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ORIGINAL COMMUNICATION

Fasciculations and cramps: how benign? Report of four cases progressing to ALS

Varun Singh · John Gibson · Brendan McLean · Mike Boggild · Nicholas Silver · Richard White

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Abstract Clinical diagnosis of amyotrophic lateral sclerosis (ALS) in patients presenting with cramps and fasciculations may not be evident at the first consultation. Sequential reviews, clinical and neurophysiological, form an important part of clinical practice in such cases. Recent attempts to delineate a more benign group with cramps and fasciculations have lacked information on the long term profile, both clinical and neurophysiological. Four patients who were initially diagnosed as suffering from benign cramps and fasciculations, but who subsequently progressed to ALS, are described. We propose that a diagnosis of benign cramps and fasciculations should not be considered secure without a minimum follow up of 4–5 years.

Keywords ALS · Fasciculation · Cramps · Myokymia · Cramp-fasciculation syndrome

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V. Singh (✉) · M. Boggild · N. Silver · R. White
Department of Neurology,
The Walton Centre for Neurology
and Neurosurgery, Lower Lane,
Liverpool L9 7AJ, UK
e-mail: varun.singh@thewaltoncentre.nhs.uk

J. Gibson
Nuffield Hospital, Plymouth,
Devon PL6 8BG, UK

B. McLean
Department of Neurology,
The Royal Cornwall Hospitals NHS Trust,
Treliske, Truro, Cornwall TR1 3LJ, UK

Introduction

The association of fasciculations with cramps is considered an integral part of the clinical presentation of amyotrophic lateral sclerosis (ALS). The disclosure of the diagnosis in those presenting with fasciculations, in view of the invariable fatal outcome of ALS, can only be made after all doubts and uncertainties about the diagnosis have been eliminated. The dilemma facing a clinician whether to make the patient aware of the possibility of the diagnosis is compounded by the observation that cramps and fasciculations are also seen in normal healthy individuals [1–3]. Questionnaire surveys have established that random muscle twitches [4] and a combination of random twitches and cramps [5] are experienced by healthy subjects. Unfortunately, the long term outcome of fasciculations and cramps either in isolation or combination has never been fully defined in terms of the clinical profile of those who progress to ALS as opposed to those who do not.

The only study addressing this issue [6] involved a telephone survey of subjects identified retrospectively as suffering from fasciculations. One hundred and twenty-one patients were interviewed. The longest duration recorded was 32 years, but whether those with the longest history were one of the 39 cases in whom no fasciculations were recorded on electromyography was not stated. Random muscle twitches in healthy individuals have also been recorded electrophysiologically. Mitsikostas et al. [7] and Van der Heijden et al. [8] were able to demonstrate that discharges can be recorded from the distal hand, foot and leg muscles in healthy volunteers.

A number of clinical reports have proposed a 'benign' status for a combination of cramps and fasciculations because it did not progress to ALS [2, 4–6]. Two eponyms have been applied, 'muscle pain and fasciculation

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syndrome' [9] or 'cramp-fasciculation syndrome' [11–14]. Two studies [12, 13] based the identification of a 'benign syndrome of cramp-fasciculations' on the strength of a single neurophysiological technique. Three further reports describing single cases have recommended caution in making a diagnosis of benign fasciculations and cramp, as all three cases reported progressed to ALS after 3 years [15, 16] and 12 months [17]. We present four further cases to emphasize that caution is needed in diagnosing cramps and fasciculations as a benign disorder on the basis of a single clinical and neurophysiological consultation. All four male patients had been diagnosed initially as suffering from benign fasciculations and cramps and are part of a larger cohort of patients with cramps and fasciculations who have been seen or are being followed up at the Walton Centre, Liverpool, UK.

Case histories

All neurophysiological evaluations were carried out by experienced neurophysiologists. Nerve conduction studies were studied in at least two limbs and electromyography consisted of sampling of muscles in two or three limbs. Axial muscles such as genioglossus, sternomastoid, thoracic paraspinals and rectus abdominis were examined as appropriate. A 500 Hz high-pass filter, as recommended by the new Awaji criteria, was not applied in these studies. Table 1 lists the muscles examined on the first neurophysiology assessment in the four patients.

