Muscle cramps and contractures: causes and treatment

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ABSTRACT

Muscle cramps are painful, sudden, involuntary muscle contractions that are generally self-limiting. They are often part of the spectrum of normal human physiology and can be associated with a wide range of acquired and inherited causes. Cramps are only infrequently due to progressive systemic or neuromuscular diseases. Contractures can mimic cramps and are defined as shortenings of the muscle resulting in an inability of the muscle to relax normally, and are generally myogenic. General practitioners and neurologists frequently encounter patients with muscle cramps but more rarely those with contractures. The main questions for clinicians are: (1) Is this a muscle cramp, a contracture or a mimic? (2) Are the cramps exercise induced, idiopathic or symptomatic? (3) What is/are the presumed cause(s) of symptomatic muscle cramps or contractures? (4) What should be the diagnostic approach? and (5) How should we advise and treat patients with muscle cramps or contractures? We consider these questions and present a practical approach to muscle cramps and contractures, including their causes, pathophysiology and treatment options.

INTRODUCTION

What is a muscle cramp? The conventional definition is an 'unexpected, involuntary and painful contraction of a single muscle or a muscle group, relieved by stretching the cramping muscle'. Muscle cramps are thought to arise from spontaneous ectopic discharges of motor nerves or the terminal branches of motor axons.[1] However, their precise pathophysiology remains unknown. A muscle contracture is the shortening of the muscle resulting in an inability of the muscle to relax, and normally has a myogenic cause.

Muscle cramps are common and part of the spectrum of normal human physiology, affecting 37% of the healthy population per year in an epidemiological survey, and are therefore frequently reported to general practitioners and neurologists.[2] Muscle cramps can accompany conditions that affect any part of the lower motor neurone: anterior horn cell, nerve root and peripheral nerves. They are also common in many non-neuromuscular neurological disorders, including Parkinson's disease, central inflammatory disorders and stroke, and many non-neurological conditions, including from electrolyte imbalances, medications and in primary endocrine disorders. Box 1 presents a typical example.[2 3]

IS IT A MUSCLE CRAMP, CONTRACTURE OR A MUSCLE CRAMP MIMIC?

Patients often refer to various symptoms as 'muscle cramps' and it is therefore important first to determine whether the reported symptom is truly a muscle cramp or a mimic. A muscle cramp is an involuntary and painful shortening of a muscle due to a non-physiological supramaximal muscle contraction. The muscle feels suddenly tightened, and the contraction may lead to an abnormal position of the affected limb. Cramps are very common and often occur during or after exercise, but the cause may differ. Some people get muscle cramps, especially leg cramps, at night. They can be painful, and they may last a few seconds to several minutes. The supramaximal contraction disrupts the muscle fibre plasma membrane, which can result in an increased serum creatine kinase (CK) and persistent myalgia. Passive or active stretching of the affected muscle usually provides relief.

A muscle contracture is the shortening of the muscle resulting in an inability of the muscle to relax normally, due to a myogenic cause. Patients often describe contractures as exertional muscle stiffness or muscle cramping after arbitrary

Box 1 An athlete with cramps

A 58-year-old athletic man reported 3 years of muscle cramps in his legs. These initially occurred only during running but gradually developed into painful nocturnal cramps, with some relief from stretching. He had been taking atorvastatin for hypercholesterolaemia before symptom onset and stopping this did not resolve the symptom. He drank eight cups of coffee per day and four units of alcohol per week.

On examination, he had normal muscle bulk and strength. There was visible fasciculation in his calves, but not elsewhere. Vibration sense was diminished, and the Achilles tendon reflex was decreased bilaterally. Laboratory testing was normal except for vitamin D insufficiency (32 nmol/L, normal ≥50). Serum creatine kinase was 346 IU/L (24–195). Nerve conduction studies and electromyography found no signs of polyneuropathy, but there were features of previous bilateral S1 radiculopathy (right>left).

The treating physician concluded that the cramps were caused by a combination of an old S1 radiculopathy and a hypovitaminosis D, with confounding factors of strenuous exercise, caffeine and statin use. The patient was advised to stop caffeinated drinks and to take a vitamin D supplement. As this was only partial effective, the patient subsequently also started magnesium, vitamin B complex and diltiazem on a trial basis. Diltiazem combined with non-pharmacological treatment were most effective, with almost complete resolution of his symptoms.[48]

Box 2 Exertional contractures and rhabdomyolyses

A 26-year-old man had recurrent episodes of myoglobinuria and rhabdomyolysis (with recurrently raised serum creatine kinase (CK) >10.000 IU/L. There was a history of myalgia and frequent exertional muscle contractures since childhood, poor endurance and episodic swelling of muscles. He had no fixed weakness or second-wind phenomena. There was no family history of similar complaints.

Neurological examination was normal, except for myalgia during manual muscle strength testing. Serum CK remained elevated (960–2026 IU/L) between episodes of myoglobinuria. A quantitative muscle ultrasound scan was normal. Initially an inflammatory myopathy was suspected; however, muscle biopsy showed only minor non-specific myopathic changes without signs of inflammation or necrosis. Histochemical staining for myophosphorylase showed no activity. Subsequently performed genetic testing identified a pathogenic homozygous mutation in the *PYGM* (muscle glycogen phosphorylase) gene (c.148C>T (p.(Arg50*)), confirming the diagnosis myophosphorylase deficiency (McArdle disease). The patient was referred to the rehabilitation team for training and dietary advice. He was also provided with a medical alert card and advised on how to prevent contractures and rhabdomyolysis.[49] We also referred him to the International Association for Muscle Glycogen Storage Disease (iamgsd): https://www.iamgsd.org/.

movement such as lifting heavy objects for more than a few seconds or after repetitive movements. Stretching the affected muscle during a contracture does not provide relief, and contractures generally last longer than muscle cramps. Painful contractures are prominent in metabolic myopathies.[4] Patients with McArdle disease—an autosomal recessive glycogen storage disease caused by a deficiency of myophosphorylase—report painful muscle contractures during normal physical activities of daily life, such as carrying a bag of groceries or walking up stairs. Patients with McArdle disease may also experience the 'second wind' phenomenon, progressive muscle weakness, fatigue and myalgia.[4] Painless contractures occur in Brody disease, a rare autosomal recessive myopathy with reduced sarcoplasmic/endoplasmic reticulum calcium-ATPase1 activity delaying muscle relaxation.[5] Box 2 presents an example of a patient suffering from muscle contractures.

