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## Primary lateral sclerosis

### A heterogeneous disorder composed of different subtypes?

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**Abstract—Objective:** To determine identifiable subgroups of patients with primary lateral sclerosis (PLS) with distinct clinical features as a first step in identifying patients likely to have the same disorder. **Methods:** Twenty-five patients meeting previously proposed diagnostic criteria for PLS were seen for examination, measurement of gait and finger tapping speed, and physiologic tests to assess motor pathways. Motor cortex excitability and central motor conduction time were assessed with transcranial magnetic stimulation. Brainstem motor pathways were assessed by the acoustic startle reflex. MRS was performed in a subgroup of patients to assess metabolites in the motor cortex. **Results:** Fifty-six percent of the patients with PLS had a similar pattern of symptom progression, which the authors termed ascending. In these patients spasticity began in the legs and progressed slowly and steadily. Spasticity in the arms developed 3.6 years after the legs, on average, and speech impairment followed 1.5 years later. Motor evoked potentials were absent. MRS showed a mean reduction of *N*-acetylaspartate/creatinine in the motor cortex. The remaining patients with PLS had heterogeneous patterns of symptom progression and physiology. **Conclusions:** Patients with PLS with an ascending progression of symptoms form a distinct clinical subgroup that may be amenable to investigations of etiology and treatment.

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Primary lateral sclerosis (PLS) was first described as a selective degeneration of the corticospinal tract.<sup>1–7</sup> Clinical diagnostic criteria were later proposed that define PLS as a condition of progressive spasticity after known disorders have been excluded.<sup>6,8</sup> Recent reviews debate whether PLS should be considered as a distinct disorder or a syndrome with multiple etiologies.<sup>8,9</sup> Some view PLS as a variant of ALS,<sup>10–13</sup> further enlarging the clinical scope of PLS. Although an expanded definition of PLS is beneficial for clinical care, research into the causes of PLS would be facilitated by identifying subsets of patients likely to have the same underlying disorder.

Because PLS is a rare condition without an obvi-

ous hereditary basis, we turned to clinical and physiologic features to classify subgroups of patients with PLS. Patients with the clinical diagnosis of PLS were solicited from neurologists throughout the country. Central motor pathways were assessed physiologically using transcranial magnetic stimulation (TMS) of the motor cortex and assessment of the primary startle reflex, which originates in the brainstem and is transmitted by rapidly conducting reticulospinal pathways.<sup>14,15</sup> We anticipated that these physiologic measures might provide a basis for differentiating among clinical subgroups. In one clinical subgroup further evaluation was carried out using MRS to assess neuronal markers in the motor cortex.

**See also page 1252**

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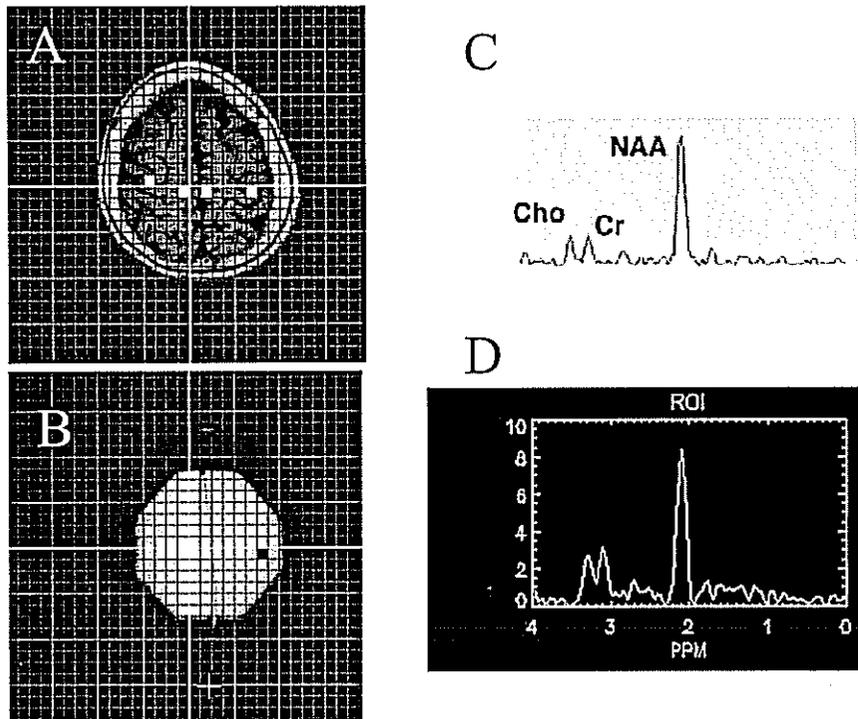


