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REVIEW

Neurogenic muscle cramps

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Abstract Muscle cramps are sustained, painful contractions of muscle and are prevalent in patients with and without medical conditions. The objective of this review is to present updates on the mechanism, investigation and treatment of neurogenic muscle cramps. PubMed and Embase databases were queried between January 1980 and July 2014 for English-language human studies. The American Academy of Neurology classification of studies (classes I–IV) was used to assess levels of evidence. Mechanical disruption, ephaptic transmission, disruption of sensory afferents and persistent inward currents have been implicated in the pathogenesis of neurogenic cramps. Investigations are directed toward identifying physiological triggers or medical conditions predisposing to cramps. Although cramps can be self-limiting, disabling or sustained muscle cramps should prompt investigation for underlying medical conditions. Lifestyle modifications, treatment of underlying conditions, stretching, B-complex vitamins, diltiezam, mexiletine, carbamazepine, tetrahydrocannabinoid, leveteracitam and quinine sulfate have shown evidence for treatment.

Keywords Muscle crampscharlie horse · Chopper · Motor nerve hyperexcitability · Spasms

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Introduction

Muscle cramps, also known as a "charlie horses" in the United States or "choppers" in England, are a common symptom defined as sustained, painful contractions of a muscle or muscle group. Virtually everyone has experienced a muscle cramp at one point or another throughout life, particularly in situations of prolonged exercise, and with increased frequency with age. Certain physiological settings, medical conditions and neurological disorders are associated with muscle cramps, and as such new-onset or sustained cramps often present to medical professionals. Although muscle cramps can originate directly from muscle in the setting of myopathy, the remaining causes of muscle cramps are neurogenic and are thought to share common mechanisms and treatments. Muscle cramps are often self-limiting, and management usually involves non-pharmacological interventions, however, medications may be needed if symptoms are persistent and disabling. This review presents the most recent information on the epidemiology, mechanisms, investigation and treatment of neurogenic muscle cramps.

Methods

Search strategy and selection criteria

PubMed and Embase databases were queried for English-language human articles published from January 1980 to August 2014 using "muscle cramps" or "muscle cramp" search terms and "epidemiology", "therapy", "diagnosis", "causation-etiology" and "prognosis" as search limits. Using this strategy, a total of 4,367 articles were identified. Preference was given to articles presenting original data

focusing on neurogenic muscle cramps, although select reviews, book chapters and scientific reports were also considered. Using this strategy, a total of 231 articles were reviewed to generate this article, and 66 of the articles are included in the bibliography.

Study classification for treatment studies

The American Academy of Neurology classification of studies (classes I–IV) was assessed using the following levels of evidence: class I and II related to randomized clinical trials, class III to other controlled trials, and class IV indicating all other studies including open-label studies [1].

Results

Epidemiology

The prevalence of muscle cramps have been reported to range from 37 to 95 % depending on the population studied [2–8]. Although patients of all ages are susceptible to muscle cramps, they are uncommon in children under age eight [9] and prominent in people older than 65 years of age [2, 3]. A study from the United Kingdom reported that 50 % of patients aged 65 or older experienced frequent cramps [2], and a review of elderly veterans in the United States quote a prevalence of 56 % [3], with most cramps occurring at least once per week. Prevalence rates in patients with neuropathic conditions are usually higher than those in the general population and include 44–55 % in patients with ALS [5, 6], 64 % in patients with polyneuropathy [7] and 79 % in patients with Charcot Marie Tooth (CMT) [8]. In addition to causing acute pain and prolonged post-cramp soreness [10], muscle cramps can also interfere with quality of life and interfere with sleep [11, 12]. In patients with underlying medical conditions such as diabetes or neurological conditions such polyneuropathy, muscle cramps are often more frequent, painful, prolonged and more disabling compared to otherwise healthy people who experience cramps [7, 13]. In patients with CMT, cramps have been described as one of the symptoms with prominent effects on quality of life [14]. Patients with idiopathic nocturnal muscle cramps and length-dependent neuropathies most often experience cramps in the distal legs and feet, particularly in the calves [15]. Patients with non-length dependent neuromuscular pathology such as radiculopathy [16] or medical conditions such as diabetes [13] can also often experience cramps in the proximal legs, trunk and upper extremities.