In contrast to muscle cramps, electromyography (EMG) shows no electrical activity (and is electrically silent) during a contracture. This is due to an insufficient amount of ATP available to break the actin-myosin bonds to relax the muscle and it is therefore a metabolic failure rather than an electrical mechanism (the same phenomenon explains rigour mortis). In the acute moment of a contracture happening, it is often not possible to perform an EMG. Patients can be asked if they can provoke it during the examination.

It is important to distinguish muscle cramps and contractures from muscle cramp mimics, including other (often unpleasant) symptoms such as dystonia or myotonia, which are discussed in more detail in table 1. The (pharmacological) treatment of these mimics differs from the treatment of true muscle cramps and is beyond the scope of this review.

ARE THE CRAMPS EXERCISE-INDUCED, IDIOPATHIC OR SYMPTOMATIC?

Based on the pattern and presumed cause, muscle cramps are classified as exercise-induced (or physiological), idiopathic (often nocturnal) or symptomatic cramps (secondary to an underlying condition and / or evoked by exogenous triggers). In many patients, particularly in the elderly, symptomatic cramps are multifactorial, resulting from a combination of endogenous factors and exogenous triggers that together exceed the threshold for developing muscle cramps (figure 1). In our neuromuscular and general practice experience, only a minority of patients experiencing muscle cramps is eventually diagnosed with an underlying neuromuscular disease.[1]

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Table 1 Clinical features of muscle cramp and its mimics

	Clinical features			
Phenomenon	**Definition**	**Occurrence**	**EMG**	**History**
Muscle cramp	An involuntary and painful shortening of a muscle due to a non-physiological supramaximal muscle contraction.	Muscle cramps can occur exercise-induced, idiopathic (often nocturnal) or secondary to an underlying condition or exogenous trigger (tables 2–4).	Continuous motor unit action potential activity, with activity increasing in the antagonist muscle when the patient is asked to move the agonist muscle.	The muscle feels tightened, and the contraction may lead to an abnormal position of the affected limb. Muscle cramps are described as very painful. Stretching the affected muscle will provide relief.
Contracture	Shortening of the muscle resulting in an inability of the muscle to relax normally.	Painful contractures occur in metabolic myopathies (eg, McArdle) and in Brody's disease. Besides, contractures can occur in thyroid disease (hypothyroidism) and rippling disease (mounding of myoedema).	No electrical activity during a contracture due to an insufficient amount of ATP available to break the actin–myosin bonds to relax the muscle; it therefore represents a failure of metabolism, rather than an electrical mechanism, hence it is referred to as electrically silent.	Patients will often describe contractures as exertional muscle stiffness or muscle cramping. Stretching the affected muscle will not provide relief during a contracture and contractures will last longer than a muscle cramp.
Dystonia	Simultaneous contraction of agonist and antagonist, leading to an altered position of the joint and frequently repetitive movements and postures. This can be either focal or generalised.	The main examples of focal dystonia are cervical dystonia, blepharospasm and writer's cramp. However, dystonia can also occur in hand or foot.	EMG shows continuous motor unit action potential activity, with activity increasing in the antagonist muscle when the patient is asked to move the agonist muscle.	Patients may experience pain and rigidity from the muscle contractions as a result of dystonia.
Myotonia	Delayed muscle relaxation after voluntary contraction or sensory stimulation.	This occurs in both myotonic dystrophy as well as in the non-dystrophic myotonias.	Needle EMG shows an abnormal spontaneous repetitive muscle fibre discharge with characteristic waxing and waning of frequency and amplitude.	Patients may describe myotonia as muscle stiffness, muscle discomfort or a sensation of "the muscle getting stuck". They may also describe a warm-up phenomenon, where this sensation lessens with repeated movement.
Myokymia	Continuous involuntary rippling movements of the muscle.	This occurs in healthy people in the orbicularis oculi muscle (eyelid myokymia) and is harmless. It may occur in episodic ataxia type I characterised by persistent myokymia and brief episodes of generalised ataxia, dysarthria, titubation, nystagmus, vertigo or tremor lasting for a few minutes, neuromyotonia and Morvan syndrome.	EMG shows abnormal spontaneous repetitive muscle fibre discharge with characteristic waxing and waning of frequency and amplitude.	Patients may report wave-like or worm-like rippling of the muscle, which may be felt on palpation.
Restless legs syndrome	Unpleasant sensations in the legs combined with the urge to move. Resolves when patient begins to move their legs.	Restless legs syndrome occurs most frequently during the evening and night.	–	Patients and doctors often have difficulty distinguishing muscle cramps from restless legs, as both present with the urge to move. Patients typically describe the urge to move during restless leg syndrome as being very unpleasant. There is usually no muscle stiffness.
Periodic limb movement disorder	Characterised by periodic episodes of repetitive limb movements (typically every 20–40 s) during sleep.	This occurs only during sleep.	–	Patients are usually unaware of the movements but may report daytime somnolence or poor sleep and waking several times during the night.
Spasticity	Spasticity is characterised by increased tone affecting different muscle groups to a different extent. The resistance of an affected muscle is most prominent when starting passive movement and lessens as the movement proceeds.	Spasticity occurs in upper motor neurone lesions such as stroke (motor cortex) or motor neurone disease (corticospinal tract).	–	Symptoms of spasticity may vary from mild stiffness and tightening of the muscle to painful and uncontrollable spasms.

