Muscle Cramps

Reliable and validated outcome measures and new treatments are needed.

By Hans D. Katzberg, MD, MSc, FRCPC and Hamid Sadeghian, MD, FRCPC


What Is a Muscle Cramp?

A muscle cramp is a hyperexcitable neurologic phenomena of excessive, involuntary muscle contractions.[1,2] It is important to distinguish between myogenic and neurogenic muscle cramps, because each has unique pathophysiology and management.[3] The conventional definition of a muscle cramp is a painful contraction of a muscle or muscle group, relieved by contraction of antagonist muscles.[4] Colloquially, muscle cramps are known by a number of different terms depending on the country, including *charley horse* in the US, *chopper* in England, and *corky* in Australia.[5] Care must be taken to avoid confusing muscle cramps with other phenomena including central hyperexcitability (eg, dystonia, spasticity, seizures, and stiff person/stiff limb syndromes) and peripheral processes, including tetany, myokymia, myotonia, neuromyotonia (focal muscle stiffness), or myalgia.[6]

The origin and propagation of neurogenic muscle cramps localizes to peripheral and central targets (Figure 1), including the neuromuscular junction, where mechanical disruption and electrolyte disturbances can influence hyperexcitability and cramp generation. Injury to peripheral nerve components including the motor neuron cell bodies or the motor axons can result in ephaptic transmission and development of muscle cramps. Dysfunctional intramuscular small fiber sensory afferents (eg, mechanoreceptors and spindles) are also proposed to be involved in cramp generation.[7-10] Centrally, persistent inward currents mediated by GABAergic transmitters at the spinal level can amplify incoming sensory input and lead to the propagation and amplification of cramp potentials.[11]

