Eur Arch Psychiatr Neurol Sci (1990) 239:337–342

European Archives of Psychiatry and Neurological Sciences

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Muscle Cramp: Main Theories as to Aetiology

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Received July 20, 1989

Summary. Historically relevant hypotheses on the pathophysiology of muscle cramp are reviewed. Psychosomatic, static, vascular, myogenic and neural theories are highlighted from a clinician's point of view. Modern neurophysiological research leaves little doubt that true muscle cramp is caused by explosive hyperactivity of motor nerves. Several mechanisms may be involved including spinal disinhibition, abnormal excitability of motor nerve terminals and spreading of muscle contraction by ephaptic transmission or axon reflexes.

Key words: Muscle cramp – Aetiology

Introduction

In a true muscle cramp, there is sudden involuntary and painful shortening of muscle, attended by visible or palpable knotting of muscle, often with abnormal posture of the affected joint, and relieved by stretching or massage [44]. This description separates muscle cramp from other painful muscle disorders without shortening of muscle (e.g. myositis and myalgia) on the one hand, and shortening of muscle without pain (e.g. myotonia, tetany, myopathic muscle contracture or occupational cramp) on the other [19]. Muscle cramp is excruciatingly painful and afterwards the affected muscle may remain sore and tender for a period of days. In most persons muscle cramp occurs rarely, but some people are truly disabled by unusual propensity to cramp.

A recent neuroepidemiological survey of the adult population of The Netherlands showed an overall incidence of muscle cramp in the previous year of 37%. For a symptom so common and distressing, muscle cramp has attracted surprisingly little attention. Nevertheless several theories have been developed to explain the sudden occurrence of painful muscle cramp in otherwise healthy individuals.

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Psychosomatic Origin of Muscle Cramp

At the turn of the century prominent French and German neurologists were of the opinion that muscle cramp represented a psychosomatic disorder. Féré in 1900 attributed the appearance of muscle cramp to extreme muscular contraction or passive shortening of muscle, accompanied by hypotonia of antagonists [10]. In his opinion states of irritability and fatigue, provoked by strenuous exercise, nervousness, neurasthenia or hysteria, would favour muscle cramp. Then musculature, particularly the heavily burdened calf musculature, would be easily irritated by action of chemical fatigue products of unknown composition either on the muscle fibres themselves or on the nerve fibres which innervated them, or on both of these. Accumulation of fatigue products in the daytime would explain nocturnal muscle cramp.

In the same year Vold suggested that in nervous individuals musculocutaneous irritation from calf musculature could even give rise to psychopathological phenomena like visual hallucinations of cramped calves, both during daytime *(Wachhallucinationen)* and during dreams at night [49].

Näcke suggested an inverse relation between dreams at night and nocturnal muscle cramp, pointing out that accidental leg movements, e.g. extension of the foot during terrifying dreams, may cause muscle cramp [36].

Kehrer [20] in 1923 wondered if muscle cramp, originating from a local cause, could by way of a conditioning reflex become a hysterical symptom, and thus a way of behaviour.

Psychosomatic theories held out until the sixth decade of this century, as seen in the chapter on muscle spasms, professional cramp and backache by Holmes [17].

According to Holmes, patients exhibiting these disorders are tense, anxious and insecure individuals, who seldom get lasting satisfaction from their endeavours. They are quick to react to threatening life situations with feelings of resentment, frustration, hostility, humiliation and guilt. They strive assiduously to gain approval, approbation and immunity from criticism and at the same

time maintain a constant state of readiness to protect themselves from what appears to be an ever-threatening, unpredictable environment.

As a protective reaction involving hyperfunction of the skeletal musculature, being on guard is well tolerated by the body for brief periods of time. Difficulties ensue, however, when failure of this technique to provide security and satisfaction leads to a protracted state of readiness for action. In such a setting the sustained hyperfunction of the skeletal muscles becomes productive of discomfort and disability, precipitating backache, muscle spasms and professional cramp. Finally, a vicious circle ensues in which the engendered somatic and psychic reactions become matters of concern to the patient and further enhance and perpetuate the symptoms.

Vascular Origin of Muscle Cramp

At the end of the third decade of this century the concept was developed of vascular insufficiency during muscle contraction as a primary factor in the production of muscle cramp. Arterial insufficiency (intermittent claudication) as well as venous insufficiency (varicosis, *Krampfadern*) was considered as a cause of muscle cramp.

