Somatosensory evoked potentials in amyotrophic lateral sclerosis

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SUMMARY Forty five patients with amyotrophic lateral sclerosis were investigated, by means of somatosensory evoked potentials, in order to detect the presence of subclinical sensory changes. Cervical SEPs from the median nerve and cortical SEPs from the median and tibial nerve were recorded, showing a delay of N13 and subsequent components; the latency of the first constant cortical potential was also increased in many patients. Only the SEPs from the tibial nerve showed a decrease of amplitude. These results suggest a pathological slowing of conduction along the central sensory pathways in amyotrophic lateral sclerosis.

Amyotrophic lateral sclerosis is generally considered to be a system disease because of selective involvement of upper and lower motor neurons. Sensory disturbances characteristically are absent in typical amyotrophic lateral sclerosis, although cramps and paraesthesias may occur; nevertheless a certain number of detailed pathological studies have claimed to show the presence of changes in sensory nerve myelinated fibres,^{1,2} in spinocerebellar pathways,³ Clarke's nucleus,⁴ posterior columns⁵⁻⁷ and thalamus.⁸ These changes have been reported more frequently in familial than in sporadic amyotrophic lateral sclerosis.⁹ A patient with a chronic pain syndrome associated with amyotrophic lateral sclerosis has recently been described.¹⁰ In a series of investigations about the possible involvement of subsystems other than motor neurons in sporadic amyotrophic lateral sclerosis, we have examined somatosensory evoked potentials (SEPs) in 45 patients in an attempt to detect the presence of subclinical alterations.

Materials and methods

Forty five patients with amyotrophic lateral sclerosis (34 males and 11 females) of mean age = 51.7 years (range

22-67) were investigated. The diagnosis of amyotrophic lateral sclerosis was made by at least two different neurologists on the ground of usual clinical and investigation features, after a follow-up period ranging from six to 14 months. There were no familial cases.

The clinical picture of these patients were divided into: *typical amyotrophic lateral sclerosis* without bulbar signs, *typical amyotrophic lateral sclerosis* with bulbar signs, *bulbar and pseudobulbar amyotrophic lateral sclerosis* and *amyotrophic lateral sclerosis with predominant lower motor neuron involvement* (without pyramidal signs). The patients were further divided into three groups, according to the duration of the disease: I = up to 12 months, II = from 13 to 24 months, III = more than 24 months. The muscular impairment was classified as light, moderate or heavy, according to the clinical evaluation of the functional capacity. The tallness of the patients and the presence or the absence of cervical spondylosis on plain radiographs was also considered. These clinical features are shown in table 1.

The control cases, matched for age, sex and tallness were sampled from normal subjects of the laboratory. The patients, relaxed in an arm-chair, in a silent room, were requested to close their eyes. The stimulating electrodes were placed on the skin overlying the median nerve at the wrist and the tibial posterior nerve at the ankle; both sides were sometimes examined. The stimulus had a duration of 0.1 ms, a frequency of 3 Hz and an intensity of 20% above that required to induce a modest muscular twitch. The recording silver-silver chloride electrodes were placed at C3 or at C4-Fpz (cortical SEPs after stimulation of the median nerve), at Cz-Fpz (cortical SEPs after stimulation of the tibial nerve), according to the 10-20 International System and above 7th cervical spine (C7-Fpz) for cervical SEPs after stimulation of the median nerve. Electrode impedance was low, less than 3 kohm. Signals were amplified and averaged by a Neuroaverager OTE-Biomedica 1239-512 words (bandpass 1-6-1000 Hz, bin-

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Table 1 Clinical data in 45 patients with amyotrophic lateral sclerosis

Clinical forms	Number of cases	Mean age (yr)	Duration of the disease	Number of cases	Mean age (yr)
Typical amyotrophic lateral sclerosis without bulbar signs	16	48.9	Group I (≤ 12 months)	12	49.7
Typical amyotrophic lateral sclerosis with bulbar signs	12	51.5	Group II (12–24 months)	16	49.9
Bulbar involvement alone	2	60.5	Group III (> 24 months)	17	52.1
Lower motor neuron involvement	15	56.8			
Total	45	51.7			