Continued

Table 1 Continued

Phenomenon	Clinical features			
	Definition	**Occurrence**	**EMG**	**History**
Stiff person syndrome	Characterised by stiffness in axial and limb muscles with periods of muscle contractions precipitated by sudden movements, noise or emotions. Anti-GAD antibodies are often present.	Stiff-person syndrome is associated with diabetes mellitus type 1, paraneoplastic syndromes and other autoimmune diseases.	Continuous motor unit action potential activity, typically ameliorated by intravenous benzodiazepine, sleep and anaesthesia.	Patients may report stiffness, muscle pain and muscle cramps often starting in the lumbar region.

EMG, electromyography.

Exercise-induced muscle cramps are the most common form and are a physiological response to prolonged and excessive exercise.[1 6] Interestingly, their incidence increases during the last trimester of pregnancy.[7] There are currently two possible hypotheses for their cause:

- The dehydration and electrolyte hypothesis (based on only low-level evidence[8 9]) states that exercise-induced muscle cramps result from hyperhidrosis (during exercise) combined with inadequate rehydration, leading to increased extracellular fluid osmolality. This causes intercellular fluids to migrate and expand to the extracellular space. This increases pressure on certain nerve pathways, alters excitability and causes electrolyte deficits, consequently leading to a muscle cramp.
- The neuromuscular hypothesis (supported by more convincing evidence[9–11]) states that the onset of an involuntary muscle cramp is affected by altered afferent synaptic feedback caused by muscle fatigue, leading to increased excitatory afferent activity and decreased inhibitory afferent activity resulting in increased alpha motor neurone activity and, ultimately, increased muscle cell activity leading to muscle cramps (figure 2).

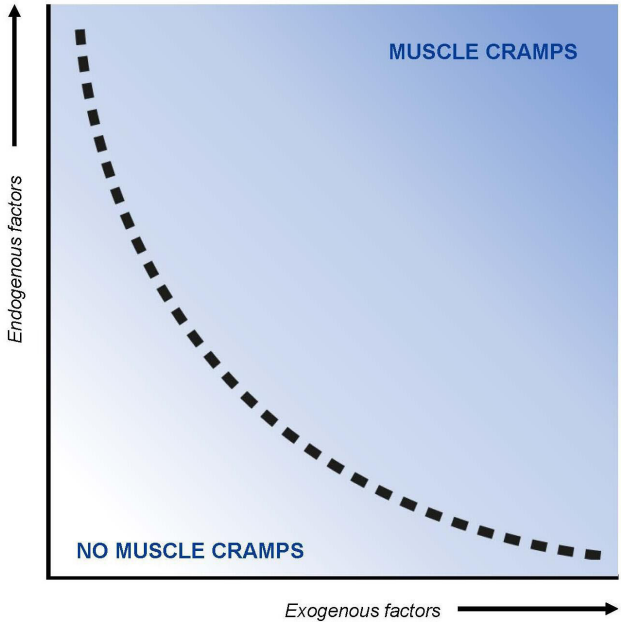

Figure 1 Threshold for endogenous and exogenous triggers causing muscle cramps.

Idiopathic, often nocturnal muscle cramps have no identifiable underlying cause; they affect mainly elderly people and typically involve the calf or foot muscles.[12 13] They occur mostly at night, probably because the foot is then passively plantar flexed; the maximum tensionless shortening of the calf muscles means these muscles have uninhibited nerve stimulation, leading to sudden uncontrolled cramping.[14 15]

Symptomatic muscle cramps are caused by a wide range of neurological or systemic conditions and are generally neurogenic (table 2). They can be provoked or intensified by exposure to certain drugs or other exogeneous triggers (figure 3.)

WHAT IS/ARE THE PRESUMED CAUSE(S) OF SYMPTOMATIC MUSCLE CRAMPS OR CONTRACTURES?

Exercise-induced and idiopathic muscle cramps are often benign and non-progressive. In these cases, the main principle for treatment is prevention of exogenous triggers. However, when suspecting a symptomatic cause, the differential diagnosis is extensive.

Muscle cramps in adults often develop in neurological and neuromuscular disorders such as motor neurone disease, radiculopathies and peripheral neuropathies. In metabolic or mitochondrial myopathies, there is a lack of ATP that causes a disturbance of muscle relaxation, which particularly occurs during exercise and is referred to as contracture. However, the occurrence during exercise does not distinguish (neurogenic) cramps from (myogenic) contractures but a comprehensive history and a thorough neurological examination will aid the differentiation. Tables 2 and 3 provide an overview of the different causes of symptomatic muscle cramps and contractures; table 4 summarises the most frequent triggers. Box 3 is an example of symptomatic muscle cramps. Figure 4 shows pictures of different clinical clues in symptomatic muscle cramps.

WHAT IS THE BEST DIAGNOSTIC APPROACH TO MUSCLE CRAMPS OR CONTRACTURES?

The challenges in assessing cramps and contractures are first the vast number of potential causes and second the need to decide whether the symptom lies outside the range of normal physiology.[16] Addressing this can avoid unnecessary investigation and psychological