In 1928 Erben [9] postulated that isometric contraction of a muscle that is already maximally shortened causes excessive stretching of the fascia (perimysium) surrounding the muscle. This stretching would not only cause the characteristic cramping pain but also obstruct the vessels that perforate the surrounding fascia. This would lead to vascular insufficiency of the affected muscle fibres with accumulation of metabolites, e.g. lactic acid. As lactic acid was thought to effect muscular contraction, accumulation of this substance would be followed by persisting involuntary contraction and muscle cramp. Stretching of a cramped muscle causes lengthening and narrowing of the muscle and therefore relaxation of the extended surrounding fascia. This would not only stop the pain but also re-establish muscular circulation, remove the intracellular accumulation of lactic acid and end the muscle cramp. Vascular disease like intermittent claudication or varicose veins, vasospasm caused by nicotine, alcohol, diabetes or uraemia and hypovolaemia caused by cholera, typhpoid, hyperhidrosis or strenuous exertion would all predispose to vascular insufficiency during muscle contraction and thus muscle cramp.

To combat hypovolaemia and warrant sufficient muscular circulation, patients suffering from muscle cramp were advised to eat large amounts of heavily salted food.

The frequent occurrence of nocturnal muscle cramp was explained by the human habit of sleeping with extended feet and thus shortened calve muscles. Sudden straightening of a leg during sleep or after awakening causes isometric contraction of already shortened calve muscles and therefore excessive stretching of the surrounding fascia.

This theory crossed the Atlantic Ocean. In 1947, at the Twentieth Scientific Meeting of the American Heart Association, Moss and Herrmann [35] presented a theory, based on the assumption that muscle cramp results from the stimulation of muscle by accumulated metabolites. This accumulation could result from venous stasis due to varicose veins and deep venous occlusion, from increased venous pressure in the legs in pregnant women, from an increase in metabolic by-products following exercise or from the products of abnormal muscle metabolism such as is observed in patients with diabetes mellitus.

In 1973 Rivlin [43] blamed nocturnal calf cramp on varicose veins. Involuntary stretching of the leg and foot during sleep would suddenly pump blood out of the dilated veins into the calf-muscle sinuses, leading to cramp. His simple remedy was emptying the veins by raising the foot of the bed 9 in. It is not until the bed is tilted to this height that the heart is sufficiently below the level of the leg veins to allow drainage.

Static Origin of Muscle Cramp

The occurrence of muscle cramp, especially in the calves and feet, has also been attributed to static deformities of the back, the pelvis, the legs and feet. There are two separate aetiological theories on the mechanism by which static deformities may induce muscle cramp. The first theory presumes that certain muscle groups in the calves and feet are strained by static deformities of the lower extremities or abnormal posture, e.g. walking on high heels. Both abnormal posture and static deformities might contribute to prolonged muscular contraction in the legs and feet, and thus to abnormal muscle fatigue, predisposing to muscle cramp [13, 41]. This hypothesis in a way joins with the theory of a primary myogenic origin of muscle cramp, which will be discussed later.

The second theory is far more interesting and dates from the fourth decade of this century. Although this theory was developed in the United States of America, it is probably based on earlier British ideas on the origin of epilepsy. In the first half of the 19th century Marshall Hall proclaimed the concept of reflex epilepsy. According to this theory epileptic convulsion were caused by affections of the extremities, e.g. injuries, that irritate the peripheral nerves and spinal cord (eccentric epilepsy). From here through a spinal reflex arc epileptic convulsions would occur primarily in the affected extremities and could generalize secondarily [2].

Everyday clinical examples like trismus in mandibular abscess or abdominal rigidity in appendicitis illustrate the relation between irritative processes and muscular hypertonia.

This second theory, presented in 1943 by Gootnick [14], therefore bears analogy to the mechanism of abdominal rigidity encountered in acute intraperitoneal disease. Essentially, it represents a variety of the segmental visceromotor reflex, except that here the irritative focus in the spinal cord is produced not by visceral disease but by change in skeletal structures of the same segmental distribution as the muscles affected. Muscle cramp in the lower extremities appears to be due to reflex bombardment of the myoneural junctions by a stream of impulses originating from some neighbouring source

of irritation. This source of irritation may be arthritis, a traumatic skeletal deformity or some other pathological condition of the weight-bearing joints, nerves or ligaments of the lower extremities.

Another factor could also precipitate cramp attacks. In muscles already abnormally stimulated by impulses radiating from an irritated segment of spinal cord, extension of the extremity could constitute a trigger mechanism sufficient to throw the stretched muscle group into cramp. The sharp contraction of the gastrocnemius and soleus muscles in response to momentary lengthening of the leg was blamed on a exaggeration of the myotatic or stretch reflex.