Muscular impairment	Number of cases	Mean duration of disease	Cervical spondylosis	Number of cases	Mean age
Light	14	18.6 months	Present	32	54.5
Moderate	20	23.6 months	Absent	13	44.6
Heavy	9	19.6 months			

width 0.195 ms, averaging of 256–512 responses for the cortical SEPs; bandpass 16–3000 Hz, binwidth 0.039 ms, averaging of 512–1024 responses for the cervical SEPs). The peaks were visually identified; the latencies were measured by a marker on the oscilloscope and checked after transcription by means of an x-y plotter; the amplitudes were measured peak to peak. For the cervical SEPs recorded after stimulation of the median nerve the following parameters have been considered: N9, N11, N13 latencies and N9–N11, N11–N13, N9–N13 intervals. For the cortical SEP recorded after stimulation of the median nerve we have identified and measured the latencies and the amplitudes of the first six peaks from P15 (it was seldom absent due to the frontal reference): N19, P26, N34, P44, N63. For this investigation were considered specifically the N19 latency, the N19/P26 amplitude and the Cervical N13–Cortical N19 interval; this latter parameter has been considered indicative of the Central Conduction Time. For the cortical SEPs recorded after the stimulation of the tibial nerve we have identified and measured the latencies and the amplitudes of the first five peaks: N34, P45, N52, P63, N79; we have considered specifically the N34 and P45 latencies, and the N34/P45 amplitudes. The conduction velocity of the sensory fibres of the median and tibial nerves was determined in a few of patients and it was always normal. The difference have been statistically evaluated by means of Student's *t* test.

Results

Cervical SEPs from the median nerve: (table 2, figs 1–2) in the cervical SEPs (47 recordings) the N13 peak was always present, while N9 and N11 peaks were sometimes unclear or absent. The N9 and N11 latencies were slightly but insignificantly increased, while the mean value of N13 latency was significantly increased ($t = 3.61$; $p < 0.001$); only in two cases out of 47 determinations (4.25%) was the value clearly abnormal ($+ 3$ SD). The N9–N11 interval was in the normal range, the N11–N13 interval was significantly increased ($t = 3.67$; $p < 0.001$); it was abnormal ($+ 3$ SD) in 11 deter-

minations out of 42 (26.2%); the N9–N13 interval was significantly increased ($t = 2.86$; $p < 0.01$) and it was abnormal ($+ 3$ SD) in five determinations out of 40. This latter significant increase is likely to be due to the increase of the N11–N13 interval.

The central conduction time was significantly increased ($t = 2.69$; $p < 0.01$): 11 determinations out of 47 (23.4%) showed values higher than $+ 3$ SD.

Cortical SEPs from the median nerve: (table 2 figs 1–2) the mean value of N19 latency was significantly increased ($t = 2.72$; $p < 0.01$) as compared to controls: the value was abnormal ($+ 2.5$ SD) in six determinations out of 53 (11%). The amplitude measured peak to peak of N19/P26 was $7.2 \mu V \pm 4.1$ (range 2–18 μV) in amyotrophic lateral sclerosis and $7.7 \pm 3.05 \mu V$ (range 1–22 μV) in controls. This difference was not significant.

Cortical SEPs from the tibial nerve: (table 3, fig 3) N34 and P45 latencies were significantly increased ($t = 5.43$ for N34 and $t = 4.18$ for P45; $p < 0.001$): N34 was abnormal ($+ 2.5$ SD) in 19 determinations out of 33 (57.6%), P45 was abnormal ($+ 2.5$ SD) in nine determinations out of 33 (27.3%). The N34/P45 amplitude measured peak to peak was significantly reduced ($t = 4.69$; $p < 0.001$) in amyotrophic lateral sclerosis patients: mean value $1.7 \pm 1.4 \mu V$, range 0.5–7 μV ; controls $3.5 \pm 1.7 \mu V$, range 1.4–8.5 μV . The amplitude was altered (below the minimum value of control) in 19 determinations out of 33 (57%).