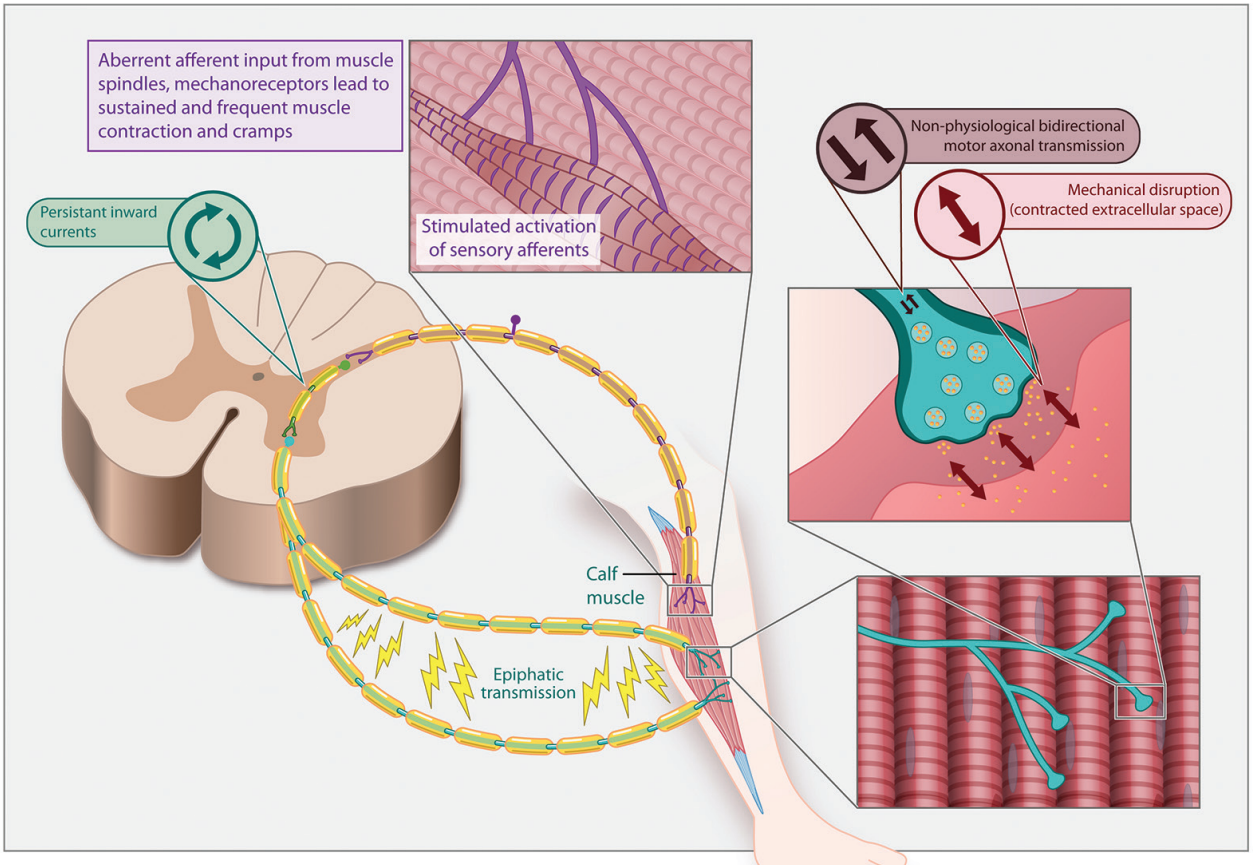

Figure 1: Pathophysiology Underlying Neurogenic Muscle Cramps.

Disruption of chloride, sodium, and potassium channels and inadequate amino acids concentrations (eg, taurine) disrupt membrane currents to generate muscle cramps.[12,13]

The pathophysiology of myogenic muscle cramps, in contrast, is usually the result of disrupted energy production in muscle cells and occurs most commonly in metabolic myopathies associated with disorders of glycogen, lipid, or mitochondrial metabolism.[14] Metabolic myopathies cause deficient ATP levels.[14] Because muscle relaxation is an adenosine triphosphate (ATP)-dependent active process, actin and myosin chains do not disengage, causing an electrically silent cramp (ie, contracture). The metabolic defect may also cause accumulation of potentially toxic metabolites that further aggravate ATP deficientcy. Myopathic cramps are also a potential symptom of myopathies linked to muscle membrane or intramuscular structural dysfunction in acquired and hereditary myopathies (eg, muscular dystrophy, congenital myopathies, and inflammatory myopathy).[15]

Assessment of Muscle Cramps

Most often, a muscle cramp is confirmed with clinical history. Although cramps are not usually induced during motor examination or electrophysiologic tests, muscle cramps can rarely be seen incidentally during these assessments. If a cramp occurs in a muscle during needle EMG, the electrically silent nature of myogenic cramps or the characteristic high frequency (≤150 Hz) of involuntary cramp potentials in neurogenic muscle cramps may be seen along with classic EMG neurogenic or myopathic recruitment and morphologic features.[16] Needle EMG can identify electric activity that often accompanies muscle cramps (eg, fasciculations) or distinguish between other peripheral hyperexcitable phenomena (eg, myokymia, myotonia, or neuromyotonia). Low-frequency (1-5 Hz) repetitive nerve stimulation can, on occasion, generate varying levels of postcramp discharges and clinical or subclinical cramp potentials (Figure 2).[17] Higher frequency stimulation paradigms in the foot using the tibial nerve and intrinsic tibial innervated foot muscles have been developed to induce and study muscle cramps; however, this is usually used in research rather than clinical practice.[18] Cramp frequency is often used to quantify severity because individuals affected by cramps can usually count distinct episodes and distinguish these from postcramp soreness. Cramp intensity and location can also be considered to quantify severity. A patient-based reliable scale to further assess muscle cramps is an unmet need.

Causes of Muscle Cramps and Investigations

Table 1 outlines physiologic and pathologic processes that can lead to muscle cramps, which are nearly ubiquitous throughout the lifespan, occurring rarely before age 8, more commonly in certain physiologic states (eg, pregnancy), and frequently in people more than age 65.[19,20] When no underlying cause is found, the term *idiopathic muscle cramps* is used. When idiopathic cramps occur in patients more than age 65—primarily nocturnally in the calves—the term *nocturnal leg cramps of the elderly* (NLCE) has been used.[21] Physiologic stressors are a common precipitant to muscle cramps. The

