SHORT REPORT

The onset of amyotrophic lateral sclerosis

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Two patients in whom both the neurological examination and electromyography (EMG) were normal prior to the onset of amyotrophic lateral sclerosis (ALS) are reported. In each patient, the onset of ALS some 18 months later was clearly defined clinically and confirmed by subsequent EMG studies. These unique observations show that ALS commences at a defined time, and that there is early generalisation with an initial phase of rapid progression.

The onset of sporadic amyotrophic lateral sclerosis (ALS) is usually uncertain, although patients often believe that they can define it. There are very few clinical observations relevant to this issue, which is important in understanding the dynamics of progression in the disease.^{1,2} Here we describe two patients who were observed clinically and by electromyography (EMG) before and shortly after the onset and then during the course of the disease. All EMG studies were performed by the same neurophysiologist (MC). Our observations show that sporadic ALS, like familial ALS,³ seems to have a relatively abrupt onset.

CASE REPORTS

Patient 1

A 68 year old woman presented to a rehabilitation service with low back pain provoked by gardening. Neurological examination was normal, and a CT scan of the lumbosacral spine was normal. Two months later, as her symptoms had persisted, an EMG investigation was performed, which was normal (table 1), with no radicular signs. Her back pain resolved with active physiotherapy and painkillers. Eighteen months later she returned with predominantly distal, progressive leg weakness, more marked on the left side, without pain or sensory loss, which had commenced 1 month previously. Magnetic resonance imaging (MRI) of the lumbosacral spine was normal. The creatine kinase level investigated 2 months after onset was 208 U/ml (normal <180), but all other biochemical and haematological tests were normal. Four months after onset of these symptoms (21 months after the first EMG) a second EMG showed neurogenic change in both legs, with fasciculation and fibrillation potentials, and severe loss of motor units, but normal motor and sensory conduction (table 1). There were slight abnormalities in the arms, but no changes in bulbar muscles. She was referred for neurological examination, which revealed distal wasting and weakness in both legs, not in a single root or with peripheral nerve distribution, and without sensory changes. There were fasciculations in all four limbs and in the tongue. Reflexes were increased. The left plantar response was absent and the right was flexor. Cerebrospinal fluid was normal. ALS Functional Rating score (ALS-FRS) was 38/40.⁴ There was rapid progression of her symptoms with symptomatic respiratory involvement 7 months after symptom onset, with weakness in the left hand. The ALS-FRS score was 35/40. Her weakness and

respiratory failure progressed and she died 2 years after symptom onset.

Patient 2

A 54 year old man presented with localised cervical pain, and intermittent tingling in the right hand. Neurological examination and a CT scan of the cervical spine were unremarkable. An EMG study, 1 month after presentation was normal (table 1). These symptoms resolved spontaneously but, 20 months after this EMG, he developed diffuse right lower limb weakness, with generalised fatigue. There were no sensory symptoms. Neuroradiological investigation, including MRI of the whole central nervous system, was normal apart from mild spondylotic changes in the cervical spine, without cord or root compression. The patient gradually developed spasticity, increased tendon reflexes, and weakness in both legs and both arms, more severe on the right side. There was widespread fasciculation in all four limbs, but bulbar muscles were not involved. The muscles on the right side of the body were atrophic. A second EMG, 5 months after the onset of weakness revealed chronic partial denervation, with fasciculation and fibrillation in both upper limbs, and the right leg. Motor unit loss was most severe in the right arm (table 1). Transcranial magnetic stimulation revealed no motor responses in any limb. He consulted another neurosurgeon who, at the patient's request, performed cervical laminectomy 6 months after the onset of weakness. Following this operation there was a phase of very rapid progression so that the patient became wheelchair dependent 3 months later, and 6 months after surgery he experienced respiratory fatigue (forced vital capacity 58% of the predicted value). In this 6 month period, his ALS-FRS declined from 34 to 17. A third EMG study (table 1) disclosed marked neurogenic changes in bulbar and respiratory muscles.

