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Fasciculation-cramp syndrome preceding anterior horn cell disease: an intermediate syndrome?

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ABSTRACT

Cramp-fasciculation syndrome (cramp-FS) is an ill-defined condition with uncertain clinical limits. We studied a 55-year-old man with progressively more severe, widespread fasciculations and cramps during a six-year period. Mild progressive lower motor neuron loss, shown by MUNE and multiMUP analysis, developed during the four years after onset, which stabilized during a further 2-year follow-up. Cramp-FS is generally a benign syndrome, probably with several causations. Our patient developed a limited form of anterior horn cell degeneration perhaps representing a syndrome transitional with amyotrophic lateral sclerosis. Cramp-FS merits more detailed study.

INTRODUCTION

The cramp-fasciculation syndrome (cramp-FS), occurring without weakness or atrophy, is generally regarded as a benign, non-progressive disorder.¹ However, the clinical limits of this syndrome are ill-defined. Indeed, fasciculations occur frequently in normal subjects.^{2,3} Cramp-FS probably represents hyperexcitability in lower motor neurons, causing after-discharges and myokymia-like spontaneous activity on EMG.^{4,5,6,7,8,9} Since patients with amyotrophic lateral sclerosis (ALS) often describe fasciculation and cramp before progressive weakness develops,^{10,11} these symptoms not infrequently raise fears of ALS. We report an atypical patient whose clinical and EMG features bridge the benign condition of cramp-FS and ALS, as defined by anterior horn cell disease without upper motor neuron features.

METHODS

We have followed convention in describing fasciculation potentials (FPs) as spontaneous, non-volitional, potentials causing a muscle twitch with an

EMG morphology similar to the motor unit potential, typically with shape variability, in the absence of myokymia and after-discharges.^{2,12} Cramps were defined as painful sudden muscle contractions with electrical activity on EMG, induced by muscle contraction and relieved by muscle stretching. Motor unit number (MUNE) in hand muscles was calculated by the incremental technique, as described elsewhere.¹³ Conventional MultiMUP analysis was used to study motor unit potentials and FPs in concentric needle EMG recordings.

CASE REPORT

A 55-year-old man presented with widespread fasciculations, involving upper and lower limb muscles and chest muscles, but not cranial muscles, and with prominent subjective fatigue. Fasciculations were present at rest, and not apparently triggered by exercise. He was not taking medication. There was no relevant personal or family history. Clinical examination and laboratory work-up were normal. EMG studies (not shown in Table 1) performed shortly after symptom onset (MdeC) showed no abnormality other than FPs of normal morphology in biceps and gastrocnemius muscles bilaterally. In these muscles, and in first dorsal

interosseous (FDI), tibialis anterior and vastus medialis, motor units were stable and of normal morphology without fibrillations or positive sharp waves (fibs-sw). Nerve conduction studies were normal. He was anxious and complained of mild headache; a brain MR scan was normal. A diagnosis of benign fasciculations was made and an anxiolytic was recommended.

Two years later he developed cramps, provoked by mild muscular contraction, affecting trunk, abdominal, neck, and upper and lower limb muscles. Cramps were also present at night. In addition, fasciculations seemed more frequent. He consulted a neurosurgeon who arranged cervical, dorsal and lumbosacral MR imaging, which was unremarkable. Laboratory tests, including ESR, electrolytes, creatinine clearance, serum calcium and phosphorous, magnesium, protein immunoelectrophoresis, and thyroid and parathyroid hormone levels were normal. Anti-ganglioside antibodies were negative. He declined CSF examination. He was referred to us.

He was anxious but unaware of a possible diagnosis of amyotrophic lateral sclerosis (ALS). Fasciculations were noted in arms and legs, mainly in proximal muscles. Voluntary contraction of thigh, calf, forearm,

abdominal and paraspinal muscles induced prominent cramps. Cranial muscles were normal. Strength was normal in all muscle groups and there was no atrophy. Tendon reflexes were normal, plantar responses were flexor and sensory examination was normal. Respiratory function tests were normal. On neurophysiological examination nerve conduction studies and skin sympathetic responses were normal. Repetitive stimulation of the right posterior tibial nerve at 2Hz and 5Hz did not induce sustained after-discharges of the abductor hallucis brevis muscle,⁶ indicating no increased motor nerve excitability. There was no conduction block and F-wave studies were normal. Concentric needle EMG sampling (Table 1; investigation A) revealed FPs in both biceps, tibialis anterior and vastus medialis muscles and in the left FDI, with large polyphasic motor units in left biceps and FDI and both tibialis anterior muscles, confirmed by multiMUP analysis. FPs showed complex morphology and moderate instability but there were no fibs-sw. Quantitative EMG analysis of the FPs revealed large potentials of long duration. There was no other spontaneous motor unit activity.

