Treatment of segmental continuous hypertrophic myokymia of the limb with botulinum A toxin

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Abstract
Myokymia is defined as fluctuating hyperexcitability of muscle fibers caused by repetitive spontaneous contraction of motor units. Myokymia is generally benign with self-resolution, although symptomatic treatment with benzodiazepines, anticonvulsants, and muscle relaxants can be used. Botulinum toxins can also be utilized, although they are mostly used for symptomatic facial myokymia. Here, we report two patients who developed continuous myokymia, resulting in secondary hypertrophy, stiffness, and discomfort in the affected muscles. The first patient had a history of a tethered spinal cord and developed continuous myokymia in the S1 and S2 radicular regions of the left leg. The second patient underwent radiation therapy for lung cancer and developed brachial plexopathy with abnormal activity in the muscles supplied by the musculocutaneous nerve in the right arm. Both patients experienced sleep disturbance, focal discomfort, and restlessness. The anticonvulsants and muscle relaxants were ineffective. Chemodenervation with botulinum A toxin was initiated using either onabotulinumtoxinA or abobotulinumtoxinA. Both patients experienced a substantial reduction in myokymia, with ongoing reversal of muscle hypertrophy and significant improvement in reported subjective symptoms. Treatment with botulinum toxins can be highly effective in patients with symptomatic segmental continuous hypertrophic myokymia and may be considered first-line therapy.

Keywords
Botox, botulinum A, myokymia, onabotulinumtoxinA, radiation, plexopathy, limb, chemodenervation

Date received: 4 June 2022; accepted: 19 October 2022

Introduction
The term myokymia is derived from the Greek words myo (muscle) and kymos (wave). Myokymia is insufficient to move a joint and typically manifests as frequent wriggling or rippling muscle movements that resemble worm-like motion. They are caused by involuntary abnormal muscular contractions due to spontaneous electrical activity, resulting in increased action potentials.¹

The pathophysiology of myokymia is only partially understood and may vary based on the cause. However, spontaneous discharges are thought to originate either from the demyelinated motor axons or near the anterior horn cells of the spinal cord, resulting in impulse transmission to the numerous muscle fibers innervated by each muscle unit.² Electromyography (EMG) detects electrical myokymia, which consists of rhythmic or semi-rhythmic bursts of waveforms representing single motor units. The frequency varies from 2 to 60 Hz, and the total burst duration is usually 100–900 ms. These bursts tend to repeat at a frequency of 2–10 Hz. Myokymic discharges are usually spontaneous and not affected by electrical stimulation, percussion, or exercise.

Myokymia can be classified as focal, usually limited to extraocular or facial muscles; segmental myokymia affecting the limb; or generalized, typically associated with myokymia.
affecting mostly the distal limbs or trunk muscles. Myokymia is often self-limiting and no therapy is necessary for most patients. Pharmacotherapy with benzodiazepines, anticonvulsants, and muscle relaxants can be used to relieve symptoms. However, the systemic use of these medications may be associated with several characteristic side effects, most commonly with sedation. Botulinum A toxin treatment has been reported in a few patients with upper eyelid facial myokymia, which may represent a cosmetic or functional problem.

Here, we report the cases of two patients who developed continuous myokymia affecting a single limb. This resulted in secondary hypertrophy of the affected muscles, which is associated with stiffness and discomfort. Repeated botulinum toxin A injections provide sufficient symptomatic relief and reversal of secondary hypertrophy.

Case presentations

The first patient was a 22-year-old man who developed intermittent cramping of the left calf exacerbated by sports activities approximately 8 years ago. The cramping was progressive and more frequent, and he began to experience near-constant muscle twitching, primarily in the left calf, as well as in the hamstring and gluteus muscles. This was associated with perceived stiffness of the left leg and occasional cramps.

Physical examination revealed continuous myokymia, predominantly in the left lower extremity, and occasional myokymia in the right leg. Lumbar magnetic resonance imaging (MRI) revealed tethered spinal cord radiological signs with a low-lying conus at approximately the level of L4 and dural ectasia (Figure 1). He underwent an untethering procedure in 2015 with no improvement in symptoms.

In 2020, his examination showed nearly continuous myokymia affecting his left gastrocnemius muscles, with additional intermittent myokymia in both hamstrings and the left buttock. His left calf was hypertrophic with a circumference of 41 cm, and his right calf had a circumference of 38 cm. Sensory examination results and strength were normal (Supplemental Material, Video 1).

After his spinal surgery, EMG detected spontaneous continuous myokymia involving multiple motor units, each firing 1–5 times per second with the average duration of approximately 800 ms. It was detected in multiple muscles of the left S1 and S2 myotomes. Occasional myokymia activity was also detected in the right S1 and S2 myotomes, but this activity was much lower. A paraneoplastic panel showed negative results.

Baclofen at the maximum dose of 60 mg per day and gabapentin with the maximum dose of 3600 mg per day were administered for the minimal duration of 4 weeks. Both medications were well tolerated but provided no relief. We offered chemodenervation with botulinum A toxin, and abobotulinum A toxin was selected. Initially, we targeted the most affected muscles of the left calf, which is the site of the most bothersome symptoms. The initial dose was 500 U of abobotulinumtoxinA with 100 U into each head of gastrocnemius muscle and 300 U into the left soleus. The first cycle was well tolerated and resulted in limited symptom improvement. The dose was increased to 1000 U with 150 U injected into each head of the gastrocnemius muscle, 400 U into the soleus, 150 U into the long head of the biceps femoris muscle, and 150 U into the semitendinosus muscle on the left side. This was well tolerated, and the patient reported significant reduction in twitching and less subjective stiffness. After the third cycle, his left calf circumference was 38 cm, which was the same as that on his right side. Reduction of muscle myokymias was also observed after 4 and 6 weeks after the injections.

