INVITED REVIEW

ABSTRACT: Muscle cramps are a common problem characterized by a sudden, painful, involuntary contraction of muscle. These true cramps, which originate from peripheral nerves, may be distinguished from other muscle pain or spasm. Medical history, physical examination, and a limited laboratory screen help to determine the various causes of muscle cramps. Despite the "benign" nature of cramps, many patients find the symptom very uncomfortable. Treatment options are guided both by experience and by a limited number of therapeutic trials. Quinine sulfate is an effective medication, but the side-effect profile is worrisome, and other membrane-stabilizing drugs are probably just as effective. Patients will benefit from further studies to better define the pathophysiology of muscle cramps and to find more effective medications with fewer side-effects.

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MUSCLE CRAMPS

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Muscle cramps are a common complaint encountered by both neurologists and primary care physicians. Indeed, the prevalence of "true" muscle cramps was reported to be 95% in a group of young students recently enrolled in an exercise class.[62] In more recent studies of several hundred elderly outpatients, the prevalence of cramps was 35%–60%[1,58,64]; 40% reported having cramps more than three times per week in one study.[58] This common experience of ordinary cramps can be exploited in taking a history to help distinguish between true muscle cramps and other types of muscle pain or spasm.

The significance of cramps ranges from a benign, infrequent muscle pain to one of the symptoms heralding a devastating neurological disease such as amyotrophic lateral sclerosis (ALS). A detailed history and neurological examination usually differentiates between the various etiologies.

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Abbreviations: ALS, amyotrophic lateral sclerosis; ATPase, adenosine triphosphatase; CK, creatine kinase; EMG, electromyogram; FDA, Food and Drug Administration; NMJ, neuromuscular junction

Key words: amyotrophic lateral sclerosis (ALS); cramp–fasciculation; fasciculation; muscle pain; myalgia; quinine; spasm

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The word "cramp" is most likely derived from "cram," whose old High German and Norse roots suggest squeezing, pressing, or pinching uncomfortably. We recognize a cramp by the sudden, uncomfortable squeezing or contraction of a muscle, lasting seconds to minutes, often with a palpable hard knot in the affected muscle. Stretching the muscle or contraction of its antagonist muscle speeds relief from the cramp. On electromyogram (EMG), the involuntary muscle contraction is associated with repetitive firing of motor unit action potentials at high rates (up to 150 per second). The number of motor units activated and the frequency of their discharges increase gradually during the cramp and then subside gradually with an irregular firing pattern toward the end (termed "cramp discharge" in the American Association of Neuromuscular and Electrodiagnostic Medicine Glossary of Terms). This painful muscle contraction associated with electrical activity is termed a "true cramp," which is the main focus of this review. The clinical features of cramps are summarized in Table 1.

PATHOPHYSIOLOGY OF MUSCLE CRAMPS

An important question in the pathophysiology of muscle cramps is the site of their origin. Several lines of evidence suggest that cramps arise from spontaneous discharges of the motor nerves rather than from within the muscle itself. First, EMG during a muscle cramp reveals involuntary repetitive firing of

Table 1. Clinical features of cramps.

Acutely painful and may result in persistent (48–72 hours) soreness, swelling and with elevated serum creatine kinase
Explosive onset, variable rate of improvement. Visible, palpable contraction
Usually in one muscle or part of a muscle
Associated with both trivial movements and forceful contraction (especially in already shortened muscle)
Start and end with EMG evidence of muscle twitching that waxes and wanes independently in different parts of the muscle
Stretching the muscle usually terminates cramp

motor unit action potentials at high frequency, a characteristic that is unlikely to represent spontaneous muscle activity. Second, EMG during cramps also demonstrates fasciculations both at the beginning and end of cramps.[23] Fasciculations originate in the peripheral nerve.[51] Third, loss or damage to lower motor neurons is associated with cramps; diseases of muscle are not. Thus, it is clear that cramps originate within the motor nerves. Are these high-frequency discharges characteristic of cramps driven by the central nervous system or spontaneously generated within the peripheral nervous system? As has been reviewed previously,[51] there are data that support both possibilities, although the evidence favors a peripheral origin.