Pathogenesis (Fig. 1)

While the generation of a neurogenic muscle cramp ultimately occurs from high-frequency firing of motor neurons leading to coordinated contraction of muscle, the origin and propagation of muscle cramps has been postulated to have various central and peripheral targets [17]. Intramuscular nerve terminals, as well as proximal structures including the motor axon and motor neurons are among the peripheral targets implicated, vulnerable through various mechanisms to injury [18]. In patients with motor neuron disease/amyotrophic lateral sclerosis for example, damage to the anterior horn cells may result in lone fasciculations or continuous firing leading to more coordinated contraction in muscle cramps [19]. In this situation, after-discharges observed occurring after the F-wave are thought to occur from lower motor neuron bi-stability in which the cell membrane has two equilibrium levels, the higher level protecting against spontaneous motor neuron discharges. A similar low threshold state is thought to occur throughout the motor axon from direct axonal injury or demyelination, where ephaptic transmission and regional spread of firing can cause development and propagation of muscle cramps [20].

Abnormal excitability has also been shown to occur at the level of the intramuscular nerve terminal [21], and also be vulnerable to physiological effects such as changes in electrolyte concentration around motor end-plates [22]. Mechanical effects affecting the terminal endplates predispose to muscle cramps and include tendon shortening, which can occur in older age and during prolonged inactivity [23]. Central hypothesis of muscle cramps generation includes the presence of persistent inward currents, mediated by γ-aminobutyric acid (GABA), which may lead to muscle cramps by amplifying the incoming sensory input as it connects to motor neurons at the spinal level [24]. Disruption of sensory inputs themselves may also lead to muscle cramps, as these afferents have been shown to mediate the generation and extinction of motor discharges [25].

Similar to mechanisms implicated in neuropathic pain, peripheral sensitization in intramuscular motor nerve terminals occurs through interaction with endogenous compounds and is enhanced by released substance-P and calcitonin gene-related peptide [26]. At the cellular level, disruption of chloride, sodium and potassium channels and inadequate concentrations of amino acids such as taurine have been directly implicated in the generation of muscle cramps by disrupted membrane currents [27, 28].

Differential diagnosis (Table 1)

Neurogenic muscle cramps have a characteristic electrophysiological pattern: spontaneous, 50–150 Hz electrical discharges. On clinical grounds, it may be difficult to distinguish other patterns of increased muscle activity

