**Cramp-fasciculation syndrome: A treatable hyperexcitable peripheral nerve disorder**

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**Article abstract**—We report nine patients with muscle aching, cramps, stiffness, exercise intolerance, and peripheral nerve hyperexcitability. Neurologic examination showed calf fasciculations in seven, quadriceps myokymia in two, and deltoid myokymia in one patient. Two patients had mild increase in serum creatine kinase. Muscle biopsy showed either no abnormality (three patients) or mild neurogenic changes (four patients). Fasciculations were the only abnormality on routine electrodiagnostic studies. Supramaximal stimulation of the median, ulnar, peroneal, and posterior tibial nerves at frequencies of 0.5, 1, 2, and 5 Hz produced showers of electrical potentials following the M response in at least one nerve. In three patients, the fasciculations and evoked electrical potentials were abolished by regional application of curare but not nerve block. Carbamazepine therapy caused moderate-to-marked reduction of symptoms and nerve hyperexcitability. We designate this hyperexcitable peripheral nerve disorder as the "cramp-fasciculation syndrome."

**Muscle aching, cramps, and exercise intolerance are common complaints from patients presenting to a muscle clinic. Only one-third of these patients are found to have a specific muscle abnormality after exhaustive studies, including serum chemistries, electroneuromyography, and muscle biopsy.**

A treatable hyperexcitable peripheral nerve disorder may present with similar symptoms. To identify patients with myalgia who have peripheral nerve hyperexcitability, we performed an evocative test on 150 consecutive patients and found nine such patients. We report the clinical characteristics, muscle biopsy findings, electrodiagnostic features, and therapeutic response for these nine patients.

**Clinical features.** The clinical characteristics of the nine patients are summarized in the table. Cramps, defined as painful muscle contractions of sudden onset precipitated by movement and relieved by passive muscle stretching, and aching in thigh and calf muscles were reported by each patient. Three patients also had cramps and aching in arm muscles. These symptoms were intensified by walking. Three patients were unable to work or assist in household activities (severe disability), five were unable to work but could assist in household activities (moderate disability), and one continued working at light duties. None had a family member with similar symptoms.

The medical and neurologic examinations showed calf fasciculations in seven, quadriceps myokymia (continuous rippling activity) in two, and deltoid myokymia in one. Muscle atrophy was not present, and individual muscle testing showed full strength. Sensation was intact, and deep tendon reflexes were normal.

**Laboratory examinations, including CBC, biochemical profile, thyroid function tests, and immunoelectrophoresis, were normal. Ischemic lactate tests were normal. CK was modestly elevated (less than twice normal) in two patients. Quadriceps muscle biopsy was performed following femoral nerve block in seven of the nine patients. Routine light microscopy, histochemistry, and electron microscopy were performed. Two biopsies showed type grouping, and two additional biopsies showed angulated fibers. The phosphorylase and adenylyl deaminase stains were normal. No other significant abnormalities were noted.**

**Electrodiagnostic studies.** Nerve conductions and monopolar needle electromyography were performed according to established techniques with a TECA-42 electromyograph. Studies were performed on the most affected arm and leg. The sensory and motor amplitudes, latencies, and conduction velocities were normal. Upon completion of each nerve conduction, the time sweep was set at 100 msec/division (total sweep time of 1 second), and the amplification was set at 100 µV/division. With the patient completely relaxed, spontaneous electrical activity was always noted when recording with surface electrodes from either the abductor hallucis or extensor digitorum brevis muscles. Simultaneous surface and monopolar needle recordings showed this electrical activity to be the spontaneous single discharge of different motor units. Spontaneous electrical activity was infrequently noted during recording with surface electrodes over the abductor pollicis brevis and abductor digiti minimi muscles. Five supramaximal stimuli were then given at frequencies of...
0.5, 1, 2, and 5 Hz to the median and ulnar nerves at the wrist and the peroneal and posterior tibial nerves at the ankle. In each patient, stimulation of at least one nerve produced a shower of electrical potentials, afterdischarges, which occurred immediately following the M response (figure). Afterdischarges occurred most often at the higher rates of stimulation. Repetitive nerve stimulation at proximal sites produced afterdischarges similar to those that occurred following distal nerve stimulation. Simultaneous surface and monopolar needle recordings showed these afterdischarges to be motor unit potentials.