Benign status on a neurophysiological basis was dictated by absence of both active denervation such as fibrillation potentials and positive sharp waves, as well as absence of changes of chronic partial denervation such as polyphasic configuration of MUPs. Subtle and occasional variations when noted were not considered sufficient to raise concerns. For instance, in case-3 an occasional FP with polyphasic configuration was recorded from the right biceps and some MUPs in the right first dorsal interosseus muscle were large and polyphasic. Therefore, MUP configuration in all instances was normal.

All patients also underwent screening for any underlying systemic disorders by blood tests as well as appropriate MR imaging. Figure 1 provides a graphical illustration of the evolution of fasciculations and cramps in the four patients described.

Case-1

A 37-year-old man first consulted a physician privately in 1999 for fatigue and disturbed sleep. The patient had remained under regular review of the same physician, who was unable to find any abnormality on examination in 2002 when the patient reported that his legs felt rubbery. In February 2004 he was referred by the general practitioner to a neurologist for intermittent sensory symptoms and odd muscle twitching and cramps in different locations including the face. Neurological examination failed to reveal any abnormality, and in view of the long history (5 years) of non specific symptoms, investigations such as electrophysiology were not considered indicated. He was referred for a further neurology opinion 2 years later. When seen in June 2006 he reported increasing random twitching and cramps. Examination showed widespread fasciculations in upper and lower limbs but normal muscle bulk, tone, power and reflexes. A diagnosis of 'cramp-fasciculation syndrome' was made, and carbamazepine prescribed. Neurophysiological studies carried out at that time showed reduced amplitude of the right median motor action potential (CMAP).

In the ensuing 4 months the patient progressively developed wasting and weakness of the proximal right scapular and shoulder muscles. Repeat neurophysiological study in October 2006, apart from showing widespread changes of active and chronic partial denervation (including the paraspinal muscles) also revealed conduction blocks. A low CMAP had already been noted in June 2006 in the right median nerve when clinically the muscles in the right hand were normal. Although, by October signs of early wasting were evident in the right hand muscles, muscles of the left hand were normal in bulk and power. As the CMAP amplitude in the right median nerve was noted to be low (1.2 mV) conduction block was not tested. Conduction blocks were documented in the following nerves:

1. Right ulnar nerve below elbow: [CMAP, Wrist 5.2 mV; below elbow 2.3 mV—drop of 56%. Proximal CMAP in upper arm 2.0 mV (change of −6%, CMAP in axilla at 2.8 thought to be artefactual due to volume conduction)].
2. Left median nerve at cubital fossa: [CMAP, wrist 2.2 mV; cubital fossa 1.2 mV—drop of 45%. CMAP in Axilla 1.3 mV and Erb's point 1.4 mV (change of +8 and 16%)].
3. Left ulnar nerve at Erb's point: [CMAPs, wrist 3.3 mV; below elbow 3.2 mV; above elbow 3 mV (change of −2 and −9%, respectively) with a drop to 0.3 at Erb's point of 90%].

In view of the atypical presentation as well as documented conduction blocks multifocal motor neuropathy (MMN) was considered a possibility. This possibility was subsequently abandoned despite the conduction blocks as no clinical improvement occurred after repeated infusions of intravenous immunoglobulin. His condition continued to progress until his death in March 2007. Death was caused by respiratory failure.

Table 1 All fasciculations had simple configuration with the exception of those marked * where some FPs had a polyphasic configuration

Muscle	Case-1		Case-2		Case-3		Case-4	
	FP	Denervation	FP	Denervation	FP	Denervation	FP	Denervation
Genioglossus			0	No				
Sternomastoid-R			0	No	++*	No†		
Sternomastoid-L					++*	No†		
Deltoid-R	++	No						
Deltoid-L								
Biceps-R	++	No	0	No	++*	No	0	No
Biceps-L								
Triceps-R	++	No						
Triceps-L								
EDC-R			+	No			0	No
EDC-L			+	No				
APB-R	0	No						
FDIO-R	0	No	+	No	0	No	0	No
FDIO-L			+	No				
Rectus abdominis			0	No				
Vastus-R	++	No	++	No	++	No	+	No
Vastus-L								
Tib ant-R	0	No	+++**	No	0	No	+	No
Tib ant-L								
Gastrocnemius-R	+	No	+++**	No	++	No	+	No
Gastrocnemius-L								
EHL-R					0	No		
EHL-L								