The central argument (favored by many neurologists at the time) was bolstered by a 1957 EMG study by Norris and colleagues.[62] When normal subjects induced cramps by forceful contraction of an already shortened muscle, they noticed synchronous activation of different motor units, suggesting a proximal (presumably central) trigger. In addition, cramp discharges were reduced by voluntary contraction of the antagonist muscles, suggesting spinal reflex inhibition by a presumed centrally mediated maneuver. However, central mechanisms cannot drive motor neurons to discharge at rates of >50 Hz, and discharge rates in cramps are typically 150 Hz. The peripheral localization of cramps was favored by Denny-Brown, one of the pioneers of electromyography, who made the following observations: (1) cramps begin as local fasciculations and spread to adjacent regions of muscle; and (2) the fasciculations vary in shape.[23] Because discharges originating more proximally would be expected to have a consistent, similar shape (as is the case with the double or triple discharges of tetany) and because the fasciculations spread to adjacent regions of muscle, he reasoned that cramps must originate in the intramuscular nerve terminals. Lambert provided unambiguous evidence that cramps can be generated peripherally. He induced cramps in human volunteers by repetitive stimulation of a peripheral nerve distal to a complete nerve block.[50] Bertolasi and colleagues[10] confirmed Lambert's observations and used this experimental paradigm to study the effect of muscle lengthening on cramps. Muscle stretching caused an abrupt cessation of a cramp induced either by voluntary contraction of a shortened muscle or by electrical stimulation distal to a nerve block. The conclusion from this latter finding is that the influence of lengthening the muscle must also primarily be a peripheral rather than central phenomenon. Although these findings do not exclude the possibility of central influence on cramps, perhaps by increasing or decreasing cramping thresholds in a given nerve, the current data point clearly to a peripheral nerve or neuromuscular junction etiology.

ETIOLOGY OF CRAMPS

True muscle cramps occur in diseases of the lower motor neuron; in certain metabolic disorders; following acute extracellular volume depletion; in inherited syndromes; as a side-effect of medications; and in some patients, especially the elderly, for unknown reasons (Table 2).

Cramps with No Apparent Cause. Recurrent, nocturnal leg cramps are common in the elderly, but may occur in any age group. The cramps typically involve the calf or foot muscles, frequently awaken the patient from sleep, and are of unknown cause.[90] Per-

Table 2. Etiology of cramps.

No apparent cause
Nocturnal leg cramps in the elderly
Exercise-related
Lower motor neuron disorders
Amyotrophic lateral sclerosis
After poliomyelitis
Radiculopathy
Neuropathy
Metabolic disorders
Pregnancy
Uremia
Cirrhosis
Hypothyroidism
Hypoadrenalism
Acute extracellular volume depletion
Perspiration, "heat cramps"
Hemodialysis
Diarrhea, vomiting
Diuretic therapy
Medications
Hereditary disorders
Antibodies to voltage-gated potassium channels

haps they are secondary to mild loss of motor neurons innervating those muscles and thus represent a similar phenomenon to patients with ALS, but on a more protracted, slow scale. There is ample evidence for such mild loss (about 25%) of motor neurons in the elderly.[84] Studies also suggest that the degree of atrophy is far greater in lower-limb muscles than in those of the upper limbs,[44,66] perhaps accounting for the propensity for cramps to occur in the legs. The implication of this hypothesis is that elderly individuals with leg cramps should show more evidence of mild reinnervation in calf muscle than a similar cohort without such symptoms. As far as we are aware, this has not been studied. Although nocturnal leg cramps are usually benign, in that they do not progress to motor neuron disease or cause significant daytime disability, their effect on sleep and quality of life may be pronounced.

Cramps have been associated with exercise, especially with beginning a new exercise program. They may occur during the exercise, but often occur during rest after exercise. Among students recently enrolled in an exercise class, cramps were a nearly universal phenomenon (95%), although how well the students were coached to report true cramps compared with other muscle aching is not entirely clear.[62] For others, even after extensive training, cramps occur frequently with exercise and may limit performance. These exercise-induced cramps may be secondary to dehydration, electrolyte shifts, or accumulation of metabolites in exercised muscle, although defining the difference has remained elusive. In a study comparing marathon runners who developed cramps during a race and those who did not, there was no difference in plasma volume, serum sodium, or serum potassium levels.[54] There is a clinical impression that some patients with large calves and benign fasciculations also have frequent leg cramps.

Lower Motor Neuron Disorders. A variety of diseases associated with damage to the lower motor neuron are associated with cramps, including ALS,[57] recovered poliomyelitis,[29] multifocal motor neuropathy, peripheral nerve injury,[24] nerve root compression,[72] and polyneuropathies.[42] Wasting of muscles, weakness, evidence of denervation and reinnervation on electrodiagnostic studies, and—in the case of ALS—upper motor neuron signs distinguish these syndromes from other causes of cramps. Although not specific to ALS, cramps appear to be more common in this disease than in other lower motor neuron diseases. This remains unexplained. Perhaps, the neuromuscular junction (NMJ) localization of the very earliest pathology in ALS may provide some insight. Recently, studies of the NMJ in rodent ALS models and in a human patient demonstrated striking changes in the NMJ at a time when there was no loss of axons proximally.[30] The abundance of distal motor nerve sprouting in ALS may also be a factor, because most cramps appear to arise in the nerve terminals.