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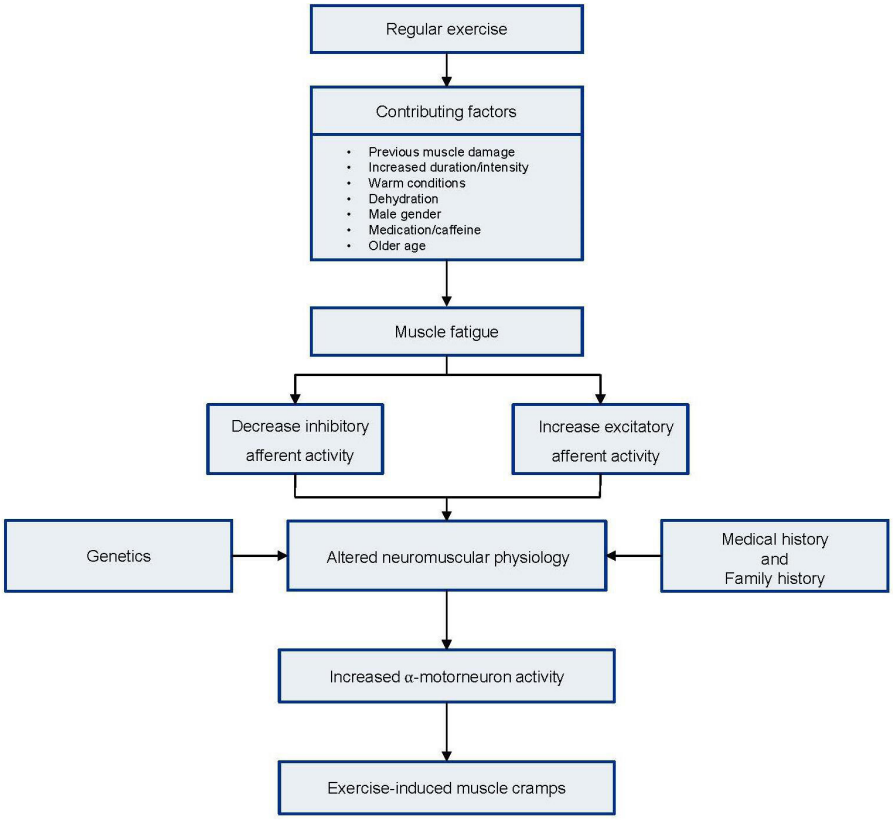

Figure 2 Factors associated with exercise-induced muscle cramps.[10]

harm, including from incidental findings. The standard diagnostic approach includes a focused medical history and a thorough neurological and systemic examination. The presence of any 'red flag' features (eg, second-wind or warm-up phenomena, de novo cramps at middle age, widespread cramps or involvement of other muscles than calves and feet) should prompt additional ancillary investigations, such as laboratory testing, EMG, genetic testing and/or a muscle biopsy.

History

The history should include questions concerning duration, frequency, severity, muscle groups involved, timing and context of muscle cramps, the presence of specific exogenous factors (in particular, triggering, aggravating or alleviating factors) and any previously used treatments. Furthermore, any chronic medical conditions, family history and relevant medication should be identified. The possibility of (chronic or acute) intoxication should also be considered. Box 4 provides key points in the history.

Examination

All patients presenting with muscle cramps should undergo a detailed systemic and neurological examination. Specific signs may point to an underlying cause and inform additional diagnostic testing.[17] Box 5 provides key points in the neurological and systemic examination.

Laboratory testing

Patients with suspected idiopathic cramps and a normal systemic and neurological examination do not require any laboratory testing. However, when investigating potential causes of muscle cramps, several blood tests are relevant depending on the clinical presentation as highlighted in tables 2 and 3.

EMG/nerve conduction studies

Muscle cramps on EMG are associated with the involuntary repetitive firing of motor unit action potentials. These discharges have a high frequency of up to 150 per second. The number of motor units and the discharge frequency often increase gradually during a muscle cramp, before subsiding gradually with an irregular discharge firing pattern at the end.[1] The EMG is particularly useful when neurological examination implies a neurogenic cause (motor neurone disease, radiculopathy or polyneuropathy). Furthermore, the EMG can distinguish contractures (electrically silent cramps) from myotonic discharges and signs of peripheral nerve hyperexcitability (neuromyotonic discharges, like fasciculations, after discharges).

Table 2 Symptomatic muscle cramps and contractures: neuromuscular causes[5 12 50–62]

Diagnosis	Clinical features/clues	Diagnostic tests
Neurogenic causes		
Anterior horn cell		
Motor neurone disease	▶ Muscle cramps ▶ Progressive proximal unilateral limb muscle weakness and atrophy ▶ Fasciculation ▶ Reduced or exaggerrated reflexes, or the presence of pathological reflexes ▶ Fatigue ▶ Bulbar dysfunction ▶ Cognitive dysfunction	▶ EMG ▶ Ultrasound scan of muscle
Spinobulbar muscular atrophy	▶ Muscle cramps ▶ Males only ▶ Limb-girdle weakness ▶ Atrophy, perioral fasciculation ▶ Sensory neuropathy ▶ Postural tremor ▶ Gynaecomastia ▶ Infertility ▶ Positive family history	▶ EMG ▶ *AR* gene testing
Spinal muscular atrophy	▶ Muscle cramps ▶ Symmetric limb girdle weakness and atrophy ▶ Fasciculation	▶ EMG ▶ *SMN* gene testing
Nerve roots		
Radiculopathy	▶ Muscle cramps ▶ Pain ▶ Sensory loss ▶ Paraesthesia	▶ EMG ▶ MR scan of spine
Peripheral nerves		
(Hereditary) motor and sensory peripheral neuropathies	▶ Muscle cramps ▶ Slowly progressive muscle weakness ▶ Feet deformities (pes cavus, hammer toes) ▶ Distal sensory loss and muscle atrophy ▶ Often a positive family history	▶ EMG ▶ Neuropathy genetic panels/ single gene testing, if appropriate
Peripheral nerve hyperexcitability ▶ Cramp-fasciculation syndrome	▶ Muscle cramps ▶ Fasciculation ▶ Positive family history	▶ EMG ▶ Ultrasound scan of muscle
▶ Morvan syndrome	▶ Muscle cramps ▶ Myokymia ▶ Fasciculation ▶ Muscle hypertrophy ▶ Autonomic dysfunction, for example, constipation, hyperhidrosis, central nervous system symptoms (eg, encephalopathy, insomnia, headache, drowsiness and hallucinations)	▶ EMG ▶ Anti-LGI1, anti-CASPR2 antibodies
Neuromyotonia	▶ Muscle cramps ▶ Myokymia ▶ Fasciculation ▶ Muscle hypertrophy and hyperhidrosis, associated with autoimmune disorders, for example, myasthenia gravis, vitiligo, Hashimoto's thyroiditis	▶ EMG ▶ Anti-LGI1, anti-CASPR2 antibodies
Myogenic causes		
Muscular dystrophies, for example, ▶ Becker and Duchenne muscular dystrophy ▶ Limb girdle muscular dystrophies	▶ (Painful) muscle stiffness ▶ Limb muscle weakness ▶ Positive Gowers' sign ▶ Waddling gait ▶ Lumbar lordosis ▶ Calf hypertrophy ▶ Cardiomyopathy ▶ Respiratory involvement ▶ Cognitive dysfunction ▶ Often positive family history	▶ Serum CK ▶ EMG ▶ *DMD* gene testing ▶ Next-generation gene sequencing
Myotonic dystrophy	▶ (Percussion) myotonia ▶ Muscle weakness and atrophy ▶ Multi organ system involvement (eg, cardiac, respiratory, endocrine, gastrointestinal) ▶ Hypersomnia/fatigue ▶ Cognitive dysfunction ▶ Cataract	▶ EMG ▶ *DMPK* gene testing