No†denotes a small degree of motor unit instability. High firing rate of FPs with doublets and triplets in case-2 is indicated by +++**

EDC extensor digitorum communis, *FDIO* first dorsal interosseus, *Tib* ant-tibialis anterior, *EHL* extensor hallucis longus

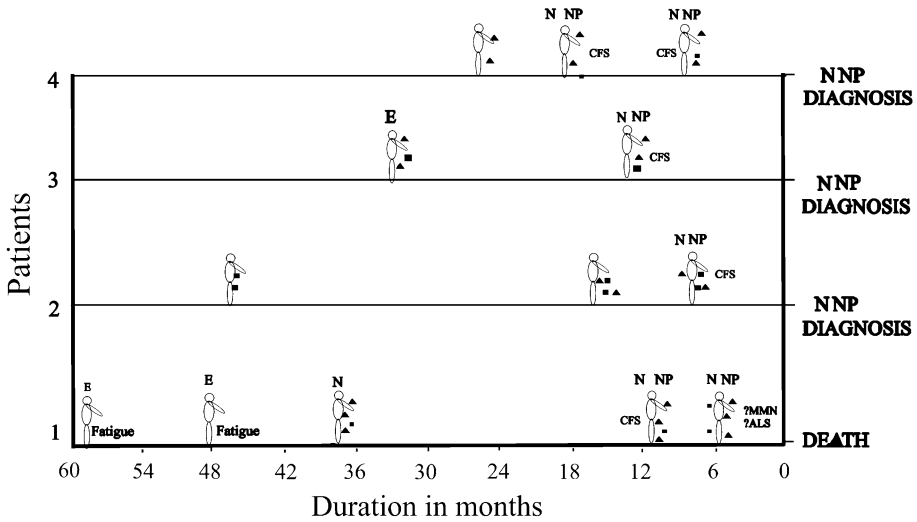

Fig. 1 Schematic representation of the evolution and progression of cramps and fasciculations. The *end point* in the graph is reached when the diagnosis of ALS is confirmed. This was achieved in all four cases by EMG, *triangle* fasciculation, *square* cramp, *E* examined by a non-neurologist, *N* examined by a neurologist, *NP* neurophysiology examination, *MMN* multifocal motor neuropathy, *CFS* cramp-fasciculation syndrome

Autopsy revealed severe atrophy of anterior horn cells and anterior roots through out the spinal cord. Although assessment of ubiquitin inclusions in the anterior horn cells could not be made as a result of damage to the cord during removal before being sent to the neuropathologist, ubiquitin inclusions were seen in the hypoglossal nuclei. Changes involving the pyramidal tracts in the medulla were also recorded.

Case-2

A 55-year-old man presented with 3- to 3½-year history of cramps in the lower abdominal muscles, calves and occasionally in the hamstrings. Bending, which his work as a blacksmith required, aggravated the abdominal cramps which were short lived (1–2 min) and were relieved by stretching. For a period of 6–8 months before being first seen in July 2008, he had become aware of muscle twitching in the lower abdomen, arms and legs. The twitches occurred randomly but daily and were often quite frequent. He had tried quinine and clonazepam without benefit. On neurological examination, apart from the fasciculations in the lower abdomen and thighs, no abnormality was evident (no wasting, weakness, or evidence of upper motor neurone involvement). A provisional diagnosis of 'cramp-fasciculation syndrome' was made.

When re-assessed in February 2009, almost a year from the time of appearance of FPs, there was evidence of wasting and weakness of the small hand muscles. The patient also complained of fatigue and deep tendon reflexes were also found to be brisk. Repeat EMG showed changes consistent with a diagnosis of ALS: widespread active denervation in both upper and lower limbs as well as rectus abdominis. Many of the FPs on this occasion displayed a complex configuration. He has continued to deteriorate, having developed upper motor neurone signs and requires non-invasive ventilation.

