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Progressive sensory nerve dysfunction in amyotrophic lateral sclerosis: a prospective clinical and neurophysiological study

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Abstract. Sensory nerve function was determined in 19 patients with amyotrophic lateral sclerosis (ALS), using a battery of clinical and neurophysiological tests. This assessment was repeated on 12 patients after intervals of 6–18 months. Twelve controls were also studied. In the ALS group, only 2 patients had noticed mild sensory symptoms and none had sensory signs. Between successive studies the vibration thresholds increased, but not to a significant degree. ALS patients showed a significant fall in amplitude of the sensory nerve action potentials in the median, radial, and sural nerves ($P < 0.04$); sensory nerve conduction velocity did not alter. The median nerve somatosensory evoked potential N19 latency showed a highly significant increase ($P < 0.008$). Significant subclinical deterioration in sensory nerve function occurs in ALS, and parallels the progressive motor decline. Neuronal degeneration in ALS is not restricted to motor neurons.

Key words: Amyotrophic lateral sclerosis – Sensation – Neurophysiology – Neurodegenerative disease

Introduction

Neurodegeneration in sporadic amyotrophic lateral sclerosis (ALS) is commonly regarded as being confined to the corticospinal tracts and alpha motor neurons, causing muscular wasting and weakness without sensory disturbance [47]. However, there is pathological evidence that other neurons are also involved, particularly those with large calibre axons such as peripheral sensory and spinocerebellar tract neurons [17, 44, 50]. Recently, several authors have described abnormalities in vibration thresholds [38] and somatosensory evoked potentials (SSEP) in patients with ALS [53]. Despite this, reports of significant sensory abnormalities are relatively rare and sensory findings have been considered inconsistent with the diagnosis of ALS [19].

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Given our ignorance of the aetiology underlying ALS, it is of fundamental importance to establish whether the neuronal degeneration is restricted to motor neurons, or whether these merely take the brunt of a more generalised neurodegenerative disorder [36]. We have conducted a prospective study of patients suffering from ALS, in order to determine whether sensory nerve function declines in parallel with motor loss. Sensation was assessed clinically and neurophysiologically at the time of diagnosis and 6–18 months later when motor function had deteriorated significantly. The aim was to detect subtle change in sensory nerve function, even if these occurred within the normal range.

Patients and methods

Patients with a diagnosis of probable ALS were recruited into the study, which was approved by the local ethics committee. They were examined clinically and neurophysiologically by one of us (R.P.G.) and their diagnosis of ALS confirmed according to the following criteria [51]:

1. Clinical evidence of progressive upper and lower motor neuron degeneration, mixed in at least one limb.

2. Absence of significant sensory symptoms or signs at presentation.

3. Electromyographic evidence of denervation in all four limbs, without peripheral motor neuropathy, multifocal conduction block or significant sensory abnormality.

4. Age at onset greater than 25 years.

5. No relevant family history.

6. No evidence of other underlying illness such as compressive myelopathy, diabetes mellitus, malignancy or paraproteinaemia.

Nineteen patients were entered into the study having obtained full informed consent. The patient details are shown in Table 1 (15 males and 4 females, mean age at onset 58.1 years, range 32–75). It is well recognised that patients become less willing and able to tolerate unpleasant and prolonged neurophysiological studies as their disease progresses [33], which may limit the follow-up rate. To limit this, patients' follow-up studies were often conducted in their own homes. To ensure that a systematic bias was not introduced between the two assessments, a control group was also

Table 1. Patient details: A, arms; L, legs; B, bulbar

Patient	Sex	Age at onset (years)	Symptoms	Study interval (months)	Comment
A	M	57	A + L	18	No deterioration
B	M	54	A		Died 4 months
C	F	57	A + L + B	10	Dysphagia
D	F	62	A + L	12	
E	M	44	B + A + L		Declined
F	M	52	B + L + A	7	
G	M	60	L + A + B	14	
H	M	53	A + L + B	15	Dysphagia
I	M	58	L + A	17	Past polio (Sens symptoms)
J	F	71	L + A		Died 5 months (Sens symptoms)
K	M	70	A + B	8	
L	M	36	A + L	12	
M	M	65	A + L + B	11	
N	M	75	L + A	14	
O	M	63	A + L		Died 9 months
P	F	66	B + L	6	
Q	M	63	A + L	15	No deterioration
R	M	66	A + L		Died 2 months
S	M	32	A + L	6	

followed consisting of 6 patients recruited from general medical outpatients who did not have any evidence of neurological or other significant disease (4 males and 2 females, mean age 60.2 years range 31–81), and 6 patients who were wheelchair-bound by multiple sclerosis (4 males and 2 females, mean age 45.3 years, range 40–51). This latter group were often more disabled than the ALS patients.