Metabolic Disorders. The third trimester of pregnancy is associated with leg cramps in up to 30% of women.[39] Differences between pregnant women with and without cramps have not been recognized. The cause is unknown, but presumably is secondary to the metabolic changes associated with pregnancy. However, cramps in the third trimester of pregnancy could be secondary to the physical distortion of the NMJ as a byproduct of the fluid retention and joint laxity that accompanies the later stages of pregnancy. The cramps subside after delivery.

Endocrine disorders including thyroid disease and hypoadrenalism may be associated with cramps. Among hypothyroid patients, 20%–50% complain of muscle pain or cramps. There are three phenomena among hypothyroid patients that may be described as "cramps." The first is a slowing of relaxation of the muscles, which may be noticed by the physician as a "hung-up," slow reflex or by the patient as stiffness. The second is myoedema, which is a localized muscle contraction caused by mechanical irritation or distortion of the muscle. On examination, percussion of the muscle may produce this hard knot. Myoedema is produced by an electrically silent contracture (discussed later). The third symptom experienced by those with hypothyroidism is true cramps, that is, sudden painful muscle spasms.

Nocturnal leg cramps occur in up to 50% of patients with uremia and do not appear to be related to any secondary neuropathy caused by the kidney disease.[60,61] Hemodialysis may also precipitate cramps, as described in what follows.

Liver disease and cirrhosis seem to be associated with increased cramps.[2,4] One study suggests that this is because of decreased intravascular volume in these patients, because infusion of human albumin compared with placebo infusions decreased the frequency of cramps in 12 cirrhotic patients with more than three cramps per week.[4]

Performing intense muscular work in a hot environment and replacing fluid losses with water has long been associated with cramps. These heat cramps[81] are well-recognized in miners, stokers, cane-cutters, firemen, and athletic teams not acclimatized to high temperatures. The cramps typically

develop in the muscles that have been performing the labor, although they may occur in any muscle. They may occur during the work or up to 18 hours later. Patients with heat cramps show evidence of volume depletion and hyponatremia. Taking salt tablets during the work may help prevent heat cramps. Intravenous saline, but not hypertonic dextrose, will relieve the established cramps. This suggests that heat cramps are caused by both volume contraction and hyponatremia.

Acute Extracelluar Volume Depletion. Nearly one third of patients undergoing hemodialysis complain of muscle cramps.[41] The cramps tend to occur at the end of dialysis, and may be relieved by volume expansion with either hypertonic dextrose or saline solutions, implying that volume expansion rather than shifts in sodium concentration are the most important factor. Intentionally varying the sodium content of the dialysis fluid during the course of the dialysis session—a procedure called sodium profiling—has sometimes been used to help preserve the plasma volume during the last period of dialysis. This decreases the incidence of cramps in some cases.[21,22]

Similar to heat cramps, any acute extracellular volume depletion may precipitate cramps. This can occur with excessive perspiration, diarrhea, vomiting, or diuretic therapy. We have seen one case in which severe cramps occurred during intravenous infusion of 10% dextrose in water. Presumably, the infusion caused a rapid shift of water from the extravascular to intravascular compartment.

Medications. Given the challenges in distinguishing muscle pain and other side-effects from true muscle cramps, clear data linking medications to cramps are lacking. However, many medications that cause myopathy, such as statins (HMG-CoA inhibitors that reduce cholesterol levels), beta-adrenergic agonists, and clofibrate, often cause muscle pain.[82] Diuretics are associated with cramps, probably as a result of their intended effect—volume depletion—rather than secondary to any adverse effect of the medication.

Cramp–Fasciculation Syndrome. Most patients with benign fasciculations do not have frequent cramps. Similarly, patients with frequent muscle cramps of unknown cause do not have frequent fasciculations. Indeed, the two are most commonly encountered together in motor neuron diseases such as ALS. In 1991, Tahmoush and colleagues described patients with both fasciculations and cramps under the rubric "the cramp–fasciculation syndrome." These patients complained of muscle aching, cramps, and stiffness aggravated by exercise.[80] Although the neurological examination was normal (other than showing frequent fasciculations), 8 of 9 of their original group of patients were unable to work because of these symptoms. EMG revealed frequent fasciculations, and repetitive nerve stimulation resulted in "showers of electrical potentials," termed afterdischarges. The specificity of these afterdischarges remains unclear.[85] Curare, but not a nerve block, abolished the fasciculations and abnormal electrical potentials. Serum antibodies to voltage-gated potassium channels were recently found in some patients meeting criteria for this disorder.[37,59] Similar to other patients with cramps, carbamazepine is effective in treating the cramps. However, it remains unclear exactly how different these patients are from those with cramps with no apparent cause. Currently, the presence of antibodies to potassium channels is of research interest but does not have practical ramifications, and thus we do not routinely screen for this disorder.