This second theory is attractive in several ways. In the first place it is able to explain the high incidence of muscle cramp in the lower extremities in old age by pointing out the frequent degenerative skeletal changes in the heavily burdened weight-bearing joints of the lower extremities. In the second place it explains the frequent occurrence of nocturnal muscle cramp by the fact that in daytime the calf muscles maintain a considerable degree of tone and are in a state of partial contraction against various degrees of pull. At night, during sleep in a recumbent posture, muscular relaxation and lengthening occur, so that straightening of the leg may elicit the stretch relex.

Finally, the beneficial effect of complete rest in exercise-induced muscle cramp is explained as an argument in favour of this theory, as rest diminishes spinal irritation by inflammatory changes in the muscle itself [38].

Muscular Origin of Muscle Cramp

In 1910 Bittorf [3], practising in the same clinic as von Strümpell, suggested a disturbed muscular metabolism as an important causal factor in muscle cramp.

In 1921 von Strümpell [48], a great authority in his field, expressed the opinion that muscle cramp had a primary myogenic origin, analogous to myotonia. Not contraction of the striated fibrils inside skeletal muscle fibres, producing voluntary muscle contraction, but contraction of the sarcoplasm, contained in muscle fibres, would cause muscle cramp. Therefore typical cramp pain would resemble violent colics that originate in smooth musculature, not containing striated muscle fibrils.

In 1927 Grund [15] openly opposed this view. The mere fact that muscle cramp happens to occur in otherwise healthy individuals *("bei sonst durchaus muskelgesunden Menschen")* precluded in his opinion a myopathic origin of cramp.

The descriptions of myopathic muscular contracture in muscle phosphorylase deficiency by McArdle [33] in 1951 and in muscle phosphofructokinase deficiency by Layzer et al. [31] in 1967 once more stressed the relation between metabolic myopathy and muscle spasm, clinically imitating muscle cramp. Myopathic muscle contracture resembles rigor mortis [32]. Both affections result from lack of sufficient metabolic energy to effect muscular relaxation. Myopathic muscle contracture is less painful than true muscle cramp. It may last an hour or more, while true muscle cramp is self-limiting within a period of several minutes [26].

Muscle contracture never occurs spontaneously. It is induced by vigorous exercise, ischaemic conditions or hyperthermia. Because of a marked disproportion between the intense muscular shortening and the paucity of accompanying electrical activity, contractures are called EMG silent [30]. Electromyography during true muscle cramp shows high-amplitude, high-frequency discharge of potentials resembling motor unit potentials [40].

In 1951, Shuman [45] suggested that impaired muscular relaxation because of lack of metabolic energy and an insufficient oxidative metabolism in muscle tissue might play an appreciable part in muscle cramp in diabetes mellitus.

In recent years there has been speculation on a possible myogenic origin of dialysis-induced muscle cramp. Chillar and Desforges [4] in 1972 blamed muscle cramp during maintenance haemodialysis and in the immediate post-dialysis period on acute oxygen deficiency in the musculature. They observed a significant rise in arterial pH to alkalotic levels and a significant drop in red-blood-cell 2,3-diphosphoglycerate after dialysis. These findings would prevent compensating mechanisms from lowering the haemoglobin-oxygen affinity (Bohr effect) and in combination with uraemic anaemia lead to acute oxygen deficiency in metabolically active muscle tissue.

In the same year Stewart et al. [47] suggested that the prime factor producing dialysis cramp is plasma volume contraction. They found that 49% of dialyses with low sodium dialysate (132 mmol/l) were accompanied by muscle cramp, compared with only 23% of dialyses with high sodium dialysate (145 mmol/l). During high-strength dialysis episodes of cramp occurred only during periods of significant ultrafiltration or towards the end of a dialysis treatment. An increase in intracorporeal blood volume was in itself sufficient to relieve cramp before there had been any change in plasma sodium concentration or cell water content.

In 1975 Jenkins and Dreher [19] postulated that plasma or muscle cell hypo-osmolality or sodium concentration may be the major factor causing muscle cramp during dialysis, rather than plasma volume contraction alone. They treated dialysis cramp, once it occurred, by administration of 500 ml or more of isotonic saline, several hundred millilitres of 3% saline or a bolus of very hypertonic 17.5% or 23.4% saline solution.

A point emphasized is that changes in the blood pH in these patients should have aggravated muscle cramp, if due to oxygen deficiency. In spite of alkalinization muscle cramp was relieved [1].