Continued

Table 2 Continued

Diagnosis	Clinical features/clues	Diagnostic tests
Glycogen storage disease V (McArdle disease)	▶ Painful muscle contractures especially during physical activities in daily life, for example, walking upstairs, cycling uphill, carrying grocery bag ▶ Fatigue ▶ Myalgia ▶ Muscle hypertrophy ▶ Exercise intolerance and progressive muscle weakness ▶ Positive family history	▶ Serum CK ▶ Myoglobinuria ▶ *PYGM* gene testing
Carnitine palmitoyl transferase II (CPTII) deficiency	▶ Muscle contractures during prolonged exercise, sports, fasting and infection ▶ Myalgia ▶ Myoglobinuria	▶ Myoglobinuria ▶ *CPT2* gene testing
Brody disease	▶ Painless contractures starting in early life ▶ Pseudomyotonia ▶ Exercise-induced muscle stiffness exacerbated by cold ▶ Muscle hypertrophy ▶ Fatigue ▶ Often positive family history	▶ Serum CK ▶ EMG ▶ *ATP2A1* gene testing
Rippling muscle disease	▶ Painful muscle stiffness/contractures ▶ Muscle hypertrophy ▶ Muscle hyperirritability triggered by stretching or percussion ▶ Episodic wave-like muscle movements ▶ Mounding ▶ Percussion-induced rapid contractures	▶ EMG, ▶ Serum CK ▶ *CAV3* gene testing

CK, creatine kinase; EMG, electromyography.

Additional testing

Patients strongly suspected of having a myopathy need targeted additional testing. Ultrasound scan of muscle is a non-invasive method that provides detailed information on its echogenicity, size and thickness, muscle movements and appearances of the surrounding fascia. Muscle ultrasound can be used for screening purposes and can be useful in the differential diagnosis.[18 19] Genetic testing is indicated in people with a suspected genetic disease associated with muscle cramps or contractures (including various forms of muscular dystrophy, congenital myotonia, glycogen storage disease or Brody disease), and may be complemented with a muscle biopsy if results are uninformative or equivocal.[17] No invasive diagnostic testing is needed when other causes sufficiently explain the presence of the muscle cramps.

HOW TO TREAT AND WHAT TO ADVISE PATIENTS WITH MUSCLE CRAMPS AND CONTRACTURES

Patients with exercise-induced or idiopathic muscle cramps should be advised that muscle cramps are common and usually harmless, are often due to a combination of factors. Exercise-induced cramps do not in themselves suggest an underlying neuromuscular, neurological or systemic disease. Sometimes reassurance can be sufficient, but some patients may want to seek symptom relief.

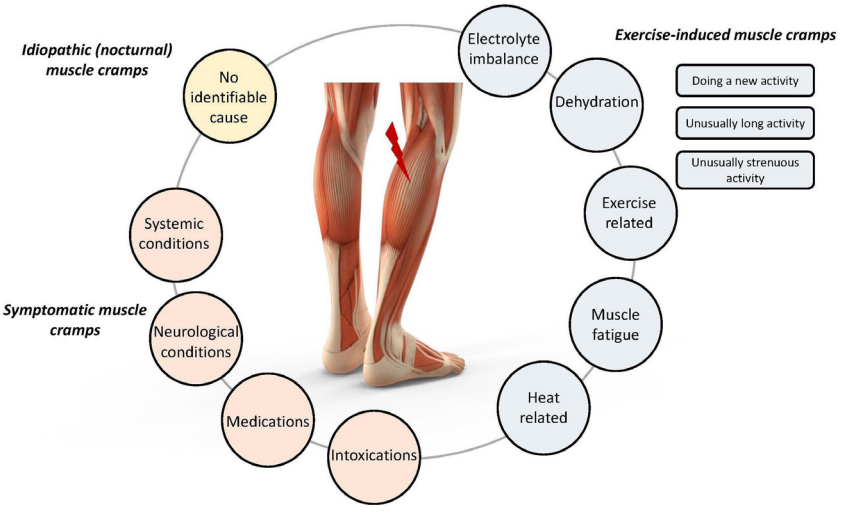

Figure 3 Triggers for developing muscle cramps.

Table 3 Symptomatic muscle cramps and contractures: non-neuromuscular causes

Diagnosis	Clinical features/clues	Diagnostic tests
Non-neurological causes		
Systemic metabolic		
Electrolyte imbalance	▶ Muscle cramps	▶ Creatine kinase, albumin, sodium, calcium, potassium, magnesium, glucose
Hepatic and renal dysfunction	▶ Muscle cramps ▶ Symptoms of hepatic or renal disease	▶ ASAT, ALAT, renal function
Vitamin deficiency	▶ Muscle cramps	▶ Vitamins B, C and D
Endocrine		
Diabetes mellitus	▶ Muscle cramps	▶ Sodium, potassium, renal function, glucose
(Para)thyroid dysfunction	▶ Contractures ▶ Symptoms of (para)thyroid disease	▶ TSH, T3/T4, PTH, calcium, ▶ Bone profile
Other endogenous causes		
Chronic venous insufficiency	▶ Nocturnal muscle cramps ▶ Pain and limb discomfort ▶ Varicose veins ▶ Oedema ▶ Skin pigmentation changes ▶ Venous ulceration	▶ Duplex ultrasonography

PTH, parathyroid stimulating hormone; TSH, thyroid stimulating hormone.