Over the next 4 years abundant fasciculations and frequent cramps, often elicited by mild muscular effort, with fatigue, continued to be

troublesome. Muscle power and deep tendon reflexes remained normal. Repeated clinical and neurophysiological evaluations were performed at 6 month intervals during this period (Table 1). Overall, the EMG results showed that the lower motor neuron pool, as shown by MUNE studies, decreased between the second and fourth years after presentation, but remained constant during the next two years. Chronic partial denervation developed during this time, although fibs-sw were not detected. A recent gadolinium-enhanced MRI of the brain and spinal cord requested by another neurologist showed no abnormality.

DISCUSSION

The causation of cramp-FS is not understood; it may represent a spectrum of disorders.² Early descriptions illustrate this. For example, Denny-Brown and Foley⁴ described two patients with myokymia and cramps who perspired profusely, and had neuromyotonic discharges on needle EMG. They noticed that the FPs cancelled out a series of recruited motor units indicating a peripheral origin for FPs in the distal axonal arborisation. In addition, mild exercise during circulatory occlusion was effective in precipitating fasciculation and cramps in predisposed subjects. They suggested that myokymia had a proximal origin and that it could be

induced by release from limb ischaemia. Neuromyotonia is characterised by recurrent axonal discharges causing repetitive motor unit potentials in EMG recordings; it has subsequently been recognised as an auto-immune disorder due to antibodies to voltage-gated potassium channels at motor end-plates.⁵

In 1978 Hudson and co-workers¹⁴ described five patients with fasciculations, muscle pain and cramps. Four showed signs of active denervation in lower limb muscles suggesting a diagnosis of peripheral neuropathy, anterior horn cell disease or root lesion. In another report¹⁵ two patients with neuropathy associated with typical features of neuromyotonia were described as “neurogenic benign fasciculations”, a terminology that invited confusion. In 1991 Tahmouh and co-workers⁶ defined cramp-FS as characterized by myalgia, cramps, stiffness, exercise intolerance and increased peripheral nerve excitability. Their nine patients had fasciculations or myokymia, mostly in calf muscles. However, this description most likely represented neuromyotonia, which is associated with stiffness (60%) cramps (12%), weakness (12%) and muscle twitching (4%).¹⁶ Tahmouh et al⁶ did not describe their EMG findings in

detail, but repetitive nerve stimulation at 5 Hz in lower limb nerves induced after-discharges following the M-waves. After-discharges are often noted during nerve conduction studies of patients with peripheral neuropathies, as described by Warmolts and Mendell in 1980,⁷ either immediately following M-waves (peripheral hyperactivity) or after the F-wave (lower motor neuron hyperexcitability).⁸ Baldissera and co-authors¹⁷ presented evidence that myokymia and cramps may occur as manifestations of lower motor neuron bistability, an anomalous condition in which the motor axonal cell membrane has two equilibrium levels, a lower level near the resting membrane potential and a higher one above the threshold for generation of self-sustained rhythmic firing.

Fasciculation potentials were defined by Buchthal¹² as brief, small muscle twitches, representing motor units or parts of motor units. A FP is a spontaneous action potential similar in size and duration to a motor unit potential. In ALS or other neurogenic disorders, FPs show differing morphology in consecutive twitches, and may be more or less complex. In normal human subjects, they can be induced by cholinergic drugs, and they are abolished by curare in doses insufficient to block neuromuscular

transmission, suggesting an effect on motor nerve terminals. Cramps may result from regional spread of successive fasciculations of distal origin; therefore, they also originate in the intramuscular nerve terminals,² as well as proximally from motor nerve cells.¹⁷

Since many patients with ALS report that their first symptom was fasciculation, either focally in a group of muscles or more diffusely, there is often concern at presentation as to whether cramp-FS might represent the onset of ALS. Indeed, we have reported such a case.¹⁰ In ALS, however, other features such as muscle fatigue, weakness, muscle atrophy and upper motor neuron signs, are necessary to make the diagnosis, and in cramp-FS follow-up generally excludes a diagnosis of ALS. Moreover, in ALS, FPs are complex, and polyphasic, with striking variability in shape, due to jitter and blocking within the potential.¹⁸ In cramp-FS, FPs are of simple morphology, without associated reinnervated, neurogenic change.¹