Relations with clinical parameters: the mean latency of N19 was 20.0 ms (± 0.8), 20.10 ms (± 1.4), 21.7 ms (± 2.1) respectively in patients with duration of the disease up to 12 months (group I), from 13 to 24 months (group II) and more than 24 months (group III). There was a significant difference ($t = 2.90$; $p < 0.01$) between groups I and III on Student's *t* test; the difference was significant also between groups II and III ($t = 2.95$; $p < 0.01$). The N13–N19 interval

Table 2 SEPs from median nerve

Components	Amyotrophic lateral sclerosis				Controls		
	Number of Determination/cases	Mean value	SD	Range	Mean value	SD	Range
N9 latency (ms)	40/39	9.6	0.9	8.1-11.8	9.2	0.9	7.4-10.9
N11 latency	42/39	11.7	1.0	9.5-14.3	11.3	0.9	9.6-12.5
N13 latency	47/39	14.0†	1.0	11.4-16.7	13.2	0.8	11.6-14.5
N19 latency	53/45	21.0*	2.5	18.7-24.7	19.9	1.2	18.0-22.0
N9-N11 interval (ms)	37/39	2.2	0.4	1.5-3.5	2.1	0.3	1.5-2.5
N11-N13 interval	42/39	2.3†	0.6	1.5-3.5	1.9	0.3	1.4-2.6
N9-N13 interval	40/39	4.4*	0.7	3.3-5.7	4.0	0.3	3.1-4.6
N13-N19 interval	47/39	6.2†	1.2	5.0-10.2	5.6	0.4	5.0-6.1

* $p < 0.01$ † $p < 0.001$

Fig. 1 Cortical (a, c) and cervical (b, d) SEPs from median nerve at wrist in one amyotrophic lateral sclerosis patient (a and b) and in a control case (c and d); central conduction time is markedly increased in the amyotrophic lateral sclerosis patient.

increased with the duration of the disease: 5.7 ± 0.46 ms in group I, 5.78 ± 0.66 ms in group II and 6.93 ± 1.58 ms in group III. There was a significant difference between groups I and III ($t = 2.35$; $p < 0.05$) and between groups II and III ($t = 3.24$; $p < 0.001$) at Student's t test.

We observed that the N9 latency was increased in the group with spondylosis (9.8 ms ± 0.8) as compared to the group without spondylosis (9.1 ms ± 0.9) ($t = 2.45$; $p < 0.02$). The N11 latency was $12 \pm$

Table 3 SEPs from tibial nerve

Components	Amyotrophic lateral sclerosis				Controls		
	Number of Determination/cases	Mean value	SD	Range	Mean value	SD	Range
N34 latency (ms)	33/30	39.6*	5.2	31.1-48.2	34.2	1.4	31.0-36.5
P45 latency	33/30	48.5*	5.9	41.5-70.0	45.5	2.9	37.2-47.6
N34/P45 amplitude (μ V)	33/30	1.7*	1.4	0.5-7.0	3.5	1.7	1.4-8.5

* $p < 0.001$

Fig. 2 Cortical SEPs from median nerve in one amyotrophic lateral sclerosis patient (a) and in a control subject (b): N19 appears delayed (3.1 ms) in amyotrophic lateral sclerosis.

Fig. 3 Cortical SEPs from tibial nerve at ankle in one amyotrophic lateral sclerosis patient (a) and in a control subject (b): N34 appears markedly delayed (16 ms) in amyotrophic lateral sclerosis.

0.9 ms in the group with spondylosis and $11.1 \text{ ms} \pm 0.9$ in the group without spondylosis this difference being significant ($t = 2.90$; $p < 0.01$).