In cases of symptomatic muscle cramps, treatment is directed towards the underlying cause(s). For muscle contractures, patients are often much helped with a detailed explanation of the underlying mechanism and physical therapy to increase physical fitness and to improve understanding of the daily activities that my provoke contractures.[4]

Unfortunately, there is limited research evidence on the symptomatic treatment of muscle cramps, and existing guidelines are based mainly on expert opinion.[20] Non-pharmacological interventions are the cornerstone of muscle cramp treatment and these often give sufficient relief; however, many patients may have already tried one or more of these without success before seeking medical help.[21] Patients whose muscle cramps remain debilitating may wish to try pharmacological treatment. The treatment options discussed below are mainly based on the review by the Therapeutics and Technology assessment subcommittee

Table 4 Exogenous triggers of muscle cramps

Class	Group	Drugs
Intoxication	Caffeine Alcohol Illicit drugs	Amphetamine, cocaine, heroin
Medication	Lipid-lowering medication	Statins Fibrates
	Cardiovascular medication	Diuretics Anti-arrhythmic medication Nifedipine/amlodipine
	Antibiotics	Ciclosporin Penicillin
	Retroviral medication	
	Chemotherapeutics	
	Beta-adrenergic agonist (incl. salbutamol)	
	Corticosteroids	
	Opioids	
	Cholinesterase inhibitor	
	Depolarising muscle relaxant	
	Selective oestrogen receptor modulators	
	Other	Lithium Cimetidine Methylphenidate Nicotinic acid (vitamin B_3)

Box 3 Muscle cramps and fasciculation

A 51-year-old man, previously healthy, developed cramps in the thenar muscles and in the base of the tongue when yawning. He had also noted involuntary muscle twitching in his arms, chest and abdomen for 6 months. He had no limb muscle weakness. When specifically asked, he mentioned varying dysphagia and dysarthria.

On examination, there was fasciculation in both arms and chest muscles without muscle atrophy or weakness. The left Hoffmann's reflex was present and palmomental reflexes noted bilaterally. The remaining examination was normal.

Ultrasound scan of muscle showed fasciculation in the cervical and thoracic region, without atrophy or increased muscle echogenicity. Nerve conduction studies were normal. Electromyography identified lower motor neurone involvement in muscles of bulbar, cervical and thoracic regions. There was no myotonia.

We made a clinical diagnosis of motor neurone disease. Over the following months, his symptoms increased. Muscle weakness and atrophy developed, with behavioural changes (uncontrollable episodes of crying and laughing). After the onset of painful nocturnal muscle cramps, carbamazepine was started but with only limited benefit.

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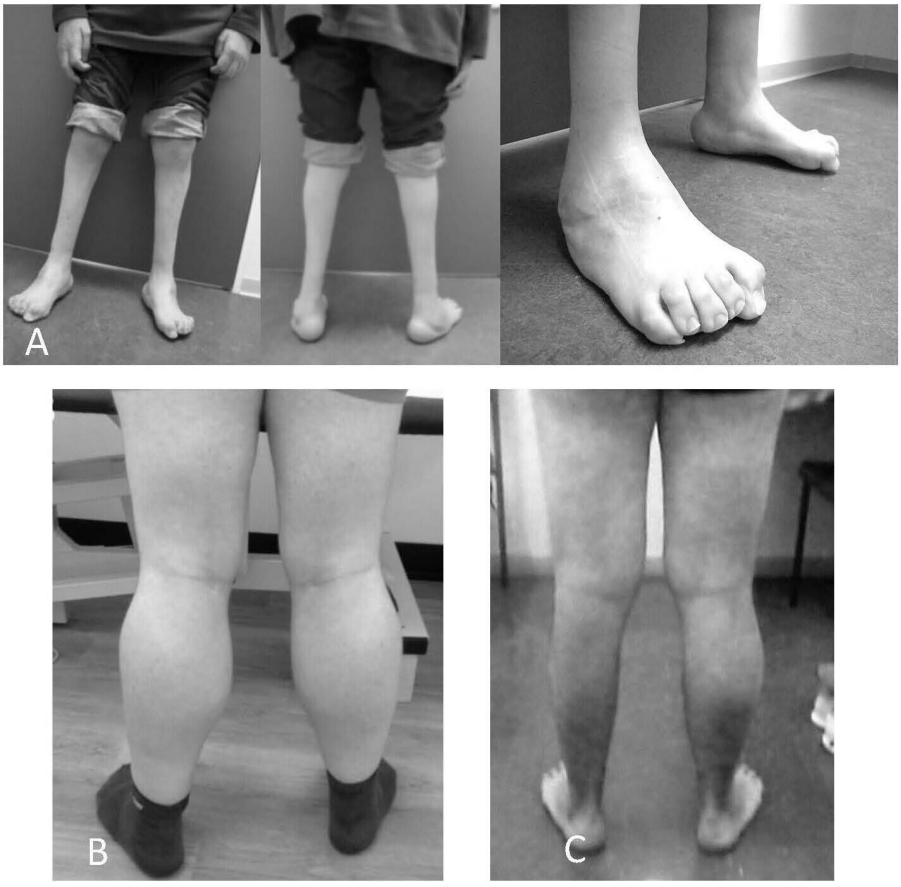

Figure 4 Clinical clues for symptomatic muscle cramps. (A) Atrophy of ventral and posterior lower leg and foot deformities in hereditary motor and sensory neuropathy. (B) Hypertrophy of the calves in Becker muscular dystrophy. (C) Asymmetric atrophy of the left medial calve in limb-girdle muscular dystrophy.

of the American Academy of Neurology published in 2010.[21]

Non-pharmacological treatment of muscle cramps

Correction of metabolic disturbances

Treatable causes and triggers of muscle cramps, for example, electrolyte imbalance, hypothyroidism and/or vitamin deficiencies should be treated in the first instance.[22]