In our patient an EMG soon after the onset of symptoms disclosed no abnormality apart from FPs of benign morphology. Two years later

reinvestigation revealed neurogenic changes in limb muscles, raising a suspicion of anterior horn cell disease, although muscle strength was normal, and there was no muscle atrophy or upper motor neuron sign. Six years after onset of cramp-FS, there were EMG features of chronic partial denervation, with increased complexity and moderate instability of motor unit potentials and FPs. After-discharges and myokymia were not found,⁶ and there were no features suggestive of peripheral neuropathy. We concluded that this was an acquired, non-progressive anterior horn cell disorder, that represented a benign variant of the progressive muscular atrophy form of motor neuron disease

The somewhat ill-defined clinical syndrome of cramp-FS without myokymia or after-discharges deserves more attention. It is likely to subsume a number of different disorders ranging from a benign condition(s) to the onset of ALS. Our observation of transition from cramp-FS to anterior horn cell disorder, entering a period of stability after a phase of initial progression, has implications for understanding the onset of ALS, since ALS is often heralded by fasciculations, representing spontaneous motor unit activity. In particular, it contributes to

understanding ALS patients who stabilize after an initial progressive phase.¹⁹ In contrast to our patient in an Australian family with a SOD1-related familial form of ALS, a remarkably abrupt loss of motor units was noted some weeks prior to the onset of detectable muscle weakness.²⁰

The wide range of severity and progression of lower motor unit involvement in the early stages of ALS syndromes is a characteristic but ill-understood feature of the disease. Indeed, understanding the dynamics of ALS onset and of the different syndromes that are currently included in the classification of the common forms of motor neuron diseases is a fundamental question that at present remains unresolved.

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Table 1. Neurophysiological studies:

There was a reduction in motor unit number between the 2-year and the 4-y studies, and MUP amplitude and duration increased. In the last 2y period there was no further progression. Only 2y interval data is shown.

	A; 2y after onset					B; 4y after onset					C; 6y after onset				
Muscle	Fibs/ sw	FPs	MUPA mpl	MUPD ur	MUP% phases	Fibs/ sw	FPs	MUPA mpl	MUPD ur	MUP% phases	Fibs/ sw	FPs	MUP Ampl	MUP Dur	MUP% phases
R Biceps	0	+	0.32	10.9	0	0	+	0.80	13.7	10	0	+	0.84	14.0	15
L Biceps	0	+	0.60	14.8	30	0	+	0.87	12.6	25	0	+	0.91	11.7	15
R Deltoid	0	0	N	N	N	0	+	↑	↑	↑	0	+	↑	↑	↑
L Deltoid	0	0	N	N	N	0	+	↑	↑	↑	0	+	↑	↑	↑
R FDI	0	0	N	N	N	0	+	↑	↑	↑	0	+	↑	↑	↑
LFDI	0	+	↑	↑	N	0	+	↑	↑	↑	0	+	↑	↑	↑
R Tib anterior	0	+	0.87	12.2	15	0	+	1.15	15.0	20	0	+	1.21	15.2	10
L Tib anterior	0	+	+	↑	↑	0	+	↑	↑	↑	0	+	↑	↑	↑
R V medialis	0	+	N	N	N	0	+	↑	↑	↑	0	+	↑	↑	↑
L V medialis	0	+	N	N	N	0	+	↑	↑	↑	0	+	↑	↑	↑
R SCM	0	0	N	N	N	0	0	N	N	N	0	0	N	N	N
R Paraspinal T5	ND	ND	ND	ND	ND	0	+	↑	↑	N	0	+	0.99	13.8	20
MUNE studies															
R ADM	143					88					79				
L ADM	114					72					65				

All investigations, including the first EMG (see text), were done by the same neurophysiologist (MdeC).

R-right; L-left; FDI-1st dorsal interosseous; SCM-sternocleidomastoid; MUNE-motor unit number estimation (incremental technique, using the proprietary software of the Allpine-Keypoint device): ADM-abductor digiti minimi; Fibs/sw-fibrillations and sharp-waves; FPs-fasciculation potentials; Ampl-mean amplitude; Dur-mean duration. ND- not done.

Normal values for MUP analysis: Biceps (mean ampl 0.3-0.66mV; duration-9.4-13.5ms; % polyphasic <35%); T anterior (mean ampl 0.32-0.80mV; duration 10.9-14.0 ms; % polyphasic <40%); paraspinal T5 (mean ampl 0.34-0.90mV; duration-9.6-13.0 ms; % polyphasic <40%). MUNE (ADM), normal >90.