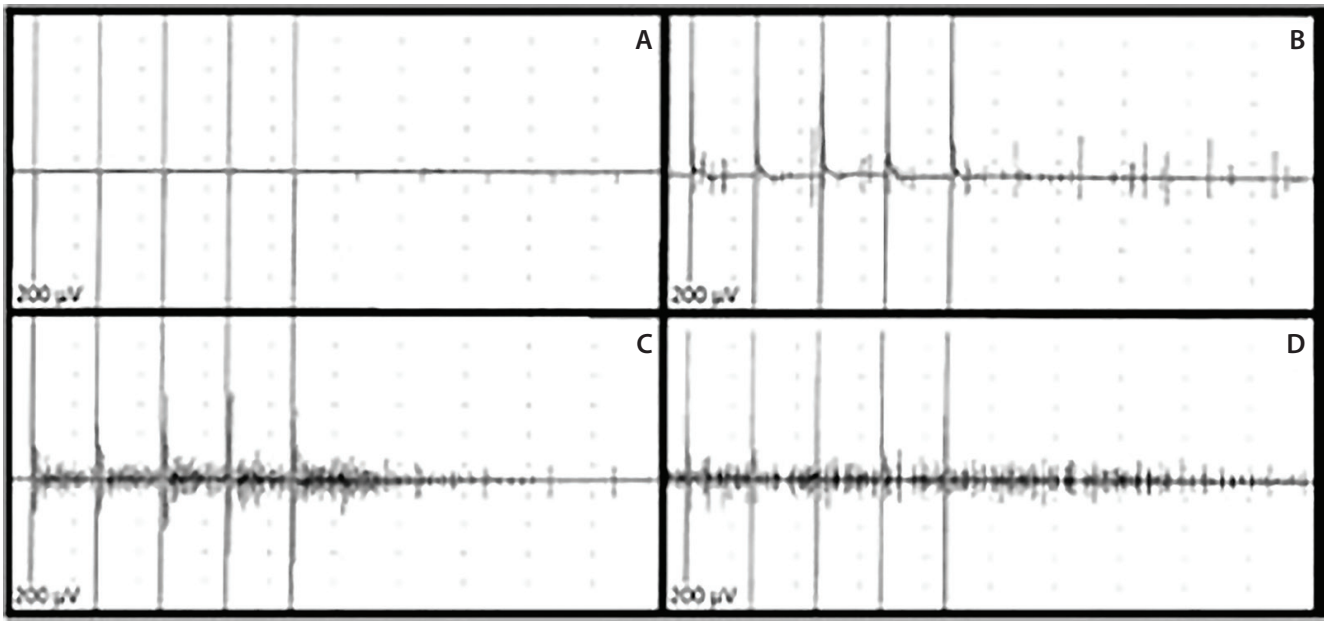

Figure 2: Cramp-Potentials and After-Discharges in Response to Slow Repetitive Nerve Stimulation. Panels A-C indicate increasing levels of after-cramp discharges, and panel D indicates a continuous cramp potential in response to 1 Hz repetitive nerve stimulation stimulating the tibial nerve and recording from the abductor hallicus.

TABLE 1. COMMON CAUSES OF MUSCLE CRAMPS	
Physiologic	Dehydration
	Exercise-induced
	Idiopathic
	Nocturnal leg cramps of the elderly
	Pregnancy
Metabolic	Cirrhosis
	Hypothyroidism
	Malnutrition (vitamin B, D, Mg^{2+} deficiencies)
	Uremia/hemodialysis
Medications	Beta-agonists
	Diuretics
	Statins
Neuromuscular disorders	Amyotrophic lateral sclerosis
	Charcot–Marie–Tooth disease
	Cramp-fasciculation syndrome
	Acquired neuropathy
	Radiculopathy
	Isaac's syndrome (neuromyotonia)
	Metabolic myopathies (McArdle's)
Other neurologic conditions	Parkinson's disease
	Dystonia
	Multiple sclerosis
	Stroke

most common is dehydration, in which electrolyte loss disrupts neuromuscular junction function and membrane stability. Other physiologic stressors include unusually prolonged or strenuous exercise, particularly in a deconditioned state in which muscle tendon shortening is common.[22]

Pathologic states that disrupt the homeostatic environment or structural integrity of the neuromuscular axis or spinal connections also lead to muscle cramps. People with medical conditions in which fluid shifts occur (eg, cirrhosis or renal failure) are especially vulnerable to muscle cramps.[23,24] For individuals being treated with hemodialysis, muscle cramps as part of dialysis disequilibrium syndrome are common, because changes in dialysate, flow rates, and dialysis parameters can cause fluid shifts.[25] In people with cirrhosis, prevention with albumin infusion is a long-known strategy to mitigate this symptom. For individuals who are dehydrated or malnourished, muscle cramps may arise from electrolyte loss or vitamin B or D deficiency.[26] People with endocrine disorders (eg, parathyroid abnormalities) that affect electrolyte levels (eg, Ca^{2+} or $PO4^{+}$) may also have muscle cramps and spasms.[27] Muscle cramps are common in the setting of diabetes through a variety of mechanisms, the most important of which are neuropathy and nephropathy.[28] Medications can also cause cramps, including thiazide diuretics statins, beta-agonists, acetylcholinesterase inhibitors (often used for treatment of myasthenia gravis), cimetidine, steroids, morphine, penicillamine, some immunosuppressants, cardiotropics, antiretrovirals, and psychotropic medications.[29]

