by Epworth Sleepiness Scale and Medication Use

patients' waiting area. He reported persistent dysesthesias in his posterior calves and anterolateral thighs, with extension up his back. His medications included gabapentin 300 mg QID; acetaminophen 325 mg plus oxycodone 5 mg, 5 to 6 tablets per day; and pramipexole, 2 mg BID. Three times a week, he used zolpidem 5 mg to initiate sleep. He reported good compliance with nightly CPAP. His other medications included doxazosin, hydrochlorothiazide, simvastatin, levothyroxine, niacin, and fexofenadine.

On exam (late in the afternoon), he moved his legs frequently. He could temporarily suppress the movements, but, if he did so for extended periods, he experienced increased discomfort. He rubbed his anterior thighs intermittently to alleviate his uncomfortable sensations. A detailed neurologic exam was normal, with no evidence of a neuropathy.

The patient received injections of a total of 320 units of BTX-A (100 units per cc) bilaterally in his lumbar paraspinal muscles (40 units per site, in 2 sites per side), his gastrocnemii (20 units per site and 2 sites per leg), and his quadratus femorii (20 units per site and 2 sites per leg).

The patient reported significant relief 3 days after injections. He reported a complete resolution of sensory symptoms even when sedentary. He experienced refreshing sleep with improvement in his daytime cognition. He reported a limit of this effect on his back that corresponded to the upper limit of injections. Below this border, he had complete relief, while above it he experienced his usual discomfort. Four weeks later, his ESS score had dropped from 18 to 12 (Figure). He temporarily stopped taking opiates and gabapentin as needed.

Over the last 2 years, he has continued to receive injections every 3 months without escalation of dose. After each injection cycle, he reports complete relief of his lower-extremity symptoms within 7 to 10 days and 75% relief of his back symptoms. His ESS score drops during this time period from 20 to 21 to 4 to 7, and his Percocet use drops to 1 per day. He has resumed working as a dean of a graduate school. He has experienced no untoward effects.

Case 3

A 38-year-old woman presented for an evaluation of migraines and reported moderately uncomfortable sensations in her posterior calves bilaterally. The urge to move and restlessness were a

less prominent complaint than the discomfort. The phenomenon recurred nightly and delayed the onset of sleep. She had difficulty describing the sensation but reported it most like an itch. Ambulation and rubbing ameliorated the symptoms. She reported multiple family members with similar symptoms. She took no medications aside from occasional ibuprofen and aspirin for migraines. She had taken propranolol and topiramate in the past as migraine prophylaxis, but she had to discontinue the medication due to untoward effects. She outlined a crescentic area of discomfort in her posterior calves and popliteal fossae. Aside from mild hypertension, her neurologic exam was normal. A complete blood count and iron studies were normal.

Once diagnosed with RLS, she refused any medical treatment because of a concern about untoward effects. A trial of botulinum toxin injections was offered. A total of 70 units of BTX-A (50 units per cc) were administered subcutaneously in the dysesthetic areas (5 units per site and 7 sites per leg).

Within 2 days, her discomfort had dropped from 10 on a scale with a maximum score of 10 to 3 out of 10. She subjectively noted marked improvement in her discomfort. Her husband reported decreased nocturnal movement. After each of 3 subsequent injection cycles, the effect waned after 12 weeks.

DISCUSSION

RLS is a common disorder affecting up to 20% of the population.^{2,3} The first modern characterization was by Ekbom, who described the uncomfortable sensations in 2 forms: one with prominent paresthesias, “asthenia crurum parasthetica” and the other with prominent pain, “asthenia crurum dolorosa.”⁴

Today, RLS is defined by the following 4 criteria: (1) an urge to move the limbs usually associated with paresthesias or dysesthesias, (2) worsening symptoms at rest or with inactivity, (3) at least partial and temporary relief by activity, and (4) worsening symptoms in the evening and at night.⁵ The unpleasant sensory component of this illness can be a prominent feature of this condition.

The pathogenesis of RLS is unclear, but loci from the basal ganglia to the spinal cord have been implicated. One line of research has focused on dysfunctional descending control of spinal function in RLS. Recent literature has found mechanical hyperalgesia and enhanced flexor reflexes in patients with RLS and PLMS, respectively.^{6,7}

While effective, current therapies can have limitations. Dopamine-receptor agonists are considered the first-line medication, but up to 80% of patients develop augmentation to levodopa and may require increased dosing for physiologic tolerance.⁸ Augmentation is associated with long-term use of dopaminergic agents, and it can be extremely debilitating.⁸ It is characterized by (1) a temporal expansion of RLS symptoms that is retrograde (occurring earlier relative to the time the medication was taken); (2) a relative increase in symptom intensity; (3) a decreased duration of rest-free time before symptoms start; and (4) increasing body involvement to involve other limbs. The newer dopaminergic agonists can also manifest augmentation at lower though significant rates.

Other agents, such as opiates, benzodiazepines, and anticonvulsants have significant side effects as well, including dependency, abuse potential, over sedation, and toxicity. In fact, withdrawal of opiates has been identified as a potential contributing factor to the

development of RLS.