Satoyoshi Syndrome. In 1978, Satoyoshi described 15 patients with a progressive disorder characterized by intermittent painful muscle spasms, alopecia, diarrhea, and skeletal abnormalities.[75] The average age of onset was 10 years in the original series, although adult-onset cases have also been described.[43] Amenorrhea is a common complaint in women. The muscle cramps initially are in the limbs. As the disease progresses, they involve neck, trunk, and masticatory muscles. An autoimmune etiology has been suggested, and some cases respond well to immunosuppressive therapies.[7,15,27]

Hereditary Disorders. Several families have been described with autosomal-dominant inherited generalized muscle cramps.[36,46,71,83] In these families, the cramping is often first recognized and most severe during adolescence; muscle enzymes are mildly elevated. In two families, EMG and muscle biopsy suggested a neurogenic origin.[71,83] In one family, muscle biopsy was compatible with a myopathy.[36]

APPROACH TO DIAGNOSIS

Accurately Defining a Cramp Syndrome. The first challenge in evaluating a patient with spasms or muscle pain, or both, is to determine whether the patient is experiencing true cramps or some other symptom. Disturbance of the central nervous system, peripheral nervous system, or muscle can cause symptoms reflected in muscle discomfort or spasms. Muscle spasm is a term that refers to any involuntary,

Table 3. Generalized muscle pain.

With muscle weakness
Inflammation (polymyositis, dermatomyositis)
Infection
Trichinosis
Toxoplasmosis
Poliomyelitis, West Nile virus infection
Viral syndrome
Secondary to bacterial toxin, e.g., toxic shock syndrome
Toxic and metabolic disorders
Hypophosphatemia
Potassium deficiency
Acute alcoholic myopathy
Total parenteral nutrition (essential fatty acid deficiency)
Necrotic myopathy secondary to malignancy
Hypothyroid myopathy
Medications
Carnitine palmityltransferase deficiency
Amyloidosis
Osteomalacia, hyperparathyroidism
Acute polyneuropathy (Guillain–Barré syndrome, porphyria)
Without muscle weakness
Polymyalgia rheumatica
Myalgia in infection or fever
Myalgia in collagen-vascular disease
Steroid withdrawal
Hypothyroidism
Parkinsonism
Fabry's disease
Fibromyalgia
Muscle pain–fasciculation syndrome

abnormal muscular contraction, regardless of whether it is painful. In all cases, spasms will need to be described further.

Muscle pain without contractions is referred to as myalgia. Generalized myalgias have a broad differential (Table 3), from benign postexertional pain in those unaccustomed to exercise to an inflammatory disorder of muscle. Determining whether weakness is present helps distinguish the various etiologies. In spite of some overlap, focal muscle pain often leads to a different set of diagnoses (Table 4). The tempo of onset of focal pain and the presence of swelling or induration helps to distinguish these disorders.

Contractions may occur without muscle pain. "Cramps" have been associated with numerous specific activities and occupations. These occupational cramps are best considered focal dystonias rather than cramps. Agonist and antagonist muscles contract simultaneously to prevent the performance of a specific task, despite the agility, strength, and sensation to perform other manual motor tasks of similar difficulty. The specific tasks are often "overlearned," such as in writer's cramp or in the playing of a musical instrument. The restriction of the "cramp" to certain tasks differentiates these disorders from true muscle cramps. Although often uncomfortable, these occupational cramps are not usually associated with the violent seizing-up and pain characteristic of a true cramp. Myotonia may be associated with involuntary muscle contractions, but these are not usually painful.

Muscle pain associated with contraction of muscle occurs in disorders other than true muscle cramps. The most common scenario is the focal muscle spasm around an injured or inflamed skeletal structure. Low back pain often fits into this category. Palpation of the lower back of those suffering from a recent increase in their pain often reveals hardened, tight paraspinal muscles on the most affected side. "Stiff person syndrome" presents with

Table 4. Focal muscle pain.

With swelling or induration
Neoplasm
Trauma (hematoma)
Ruptured tendon
Ruptured Baker cyst
Thrombophlebitis
Infection
Streptococcal myositis
Gas gangrene
Pyomyositis
Trichinosis, hydatid cysts, sparganosis
Influenza in children
Inflammation
Sarcoidosis (nodular form)
Localized nodular myositis
Proliferative myositis
Pseudomalignant myositis ossificans
Eosinophilic fasciitis
Ischemia
Muscle necrosis following relief of large artery occlusion
Diabetes (infarction of thigh muscle)
Embolism
Azotemic hyperparathyroidism
Toxic and metabolic disorders
Acute alcoholic myopathy
Exertion muscle damage
Normal persons (e.g., military recruits)
Metabolic myopathies
Myoglobinuria in drug-induced coma
No swelling or induration
Exertional myalgia
Normal persons
Vascular insufficiency (intermittent claudication)
Metabolic myopathies
Acute brachial neuritis
Parkinsonism
Ischemic mononeuropathy
Restless legs syndrome
Growing pains

focal, painful spasms, often provoked by sensory stimulation or emotion. The spasms and stiffness of this syndrome are often most prominent in the axial muscles. Simultaneous contraction of both abdominal muscles and back extensors is typical of this central disorder, which is often associated with antibodies to glutamic acid decarboxylase.