Withdraw or reduce iatrogenic causes

Clinicians should consider possible iatrogenic causes of muscle cramps. Medications well known to cause muscle cramps as a side effect (such as statins, diuretics and inhalation β2 sympathomimetics) should be stopped or replaced if possible. However, note that muscle cramps from diuretics are often caused by the desired volume depletion rather than being a primary muscle effect.[1 23] Table 4 overviews the medications associated with muscle cramps.[3 22]

We also advise patients to stop smoking and limit their alcohol and caffeine consumption. Reducing caffeine consumption, particularly in the evenings, might particularly help nocturnal muscle cramps, although there is little evidence to support this.[23 24]

Patients should also maintain adequate hydration (a daily fluid intake of 1.5–2 L), mainly to prevent exercise-induced- muscle cramps, although again there are no formal studies supporting this recommendation.[21]

Some patients use an orthosis to prevent hyperextension of the foot during the night. Two studies have investigated the effect of forced passive muscle stretching to prevent cramps. The first showed reduction of nocturnal muscle cramps in patients who stretched their calves three times a day.[25] The second study showed that stretching did not benefit the severity or frequency of muscle cramps.[26] Forced passive muscle stretching before physical activity appears to help prevent muscle cramps.[1]

Muscle cramps can be relieved quickly by stretching the affected muscle or by active contraction of its antagonising muscle.[1 26] Massaging the affected muscle and applying heat—for example applying a hot-water bottle, shower or bath—may also relieve pain. However, again these interventions have not been formally studied.

Non-Pharmacological treatment of muscle contractures

Metabolic myopathies cannot be cured but the symptoms can be kept under control by learning techniques

Box 4 Key points in history

- Duration, frequency, severity, timing and pattern of muscle cramps:
  - Involvement of other muscles than calves and feet is suggestive for neuromuscular diseases
  - Widespread cramps might suggest motor neurone disease.
  - Second-wind phenomenon (suggests glycogen storage disease) or warm-up phenomenon (suggests myotonia).
- Context in which the cramps occur (eg, exercise, rest, nocturnal).
- Triggers (eg, exercise, dehydration) and alleviating (eg, stretching) factors.
- Associated symptoms (fatigue, weakness, stiffness, pain, sensory loss).
- Risk factors contributing to electrolyte imbalances (vomiting, diarrhoea, excessive exercise, malnutrition, pregnancy, etc).
- Family history.
- Medication use (see table 4).
- Chronic medical conditions (eg, diabetes mellitus, hepatic, renal or thyroid dysfunction).
- Chronic or acute intoxications (eg, caffeine, alcohol, illicit drugs).
- Effect of previously used treatments.

for doing exercise and staying fit. This is best done by working with a physiotherapist. We recommend regular moderate exercise, such as walking. To manage a cramp or contracture, we recommend stopping the activity that caused it until the pain resolves. Unlike stretching of muscle cramps, stretching of a muscle in contracture may cause further muscle damage, and should be avoided. In McArdle disease, oral sucrose supplementation improves exercise capacity, and a carbohydrate-rich diet can relieve symptoms more than a protein-rich diet.[4]

Box 5 Key points in the examination

Findings suggesting a neuromuscular disease:

- Atrophic or (pseudo)hypertrophic muscle (the latter suggests muscular dystrophies).
- Widespread cramps combined with muscle weakness.
- Muscle weakness, fasciculation, hyperreflexia and spasticity suggest motor neuron disease.
- Sensory loss or pain suggest polyneuropathy or (poly) radiculopathy.
- Focal hyporeflexia or absent reflexes suggest a radiculopathy or polyneuropathy.

Findings suggesting a non-neurological disease:

- Features of liver disease such as abdominal pain, jaundice, easy bruising, lower limb oedema, fever, weight loss, pruritus, fatigue, increasing abdominal girth or confusion.
- Features of renal disease such as oedema, hypertension, fatigue, anorexia, vomiting or pruritus.
- Features of thyroid disease such as slow movement and speech, fatigue, cold intolerance, weight gain, constipation, cognitive dysfunction or bradycardia.

Pharmacological treatment of muscle cramps

There is little evidence concerning pharmacological treatment of muscle cramps, and the treatments mentioned below are often based on the empirical experience in our neuromuscular clinic.

There are several pharmacological treatment options for those where non-pharmacological management is ineffective. Vitamin B complex or diltiazem are the first choice. Quinine is effective, but its risk of severe side effects limits its use to short periods only (≤2 weeks).[21]

Vitamin B complex

Vitamin B complex is effective treatment for muscle cramps and has no severe side-effects[27]; however, note that B_6 hypervitaminosis can result in a neuropathy.[21 22 27] A vitamin B complex capsule comprises vitamins B_1, B_2, B_3, B_5, B_6, B_8, B_{11} and B_{12} and the recommended dosage is 50 mg once a day. Treatment should be stopped if symptoms have not improved within 2 weeks; however, if the treatment helps, we recommend continuing it for a few months.

Diltiazem

Diltiazem is a calcium-channel blocker that may prevent muscle cramps by stabilising the influx of calcium ions across the cell membrane.[21 22 28] Possible side effects include peripheral oedema, headache, dizziness, orthostatic hypotension and arrhythmias.[22] Contraindications include severe heart failure and arrythmias. The recommended dose of diltiazem is 30 mg at bedtime; if there is no benefit after 2 weeks, we advise stopping the drug.