Neurologic conditions in which peripheral nerve is affected are particularly prone to muscle cramps as a positive motor symptom. This includes motor neuron diseases, such as amyotrophic lateral sclerosis (ALS), where muscles cramps are an early and common symptom that may eventually fade as denervation becomes advanced.[30] Radiculopathies can not only produce significant weakness, numbness, dysesthesia and radicular pain, but can also cause unilateral or bilateral proximal or distal muscle cramps in the affected myotome.[31] Axonal neuropathies including hereditary neuropathies (eg, Charcot–Marie–Tooth disease [CMT]), acquired neuropathies, and idiopathic neuropathies can be associated with muscle cramps.[32] Although traditionally muscle cramps have been considered most common in neuropathies with a high burden of motor or large fiber involvement, muscle cramps have also been observed with similar frequency in people with predominantly sensory or small fiber neuropathies.[33,34] Acquired demyelinating neuropathies (eg, acute and chronic inflammatory demyelinating polyneuropathies [AIDP and CIDP]) are also associated with muscle cramps. A high proportion of individuals with nonneuromuscular neurologic conditions (eg, stroke, multiple sclerosis, and movement disorders) experience muscle cramps. Although the mechanism for this association is unclear, it could result from a combination of spinal or cortical dysfunction, deconditioning, increased age, or medications.

Myopathic cramps are common in metabolic myopathies (eg, McArdle's disease, phosphorylase kinase b deficiency, phosphofructokinase deficiency, phosphoglycerate kinase deficiency, carnitine deficiency, or carnitine palmitoyl transferase 2 (CPT 2) deficiency).[35] Myopathic cramps are almost always exertional, presenting with exercise intolerance, myoglobinuria, and exertional cramps. The most common disorder of carbohydrate metabolism is McArdle's disease (Type V glycogenosis),[35] which presents with exercise-induced myalgias and muscle cramps, pain that intensifies with exercise, and electrically silent contracture. The most common disorders of lipid metabolism are carnitine deficiency and CPT 2 deficiency, in which symptoms manifest with prolonged exercise (usually after 45 minutes).

Investigations of Muscle Cramps

Investigation can be directed when muscle cramps are particularly bothersome, severe, or frequent. A practical

approach is to consider first whether cramps are neurogenic or myogenic. Nerve conduction studies and needle EMG can be helpful in differentiating neurogenic from myogenic cramps. Serum creatine kinase (CK) levels may also be helpful as CK is often elevated over,1000 IU per L in myopathy; however, it should be noted that CK can also be elevated, particularly mildly elevated, in neurogenic processes and situations in which cramps are common (see also *HyperCKemia* in this issue). Evaluation should be directed toward potential etiology. Spinal MRI should be ordered if cervical or lumbosacral radiculopathy is suspected. Reccomended laboratory tests include a complete blood count (CBC), creatinine and urea, liver enzymes, albumin, extended electrolytes, serum B-vitamin levels including B_{12} and B_6 levels, 2-hour glucose tolerance test, hemoglobin A1C, thyroid-stimulating hormone (TSH), and serum protein electrophoresis. If appropriate, for advanced work-up of neuropathy additional tests include serum immunoelectrophoresis, antinuclear antibody (ANA), rheumatoid factor (RF), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), Sjögren's-syndrome-related antigen A (anti-SSA) and B (anti-SSB), and antinuclear cytoplasmic antibodies (ANCA). If immune motor neuropathy is suspected, anti-ganglioside (GM1) antibody testing should be done. Serum anti-voltage gated potassium channel levels can be helpful when cramp-fasciculation syndrome or Isaac's syndrome are suspected.[36] Repetitive peripheral nerve stimulation on conduction nerve studies may show "after-discharges" in cramp-fasciculation syndrome and Isaac's syndrome.