In 1981 Neal and coworkers [37] evaluated the efficacy of hypertonic dextrose in the treatment of dialysis-related muscle cramp. Their data suggest that plasma volume contraction is important in the genesis of dialysis-related muscle cramp and that relief is related to expansion of plasma volume secondary to increased plasma osmolality. If cramps were a result of hyponatraemia 50% dextrose in water would not have relieved them as administration of dextrose in water exaggerates hyponatraemia.

Neural Origin of Muscle Cramp

Muscle cramp may be experimentally induced as well as blocked by repetitive electrical stimulation of peripheral nerves [8, 24, 25]. Furthermore, there is a strong clinical association of muscle cramp with lower motor neuron diseases like amyotrophic lateral sclerosis, old poliomyelitis, radiculopathy and neuropathy [27]. They are not associated with upper motor neuron, extrapyramidal or muscle disease. The onset and subsidence of muscle cramp is associated with muscle twitches and fasciculations; these also closely resemble those found in motor neuron disease. These facts support the notion that muscle cramp is neural in origin [7, 29, 30].

Because muscle cramp persists during sleep, general anaesthesia, spinal anaesthesia and distal to blocked or transsected nerves, there is little doubt that it originates in the peripheral nervous system [26].

The first to state clearly this assumption was Wernicke. In 1904 he described the *crampus neurosis*, a rare non-hereditary disease, accompanied by serious extensive muscle cramp, occurring with nearly every forceful, rapid active or passive motion [50]. Painful cramp of the thoracic musculature could for instance arrest the breathing of one of his patients and cause cyanosis. Wernicke postulated that muscle cramp was based on a spinal reflex, effected by irritation on the intramuscular sensory nerve endings. Toxic influences, e.g. alcohol, arsenic poisoning, cholera and diabetes mellitus, could lead to prolonged irritation of anterior horn nerve cells, causing muscle cramp. Because of the accompanying functional changes of nerve cells he preferred the term neurosis to neuritis. True muscle cramp was only infrequently observed in manifest neuritis. Electrophysiological examination of his patients led him to speak of a subneuritic state *(ein subneuritischer Zustand der Nerven)*.

In 1940 Wilder [51] introduced this crampus disease in the American medical literature, but he never found a hearing. On the analogy of his tutor he indicated a very mild polyneuritis (polyneuritis levissima), hyperuricaemia and spondylarthritis as aetiological factors.

In 1910 Bittorf [3] suggested damage to the peripheral motor neuron, especially the motor nerve terminals, as a cause of muscle cramp. He described signs and symptoms of polyneuritis in patients, suffering from muscle cramp.

In 1936 Klimke [21] considered excessive stimulation of the sympathetic nervous system as a prime factor. Sympathetic hyperactivity would indirectly stimulate nerve fibres that innervate cramped musculature. This mechanism could be brought about by exhaustion, infection, intoxication or a mental constitution, predisposing to neurovegetative irritability. Strenuous exercise, e.g. running, swimming or marching, could in his opinion give an accumulation of fatigue products like creatine in muscle. These substances would stimulate the sympathetic nervous system, promoting discharge of spinal reflex arcs and thus muscle contraction. Also infections, e.g. cholera, typhoid, and intoxications, e.g. alcoholism, arsenic poisoning, would through sympathetic hyperactivity cause muscle cramp. According to Klimke people suffering from nervousness, neurasthenia or hysteria exhibit neurovegetative irritability and therefore a special propensity to develop cramp.

Several other theories have been presented on neurogenic origins of muscle cramp, e.g. local athetosis and motor epilepsy, that never gained much support [21].

After the Second World War neurophysiological research flourished, mainly because of great advances made in the field of electronics. In 1946 Kugelberg [22] published his classic electromyographic studies on tetany.

In 1948 Denny-Brown and Foley [7] stressed the close relations between benign fasciculations and muscle cramp. He demonstrated that the onset of such cramp is associated with clinical and electromyographic fasciculations, which erupt into high-frequency bursts of action potentials resembling motor unit potentials, the intensity of the discharge waxing and waning independently in different parts of the muscle. From the nature of the discharge, he thought that the activity probably arose from abnormal excitability and spontaneous propagation of abnormal impulses in the peripheral termination of motor nerve fibres.

In 1957 Norris et al. [40] were impressed by the occurrence of synchronous electromyographic discharges of different motor units during muscle cramp. They studied the ability of spinal reflex activity to initiate and inhibit cramp discharges. Muscle cramps are provoked by forceful contraction of a shortened muscle and can be terminated by passive stretching of the muscle [6]. Active contraction of the antagonist muscles also worked, supposedly by a mechanism of reciprocal reflex inhibition. These observations made him favour an excitation of motor neuron pools in the spinal cord.