Quinine

Historically, quinine has been the most widely prescribed and studied treatment for muscle cramps.[29] Its derivatives do reduce muscle cramps, although the observed benefit is limited. However, its high risk of toxicity means that it should not be used routinely to treat muscle cramps.[21 30 31] In particular, quinine can cause rare but severe hypersensitivity reactions, such as haemolytic uraemic syndrome.[32 33] Strict contraindications for quinine derivatives are myasthenia gravis, optic neuritis, arrhythmias and tinnitus. Furthermore, quinine is not advised for elderly patients because of the increased risk of falls due to vertigo. Overall quinine is not recommended as a first-line treatment but may still be an option for people with severe muscle cramps when other medications have failed.[21]

Dijkstra JN, *et al*. *Pract Neurol* 2023;**23**:23–34. doi:10.1136/pn-2022-003574

No patient should receive quinine derivatives in the long term.[34]

Additional pharmacological treatments

Carbamazepine is a sodium channel blocker that prevents repetitive and sustained firing of an action potential and appears to have help benign fasciculation syndrome.[1 22]

Clonazepam, a benzodiazepine, is often prescribed for nocturnal muscle cramps, although its effect has never been formally investigated. The risk of benzodiazepine dependence means that clonazepam is not a first-choice treatment.

Baclofen may sometimes provide relief in muscle cramps in a low dose (5 mg) at bedtime, but there is no clinical trial evidence to support this.[21]

Tetrahydrocannabinol has been used effectively in one study of patients with motor neuron disease and muscle cramps.[22 35]

Levetiracetam appears potentially helpful for muscle cramps in people with motor neuron disease; however, the evidence is sparse, and this medication is therefore not regularly prescribed.[22 36]

There is limited evidence for magnesium supplementation outside the setting of pregnancy or magnesium deficiency.[37]

Pharmacological treatment for muscle contractures

To manage episodic occurrences of contractures in metabolic myopathies, paracetamol (acetaminophen) may be taken after activity has ceased. For more severe pain, which lasts for hours, patients may need to seek medical attention. Patients who experience chronic daily pain warrant a thorough assessment of their aerobic and muscle conditioning, as there is an inverse relationship between aerobic fitness/muscle strength and chronic pain. Furthermore, chronic use of opioid medications is not recommended, as they may mask feedback from the muscles, leading to further muscle damage and recurring pain.[4]

Different medications have been used as symptomatic treatment for muscle stiffness, contracture and myalgia in Brody disease. Verapamil and mexiletine improved symptoms in few patients but were associated with side effects.[5]

Specific considerations for children with muscle cramps

Most muscle cramps in children are benign and self-limiting and often nocturnal.[38] In general, physiological muscle cramps are less common in children than in adults. There is only limited research on muscle cramps in children. A common and benign condition in children is 'growing pains', which is often misinterpreted as muscle cramps. There is no consensus on the exact definition of 'growing pains'. Although ill defined, the term is generally used to describe a common, benign syndrome of recurrent discomfort often affecting the legs that occurs in children, mainly at age 4–14 years and with an estimated prevalence of 37%.[39 40] The absence of palpable or visible hardening (which is usually seen in muscle cramps) and the difference in duration of the pain may help to distinguish between the two. If muscle cramps are associated with (recurrent) rhabdomyolysis or other suggestive features, motor developmental delay and/or neuromuscular weakness, genetic neuromuscular conditions such as muscular dystrophies (in particular Duchenne and Becker muscular dystrophy) and metabolic myopathies (in particular glycogen storage disorders and fatty acid oxidation defects) do enter the differential diagnosis. Muscle cramps are also fairly common in children with spastic cerebral palsy and depending on the severity and treatment goal, requires tone modifying medication for management.[41]

The same diagnostic approach discussed above for adult patients can be applied in children. As in adults, the first treatment steps are non-pharmacological treatments such as adequate hydration and stretching or massaging the affected muscle. However, if necessary, pharmacological pain relief might be considered although there is little supportive evidence base. There has been no research into vitamin supplementation as a treatment option for children. Explaining the usually benign nature of muscle cramps as a symptom in children is most important.

Specific considerations for muscle cramps during pregnancy

Muscle cramps are common in pregnancy, in particular during the third trimester and mainly affecting the lower limbs.[7] About 30%–50% of women experience muscle cramps during their pregnancy, often several times per week, with a variable duration ranging from few seconds to several minutes and occurring mostly during the night.[42] The cause(s) for this association remain(s) uncertain, but contributing factors (also common outside the context of pregnancy) include metabolic disturbances, electrolyte imbalances and vitamin deficiencies.[1 43]

Treatable causes of muscle cramps should be identified and treated if possible. The same non-pharmacological treatment options advised for non-pregnant patients ought to be recommended for pregnant patients with muscle cramps.

Magnesium

There is conflicting evidence for an effect of magnesium on pregnancy-related muscle cramps.[44 45] In general, magnesium is well tolerated, but it may cause gastrointestinal side effects such as diarrhoea.[46] The recommended dose is 300–400 mg per day and can be safely administered during pregnancy.

Vitamin B

Vitamin B 100 mg daily and 'vitamin B_1 plus' 40 mg, and vitamin B_6 three times daily may reduce the frequency and intensity of muscle cramps. There are no reported adverse effects and it is safe to use during pregnancy.[47]

Additional pharmacological options

Quinine at high dose is teratogenic and may cause abortion, it is therefore strictly contraindicated during pregnancy.

CONCLUSION

Although muscle cramps are common, there has been little research regarding their treatment. Mainstays of management are evaluation and elimination of medications and lifestyle factors that may cause muscle cramps and the identification and treatment of possible underlying causes. Symptom management is primarily based on counselling the patient and families about the prevalence and origin of muscle cramps followed by non-pharmacological recommendations, emphasising the importance of stretching and lifestyle changes. If this gives insufficient relief, then pharmacological treatment may be considered. The limited evidence available suggests that vitamin B complex and diltiazem are pharmacological treatments of first choice.

Key points

- Muscle cramps have many causes, but only a minority of patients with cramps has underlying neuromuscular disease.
- Clinicians should try to identify and treat underlying (pathological and iatrogenic) causes of muscle cramps.
- Non-pharmacological first line recommendations including hydration and stretching.
- Vitamin B complex and diltiazem are the first choice of pharmacological treatment for muscle cramps; quinine should not be given for long-term treatment of muscle cramps and is contra-indicated during pregnancy.

Further reading

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