Patients with neuromyotonia (Isaacs' syndrome) are predisposed to true muscle cramps, but the other clinical manifestations of this disorder of continuous muscle fiber activity are usually even more prominent.[59] All patients with neuromyotonia have visible continuous muscle twitching, called myokymia. Abnormal postures of the limbs identical to carpal or pedal spasm are characteristic and may be either persistent or intermittent. Another feature is difficulty in relaxing muscles, which differs from true myotonia by EMG pattern, lack of percussion myotonia, and increased rather than decreased stiffness with continued activity. This disorder of children and young adults progresses insidiously, and is associated with the presence of serum antibodies to voltage-gated potassium channels. Immunomodulation is helpful in some cases, and carbamazepine or phenytoin usually controls symptoms.

Muscle contractures resemble true muscle cramps in that they are involuntary contractions of muscle that may be painful. The main difference between contractures and cramps is the striking EMG characteristic: contractures are electrically silent. Exercise-induced contractures are the hallmark of McArdle's disease and other primary deficiencies of muscle glycolytic metabolism. In those disorders, contractures are typically associated with exercise-induced muscle pain, weakness, elevated serum creatine kinase (CK) level, and myoglobinuria. Unlike cramps, these contractures never occur outside the setting of exercise. Brody's disease is an inherited disorder causing exercise-induced painless impairment of muscle relaxation, stiffening, cramping, and myalgias involving limb and facial muscles.[13] Cold exacerbates symptoms; contractures are electrically silent. Biochemical studies have revealed reduced calcium uptake and calcium adenosine triphosphatase (ATPase) activity in the sarcoplasmic reticulum of muscle fibers from these patients.[9,13,47] Because reuptake of calcium is important for skeletal muscle relaxation after contraction, this defect seems to account for the clinical symptoms, including the electrical silence of the contractures. A mutation in the fast-twitch skeletal muscle sarcoplasmic reticulum Ca–ATPase gene (*SERCA1*) has been identified.[65]

Both tetany and tetanus are conditions of motor unit hyperactivity that derive from the Greek word *tetanos*, referring to muscular spasm, and both conditions could be confused with muscle cramps. Tetany is associated with electrolyte disturbances, either hypocalcemia or alkalosis, and is caused by spontaneous peripheral nerve discharges occurring in groups. Hypocalcemic tetany was common in the 19th and early 20th centuries because of dietary vitamin D deficiency. The full manifestation of the syndrome is now rare; the clinical features of an attack are distinctive. Tingling begins in the mouth and peripheral extremities, increases in intensity, and spreads proximally. Then a sensation of spasm or tension follows the same pattern as the tingling, eventually leading to tonic spasm. In a severe attack the spasm may affect proximal and paraspinal muscles. Laryngeal muscles are commonly involved early. Tetany produces a characteristic motor posture referred to as carpopedal spasm. In the upper extremities, the thumb and fingers adduct and remain straight except for flexion at the metacarpophalangeal joints. Later, the wrists and elbows flex. In the lower extremities, the toes and foot flex with an equinovarus deviation at the ankles. Tetanus is caused by a toxin elaborated by the bacterium *Clostridium tetani*, which blocks the release of inhibitory neurotransmitters in the central nervous system.[14] Tetanus has been nearly eliminated in the developed world by immunizations and attention to wound care, although it remains a significant problem in developing countries, especially in infants. The main symptoms of tetanus are muscular rigidity and spasms. Persistent spasm of masseter muscles leading to jaw closure (trismus) and dysphagia are the typical presenting complaints. The spasms, which are extremely painful, are caused by sudden contraction of opposing muscles that last for a few seconds, but occur repeatedly for minutes. They may be either localized or generalized and are often triggered by sensory stimuli, movement, or emotion. In some cases, the spasms are severe enough to cause injury to the muscles or to fracture bones. Treatment of tetanus consists of supportive care, usually in an intensive care unit, and administering antitoxin.

Evaluation of Patients with True Cramps. Having determined that a patient is suffering from true cramps rather than another syndrome, the next challenge is to try to determine their cause. Although determination of etiology rests mainly on the history and examination findings, a few details regarding the cramps themselves may be useful. For example, cramps that occur only in the calf and foot muscles

at night in an elderly patient are likely to represent benign nocturnal cramps. Widespread cramps during the day, provoked by only minimal activity would raise more concern for motor neuron disease. However, most of these cases are also benign, in the absence of muscle weakness and atrophy. When cramps occur during or related to an activity, fluid intake status and environmental heat during the activity may be important factors.

In addition to screening for the etiologies discussed earlier, the history should focus on whether weakness or fasciculations are present. Fasciculations may occur with any of the disorders associated with cramps although they are more likely to occur with structural causes of cramps; for example, loss or damage to motor neurons. Hereditary cramping syndromes are uncommon, but a family history of cramps should be sought.

