Autosomal dominant muscle cramp syndrome in a Japanese family

S Chiba, M Saitoh, Y Hatanaka, M Kashiwagi, T Imai, H Matsumoto, R Minami

Abstract

Objectives—To identify the clinical, electrophysiological, histological, and genetic characteristics of a Japanese family with a muscle cramp syndrome.

Methods—Fourteen patients (eight men, six women) were studied in four generations of a single family. Electrophysiological examinations were performed in four cases and muscle and nerve biopsies were performed on the propositus.

Results—The mode of inheritance seemed to be autosomal dominant. The cramps occurred during both exertion and at rest, and during sleep. Electromyographic examination indicated a neurogenic aetiology. There was a decreased number of large myelinated fibres in the sural nerve, and fibre type grouping in the quadriceps femoris muscle biopsy.

Conclusions—The autosomal dominant muscle cramp syndrome in this family is probably caused by a polyneuropathy.

Keywords: autosomal dominant inheritance, muscle cramp, polyneuropathy

Painful muscle contractions during exercise or cold exposure are common complaints of patients with an inborn enzyme deficiency related to carbohydrate or lipid metabolism. Most of these disorders are either autosomal recessive or sporadic. Autosomal dominant muscle cramp syndromes without metabolic defects have been documented in only a few families. We studied 14 members of a Japanese family who, through four generations, had characteristic muscle cramps.

Figure 1 Pedigrees of the family. Shaded symbols indicate affected members.
was good. Muscle weakness or atrophy could not be detected, but there was a mildly decreased vibration sense in his toes, his knee jerks were reduced, and ankle jerks were absent. Cramps could not be induced in his limbs by ischaemic exercise. The results of laboratory tests, including serum creatine kinase (CK) and a glucose tolerance test, were normal. Limb muscle CT disclosed no abnormality. An electrophysiological examination detected a mild delay in sensory conduction with a decreased amplitude of sensory nerve action potentials in the right median, ulnar, and sural nerves (47.8, 46.4, and 38.2 m/s respectively). A delay in motor conduction (43.2 m/s) and a decreased amplitude of compound muscle action potentials (CMAPs) were found in the right common peroneal nerve. An EMG obtained from the anterior tibial and quadriceps femoris muscles disclosed high amplitude motor unit potentials and impaired interference at maximum voluntary contraction. There was no clinical myotonia. A histological examination including periodic acid Schiff and oil red O stainings of the quadriceps femoris muscle showed a mild fibre type grouping. A sural nerve biopsy disclosed a decreased number of large myelinated fibres (5784/mm²) without onion bulb formation (fig 2). Administration of diazepam and dantrolen sodium did not influence the cramps.

His 23 year old son (III-16) had a history, from his teenage years, of painful cramps in muscles lasting from several seconds to 5 minutes induced by exertion, exposure to cold, and certain postures. His 20 year old daughter (III-17) also had a more than 10 year history of muscle cramps during rest and sleep. Cramps were induced by stretching the affected muscles. Interestingly, the neck and temporal muscle cramps could be induced by yawning from the age of 20 years. The frequency of the cramps was initially two or three times each week, but this decreased when the patient avoided the muscle stretching and certain postures.

CASE 2 (II-2)

This 72 year old women had a 45 year history of muscle cramps, predominantly in the thighs, calves, and toes. The cramps occurred most often when she was aged 20–30 years. The cramps had not been influenced by pregnancy or childbirth. She had a right thalamic haemorrhage at the age of 71. A neurological examination at that time showed left hemiparesis, muscle fasciculation in the calves, and reduced bilateral ankle jerks, but muscle cramps were absent. Laboratory data, including creatine kinase and lactate concentrations, were within normal limits. Sensory conduction...
The clinical features of the other affected members of the family are shown in the table.

**Table**

<table>
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<tr>
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<th>II - 5</th>
<th>II - 6 (case 4)</th>
<th>II - 7 (case 1)</th>
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<tbody>
<tr>
<td>56/Female</td>
<td>53/Female</td>
<td>51/Male</td>
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<tr>
<td>Early 20s</td>
<td>Before 24</td>
<td>25</td>
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<tr>
<td>Late 20s</td>
<td>Late 20s</td>
<td>50</td>
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<tr>
<td>Thighs, calves, hands, and fingers</td>
<td>Thighs, calves, forearms, hands, and fingers</td>
<td>Thighs, trunk, neck, and fingers</td>
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<tr>
<td>Not examined</td>
<td>Not examined</td>
<td>Muscle fasciculation, reduced DTRs</td>
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<td>Self limiting</td>
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<td>Continuous</td>
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<td>Normal</td>
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<tr>
<td>Not examined</td>
<td>Not examined</td>
<td>Fasciculation, high amplitude potentials and impaired interference</td>
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<td>Not examined</td>
<td>Not examined</td>
<td>Mild delay (sensory and motor)</td>
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<td>Vestibular neuritis (at age 45)</td>
<td>Myoma uteri (at age 48)</td>
<td>Rheumatoid arthritis (at age 48)</td>
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<tr>
<td>III - 16</td>
<td>III - 17</td>
<td>IV - 1</td>
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<td>23/Male</td>
<td>20/Female</td>
<td>20/Female</td>
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<td>Continuous</td>
<td>6–8</td>
<td>7–10</td>
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<td>Neck, calves, hands, and fingers</td>
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<td>Continuous</td>
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<td>Normal</td>
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<tr>
<td>None</td>
<td>Colonic diverticula (at age 20)</td>
<td>None</td>
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</table>