Initial assessment

The initial assessment of patients and controls took place in hospital and the neurophysiological examination performed on a Medelec MS-6. Skin temperature was noted and if necessary the limb warmed to 33°C. The following parameters were recorded:

1. Two-point discrimination over the distal aspect of both great toes and index fingers.

2. Vibration threshold using a Somedic Vibrameter over the dorsal aspect of both first metatarsal and both second metacarpal bones.

3. Median sensory nerve action potentials (SNAP), recorded orthodromically from index finger to wrist bilaterally, using standard techniques [14].

4. Radial and sural nerve SNAPs recorded antidromically [13].

5. To confirm the diagnosis and exclude focal compressive lesions or conduction block, motor function in median nerve to abductor pollicis brevis and posterior tibial nerve to abductor hallucis were recorded. Distal motor latencies, proximal and distal amplitudes, motor conduction velocities, and F-wave latencies were noted [13].

6. Median SSEP were recorded bilaterally, using conventional techniques [13], recording the N19 latency from C3 or C4-Fpz according to the 10–20 International System.

Follow-up assessment

The follow-up assessment was performed when significant motor deterioration had occurred after intervals of 6–18 months, in order to allow any changes in sensory function to become apparent, but before severe limb paralysis threatened to cause compressive neuropathy, dysphagia and malnutrition. Patients were not included if there had been no significant decline in motor function after the 18-month study period, as this would be atypical for ALS [51]. Most subjects were examined at home using a protable Medelec MS-91 with the same filter characteristics, electrode types, stimulating and recording positions, and a skin temperature to within 2°C of that used in the initial assesment. Simultaneous comparison of the two Medelec machines on the same subjects showed no significant differences in the results obtained. Both studies were conducted by the same examiner to limit variability [9].

The control patients were also examined using the Medelec MS-6 for their initial in-hospital assessment and, after an interval of between 6 and 9 months, with the Medelec MS-91 at home. To reduce the time taken to perform the examination the neurological controls did not have vibration thresholds or SSEP performed, as abnormalities would be expected from their multiple sclerosis. Statistical analysis of results was performed using the Willcoxon signed rank test.

Results

Progress of study group

Fourteen of the 19 patients recruited completed the study (see Table 1). Four died of their disease before 6 months had elapsed, 2 from pneumonia and respiratory failure (J and R), 1 from a myocardial infarction (B), and 1 from suicide (O). One declined a second examination (E). Two other patients had a benign course with no motor deterioration during their 18-month study period (A and Q). They never displaced consistent or unequivocal signs of pyramidal tract dysfunction and, in view of their lack of progression, were considered more typical of progressive muscular atrophy and excluded from the statistical analysis. The 12 patients with typical, progres-

Table 2. Results: SNAP, sensory nerve action potential; SSEP, somatosensory evoked potential; amp, amplitude; lat, latency. * $P < 0.05$

Modality tested	Controls Median change	Patients Median change	
Vibration (μm)			
Rt foot	−0.1	0.4	($P = 0.079$)
Lt foot	−0.1	0.5	($P = 0.194$)
Rt hand	−0.1	0.1	($P = 0.328$)
Lt hand	+0.1	0.2	($P = 0.465$)
SNAP			
Rt median amp (μV)	1.0	−2.5	($P = 0.023$*)
peak lat (ms)	0.0	−0.1	($P = 0.257$)
Lt median amp (μV)	0.5	−2.0	($P = 0.041$*)
peak lat (ms)	−0.5	0.1	($P = 0.193$)
Rt radial amp (μV)	−0.5	−3.0	($P = 0.009$*)
velocity (m/s)	−1.0	−1.0	($P = 0.319$)
Lt radial amp (μV)	0.0	−2.5	($P = 0.038$*)
velocity (m/s)	0.0	−0.5	($P = 0.143$)
Rt sural amp (μV)	0.5	−1.5	($P = 0.025$*)
velocity (m/s)	−0.5	−0.5	($P = 0.181$)
Lt sural amp (μV)	0.5	−1.0	($P = 0.105$)
velocity (m/s)	0.0	−1.5	($P = 0.252$)
Median SSEP			
Rt N19 lat (ms)	0.15	+1.50	($P = 0.008$*)
Lt N19 lat (ms)	−0.20	+1.00	($P = 0.006$*)

sive ALS were studied for the second time after a mean of 11 months (range 6–17 months). The average age of these 12 patients with typical ALS was 57 years (range 32–75 years).

Sensory symptoms

Only 2 patients reported sensory symptoms, both at the onset of their illness. One noted a sensation like warm water running over the lateral aspect of one thigh that resolved after several months (I). The other experienced transient paraesthesia in both feet (J). Significant sensory signs on routine clinical examination were not found in any patient.