The examination should focus primarily on whether there is weakness and loss of muscle bulk, because this implies damage to or loss of motor neurons. Sensory loss may suggest a polyneuropathy, which is sometimes associated with cramps. Even if patients do not describe fasciculations, these should be sought on examination both by direct visualization of relaxed muscles and by palpating large proximal muscles where fasciculations are sometimes felt more easily than seen. Evidence of muscle wasting accompanied by upper motor neuron signs, such as hyperreflexia and spasticity, raises concern for ALS. Thyroid disorders are sometimes suggested by the physical examination, although screening laboratory tests are more sensitive.

Ancillary tests in evaluating a patient with cramps depend on the individual patient. With clear evidence of motor neuron loss, an imaging study often helps to exclude structural lesions such as degenerative disk disease. Electrodiagnostic studies may similarly help to demonstrate the extent of lower motor neuron loss or further define a neuropathy. Although disorders such as myotonia, neuromyotonia, cramp–fasciculation syndrome, and tetany are usually distinguished clinically, EMG is an important test that may, in some cases, prove diagnostic for these disorders. Laboratory studies that may be useful include serum creatinine, sodium, bicarbonate, calcium, magnesium, and CK levels and thyroid function studies. The serum CK may be increased by the frequent cramps alone or by motor neuron disease, and such a finding does not necessarily imply a primary muscle disease. As discussed earlier, we do not screen for voltage-gated potassium channels associated with the cramp–fasciculation syndrome.

TREATMENT OF CRAMPS

Reversing an underlying metabolic or structural disorder responsible for the cramps is clearly important. Unfortunately, the underlying cause often is not evident or not reversible, and thus other treatment strategies are required.

Nonpharmacological Treatment. Many patients will have already initiated the common, effective, nonpharmacological treatment for acute cramps; that is, lengthening or stretching the cramping muscle and activating the antagonist muscles. This method helps to stop most cramps.[20,32,87] Based on the observation that stretching treats acute cramps and that experimentally induced cramps do not occur in lengthened muscles, stretching was also tried as a preventive strategy.[19] Nocturnal leg cramps were markedly reduced in 44 patients instructed to stretch their calf three times daily. This simple, low-risk treatment should be suggested first in all patients with cramps. Stretching before exercise is probably an effective method to prevent cramps during exercise, although this has not been studied formally.

For patients with benign nocturnal cramps of the foot and calf muscles, another strategy may be to wear foot splints at night, to provide a passive stretch of the calf muscle. As far as we are aware, this has not been studied. Careful attention would need to be paid to the risk of causing falls in patients who get up frequently at night with cumbersome footwear. Strengthening training in elderly patients has shown clear improvement in strength.[84] Do such patients also have fewer cramps? Mild to moderate exercise may help prevent the cramps occurring during pregnancy.[40] One important over-the-counter treatment of exercise-related fluid losses leading to cramps has been captured by the beverage industry: sports drinks to replace fluids and electrolytes. Adding sodium (50 mmol/L) to fluid replacement has been shown to maximize fluid retention,[77] although typical sports drinks have lower sodium levels (10–25 mmol/L) to increase palatability. These drinks with lower sodium offer only slight benefit over water.[34] Perhaps ingestion of food with some salt content in addition to water provides the best combination for replacing fluid losses[55,69] and thus for preventing that component of exercise-related cramping.

Pharmacological Treatment. The old mainstay of pharmacological treatment for cramps is quinine sulfate, although the concerning side-effect profile may change that practice. Quinine had long been used for feverish illnesses such as malaria. In the

1930s, Wolf found that quinine sulfate provided excellent relief for patients with myotonic dystrophy,[88] but worsened the condition of patients with myasthenia gravis.[48] Quinine sulfate increases the muscle refractory period and decreases the excitability of the motor endplate to nerve stimulation.[38] Based on these observations, quinine sulfate was given to patients with nocturnal cramps. The initial single-blinded study demonstrated excellent relief.[56] Since then, there have been numerous trials of quinine sulfate in the treatment of muscle cramps, most with a relatively small number of patients for short treatment periods. In 1995, Man-Son-Hing and Wells[52] provided a meta-analysis of six double-blind, crossover trials.[17,26,33,45,78,86] This included 107 general ambulatory patients. They found that patients treated with quinine sulfate compared with placebo had roughly eight fewer cramps and about one third fewer nights disturbed by cramps in a 4-week period. The same investigators repeated this analysis in 1998.[53] This time they included four published trials[17,33,78,86] and three unpublished trials,[53] increasing the number of patients to 659. They reached the same general conclusion: quinine sulfate reduces cramps compared with placebo. However, including the unpublished data decreased the magnitude of the effect. Patients on quinine sulfate had 3.6 fewer cramps in a 4-week period compared with placebo. Including the unpublished data also showed that those taking quinine sulfate were more likely to drop out of the various studies and had a greater number of side-effects, especially tinnitus. A recent trial of 98 patients in general practice centers in Germany also supports the beneficial effect of quinine sulfate over placebo.[25] No difference was found in terms of side-effects.