A semiquantitative scoring system was developed to grade the number of electrical potentials occurring with repetitive nerve stimulation at 5 Hz and within 500 msec after the M response of the last stimulus (table). The numbers of afterdischarges recorded from the median, ulnar, peroneal, and posterior tibial nerves for each patient were not similar. The greatest number of electrical potentials was obtained on stimulation of the peroneal and posterior tibial nerves.

Needle examination in the most affected arm and leg showed fasciculations in some muscles in each patient. Fibrillations, positive waves, electrical myokymia, and complex repetitive discharges were not present. The motor unit potential amplitudes, durations, and recruitment patterns were normal.

The effect of limb ischemia on the evoked electrical activity was examined in four patients. A pneumatic cuff was placed on the lower leg and inflated above systolic blood pressure. Repetitive nerve stimulation of the posterior tibial nerve was performed before and every 2 minutes after cuff inflation for 10 minutes. No change in the number of afterdischarges was noted.

Three patients had peroneal nerve block performed by injecting 2% lidocaine at the fibula head. Complete nerve block was documented by monitoring the extensor digitorum brevis electrical response to stimulation above the block. No change in the number of afterdischarges evoked by repetitive stimulation below the block was noted. A regional curare test was then performed in the same leg. The M response and afterdischarges were completely abolished. Recovery from the curare-induced paralysis was associated with return of the M response and afterdischarges.

Repetitive nerve stimulation studies were also performed on 25 normal volunteers, four patients with myotonic dystrophy, three with polymyositis, and four with motor neuron disease. Only an F wave was noted following the M response.

**Follow-up studies.** Each patient was treated for 4 months with increasing amounts of carbamazepine to maximize clinical effect but not to exceed 1,600 mg/d.
Five patients had an excellent response and were able to return to normal activities. One patient had a good response (mild restriction in activities), and three patients had only a fair response (moderate restrictions in activities). Carbamazepine therapy was gradually discontinued after 2 months of maximal improvement without return of symptoms. Repeat electrophysiologically studies in each patient showed a marked reduction in the number of afterdischarges.

**Discussion.** Muscle enzyme defects, inflammatory myopathies, neurogenic disorders, and endocrine disorders may present with muscle aching, cramps, and exercise intolerance. This report identifies another disorder, the cramp-fasciculation syndrome, which presents with these symptoms. We initially used the evocative test to define this clinical syndrome. As we electrophysiologically identified additional patients, the stereotypic clinical presentation became evident. The acute onset of muscle aching, cramps, and exercise intolerance without weakness or muscle atrophy in an otherwise healthy adult is characteristic. The neuromuscular examination is normal except for fasciculations or myokymia. Electroneuromyography shows fasciculations, and muscle biopsy may show neurogenic abnormalities. Treatment with carbamazepine frequently provides good-to-excellent relief of symptoms and permits return to normal activities. A similar clinical syndrome has previously been reported as the “muscular pain-fasculation syndrome” and as a “benign motor neuron disorder.”

In the cramp-fasciculation syndrome, the afterdischarges are abolished by regional curare but persist after nerve block, suggesting an abnormality of excitability in the distal motor axon. A similar abnormality has been proposed in Isaac’s syndrome. However, the clinical features are not similar. Stiffness, continuous muscle contraction, continuous motor unit activity on needle EMG, and dramatic clinical improvement following carbamazepine therapy have been described in Isaac’s syndrome. Our patients did not have continuous muscle contraction, and needle EMG did not show continuous motor unit activity. Nerve stimulation in patients with both Isaac’s and the cramp-fasciculation syndromes produce showers of afterdischarges following the M response. We conclude that Isaac’s and the cramp-fasciculation syndromes are hyperexcitable peripheral nerve disorders and that the difference in clinical symptoms is due to a difference in hyperexcitability. In Isaac’s syndrome, the terminal axon is very excitable and continuously firing. In cramp-fasciculation syndrome, there is mild hyperexcitability with rare firings, which become more frequent following voluntary activity (exercise) or nerve stimulation.