DISCUSSION

These two patients allow definition of the onset of ALS. Both developed El Escorial definite ALS.⁵ Although patients often describe the sudden onset of fasciculation or of the recognition of weakness in a limb, clinicians have tended to regard this not so much as the onset of the disease, but of awareness of the deficit. These two patients developed ALS while under observation for spinal pain of rheumatological origin. They both had normal EMG studies <2 years prior to the onset of their ALS. In addition, patient 1 showed relatively localised EMG changes at the time of the diagnostic EMG, 4 months after the onset of ALS. At this time there were mild abnormalities in the upper limb muscles, but marked partial denervation in both legs; however, the upper limb findings indicate the change from possible to probable ALS (laboratory supported) by the revised El Escorial criteria.⁵ In patient 2, prospective neurophysiological investigation showed progressively more severe changes in the muscles that were most affected initially compared with those not affected at presentation; eventually, loss of motor units were also disclosed in the latter (table 1).

Table 1 Electrophysiological findings (skin temperature >30°C) of both patients before and after onset of ALS

	Patient 1		Patient 2		
	First	Second	First	Second	Third
	17 months before	4 months after	20 months before	5 months after	12 months after
Concentric needle examination					
Right deltoid	–	–	Normal	F	Abn++
Left deltoid	–	–	Normal	F	Abn+
Right biceps	–	Normal	Normal	Abn	Abn++
Left biceps	–	F	Normal	F	Abn+
Right triceps	–	–	Normal	Abn	Abn++
Left triceps	–	–	Normal	F	Abn+
Right flexor carpi radialis	–	–	Normal	Abn+	Abn++
Left flexor carpi radialis	–	–	Normal	Abn	Abn+
Right first dorsal interosseus	–	Abn	Normal	Abn++	0
Left first dorsal interosseus	–	Abn	Normal	Abn+	Abn++
Right vastus medialis	Normal	Abn+	–	Abn	Abn+
Left vastus medialis	Normal	Abn+	–	F	Abn+
Right peroneus longus	Normal	Abn+	–	Abn++	0
Left peroneus longus	Normal	Abn++	–	F	Abn+
Right tibialis anterior	Normal	Abn+	–	Abn++	0
Left tibialis anterior	Normal	Abn++	–	F	Abn+
Right gastrocnemius medialis	Normal	Abn+	–	Abn+	Abn++
Left gastrocnemius medialis	Normal	Abn++	–	F	Abn+
Left masseter	–	Normal	–	Normal	Normal
Right genioglossus	–	Normal	–	Normal	F
Right sternocleidomastoid muscle	–	Normal	–	Normal	F
Right internal intercostals	–	–	–	–	Abn+
Right diaphragm	–	–	–	–	Abn

F, muscle with fasciculations, slight loss of motor units with signs of chronic reinnervation; Abn, abnormal muscle, with fibrillation sharp waves, fasciculations and slight loss of motor units with unstable motor units; Abn+, abnormal muscle, with fibrillation sharp waves, fasciculations and moderate loss of motor units with unstable motor; Abn++, abnormal muscle, with fibrillation sharp waves, fasciculations and severe loss of motor units with unstable motor units; 0, abnormal muscle, with fibrillation sharp waves, no motor units.

EMG studies of the pattern of spread of denervation and reinnervation in ALS from a site of clinical presentation to other limbs have indicated that even when there is apparently focal onset of loss of motor units there are subtle abnormalities in spinal segments far removed from the site of clinical onset.⁶ This supports the usefulness of the electrophysiological studies, as laid out in the revised El Escorial criteria.⁵

Aggarwal and Nicholson³ prospectively followed a group of 17 people with a family history of ALS and known *SOD-1* mutations during a 3 year period, using motor unit number estimation and clinical assessment. Two of these subjects developed ALS during this period. Their patient 1 showed normal conventional EMG and normal motor unit number estimate (MUNE) in several muscles when he entered into the study, but 6 months later, there was a reduction in number of motor units in the extensor digitorum brevis muscle. However, symptomatic weakness developed only a year after study entry, when the EMG was diagnostic of ALS. The observations in this patient with familial SOD-1 related ALS resemble ours in sporadic ALS. There was a rather rapid onset of the loss of motor units that seems to be characteristic of the disease, which has been observed in serial studies using MUNE in patients presenting shortly after symptom onset.³ We have previously reported a patient in whom benign fasciculation and cramp preceded the onset of ALS.² Conventional EMG was normal shortly before weakness developed, but was thereafter abnormal. These observations show that ALS develops rapidly from a finite onset, and should not be regarded as a disorder gradually developing in the context of age related motor unit loss. There is usually an initial phase of rapid motor unit loss but, later in the disease, there is often relatively less rapid progression.^{1,7} It is interesting that in our patient 2 an elective surgical procedure seemed to be associated with a phase of rapid progression, which may also be an important feature.

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