Vibration sensation

The vibration thresholds in all four limbs increased during the study period (Table 2), but none reached statistical significance. There was no change in two-point discrimination measurements.

Sensory action potentials

The amplitude of both median, both radial, and the right sural SNAP fell significantly but the left sural nerve amplitude did not (Fig. 1, Table 2). Sensory nerve conduction velocities became slower overall but not to a significant degree (Table 2). Results outside the normal range were recorded in only 1 patient whose right sural SNAP

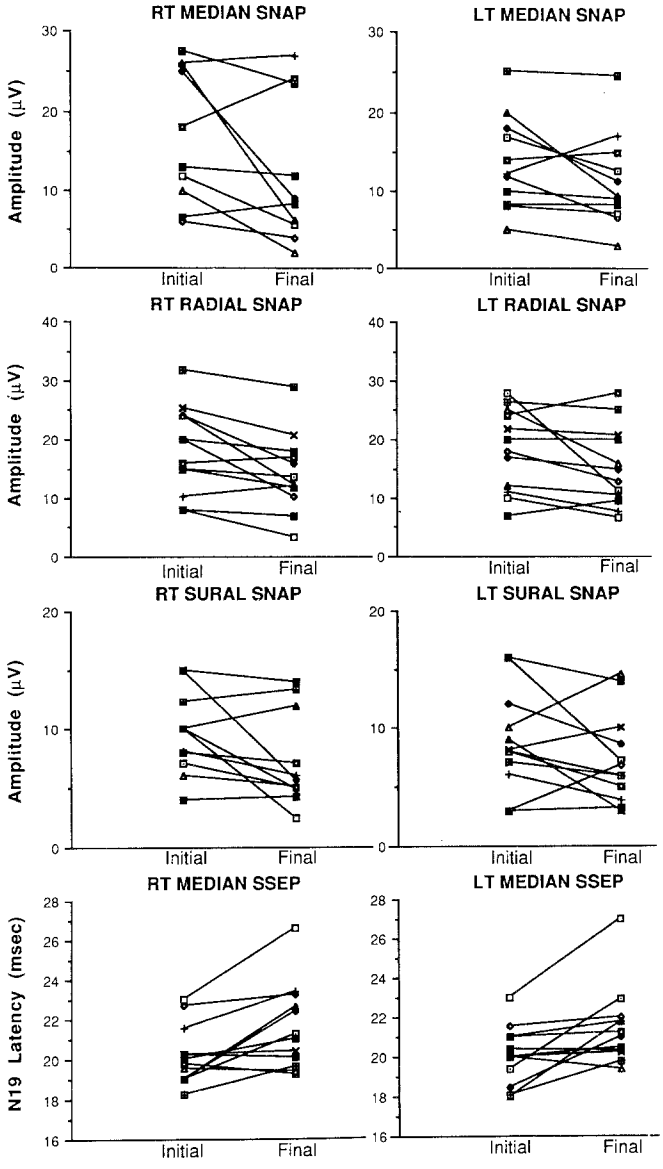

Fig. 1. Comparison of sensory nerve action potentials *(SNAP)* and somatosensory evoked potentials *(SSEP)* at intervals of 6–17 months in the 12 patients with progressive amyotrophic lateral sclerosis

was consistently absent (I). This patient also had neurophysiological evidence of a bilateral carpal tunnel syndrome and so his median SNAP were not included in the statistical analysis.

Somatosensory evoked potentials

Median SSEP N19 latencies increased in 20 of 24 measurements and in 12 this was by more than 1 ms. Only 3 measurements in 2 patients (G and I) were outside the normal range at the initial assessment (normal < 22.5 ms) [13] (Fig. 1, Table 2).

Controls

There was no significant change of any modality measured in the control groups (Table 2).

Discussion

Despite the popular conception that neurodegeneration in ALS is restricted to motor neurons, numerous pathological studies have reported neuronal degeneration outside the motor system [2, 4, 5, 8, 16, 17, 23, 25, 29, 31, 44, 46, 50]. Thus there is a discrepancy between clinical and pathological estimates of the extent of neuronal involvement in ALS. This is the first longitudinal study to address the question of subclinical deterioration in neuronal pathways outside the motor system, and to document significant deterioration in sensory nerve function which parallels clinically obvious motor deterioration. Our study suggests that ALS is a generalised neurodegenerative disorder from the outset, and that sensory neuron involvement is not merely a by-product of terminal factors such as peripheral nerve compression due to immobility, or malnutrition due to disturbed bulbar function.