For myogenic cramps, investigations should be tailored to diagnose underlying metabolic myopathies. Forearm ischemic exercise testing can be used to diagnose disorders of glycolysis. The normal result is elevated lactate and ammonia (3-4 times baseline) levels. In McArdle's disease and other glycolysis-pathway enzyme deficiencies, ammonia rises, but lactate levels do not. In contrast, in myoadenylate deaminase deficiency, lactate levels rise, but ammonia levels do not. When neither ammonia nor lactate levels increase, the test is inconclusive and indicates muscles were not adequately exercised. In myopathies due to lipid metabolism disorders, forearm ischemic exercise testing results are normal.

If the forearm ischemic test result is abnormal (in line with glycolysis pathway enzymatic deficiencies), then genetic testing for McArdle's disease is in order as the latter is the most common glycolytic pathway enzyme deficiency. If the genetic test for McArdle's disease is negative, consider muscle biopsy with metabolic analysis. If lipid metabolism disorder is suspected, order genetic testing for CPT2 deficiency, and if negative, again consider muscle biopsy with metabolic assay.

If cramps are found to be an isolated finding not associated with any identifiable neurogenic, myogenic, or metabolic source, they can be labelled as idiopathic and treated as such.

Treatment of Muscle Cramps

General Principles and Nonprescription Treatments

Infrequent cramps that do not interfere in someone's life rarely need investigation or treatment. There is no evidence that recurrent muscle cramps lead to significant long-lasting damage to muscles, and serious harm from muscle cramps (eg, tendon ruptures) is rare. If treatment is needed, the avoidance of the offending agent or appropriate electrolyte and vitamin replacement to treat the root cause are warranted. There is level B evidence that vitamin B-complex supplementation can reduce cramp frequency in people who experience at least 6 cramps per week.[37] Care must be taken with a multitude of homeopathic medications marketed or used for muscle cramps, especially if exact constituents or proportions in the remedy are unknown. This also includes cannabinoids, where the limited high-quality evidence available to date has not shown a clear treatment effect.[38]

In individuals with prominent dehydration (eg, athletes, malnourished individuals, or members of vulnerable populations), care must be taken to ensure adequate electrolyte-rich solutions, particularly high-salt formulations. In pregnant women, there is ample evidence that magnesium replacement is helpful in managing muscle cramps.[39] There is limited evidence for magnesium outside the setting of pregnancy or magnesium deficiency; however, it may be reasonable to do a limited trial of oral magnesium or lower extremity magnesium baths (Epsom salts) as some people can experience benefit. People with dialysis disequilibrium syndrome during hemodialysis usually have improvement in muscle cramps when dialysates and dialysis rates are adjusted to prevent fluid shifts.[40] Similarly, when fluid shifts and third-spacing is mitigated in persons with liver cirrhosis with albumin infusions or branched chain amino acids, muscle cramps can be avoided.[41] Regular daily stretching exercise and low-impact aerobic exercise have been shown to be helpful in preventing nocturnal muscle cramps.[42]

Prescription Medications

If cramps remain frequent, severe, and disabling, pharmacologic prescription level intervention should be considered (Table 2). Given a current lack of a validated and comprehensive cramp scale, the prescribing clinician and patient are encouraged to choose a clear goal in mind when considering treatment (eg, cramp frequency or intensity reduction) until more comprehensive and validated outcome measures become available. Quinine sulphate is the most studied medication for treatment of muscle cramps. Although there is level 1 evidence that quinine may be effective for treating muscle cramps, there are concerns about hematologic and cardiac adverse effects, including thrombocytopenia and QT prolongation in addition to visual disturbances and cinchonism.[43-46] Because of those concerns, there is a Food

TABLE 2. PRESCRIPTION MEDICATIONS FOR MUSCLE CRAMPS

Medication	Dose	Adverse Events
Quinine sulfate[a]	300 mg at bedtime	Cinchonism, thrombocytopenia, TTP, palpitations, nausea, blurry vision, bitter taste
Mexiletine[b]	Up to 300 mg 3x/day	Nausea, vomiting, dizziness, tremor, palpitation, arrhythmia
Diltiazem	30 mg/day	Edema, headache, nausea, dizziness, rash, asthenia, arrhythmia
Levetiracetam[b]	Up to 1500 mg 2x/day	Fatigue, headache, insomnia, arthralgia, edema
Carbemazepine[c]	Up to 1,600 mg/day	Confusion, dizziness, nausea, rash, SIADH, hyponatremia
Phenytoin	300 mg od	Confusion, dizziness, nausea, rash
Baclofen	Up to 50 mg daily	Confusion, dizziness, nausea, flaccid weakness, ataxia, withdrawal