Modern Pathophysiological Concepts

Two main themes emerge from the results of recent research. Firstly, there is considerable support for the notion that spinal disinhibition may play a part in muscle cramp. Secondly, hyperexcitability of intramuscular terminal motor axons may contribute to involuntary motor unit activity.

Electromyographic studies by Lanari et al. [25] in 1973 analysed the effect of electrical nerve stimulation upon developing voluntary muscle cramp. Electrical stimulus below the motor threshold was effective in blocking cramp-contractions, suggesting the possibility that afferent activation could be the main factor for cramp release. Activation of type Ib afferent fibres from Golgi tendinous and skin receptors was speculated upon as the more convincing explanation. As the inhibitory effect of Ib fibres is not exerted directly on the spinal cord motor neurons, but rather over a wider group of inhibitory interneurons, this offered an explanation for the inhibition of gastrocnemius muscle cramp by stimulation of metameric nerves, supplying a muscle of the same spinal cord level. Finally, the fact that muscle cramp can be elicited more easily when the tendinous insertion points are close together and the tendon insertions are relaxed supported the postulate of a decrease of afferent inhibitory infor-

mation from Golgi receptors as a mechanism responsible for the production of cramp. Cramps can be overcome by stretching the muscle, thus stretching the Golgi tendon organs and activating type Ib afferent fibres [5]. In the same year Fowler [11] supported this opinion.

Older clinical evidence that segmental muscle cramp is more common after laminectomy for prolapsed intervertebral disc in cases having division of sensory roots at the same segmental level as the disc are also in agreement with this spinal disinhibition theory [5].

In 1970 Stålberg and Trontelj [46] were able to demonstrate axon reflexes in human motor nerve fibres and suggested that this reflex mechanism may be involved in muscle cramp. In the same year Elmqvist [8] convincingly demonstrated the extremely peripheral triggering of muscle cramp. It could be elicited in full strength by intramuscular electrical stimulation, was unaffected after nerve block outside the muscle, and disappeared after curarization.

In 1984 Layzer [29] speculated that muscle cramp, like fasciculations, arises in the intramuscular portion of the motor nerve terminals. These speculations are based upon Denny-Brown's suggestion that muscle cramp originates in the distal portions of motor nerves [7, 26]. In this location the axonal branches, being unmyelinated, have different physiological properties from the extramuscular nerve fibres. Motor nerve terminals are prone to develop repetitive activity following tetanic stimulation or on exposure to certain drugs [39].

The unmyelinated nerve twigs in the intramuscular portion of motor nerve terminals could become hyperexcitable in several ways: diseases of the motor neurons, like amyotrophic lateral sclerosis; alterations of peripheral nerve function, as in radiculopathy and peripheral neuropathy; changes in volume or concentration of the extracellular fluid of muscle, as in dehydration and haemodialysis; and perhaps mechanical distortion of the nerve terminals during muscle shortening [1, 16, 23, 24, 26, 29, 30, 37, 42].

Changes in the extracellular fluid can initiate and terminate muscle cramp. Rapid dehydration caused by diuretic therapy or by profuse perspiration, diarrhoea or vomiting has been observed to lead to frequent cramp [16, 23, 28]. Haemodialysis cramp can be terminated by intravenous bolus injection of hypertonic fluids, suggesting that either hypo-osmolality or extracellular volume contraction is responsible for initiating and maintaining the muscle cramp.

Voluntary muscle activity might promote muscle cramps by releasing into the extracellular space chemical substances that increase nerve excitability [28, 34, 37]. Hence action potentials arising in one or more distal nerve twigs are rapidly conducted throughout the terminal arborizations by axon reflexes, activating whole motor units.

Ephaptic transmission, i.e. a cross-excitation between adjacent neurons, without utilizing specialized anatomic structures, may be involved in these axon reflexes [12].

The manner in which the involuntary cramp contraction spreads over large areas of a muscle in a relatively slow, erratic fashion might be explained by local release of a chemical substance in the muscle, activating adjacent motor nerve terminals or by spreading excitation in spinal cord circuits [30, 40].

This review underlines the fact that we know very little about the pathophysiology of muscle cramp. Nevertheless, our knowledge has grown during the second half of this century, mainly because of rapid advances made in the field of clinical electromyography. Modern techniques like single-fibre EMG and surface EMG will hopefully extend our insights. For the time being muscle cramp remains a painful problem, both for the patients and their doctors.

Acknowledgements. The authors thank Prof. Dr. B. P. M. Schulte for his valuable advice. Financial support was granted by ACF Farma B.V., 3604 BB Maarsen, The Netherlands.

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