Despite the relatively low incidence of side-effects in the clinical trials, it is the side-effect profile that caused the Food and Drug Administration (FDA) to ban over-the-counter formulations of quinine sulfate in 1994[5] and then recommended against its use for cramps in 1995, arguing that the risk/benefit ratio was too high.[6] From 1969 through June 1992, the FDA received 157 reports of health problems related to quinine sulfate use, including 23 that resulted in death. Quinine sulfate toxicity, which occurs with levels of 5–10 mg/L, is called cinchonism, a reference to the cinchona tree bark from which quinine is originally derived. Symptoms include temporary visual and hearing disturbances, dizziness, fever, nausea, vomiting, and diarrhea. Blindness may be permanent in some cases when the levels exceed 10 mg/L.[12,67] One of the most concerning side-effects unrelated to blood levels is drug-induced thrombocytopenia, a potentially serious problem whose link to quinine sulfate use may be challenging to recognize.[70] Quinine sulfate interacts with many medications.[35] For example, quinine may augment the effect of warfarin. Quinine sulfate remains an effective treatment, but the risks of treatment may be unwarranted.

The pathophysiology of cramps as just described underscores the hyperexcitability of peripheral nerves. Dampening the excitability of the nerves with sodium channel–blocking agents such as the anticonvulsants carbamazepine and phenytoin should theoretically be effective, although these medications have not been formally studied for preventing cramps. One small study comparing 12 patients taking quinine sulfate with 12 patients receiving lidocaine injections into the calf showed equal reduction in cramp frequency in both groups.[68] This treatment is obviously not practical for routine cramps, and a lidocaine patch would probably not deliver the drug sufficiently deep to have an effect.

In one open-label, unblinded trial of 30 patients, the anticonvulsant gabapentin proved particularly effective for muscle cramps, with all patients cramp-free after 3 months of therapy.[76]

Although cramps are a common complaint among women in the third trimester of pregnancy, there are few appropriate remedies because of the teratogenicity of quinine sulfate and anticonvulsants. Supplemental calcium, sodium, and magnesium have all been tried, and the best evidence favors supplemental magnesium for preventing cramps,[18,89] although this is based on a single, randomized, placebo-controlled trial.[18] A study of magnesium in 46 nonpregnant patients with nocturnal leg cramps showed marginal benefit.[74]

Botulinum toxin binds to the presynaptic side of the neuromuscular junction and relaxes muscles by preventing acetylcholine release. Bertolasi and colleagues demonstrated decreased cramping after botulinum toxin injection into the calf and foot muscles of a small group of patients with an inherited cramping syndrome.[11] Calf strength was unaffected. There was no placebo group.

In 10 hemodialysis patients taking creatine monohydrate, frequency of muscle cramps decreased by 60% compared with 10 patients receiving placebo.[16] There were no adverse effects of creatine and no difference between the two groups in terms of hematocrit, hemodynamic shifts, or electrolytes. Infusion of L-carnitine may also be beneficial for hemodialysis-associated cramping.[3] An open-label study in 38 college football players showed a decreased incidence of cramping in those taking creatine.[35]

In patients with cramps refractory to quinine sulfate treatment, Baltodano et al. found an impressive response rate (7 of 8 patients) to the calcium channel blocker, verapamil.[8] Other studies support the use of this agent.[28] There are anecdotal reports of baclofen as a treatment for cramps in motor neuron disease.[63]

Vitamin E has also been used for cramps. In patients with liver disease and cirrhosis, Konikoff et al. demonstrated lower vitamin E in patients with cramps than those without them. Replacement with oral vitamin decreased the cramp frequency.[49] In a randomized, placebo-controlled study of 40 hemodialysis patients, vitamin E was as effective as quinine sulfate in treating leg cramps.[73] A randomized, placebo-controlled study of 27 patients with nocturnal leg cramps showed benefit from quinine sulfate but not vitamin E. Although the trials are relatively few, the current data suggest that vitamin E may be beneficial for patients with liver or renal disease, but not for leg cramps in other contexts.

A recent study of ALS patients from six centers in the United States provided a glimpse into how these patients, with a 62% prevalence rate of cramps, are currently treated.[31] Unlike other symptoms such as fasciculations, which are often not bothersome, cramps were troublesome for 90% of those experiencing them. The four main drugs being used for cramps were quinine sulfate (35%), baclofen (19%), phenytoin (10%), and gabapentin (7%). In a survey on their efficacy, patients rated baclofen, phenytoin, and gabapentin between "worked sometimes or a little" and "worked, but not well" for cramps. Quinine sulfate appeared more efficacious in ALS patients, rating between "worked, but not well" and "worked fairly well."