Figure 1. Magnetic resonance imaging (MRI) of lumbosacral spine with sagittal view showing low lying spinal cord with conus at the level of L4 (arrow) with tethered cauda equina nerve roots to the posterior aspect of the thecal sac with overlying presumed closed spina bifid abnormality at the S1. Dural ectasia of the spinal canal is observed from L5 to S2 S3.
there was a trace of weakness in right arm flexion, graded as 5−/5 range, and mild sensory loss corresponding to his subjective complaints. In addition, abnormal involuntary muscle contractions of the biceps brachii and brachialis were consistent with myokymia. Occasional myokymia were also detected in the right deltoid muscle. He had mild hypertrophy of the right arm with a 15 cm circumference, and his left arm circumference was 14 cm.

EMG revealed electrical myokymia with spontaneous single motor unit discharges mostly occurring as doublets and triplets firing as semi-rhythmic bursts with a frequency of around 1.5 Hz and average duration of approximately 500 ms in C5 and C6 myotomes. The patient was diagnosed with hypertrophic myokymia secondary to post-radiation brachial plexopathy. We administered botulinum A toxin injections after failure of baclofen with the maximum daily dose of 60 mg, carbamazepine with the maximum daily dose of 1200 mg, and levetiracetam with the maximum daily dose 3000 mg, which were prescribed by an outside neurologist. Each medication was tried for at least 4 weeks, and they were all tolerated but perceived as ineffective. A starting dose of 100 U of onabotulinumtoxinA injected into both heads of the biceps muscle was partially beneficial, with relief for approximately 6 weeks. A dose adjustment of up to 275 U of onabotulinumtoxinA with 100 U injected into each head of the biceps muscle and 75 U into the brachialis muscle, controlled his symptoms for 12 weeks and did not induce any apparent weakness. Evaluation approximately 6 weeks after the injections showed a dramatic reduction in myokymia. In addition, his right arm hypertrophy normalized after three therapeutic cycles. His discomfort and cramping in the right upper arm resolved with ongoing botulinum A toxin therapy.

**Discussion**

Focal, segmental, and generalized myokymia are associated with various central and peripheral nervous system disorders. Focal myokymia is the most common type and typically presents as facial or upper lid myokymia caused by multiple sclerosis, hypothyroidism, or Bell’s palsy. Other types of myokymia are less common and less frequently reported in literature. Here, we present two patients with limb myokymia who developed segmental hypertrophy due to ongoing muscle activity. Myokymia is considered to be related to peripheral nerve hyperexcitability caused by various types of peripheral nerve injury. As demonstrated in one of our patients, the segmental form of this syndrome is most frequently observed in patients with post-radiation brachial plexopathy. They appear in 60−70% of radiation-induced brachial or lumbosacral plexopathies. Additional common causes of limb myokymia include an incomplete peripheral nerve injury, as observed in our second patient with the syndrome of tethered lumbosacral spinal cord.

**Conclusion**

We expand the literature on botulinum A toxin used for rare conditions with our report of successful treatment of limb myokymia that resulted in focal hypertrophy, subjective discomfort with spasms, and feeling of tightness in the affected extremities. Both patients reported significant subjective improvement in their symptoms, and symptomatic improvement was also objectively demonstrated by the reversal of their secondary hypertrophy. The success rate of oral medications for troublesome myokymia has not been studied; however, the adverse profile of these medications is well known. Therefore, botulinum toxins can be highly effective in patients with symptomatic focal continuous hypertrophic myokymia and may be considered first-line therapy.

**Acknowledgements**

The authors wish to express their gratitude to both patients for their consent to publish this report.

**Author contributions**

M.I.K.Y. contributed to drafting/revision of the manuscript for content, including medical writing for content, analysis, and interpretation of data. M.R.G. contributed to drafting/revision of the manuscript for content, including medical writing for content, analysis, and interpretation of data. T.D.R. contributed to drafting/revision of the manuscript for content, including medical writing for content, analysis, and interpretation of data. V.N.H. contributed to drafting/revision of the manuscript for content, including medical writing for content, analysis, and interpretation of data. M.B. contributed to drafting/revision of the manuscript for content, including medical writing for content, analysis, and interpretation of data. P.H. contributed to drafting/revision of the manuscript for content,
including medical writing for content, analysis, and interpretation of data, study concept or design. All authors read and approved the final manuscript.

**Availability of data and materials**
Data sharing is not applicable to this article as no data sets were generated or analyzed during this study.

**Consent for publication**
Written consent obtained from the patients.

**Declaration of conflicting interests**
The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

**Ethical approval**
Institutional Review Board Statement: An IRB member has reviewed your submission and determined that the project described does not meet the “Common Rule” definition of human subjects’ research. The IRB has classified this project as a non-human subject research (NHSR). Therefore, allowed the project to proceed. IRB: 22.0287.

**Funding**
The author(s) received no financial support for the research, authorship, and/or publication of this article.

**Informed consent**
Written informed consent was obtained from the patients for their anonymized information to be published in this article.

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## Supplemental material
Supplemental material for this article is available online.

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