Abbreviations: SIADH syndrome of inappropriate antidiuretic hormone secretion; TTP thrombotic thrombocytopenia purpura.
[a] Federal Drug Administration warning against use for treatment of muscle cramps, [b] Studied in amyotrophic lateral sclerosis, [c] Studied in cramp-fasciculation syndrome, [d] No high-quality evidence supporting use in muscle cramps

and Drug Administration (FDA)-advisory against use of quinine for routine treatment of muscle cramps. Quinine, however, is still prescribed with special precautions in some parts of the world.[29,47] An alternatative, mexiletine, with a similar mechanism has been studied in persons with ALS. In 2 independent studies in this population, safety and efficacy for reducing severity and frequency of muscle cramps was seen, which offers an alternative for those with ALS or other neuromuscular conditions with prominent muscle cramps. Mexiletine is also proven effective for treating nondystrophic myotonia.[48,49] It should be noted that medications studied for treatment of neuropathic pain including gabapentin, pregabalin, nortriptyline, and duloxetine have not been shown to have a significant effect on muscle cramps in clinical studies. As such, these can be tried in individuals with muscle cramps and coexisting neuropathic pain; however, if there is no effect on muscle cramps once the maximal effective dose for pain is reached, add-on medications for the cramps should be considered.[50] There is modest evidence that calcium channel blockers may be effective for cramps, and antiepileptic medications, including carbamazepine, have been found helpful for cramp fasciculation syndrome.[51,52] Although medications such as baclofen, tizanidine, and clonazepam used for treating spasticity and stiff-person syndrome can be helpful in managing neurogenic muscle cramps (likely due to the central contributions to cramp propagation), there is limited evidence for use in muscle cramps not associated with spasticity.[53] There is class II level evidence that intramuscular lidocaine is effective, but use is often limited by the multifocal nature of muscle cramps.[54] Although botulinum toxin is effective for dystonia, similar studies have not been performed for severe, refractory neurogenic cramps, and additional limitations also include the multifocal nature of cramps and potential significant weakness associated with botulinum toxin treatment.

Conclusion

Cramps are an under-recognized treatable painful symptom that affects a large number of people across normal physiologic and neuromuscular, neurologic, and medical disease states. Clinical judgement should be used to fully evaluate possible treatable causes. A rational treatment plan includes pharmacologic and nonpharmacologic options. Additional research into a reliable and validated outcome measure and new treatments for muscle cramps are areas of unmet need. ■