Velocity of the sural nerve was normal, but the amplitude of sensory action potentials was low. An EMG obtained from the quadriceps femoris muscle showed fasciculation at rest and high amplitude potentials during maximal muscle contraction.

We examined her 47 year old son (III-3) who had had painful muscle cramps since he was aged 20. The cramps occurred a few times each month for 2–3 minutes. This patient had a 20 year old daughter (IV-1) who had also had painful muscle cramps since the age of 6–7. Limb muscle cramps lasting 2–3 minutes, induced by exertion and exposure to cold, were noted several times each week and she had recently experienced neck muscle cramps. Neurological examination and laboratory and nerve conduction studies, yielded normal results.

**CASE 3 (II-3)**

This 60 year old man had a history of painful cramps in the fingers since his early 20s. When diabetes mellitus was diagnosed at the age of 48, the severity of the cramps increased. The muscle cramps improved, however, when the diabetes was well controlled.

**CASE 4 (II-6)**

This 53 year old woman had a more than 30 year history of muscle cramps in the hands and lower limbs. She developed diabetes at the age of 49 and the muscle cramps subsequently increased in frequency and intensity, and spread to affect the trunk. Her cramps also improved when the diabetes was well controlled. In addition, this patient’s 29 year old son (III-15), one of fraternal twins, had experienced muscle cramps but the problem was absent in his sister.

**Discussion**

The prominent and common symptom in this family was painful cramps of the limb and trunk muscles. These could be induced by repeated movements or by maintaining a specific posture, although cramps also occurred during full relaxation and sleep. The disorder seemed to be an autosomal dominant inheritance.

Painful muscle contractions after exercise are often attributed to disorders of carbohydrate and lipid metabolism. For example, McArdle’s and Tarui’s diseases are characterised by early onset of painful cramps during exercise, failure of lactate to increase during ischaemic exercise, electrical silence on EMG during contracture, and autosomal recessive inheritance. Records by EMG during muscle cramps were unfortunately not obtained in the family reported here, but the biochemical findings and muscle histology of our patients were not compatible with glycogen or lipid storage diseases.

Muscle cramps have been described in Isaacs’ syndrome and other forms of neuro-myotonia. Clinically and electrophysiologically, the findings of the present family differ from neuro-myotonia because of the absence of widespread fasciculation or myokymia, generalised rigidity, excessive sweating, and lack of continuous high frequency asynchronous motor unit activity, and extra discharge at rest on EMG. Painful muscle spasms induced by sudden movements have also been described in the stiff man syndrome. However, these spasms are usually symmetric, typically axial, and are inhibited by sleep.

The clinical features of this family resemble partially those reported by Jusic et al.; Lazzaro et al. and Van den Bergh et al. Except for the sphincter muscle involvement, the distribution of affected muscles in this family is similar to that reported by Ricker and Moxley.

In three of the four cases we examined nerve conduction studies disclosed a mild delay in motor and sensory nerve conduction, with decreased CMAPs. Sensory nerve action potentials indicated a predominantly axonal involvement. In addition, EMG records showed features of denervation. The histological findings of the sural nerve and those of the quadriceps femoris muscle also indicated a neurogenic origin. We have compared the aetiological aspects of the present cases with others previously reported. The common underlying abnormality in this syndrome could be a polyneuropathy.

It was interesting that patients 3 and 4 showed clinical exacerbation of the cramps when they were just diagnosed with diabetes, and that the cramps diminished when the diabetes was well controlled.

We conclude that the muscle cramps in this Japanese family may be due to chronic denervation due to a polyneuropathy with autosomal dominant inheritance. The exact
mechanism of cramps in this family remains unsolved, and further genetic studies are necessary.


**NEUROLOGICAL PICTURE**

Single thalamic-subthalamic artery and bilateral thalamic infarcts

A 68 year old woman developed intermittent somnolence and dysarthria. Four days later she was alert but disoriented and developed stereotypic behaviours such as constantly packing her belongings. Brain MRI showed bilateral symmetric thalamic infarcts. Magnetic resonance angiography and an echocardiogram were normal.

In one third of patients, the thalamic-subthalamic arteries arise from one side or from a common pedicle. In such cases an acute occlusion will lead to bilateral posteromedial thalamic infarcts that can be followed by a thalamic dementia.

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Single thalamic-subthalamic artery and bilateral thalamic infarcts

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Notes