Case-3

A 61-year-old man saw a physician for weight loss and night sweats since suffering from shingles in 2003. In May 2005 he reported frequent muscle twitches involving the upper limbs and back for the first time. The general practitioner referring him for a neurological consultation in June 2006 noted fasciculations in the arms, back and calves. The patient was also known to suffer from type II diabetes and hypertension.

When seen by a neurologist in September 2006, widespread vigorous fasciculations were observed but with normal power, tone and reflexes. No wasting was reported or observed.

When reviewed in November 2007, now 2½ years from the first report of involuntary twitches, some loss of muscle bulk in the distal muscles of the upper limbs was evident. Fasciculations were noted in the upper limbs and thighs. The patient also reported frequent cramps in both upper and lower limbs. No upper motor neurone signs were found. Repeat EMG showed many FPs with a polyphasic configuration, with evidence of abnormal active and chronic partial denervation in both upper and lower limbs as well as sternomastoid.

His condition progressively deteriorated with development in upper motor neurone signs and difficult in clearing his chest due to weakness. His breathing was assessed on 4 November 2009 and was not found impaired enough to require assistance. He died on 28 December 2009 after being admitted to a hospice 2 weeks earlier as he was regarded as in a terminal state.

Case-4

A 40-year-old man was referred for neurological consultation with a 6-month history of muscle twitching of both upper limbs and inability to increase the bulk of the upper limb muscles on exercise. On examination, widespread fasciculations were seen in both deltoids, biceps, quadriceps, left calf and abdominal muscles, but there was no wasting, weakness, or abnormality in the deep tendon reflexes. EMG showed an occasional FP in calf and thigh muscles but without signs of active denervation. Motor unit potential configuration was normal as was the configuration of the FPs.

When reviewed 6 months later, he still complained of not being able to gain upper limb muscle bulk, but was still playing football at a competitive level. Twitching of muscles and cramps were reported as before but the latter were not disabling. Examination findings were unchanged and apart from fasciculations revealed no wasting, weakness or upper motor neurone involvement. In view of the slight shift in profile which was still thought to favour a benign process, further review was recommended.

The patient returned earlier than the planned review date because of progression in his condition. When seen almost 2 years from symptom onset, there had been a dramatic deterioration with wasting and weakness in the proximal upper limb muscles, right foot drop and a fibrillating tongue. Well established upper motor neurone signs were also identified. EMG confirmed the clinical diagnosis of ALS by showing widespread changes of active denervation and complex FP configuration. He has continued to deteriorate and recently has started to experience breathing difficulties.

Discussion

By the time a final diagnosis of ALS was made in the four cases described on the strength of electrophysiology, other signs such as wasting and weakness were also becoming noticeable. All patients continued to deteriorate with case-3 dying on 28 December 2009, some 2 years after the diagnosis was made. The total absence of focal signs suggesting an active lower motor neurone process or involvement of the upper motor neurones was the basis for the initial characterization of the fasciculations as benign. This

conclusion was further supported by the absence of signs of active denervation on electromyography as the FPs had a simple, normal motor unit like configuration. In addition, no features of chronic partial denervation or MUP abnormality was evident until the time when the final diagnosis was made. Upper motor neurone signs were eventually noted in all patients with the exception of case-1 who, until his death, had a dominant lower motor neurone syndrome.

The duration from symptom onset to the point where a benign diagnostic label could no longer be applied ranged from 3–5 years. Our experience reinforces the concerns raised by the three earlier single case reports [15–17] that the application of a benign label to fasciculations with or without cramps must be made with caution. The possibility of MMN was raised in case-1 but abandoned in view of rapid progression as well no response to intravenous immunoglobulin infusions. The minimal initial changes in the a few muscles in case-3, once again, were not considered supportive of a diagnosis of ALS because of the absence of active denervation. High frequency of FPs in case-2 along with 'doublets and triplets' in the leg muscles was thought to be more in keeping with 'peripheral nerve hyperexcitability' and the syndrome of neuromyotonia. The fact that all four patients later developed ALS after having initially been thought to have a benign disorder on the strength of the absence of acute or chronic partial denervation re-enforces the new Awaji criteria [18]. Our experience also highlights the fact that a distinction between benign versus malignant fasciculations can not be used to predict whether progression to ALS will occur or not. We note the fact that the recently recommended high-pass filter setting of 500 Hz was not used in the assessment of the patients described.