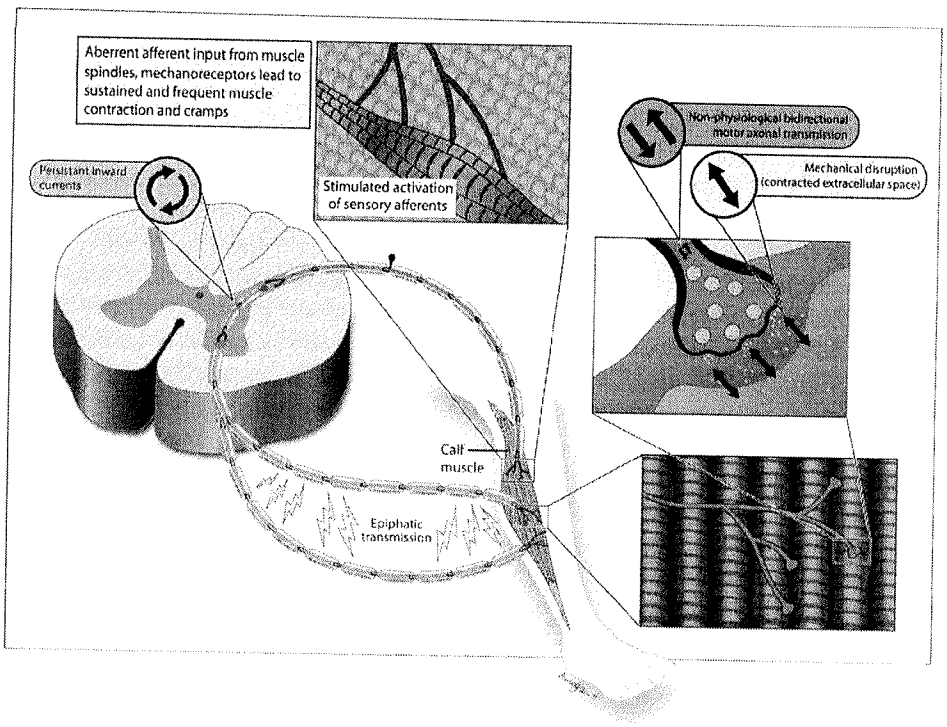

Fig. 1 Pathophysiology of Neurogenic Muscle Cramps

from muscle cramps. Increased tone can manifest as spasms or dystonia depending on whether pyramidal or extra-pyramidal tracts are involved. Dysfunction of spinal inter-neurons from the *Clostridium botulinum* neurotoxin can lead to tetanus, a diffuse contraction of skeletal limb muscles, often in an opisthotonic position. Antibodies against the inhibitory neurotransmitter GABA can lead to stiff limb syndrome, a focal form of stiff person syndrome where hypertonia and rigidity are associated with contraction of agonist and antagonist extremity muscles [29]. Myotonia is a delayed relaxation of muscle which occurs in response to voluntary activation. Myokymia is often described as a "rippling of muscle" or "bag of worms" phenomenon caused by dysfunctional peripheral nerves. Although impaired blood flow can also predispose to muscle cramps, muscle pain without cramping can also occur from vascular claudication and should be recognized as a separate phenomenon due to the distinct management including investigation with Doppler ultrasound and vascular recanalization [30]. Metabolic myopathies are characterized by electrically silent cramps, which are caused by a mismatch in the rate of ATP utilization-to-resynthesis in muscle [31]. Muscle cramps have also been implicated in non-metabolic myopathies such as Becker's muscular dystrophy [32] and toxic myopathies related to statin therapy [33], where mechanism behind cramps include fibre splitting and myofibre necrosis.

Etiologies

Physiological and idiopathic muscle cramps

Muscle cramps can occur in anyone under sufficient physiologic stress. A common stressor is strenuous exercise, particularly after periods of inactivity [34]. Dehydration and exposure to heat may also lead to muscle cramps independent of electrolyte imbalance [35]. The peripartum period is associated with cramps due factors including hypomagnesemia and dehydration [36]. When no underlying physiological, medical or neurological process can be identified, the term idiopathic muscle cramps is used. These are more prevalent with advanced age and occur most commonly in the calves and at night [2].

Medical conditions and medications

Muscle cramps have been described in a variety of medical conditions, the most common being hepatic and renal dysfunction. Possible mechanisms by which cirrhosis causes cramps include reduction in effective circulating volume and hyperexcitable nerves by disrupted homeostasis of amino acids and chloride [37]. Renal dysfunction may also predispose to muscle cramps by retention of middle molecules and disruption of potassium homeostasis. Acute changes in osmolality can also lead to muscle cramps during hemodialysis, which has been improved in

recent years by changes in dialysate and change in rates of dialysis [38]. Patients who are malnourished or with malabsorption syndromes may experience vitamin and electrolyte deficiencies leading to muscle cramps, particularly potassium, calcium, magnesium and vitamins B and D. Cramps are common during metabolic derangement such as parathyroid dysfunction [39] and diabetes mellitus [13], where multiple factors often underlie the development of cramps. Neurogenic cramps have also been described to occur more frequently in patients with central neurological conditions such as Parkinson's disease, stroke and multiple sclerosis, which may occur due to a variety of mechanisms including spinal disinhibition or mechanical factors such as immobility.

The most common medications reported to cause muscle cramps are statins [40] and diuretics such as thiazides [41]. Cramps have also been reported with acetylcholinesterase inhibitors, bronchodilators, beta-agonists, steroids, morphine, cimetidine, penicillamine, antiretrovirals, cardiotropics, immunosuppressants, psychotropic drugs, and anticancer drugs [42].