Seventeen of our 19 patients had typical progressive ALS. Only 2 reported sensory symptoms at some time during their illness; these were mild and transient and not associated with abnormalities on sensory examination. The first clinical surveys on this subject reported sensory symptoms is as many as 50% of ALS patients [21], with 10% having objective sensory changes. Similar findings were also reported by other authors [27, 32, 49], but more recent reviews point to a lower incidence of sensory abnormalities. Gubbay et al. [24] reviewed 318 patients with ALS and found only 3.5% presenting with paraesthesia. Only 2% had decreased vibration sense and less than 1% diminished joint position or light touch. Li and coworkers [34] reported sensory symptoms or signs in 5% of 553 patients presenting with ALS. It is possible that differences in these various studies may be explained in part by failure to differentiate between familial and sporadic ALS cases; a relatively high incidence of sensory involvement is well recognised in familial ALS [28, 34]. Also, improvements in diagnostic concepts and techniques may have led to exclusion of those patients with sensory symptoms caused by other conditions resembling ALS. Four patients with otherwise typical ALS all had objective sensory signs with the subsequent finding of abnormalities in the sensory pathways at postmortem examination [12, 48]. The histology was subsequently reviewed [19] and the pathological diagnosis of ALS confirmed. However, 2 of these patients also had thoracic spinal cord abnormalities consistent with compressive myelopathy, and 1 had an area of spinal cord necrosis suggesting an alternative pathology. Histopathological data from other patients with sensory symptoms has only rarely been reported and was often atypical for ALS [7, 35, 39]. Unlike patients with other muscle wasting diseases, ALS patients do not experience ischaemic parasthesiae [40], which are thought to reflect abnormalities of large sensory fibres [42].

Vibration thresholds in our patients did increase during the study but not to a significant degree. Similar findings have been reported in larger series. Mulder et al. [38] studied 80 ALS patients and found that vibration thresholds were more frequently elevated than in controls. Touch pressure sensation and thermal cooling were not significantly different in this study, though others [30] have reported thermal threshold abnormalities. Tashiro [45] found impaired vibration sense at the ankles assessed by tuning fork in almost 40% of a series of 148 ALS patients; however, only 22 patients were subsequently examined using a Vibrameter. Other workers [14] have merely demonstrated a trend to increased vibration thresholds compared with age-matched controls.

We found significant decreases in several different objective measures of sensory function which were not evident in either group of controls. The SNAP amplitude in the median and radial nerves fell with progression of the disease. This also occurred in the sural nerve, but was significant only on the right. This sensory deterioration usually occurred within the limits of the normal range and conduction velocities were not significantly altered. External compression neuropathy is unlikely to be responsible for the deterioration since we did not study vulnerable nerves, such as the ulnar or common peroneal. Similarly, nutritional factors are unlikely to play a part as dysphagia was only reported by 2 patients (C and H), and neither reported significant decline in food intake or showed evidence of malnutrition. Degeneration of dorsal root ganglion neurons is the most likely explanation for the progressive reduction in SNAP seen in our ALS patients. Loss of such neurons has been demonstrated morphometrically at autospy [31]. Wallerian degeneration could be contributing, since biopsies of sural [4, 16, 26, 46] and superficial peroneal nerves [17, 25] from ALS patients have consistently shown decreased numbers of large myelineated fibres. Near nerve recording of sural nerve sensory action potentials has shown reduction of the minimum conduction velocity consistent with regenerating fibres in the context of progressive axonal degeneration [43].

Further evidence of progressive sensory pathway involvement was provided by serial median SSEP measurements. The N19 latency became more prolonged in most of the ALS patients during the study period. This is in keeping with numerous previous reports of prolonged median SSEP latencies on single measurements [1, 10, 11, 22, 37, 41, 52, 53], although some have not confirmed abnormalities [6, 15]. The N19 latency is more likely to be delayed in patients with longer durations of disease [10]. Longitudinal studies on two individual ALS patients [11, 41] have shown progressive SSEP delays with time. Various SSEP parameters have been recorded and direct comparisons between different studies are often not possible. The commonest abnormality was in the N13–N19 interval, with normal amplitudes and peripheral conduction. This implies delayed conduction in the dorsal columns and lemniscal pathways [10]. It is not possible to differentiate peripheral from central delay in our patients as we restricted our measurements to the N19 latency for brevity and simplicity of testing.

Our findings show that subclinical deterioration of sensory nerve function occurs in parallel with motor neuron degeneration in ALS. This phenomenon is demonstrable in the majority of patients, but measure-

ments of sensory nerve function in ALS only occasionally lie outside the normal range, as has been shown in large reviews [3]. This does not contradict the commonly held view that normal sensory function on routine clinical and neurophysiological assessment is a feature supporting the diagnosis of classical sporadic ALS [18, 20]. Our study suggests that ALS may be a generalised neurodegenerative disorder from the outset and that the disease may be caused by an agent with generalised neurotoxic effects, rather than one with pathogenic effects restricted to motor neurons.

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