The clinical and electromyographic components of the syndrome called 'cramp-fasciculation syndrome' have remained undefined. The literature on the subject remains sparse and extremely limited and is listed in Table 2. It will be noted that with the exception of the most recent report of a patient with generalized fasciculations and cramps by de Carvalho and Swash [14], all previous reports had consisted of cramps and fasciculations confined to the lower limbs, in particular the leg muscles, the third case described by Fettel et al. [10] being the only exception. This patient developed generalized cramps and fasciculation when recovering from an acute illness which resulted in paralysis of all four limbs. He was profoundly disabled from severe distal wasting and weakness of the limbs. Although diagnosed as myelitis, the clinical features as described could also suggest the more recently recognized 'acute motor axonal neuropathy'. Their remaining two cases had symptoms, signs and EMG abnormality confined to the calves. Both of these patients had suffered from polio when young. Vos and Wokke also reported three cases. One of these had a family history of cramps and may well have suffered from a familial cramp disorder. Another patient suffered from cramps and muscle twitching only when experiencing bouts of upper respiratory infection. Then, four of the five cases reported by Hudson et al. [9] had been found to have neurogenic changes in the distal lower limb muscles suggesting axonal neuropathy as the underlying problem. The report by Harrison and Benatar [13] that a third of their patients had an underlying problem including radiculopathy, neuropathy and ALS indicates that the combination of cramps and fasciculations can result from diverse pathophysiological mechanisms. The case published by de Carvalho and Swash [14] is novel in

Table 2 Cited references for each report are given in brackets

Reference	Year	No	Distribution			Denervation	FUP
			Cramps/pain	FP/observed	FP/EMG		
Clinical case series published							
Denny-Brown [2]	1948	2	Calves	Myokymia-calf	1-Gastrocnemius	No	6 months
Hudson et al. [9]	1978	5	Widespread	Calves	2-leg	4-calves	No data
Fettel et al. [10]	1982	3	Calves-2	Calves-2	Leg-2	2-calves	6 years
			Generalized-1	Generalized-1	Generalized-1	1-Generalized	
Vos-Wokke [11]	1996	3	Lower limbs	Lower limbs	Leg	No	6 years
de Carvalho and Swash [14]	2010	1	Generalized	Generalized	Generalized*	**	6 years
Cases identified by repetitive nerve stimulation							
Tahmoush et al. [12]	1991	9 (150)	Calves/thigh-9	Calves-7	FPs in most affected muscles	No	6 months
			Upper limb-3	Thigh-myokymia-1			
				Shoulder-myokymia-1			
Harrison and Benatar [13]	2007	36 (108)	Not stated	Not stated	Not stated	No details	Not stated

The numbers in bracket are the total number of patients subjected to repetitive nerve stimulation

FP fasciculation potentials, *EMG* electromyography

the sense that a similar clinical picture of progression in the EMG profile with stabilization after 4 years has not been reported before. This patient may have seemed to be heading towards developing ALS but then the progress appears to have arrested spontaneously.

The two studies claiming to be able to identify the syndrome on the strength of 'repetitive nerve stimulation' deserve mention. They differed in their methodology and patient selection as well as the ideal frequency for this stimulation. While Tahmoush et al. [12] selected patients retrospectively with cramps conforming to the definition, Harrison and Benatar [13] admit that in their retrospective selection the characterization of cramps may not have been adequate. Also, while Tahmoush et al. found fasciculations on EMG in the most severely affected muscles, for Harrison and Benatar only a report by the patient was sufficient for inclusion.

Based on the current published evidence the spectrum of co-existence of cramps and fasciculations extends from normal healthy population at one end and fatal ALS at the other. Thus, there are many unresolved issues such as whether the cases who report fasciculations and cramps but have no clinical or EMG corroboration should be included in this syndrome.

In summary, on the strength of currently available evidence the clinical profile of a benign condition comprising cramps and fasciculations cannot be reliably defined. Our experience of four cases prompts us to recommend that without a structured follow up over a minimum of 4–5 years, no decision about the benign nature of fasciculations or cramps should be made.

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