Which therapy should be chosen? One impressive finding in the medication trials was the powerful effect of a placebo, with response rates in the 40%–50% range. This finding gives promise for effective treatment even with a placebo, but also emphasizes the need for well-designed, double-blind, randomized, placebo-controlled trials in choosing therapies. As detailed earlier, there have been few of these "gold-standard" trials for cramp treatment. For a condition that is uncomfortable but relatively benign, perhaps the best first choice is to advise stretching exercises three times daily, especially before going to bed and before exercise. Despite the lack of studies, maintaining passive stretching of the calves while sleeping should be effective and devices worn on the calves at night may be considered in some patients. Attention to hydration and nutrition may prevent some cramps secondary to or partially provoked by dehydration. If these measures fail and cramps remain bothersome, sodium channel–blocking drugs such as carbamazepine or phenytoin should be initiated. In our experience, these drugs are nearly always effective and often may be given exclusively in a small, bedtime dose. We do not routinely use quinine sulfate because of the side-effect profile discussed earlier, although for severe cramps its use may still be warranted. Sodium channel–blocking agents (carbamazepine, phenytoin) also have side-effects (some of them severe) and the risk/benefit profile of such off-label use of these drugs for cramps has not been formally studied. In pregnant patients, a trial of magnesium may be warranted. Therapies and side-effects are summarized in Table 5.

RESEARCH DIRECTIONS

Overall, our understanding of cramps has not progressed significantly in the last decade, although recent studies defining electrically induced cramps and interest in symptom management in diseases such as ALS may provide new insights. Building on the observations of others[10,50] that cramps may be electrically induced in normal subjects, Stone et al. studied the reliability of the cramp threshold frequency; that is, the frequency of repetitive stimulation that produces a cramp in a given subject.[79] By recording two trials on 3 separate days, they demonstrated excellent intrasession (0.84, 0.95, 0.98) and intersession (0.96) reliability. The next important study will be to determine whether the threshold frequency is correlated with the symptom of cramps. This could be studied in a given patient before and after dialysis, for example, or between patients—that is, those who do or do not report cramps. Such a study would permit objective evaluation of pharmacotherapy.

If electrically induced cramps could be produced in laboratory animals, this might provide an excellent model for quickly testing various therapeutic agents or for further testing the pathophysiology of cramps. Similar investigations could be carried out in animal models of motor neuron disease. Does the threshold frequency for inducing cramps in ALS mice or rats decrease with time? Given the well-documented pathology and disease course in these animals, correlating changes in physiology of cramps over time may yield insights into the pathophysiology of cramps.

In conclusion, muscle cramps originate from peripheral nerves. True muscle cramps may be distinguished from other disorders by the history and

Table 5. Treatment for muscle cramps.

Nonpharmacologic treatments			
Stretching before exercise and before bedtime			
Good hydration/nutrition, especially surrounding exercise			
? Nocturnal device to stretch calves			
Pharmacologic treatments			
		Side-effects	
Medication	Typical dose	Serious	Common
Quinine sulfate	260 mg at bedtime	Thrombocytopenia, disseminated intravascular coagulation, hemolytic-uremic syndrome, hepatotoxicity, interstitial nephritis, ototoxicity	Headache, hypoglycemia, nausea/vomiting, dysphagia, rash
Carbamazepine	100 to 200 mg at bedtime	Bone marrow depression, thrombocytopenia, renal toxicity, hyponatremia, hypocalcemia, arrhythmias, AV heart block, congestive heart failure, syncope, hepatitis, Stevens–Johnson syndrome	Blurred vision, double vision, dizziness, clumsiness, hypertension, hypotension nausea, vomiting, drowsiness, pruritic rash
Dilantin	100 to 200 mg at bedtime	Stevens–Johnson syndrome, thrombocytopenia, leukopenia, pancytopenia, toxic hepatitis, liver damage	Ataxia, dizziness, encephalopathy, gingival hyperplasia confusion, osteomalacia, rash
Gabapentin	300 mg at bedtime	Stevens–Johnson syndrome (rare)	Ataxia, dizziness, somnolence, blurred vision, diplopia, nystagmus, fatigue, myalgia, tremor, peripheral edema
Vitamin E	1000 units at bedtime	?	Gastrointestinal distress

Side effects are not intended to be a complete list and this table is not intended as a prescribing guide.

physical examination. In many cases, the etiology of the muscle cramp may also be determined. Despite the "benign" nature of cramps, many patients find the symptom very uncomfortable. Quinine sulfate is an effective medication, but the side-effect profile is worrisome, and other membrane-stabilizing drugs are probably just as effective. Patients will benefit from further studies to better define the pathophysiology of muscle cramps in efforts to find more effective medications with fewer side-effects.

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