No difference was evident between the different clinical groups. A pattern of increased latencies with increasing severity of the disease was observed, and probably depended on the increased duration of illness. The parameters obtained from the cortical SEPs derived from the tibial nerve were the same irrespective of the duration of the disease, the clinical features or the presence of cervical spondylosis.

Discussion

The measurement of cervical and cortical SEPs allows the recognition of subclinical sensory disturbances and their localisation along the afferent pathways; considerable progress has been made recently in the description and investigation of the potentials' pattern and sources¹¹⁻¹⁶ and their alterations in different neurological diseases.¹⁷⁻¹⁹ In amyotrophic lateral sclerosis somatosensory cortical evoked potentials were investigated by Dustman²⁰ who observed significant reduction of the peaks' amplitudes and a trend toward increased latencies. Visual evoked potentials (VEPs) were found to be normal.²⁰ Somatosensory evoked potentials were also abnormal in 62.5% and 34% of patients with amyotrophic lateral sclerosis at lower and upper limbs respectively according to Matheson²¹ and in one out of three cases according to Anziska.²² A lower percentage of patients (12%) displayed abnormal visual and brain-stem evoked potentials.²¹

Our results confirm that SEPs may be clearly abnormal in certain amyotrophic lateral sclerosis patients: the main abnormality is a significant delay of N13 and subsequent components while the amplitudes are relatively preserved. Only SEPs from the tibial nerve showed a significant decrease of amplitude. Cortical SEPs showed a generally normal waveform but the latency of the first negative (N19) component was clearly increased. So the main pathological alteration was a slowing of conduction along the sensory pathways.

We think that the level of the sensory involvement is most probably localised within the dorsal columns and the lemniscal pathways. The presence of normal amplitude and latency of N9 indicates that a normal afferent volley has been conducted along the brachial plexus after the stimulation, without any delay; abnormalities of N9 were found only in presence of lesions of the peripheral nerves.¹⁹ Moreover the conduction velocity of the sensory fibres was in the normal range in those subjects in whom it was measured.

N11, which is considered to be generated near the spinal cord entry zone,^{13 15 19} also displayed a normal latency. This fact, as well as the N9-N11 interval that was normal, seems to indicate that the roots were well preserved, at least in the subjects without cervical spondylosis; on the contrary, when spondylosis was present, the development of N11 potential was delayed and the N9-N11 interval was increased. Growing evidence supports the notion that the N13 potential is generated rostrally, in the nucleus of the dorsal columns;^{13 14 18} N13 appears constantly affected in patients with lesions of the cervical cord, caused by severe cervical myelopathy due to spondylosis.¹⁹

Hence the increased latency of N13 and consequently the increased N11-N13 and N9-N13 intervals suggest a slowing of conduction in the dorsal columns; on the other hand the increase of the so called central conduction time, that is, the N13-N19 interval, seems to indicate a delayed conduction of afferent potentials also along the lemniscal pathways up the cortex. Moreover these disturbances of the somatosensory system, clearly shown in amyotrophic lateral sclerosis, seem to progress with increasing duration and severity of the disease, as it was also indicated in the work by Dustman.²⁰

The possibility exists that these delayed evoked responses in amyotrophic lateral sclerosis might be dependent on the pathological lesions affecting the afferent pathways, recognised in necropsy studies by Charcot and Marie⁶ in 1885 and Holmes,³ and more recently confirmed.^{4 5 8} Alternatively they might be due to a loss of the pyramidal feedback acting on the somatosensory pathways and specifically on the dorsal horns, as recently suggested²⁰ on the basis of the well known relationships between the afferent and efferent systems.

Interestingly it has been recently shown that choline acetyltransferase activity is severely reduced in the spinal cord of patients with amyotrophic lateral sclerosis not only in the ventral horns, where it is associated with motor neurons, but also in the apical area of the dorsal horns,²³ the site of the spinal interneurons: this finding gives a biochemical substrate to the morphological degeneration of Clarke's nucleus.⁴

The sensory system could therefore be affected by the same abnormality involving the motor neurons, but to a lesser extent and without clinical evidence.¹

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