1. Jansen PH, Gabreels FJ, van Engelen BG. Diagnosis and differential diagnosis of muscle cramps: a clinical approach. *J Clin Neuromuscul Dis*. 2002;4(2):89-94.
2. Layzer RB. The origin of muscle fasciculations and cramps. *Muscle Nerve*. 1994;17:1243-1249.
3. Jansen PH, Joosten EM, Vingerhoets HM. Muscle cramp: main theories as to aetiology. *Eur Arch Psychiatry Neurol Sci*. 1990; 239(5):337-342.
4. Miller TM, Layzer RB. Muscle cramps. *Muscle Nerve*. 2005;32:431-442.
5. Katzberg HD. Neurogenic muscle cramps. *J Neurol*. 2015;262(8):1814-1821.
6. Sawlani K, Katirji B. Peripheral nerve hyperexcitability syndromes. *Continuum (Minneap Minn)*. 2017;23(5):1437-1450.
7. Matzner O, Devor M. Hyperexcitability at sites of nerve injury depends on voltage-sensitive Na+ channels. *J Neurophysiol*. 1994;72:349-359.
8. Mense S. Group III and IV receptors in skeletal muscle: are they specific or polymodal? *Prog Brain Res*. 1996;113:83-100.
9. Baldissera F, Cavallari P, Dworzak F. Motor neuron 'bistability': a pathogenetic mechanism for cramps and myokymia. *Brain*. 1994;117(5):929-939
10. Graven-Nielsen T, Mense S. The peripheral apparatus of muscle pain: evidence from animal and human studies. *Clin J Pain*. 2001;17:2-10
11. Obi T, Mizoguchi K, Matsuoka H, Takatsu M, Nishimura Y. Muscle cramp as the result of impaired GABA function— an electrophysiological and pharmacological observation. *Muscle Nerve*. 1993;16(11):1228-1231.
12. Jentsch TJ, Stein V, Weinreich F, Zdebik AA. Molecular structure and physiological function of chloride channels. *Physiol Rev*. 2002;82:503-568.
13. Conte Camerino D, Tricarico D, Pierno S, et al. Taurine and skeletal muscle disorders. *Neurochem Res*. 2004;2991:135-142.
14. Amato A, Russell JA. *Neuromuscular disorders*. New York, NY: McGraw Hill; 2008.
15. Gospe SM, Lazaro RP, Lava NS, et al. Familial X-¬linked myalgia and cramps. *Neurology*. 1989;39:1277-1280.
16. Weiner IH, Weiner HL. Nocturnal leg muscle cramps. *JAMA*. 1980;244:2332-2333
17. Harrison TB, Benatar M. Accuracy of repetitive nerve stimulation for diagnosis of the cramp-fasciculation syndrome. *Muscle Nerve*. 2007;35:776-780
18. Minetto MA, Holobar A, Botter A, Farina D. Discharge properties of motor units of the abductor hallucis muscle during cramp contractions. *J Neurophysiol*. 2009;102:1890-1901.
19. Leung AK, Wong BE, Chan PY, Cho HY. Nocturnal leg cramps in children: incidence and clinical characteristics. *J Natl Med Assoc*. 1999;91(6):329-332.
20. Abdulla AJ, Jones PW, Pearce VR. Leg cramps in the elderly: prevalence, drug and disease associations. *Int J Clin Pract*. 1999;53:494-496.
21. Butler JV, Mulkerrin EC, O'Keeffe ST, Zanette GP, Gasperini M. Nocturnal leg cramps in older people. *Postgrad Med J*. 2002;78:596-598
22. Bertolasi L, De Grandis D, Bongiovanni LG, et al. The influence of muscular lengthening on cramps. *Ann Neurol*. 1993;33(2):176-180.
23. Ng K, Lin CS, Murray NM, Burroughs AK, Bostock H. Conduction and excitability properties of peripheral nerves in end-stage liver disease. *Muscle Nerve*. 2007;35:730-738.