Peripheral neuropathy

Muscle cramps are more frequent, severe and prolonged in patients with polyneuropathy compared to those who are otherwise healthy [7]. Muscle cramps are also common and contribute to disability in patients with hereditary neuropathies such as Charcot Marie Tooth [8]. In amyotrophic lateral sclerosis (ALS), cramps accompany fasciculations and are particularly frequent early in the disease [5, 6]. Patients with carpal tunnel syndrome, brachial neuropathy, or radiculopathy also frequently complain of muscle cramps [16]. Although these usually occur during active compression, symptoms can remain persist for years after the initial insult.

Peripheral nerve hyper-excitability syndromes

Peripheral nerve hyper-excitability (PNH) syndromes are characterized by muscle cramps, myalgias, fasciculations or myokymia. The most benign syndrome is cramp-fasciculation syndrome (CFS), characterized by cramps and fasciculations without additional peripheral or central nervous system involvement [43]. Isaac's syndrome is characterized by continuous discharges, myokymia, neuromyotonia, cramps and hyperhidrosis. When PNH is associated with sleep disturbance, encephalopathy and autonomic disturbance, the term Morvan's Syndrome is used [44]. Voltage-gated potassium channel antibodies (VGKC) are often elevated in these conditions and in patients with central manifestations, neural antibodies such as CASPR2 and LGI1 may also co-exist [45]. An increase in the prevalence of neoplasm, the most common being thymoma, has been described in patients even with PNH, particularly in the setting of Isaac's syndrome and positive VGKC. Although no specific genetic target has been implicated in patients with muscle cramps, there may be a hereditary component in some patients as evidenced by families described with muscle cramps inherited in an autosomal dominant manner [46].

Investigations (Table 2)

Evaluation of patients with muscle cramps includes identifying underlying physiological, metabolic or neurological conditions. Careful history will identify exposure to heat, prolonged exercise, or use of medications predisposing to cramps. Cirrhosis or renal dysfunction can be identified on history and physical or laboratory testing of liver enzymes, urea, creatinine, and electrolytes. Careful neurological examination will identify polyneuropathy, mononeuropathy, radiculopathy, plexopathy or motor neuron disease. Electromyography and nerve conduction studies may be required to confirm neuromuscular localization or cramp-mimics such as myotonia, neuromyotonia or myokymia. In patients with additional neurological manifestations, brain or spine MRI and VGKC testing may be indicated. Muscle cramps associated with myopathy will be associated with proximal muscle weakness without sensory disturbances, fatigue and exercise intolerance and will often have myopathic changes on EMG with electrically silent muscle cramps. Repetitive nerve stimulation (Fig. 2) at 1–10 Hz demonstrates after-cramp discharges in peripheral nerve hyper-excitability, however, this test is not used routinely in clinical practice [47].

Non-prescription therapy

Elimination of underlying causes and triggers for muscle cramps is first line intervention in the management of muscle cramps. This includes correction of deficiencies in potassium, calcium, magnesium and vitamins B and D. Vitamin B complex including 30 mg of B_6 has also demonstrated limited evidence for efficacy in the treatment of idiopathic muscle cramps [48]. Although treatment with oral or intravenous magnesium sulfate has shown efficacy for treatment of muscle cramps in the setting of pregnancy [49], this has not translated to idiopathic muscle cramps [50, 51] and is not recommended outside the peripartum period or magnesium deficiency. In the setting of cirrhosis, albumin infusions used to treat contracted extracellular volume and replacement of amino acids have been postulated to be beneficial for cramps [52]. For patients with hemodialysis-induced cramps, changing the dialysate and prazosin have been shown to reduce the frequency of

Table 1 Differentiating muscle cramps from other hyper-excitable neurological phenomena

Phenomena	Clinical	Electromyography
Neurogenic muscle cramps	Painful contraction of a single muscle or muscle group	Spontaneous, 50–150 Hz electrical discharges
Myopathic muscle cramps	Painful contraction of muscles, usually precipitated by exercise	Electrically silent
Myotonia	Delayed relaxation of muscle	Waxing and waning "dive bomber" spontaneous discharges
Myokymia	Irregular twitching of muscle giving a rippling appearance	Bursts of electrical activity ("soldiers marching on a bridge")
Neuromyotonia	Muscle stiffness and twitching	Short bursts of high-frequency (>150 Hz), irregular spontaneous discharges
Hypertonia	Stiffness associated with upper motor neuron signs	Poor activation of motor units without abnormal sponatenous activity
Dystonia	Contraction of agonist and antagonist muscles	Continuous firing of motor units in agonist and antagonist muscles
Stiff limb syndrome	Painful, sudden muscle spasms triggered by sudden stimuli	Continuous low frequency firing in agonist and antagonists