Among the hyperkinetic movement disorders, there are similarities between RLS and tic disorders and akathisia. Tics are preceded by a premonitory urge or a disturbing sensation that prompts the patient to perform the tic, thereby temporarily relieving the sensation. In akathisia, patients describe a more generalized dysphoria and less stereotyped movements. As with tics, patients with RLS relate worsening of sensations if movements are not performed. Sensations in RLS vary, although many patients describe an aching, painful, deep-seated, and crawling sensation.⁷ In both RLS and tic disorders, premonitory sensations may be described as a feeling of discomfort.^{5,6} The resultant movements in RLS, tics, and akathisia have been described as “unvoluntary,” implying partial conscious control of the movements.

Recent case series have reported efficacy of BTX-A injections in Tourette syndrome. This medication, injected into the area of the premonitory urge (somatic musculature and/or vocal cords) has safely and effectively relieved premonitory sensations, resulting in a decreased number of motor tics.⁹ The mechanism for this improvement remains unknown, although it is theorized that peripheral treatment with BTX-A diminishes subclinical, pretic muscle activity. In turn, there is a decrease in both the severity of the premonitory urge as well as the need to tic.¹⁰

Additional evidence of the role of botulinum toxin in modulating pain was initially noted in patients with cervical dystonia. Treatment with botulinum toxin was found to diminish motor activity and was also associated with a significant improvement in cervicogenic pain. In this series, the patients identified pain as their most difficult symptom. Subsequent clinical trials have demonstrated effective pain control in patients with intractable headache and back pain, delivering relief with a distinct lack of serious side effects.¹⁰⁻¹³

The mechanism of pain relief is unknown, but there is growing evidence for its effects on neurotransmitters and neuropeptides in sensory systems. Acetylcholine, substance-P, and calcitonin gene-related protein (CGRP) are all packaged in vesicles that bind to the synaptic terminal by common docking molecules (soluble, n-ethylmaleimide sensitive factor attachment protein receptor, or SNARE proteins). The various botulinum toxin serotypes cleave different SNARE proteins, preventing exocytosis of the synaptic vesicles.

CGRP, an inflammatory neuropeptide, is colocalized with substance P in the trigeminal and sensory root ganglia. Botulinum toxin A has been noted in animals to reduce central nervous system indexes and behavioral responses to pain by inhibiting the release of substance P, glutamate, and CGRP.¹⁴ These neuropeptides trigger neurogenic inflammation. It is theorized that blocking these sensory mediators of pain and neurogenic inflammation reduce painful impulses and subsequently reduce c-FOS expression and dorsal-horn responses in the spinal cord.¹⁴

Based on the successful use of botulinum toxin for painful conditions and tics, we hypothesized that the course of RLS could be modified with the use of BTX-A. Furthermore, we were attracted to this medication given its favorable side-effect profile, lack of interactions, and apparent lack of long-term risks. Our goal was to add a palliative treatment that might allow these individuals to diminish the use and untoward effects of their oral medications.

BTX-A treatment significantly reduced the discomfort caused by RLS in these 3 individuals. Daytime symptoms markedly improved in all 3. Both patients taking oral medications were able

to significantly limit their use, resulting in fewer medication side effects. None of these patients suffered a serious untoward effect from multiple courses of injections.

The clinical response to BTX-A is consistent with a direct effect of this medication. Both the onsets as well as the durations of effect were consistent with the known pharmacologic effects of botulinum toxin. Additionally, in Patient #2, the amelioration of dysesthesias strictly corresponded to the muscle groups that were injected. In patient #3, the bedpartner noted clinical improvement in nocturnal restlessness.

We monitored 2 of our patients' response using the ESS and their self-reported use of medications (see Figure 1). The ESS is a widely used clinical instrument with a high correlation with sleep latency.²⁰ Further evaluations of the effect of BTX-A might benefit from objective measures of activity (using actigraphy), assessments of neurophysiologic parameters (polysomnography), or use of validated rating scales. It is unclear what effect, if any, botulinum toxin might have on periodic limb movements of sleep.

Ultimately, an estimated 15% to 20% of RLS patients fail treatment because of untoward effects and limited benefits. Also, subsets of the population such as the elderly may be at a higher risk of medication interactions and toxicities. For these groups, there is a need for safe and effective treatment options. BTX-A may offer a well-tolerated adjunctive treatment for targeted populations with RLS.

CONCLUSION

Our patients suffered from RLS that was recalcitrant to current pharmacotherapy or who did not tolerate oral medication. Following BTX-A injections into symptomatic areas, these individuals reported improvements in their symptoms, less daytime sleepiness, and reduced use of oral medication. This clinical response was consistent over several injection cycles and was associated with minimal side effects. The improvement in our patients respected the anatomic sites of injection and was consistent with the known pharmacokinetics of BTX-A. Further study of botulinum toxins in the treatment of RLS should be undertaken.

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