Nerve hyperexcitability has also been reported in an autosomal dominant peripheral nerve disorder, Schwartz-Jampel syndrome, following peripheral nerve injury, and in association with intrathoracic malignancy, gold therapy, and peripheral neuropathy. Additional clinical syndromes with nerve hyperexcitability probably exist, and evocative testing should assist in their detection and treatment with carbamazepine.

**Table. Clinical characteristics and estimates of the number of afterdischarges occurring at 5-Hz stimulation and within 500 msec of the last stimulus**

<table>
<thead>
<tr>
<th>Pt</th>
<th>Age</th>
<th>Sex</th>
<th>Duration</th>
<th>Disability</th>
<th>Afterdischarges</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>67</td>
<td>M</td>
<td>36</td>
<td>Mild</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>23</td>
<td>M</td>
<td>18</td>
<td>Moderate</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>29</td>
<td>F</td>
<td>12</td>
<td>Moderate</td>
<td>+ +</td>
</tr>
<tr>
<td>4</td>
<td>39</td>
<td>F</td>
<td>60</td>
<td>Moderate</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>43</td>
<td>M</td>
<td>24</td>
<td>Moderate</td>
<td>+ + + + + +</td>
</tr>
<tr>
<td>6</td>
<td>42</td>
<td>M</td>
<td>42</td>
<td>Moderate</td>
<td>+ + + +</td>
</tr>
<tr>
<td>7</td>
<td>26</td>
<td>F</td>
<td>1</td>
<td>Severe</td>
<td>0</td>
</tr>
<tr>
<td>8</td>
<td>55</td>
<td>F</td>
<td>1</td>
<td>Severe</td>
<td>0</td>
</tr>
<tr>
<td>9</td>
<td>42</td>
<td>M</td>
<td>6</td>
<td>Severe</td>
<td>0</td>
</tr>
</tbody>
</table>

* Months.
† See text for definition of grade severity.
0 No electrical potentials following M response other than F-wave.
+ 1-3 electrical potentials following M response.
+ + 4-7 electrical potentials following M response.
+++ Electrical potentials following M response are too numerous to count.

References

Both intravenous lidocaine and morphine reduce the pain of postherpetic neuralgia

Michael C. Rowbotham, MD; Lori A. Reisner-Keller, PharmD; and Howard L. Fields, MD, PhD

**Article abstract**—We studied the analgesic efficacy of an intravenous infusion of lidocaine and morphine in 19 adults with well-established postherpetic neuralgia in a three-session, randomized, double-blind, placebo-controlled trial. Compared with saline placebo, both lidocaine and morphine reduced pain intensity. Reductions in pain did not correlate with side effects produced by the infusions. For morphine, there was a significant correlation between reductions in pain intensity and blood level achieved. In the majority of subjects who reported definite pain relief, allodynia also disappeared. The results show that neuropathic pain can respond to opioids and to systemically administered local anesthetic drugs.

Herpes zoster (HZ) is an acute, topically limited recrudescence of varicella-zoster virus that has been latent in sensory ganglia. Although painful, acute HZ is usually transient. However, in many patients the pain persists after healing of the rash. This persistent pain, known as postherpetic neuralgia (PHN), occurs in about 10% of all HZ patients with the elderly at greatly increased risk. For example, more than 50% of those over the age of 60 will suffer from PHN after acute HZ. Although PHN resolves spontaneously within the first year in the great majority of cases, the pain is often relentless and may be of incapacitating severity. In some patients, PHN persists for years or even a lifetime.

As is generally the case for neuropathic pains, the treatment of PHN is presently unsatisfactory. Only tricyclic antidepressants have established efficacy in controlled clinical trials. However, many PHN patients obtain no pain relief with these drugs, and only occasionally is complete pain relief achieved. Furthermore, the cardiac and central nervous system side effects of tricyclic antidepressants greatly limit their use, particularly in the elderly population most often afflicted with PHN.

Despite the prominence and severity of the pain in PHN, there are few controlled trials of other therapeutic agents. One obvious approach is to use opioid analgesics. These drugs are potent and have a broad range of therapeutic efficacy. At the present time, there is serious controversy on the issue of whether opioid analgesics are of benefit in painful conditions, such as PHN, associated...
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