24. Kanaan N, Sawaya R. Nocturnal leg cramps. Clinically mysterious and painful-but manageable. *Geriatrics*. 2001;56(6):39-42.
25. Arieff AI. Dialysis disequilibrium syndrome: current concepts on pathogenesis and prevention. *Kidney Int.* 1994;45:629-635.
26. Naylor JR, Young JB. A general population survey of rest cramps. *Age Ageing*. 1994;23:418-420.
27. Turken SA, Cafferty M, Silverberg SJ, et al. Neuromuscular involvement in mild, asymptomatic primary hyperparathyroidism. *Am J Med*. 1989;87:553-557.
28. Katzberg H, Kokokyi S, Halpern E, et al. Prevalence of muscle cramps in patients with diabetes. *Diabetes Care*. 2014;37(1):e17-e18.
29. Garrison SR, Dormuth CR, Morrow RL, Carney GA, Khan KM.. Nocturnal leg cramps and prescription use that precedes them: a sequence symmetry analysis. *Arch Intern Med*. 2012;172:120-126.
30. Ganzini L, Johnston W, Hoffman W. Correlates of suffering in amyotrophic lateral sclerosis. *Neurology*. 1999;52(7):1434-1440.
31. Matsumoto M, Watanabe K, Tsuji T, et al. Nocturnal leg cramps: a common complaint in patients with lumbar spinal canal stenosis. *Spine*. 2009;34(5):189-194.
32. Johnson NE, Sowden J, Dilek N, et al. Prospective study of muscle cramps in Charcot-Marie-Tooth disease. *Muscle Nerve*. 2015; 51(4):485-488.
33. Lopate G, Streif E, Harms M, Carney GA, Khan KM. Cramps and small-fiber neuropathy. *Muscle Nerve*. 2013;48:252-255.
34. Maxwell SK, Kokokyi S, Breiner A, et al. Characteristics of muscle cramps in patients with polyneuropathy. *Neuromuscul Disord*. 2014;24(8):671-676.
35. Kishnani PS, Chen YT. Glycogen storage disease. In: Kliegman RM, Stanton BF, St. Geme J, Schor N, Behrman RE. (eds) *Nelson Textbook of Pediatrics*, 17th ed. Philadelphia, PA: Elsevier; 2011:492-501.
36. Shillito P, Molenaar PC, Vincent A, et al. Acquired neuromyotonia: evidence for autoantibodies directed against K channels of peripheral nerves. *Ann Neurol*. 1995;38:714-722.
37. Chan P, Huang TY, Chen YJ, Huang WP, Liu YC. Randomized, double-blind, placebo-controlled study of the safety and efficacy of vitamin B complex in the treatment of nocturnal leg cramps in elderly patients with hypertension. *J Clin Pharmacol*. 1998;38:1151-1154.
38. Weber M, Goldman B, Truniger S. Tetrahydrocannabinol (THC) for cramps in amyotrophic lateral sclerosis: a randomised, double-blind crossover trial. *J Neurol Neurosurg Psychiatry*. 2010;81(10):1135-1140.
39. Dahle LO, Berg G, Hammar M, Hurtig M, Larsson L. The effect of oral magnesium substitution on pregnancy induced leg cramps. *Am J Obstet Gynecol*. 1995;173:175-180.
40. Lindsay RM, Shulman T, Prakash S, Nesrallah G, Kiaii M. Hemodynamic and volume changes during hemodialysis. *Hemodial Int.* 2003;7:204-208.
41. Kawaguchi T, Izumi N, Charlton MR, Sata M. Branched-chain amino acids as pharmacological nutrients in chronic liver disease. *Hepatology*. 2011;54:1063-1070.
42. Coppin RJ, Wicke DM, Little PS. Managing nocturnal leg cramps: calf-stretching exercises and cessation of quinine treatment: a factorial randomised controlled trial. *Br J Gen Pract*. 2005;55:186-191.
43. Connolly PS, Shirley EA, Wasson JH, Nierenberg DW. Treatment of nocturnal leg cramps: a crossover trial of quinine vs vitamin E. *Arch Intern Med*. 1992;152:1877-1880.
44. Jansen PH, Veenhuizen KC, Wesseling AI, de Boo T, Verbeek AL.. Randomised controlled trial of hydroquinine in muscle cramps. *Lancet*. 1997;349:528-532.
45. Diener HC, Dethlefsen U, Dethlefsen-Gruber S, Verbeek P. Efficacy of quinine in treating muscle cramps: a double-blind, placebo-controlled, parallel-group, multicentre trial. *Int J Clin Pract.* 2002;56:243-246.
46. Bateman DN, Dyson EH. Quinine toxicity. *Adv Drug React Acute Poisoning Rev.* 1986;5:215-233.
47. Food and Drug Administration, Department of Health and Human Services. Drug products containing quinine; enforcement action dates. *Fed Reg*. 2006;71:75557-75560.
48. Weiss MD, Macklin EA, Simmons Z, et al.A randomized trial of mexiletine in ALS: safety and effects on muscle cramps and progression. *Neurology*. 2016;19;86(16):1474-1481.
49. Oskarsson B, Moore D, Mozaffar T, et al. Mexiletine for muscle cramps in amyotrophic lateral sclerosis: a randomized, double-blind crossover trial. *Muscle Nerve*. 2018;58(1):42-48.
50. Miller RG, Moore DH, Gelinas DF, et al. Phase III randomized trial of gabapentin in patients with amyotrophic lateral sclerosis. *Neurology*. 2001;56:843-848.
51. Voon WC, Sheu SH. Diltiazem for nocturnal leg cramps. *Age Ageing*. 2001;30:91-92.
52. Tahmoush AJ, Alonso RJ, Tahmoush GP, Heiman-Patterson TD.. Cramp-fasciculation syndrome: a treatable, hyperexcitable peripheral nerve disorder. *Neurology*. 1991;41:1021-1024.
53. Katzberg HD, Khan AH, So YT. Assessment: symptomatic treatment for muscle cramps (an evidence-based review): report of the therapeutics and technology assessment subcommittee of the American Academy of Neurology. *Neurology*. 2010;74(8):691-696.
54. Prateepavanich P, Kupniratsaikul V, Charoensak T. The relationship between myofascial trigger points of gastrocnemius muscle and nocturnal calf cramps. *J Med Assoc Thai*. 1999;82:451-459.

Hans D. Katzberg, MD, MSc, FRCPC
University Health Network
Division of Neurology
Toronto, Ontario, Canada

Hamid Sadeghian MD, FRCPC
University Health Network
Division of Neurology
Toronto, Ontario, Canada

Disclosures

HDK and HS report no disclosures.