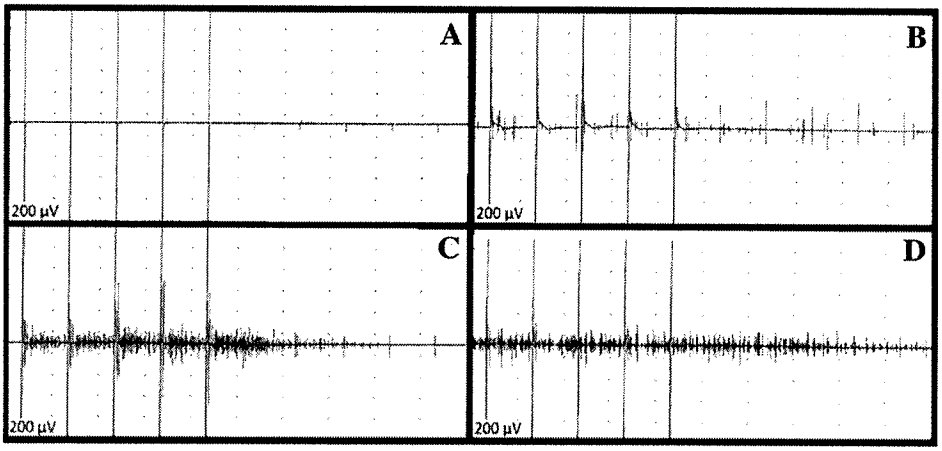

Fig. 2 Cramp after-discharge potentials. Cramp after-discharge potentials at 1 Hz repetitive nerve stimulation (RNS) of the tibial nerve recording from abductor hallicus in four different patients. **a** shows no after-discharges and panels **b–d** show increasing levels of after-discharges with 1 Hz RNS

cramps [53]. Stretching can help avoid muscle cramps prior to exercise and also prevent nocturnal muscle cramps in a sham-controlled clinical study [54]. Replacement of potassium for prevention of muscle cramps is only recommended through nutritional options including electrolyte replacement drinks and foods rich in potassium such as bananas, which typically contain up to 600 mg of potassium per serving.

Pharmacotherapy (Table 3)

The medication which has the most evidence for efficacy in the treatment of idiopathic muscle cramps is quinine sulfate [55, 56]. Since 1934, over 21 clinical trials including 2 class 1 trials evaluating quinine sulfate at doses ranging from 150 to 450 mg per day have been published, with a minimal effective dose of 300 mg po qhs. Adverse events, particularly at the higher dose ranges used for malaria has been shown to cause cinchonism (ringing in the ears), bitter taste and can cause idiosynchratic reactions such as arrthymia, idiopathic thrombocytopenic purpura (ITP) and thrombotic thrombocytopenic purpura (TTP) [57]. Due to these concerns and deaths reported to be related to quinine use since 1973, the FDA has banned to use of quinine sulfate for muscle cramps in the United States [58]. According to the American Academy of Neurology Practice Parameter, quinine was recommended for use in muscle cramps only when first line therapies have failed and if cramps are disabling [59].

Calcium channel blockers are thought to prevent muscle cramps by stabilizing inward restoring axonal currents. A double-blind, crossover study using 30 mg of diltiazem hydrochloride in the treatment of idiopathic muscle cramps showed a reduction in the number of cramps compared to placebo, with no effect on the intensity of cramps [60]. Baclofen is thought to prevent muscle cramps by enhancing GABA output and inhibiting spinal interneurons, and is often used at low doses by neurologists to treat cramps of

Table 2 Recommended investigations for muscle cramps

Screening investigations
Complete blood count
Electrolytes (including calcium, magnesium, phosphate)
Liver enzymes
Creatinine, urea, urinalysis
Fasting blood sugar, 2-h glucose tolerance test, hemoglobin A1c
Creatine phosphate kinase
Urinalysis
Advanced investigations
MRI spine
Nerve conduction studies/electromyography
Slow RNS for after-discharges
Voltage-gated potassium channels (VGKC)

Table 3 Pharmacological treatments for muscle cramps according to level of evidence

Medication	Dose	Class of evidence	Adverse events[e]
Quinine sulfate [54–56]	150–450 mg daily (300 mg)[a]	I	Cinchonism, bitter taste, arrhythmia, ITP, TTP, rash, thrombocytopenia, nausea, blurry vision
Tetrahydrocannabinol [65] (sesame oil containing Δ9-THC)[b]	10 mg daily	I	Elation, heightened awareness, asthenia, palpitations, facial flushing, amnesia, anxiety, confusion, dizziness, somnolence
Vitamin B-complex [48]	Includes 50 mg of B1,B2, B3, B6, B12 daily	II	Caution with B6 hyper-vitaminosis which can cause neuropathy
Diltiazem [60]	30 mg daily	II	Edema, headache, nausea, dizziness, rash, asthenia, arrhythmia
Natridrofuryl oxalate[c,] [67]	300 mg twice per day	II	Diarrhea, nausea, vomiting skin rash, elevation in liver enzymes, renal calculi
Mexiletine [66]	Up to 300 mg daily	IV	Nausea, vomiting, heartburn, ataxia, dizziness, tremor, palpitation, hypotension, blurry vision, arrythmia
Carbemazepine[d,] [43]	Maximum 1,600 mg per day	IV	Blurry vision, confusion, dizziness, nausea, drowsiness, Steven-Johnson Syndrome, SIADH, hyponatremia
Leveteracitam[d, b,] [63]	1,500 mg twice per day	IV	Fatigue, headache, insomnia, arthralgia, edema

TTP thrombotic thrombocytopenia purpura, *ITP* idiopathic thrombocytopenic purpura, *SIADH* syndrome of inappropriate antidiuretic hormone secretion

[a] Federal Drug Administration warning against use for treatment of muscle cramps in the United States

[b] Studied in amyotrophic lateral sclerosis

[c] Not routinely available in the United States or throughout Europe

[d] Studied in cramp-fasciculation syndrome

[e] Common and serious adverse events reported with medications, not limited to muscle cramp trials

multiple etiologies despite a lack of evidence [61]. Although often used for neuropathic pain, a trial of gabapentin in ALS showed that there was no effect on muscle cramps [62]. There are positive trials evaluating anti-epileptics such as levetiracetam in ALS [63] and carbemazepine for treatment of cramp-fasciculation syndrome [64]. A single study found tetrahydrocannabinol (THC) effective in preventing muscle cramps in patients with ALS [65]. A study of 14 patients evaluating mexiletine up to 300 mg found a benefit in reducing disability caused by idiopathic muscle cramps [66] (Table 3). A small study on 14 patients using Naftidrofuryl oxalate, which enhances utilization of oxygen and glucose in peripheral vascular disease, showed modest efficacy in the reduction of cramps, however, this medication is not routinely available for use in Europe or North America [67].

Conclusion

Evaluation of muscle cramps includes assessment of physiological stressors, pregnancy, medical and

neurological conditions using history, physical, laboratory tests and occasionally neuroimaging and electrophysiology. Management of patients with muscle cramps includes lifestyle modifications, treatment of causative etiologies, elimination of culprit medications, stretching and nutritional treatments. Although evidence is sparse, pharmacological options including calcium channel blockers, baclofen, carbamazepine, phenytoin and quinine sulfate can also be considered for disabling muscle cramps under careful clinical supervision. Clinical trials evaluating the efficacy and safety of these treatments and concurrent establishment of validated clinical tools and biomarkers for muscle cramps are urgently needed.

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Conflicts of interest Dr. Katzberg drafted the manuscript and performed literature review. He has received travel support from Genzyme Corporation and grants from CSL Behring and Grifols, Canada, Ltd. There are no direct conflicts of interest in the preparation of this manuscript.

Ethical standard This study does not contain clinical data or patient information.

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