Figure 1. MRI slice with MRS regions and spectra. (A) Regions used for the left and right hand area of the motor cortex ("knob") and left and right leg areas shown in white. (B) The most superior spectroscopy slice, coregistered with the anatomic slice in order to find the region of interest (ROI). The ROI highlighted in black puts out the spectroscopy on panel D. (C) Schematic drawing of a normal spectrum with a long echo time as we used in our experiment. The MRS program gives an arbitrary number representing the area under the curve for each spectrum.

**Methods. Subjects.** All patients gave written informed consent for a protocol approved by the Institutional Review Board. Medical records of 42 patient volunteers were screened and 30 patients were examined in person. Inclusion and exclusionary criteria (appendix) were used to select 25 patients for further physiologic and neuroimaging studies. Twenty-two healthy, age-matched controls ( $53.5 \pm 12$  years) without neurologic symptoms participated in physiologic studies, motor coordination tests, and MRS studies.

**History and physical examination.** Patients were carefully questioned about the dates of onset and progression of their symptoms, including landmark dates, such as the year when assistive devices were first used for walking or when they became unable to work. Records from referring neurologists were also reviewed for documentation of symptom onset. The presence of upper motor neuron signs in individual limbs and bulbar muscles was evaluated by neurologic examination. Reflexes were graded on a scale of 0 to 4, and presence of Babinski and Hoffman signs noted. Muscle strength was quantified using the Appel motor scale (full strength in all limbs = 140 points).<sup>16</sup> A Rydel-Seiffer tuning fork was used to assess vibration perception. A 15-second computerized tapping test was used to quantify finger movement and gait speed was quantified by determining the time to walk 20 feet. Tapping and gait tasks were performed three times, and the average taken as the final score.

Twenty-three patients have been followed for longer than a year. Fifteen returned for re-examination and eight mailed in a questionnaire regarding symptom progression.

**Transcranial magnetic stimulation.** The motor cortex was stimulated using a Magstim 200 transcranial magnetic stimulator (Magstim, UK) with the 90-mm round coil. The optimal position for obtaining a motor-evoked potential (MEP) from thenar muscles was determined and the threshold was defined as the lowest stimulus level evoking an MEP of at least 50  $\mu$ V in three of five trials, with stimulus increments of 2%.<sup>17</sup> When an MEP was obtained, central motor conduction time (CMCT) to the cervical cord was measured using intensities 130% of threshold during moderate contraction and using F-waves to calculate the peripheral conduction time.<sup>18</sup>

**Startle testing.** The acoustic startle response (ASR) was measured using methods previously described.<sup>19</sup> Briefly, patients reclined in a chair in a quiet, slightly darkened room. Hearing was tested to ensure that the stimulus would be at least 60 dB above hearing threshold. A 90-dB, 30-msec tone of 1,000 Hz was delivered through headphones at unpredictable intervals from 3 to 5 minutes. Tones were repeated until two successive tones failed to

evoke any muscle response or until eight tones were delivered, at which point testing was stopped. EMG activity was recorded from the orbicularis oculi, masseter, sternocleidomastoid, biceps brachii, flexor carpi radialis, tibialis anterior, and soleus muscles on one side. EMG was collected using a Viking IV electromyograph (Nicolet, Madison, WI). A response was deemed present when the peak-peak EMG amplitude was more than twice baseline by visual inspection. For each trial, the latency of EMG activity was measured visually by cursor placement. To provide a rough index of the exaggeration of the ASR the number of muscles activated over the eight trials was tallied.

**Imaging.** Ten patients with PLS and 12 age-matched control subjects underwent routine anatomic MRI (T1 sagittal, T1 axial, T2 axial, and axial proton density) using a GE 1.5 Tesla MRI to exclude underlying pathology. Multislice nuclear magnetic spectroscopy imaging software developed by NIH<sup>20</sup> was used to assess *N*-acetylaspartate (NAA), creatinine (Cr), choline (Cho), and lactate (Lac) levels, using a long echo time of 280 msec. Phase-encoding procedures and outer volume suppression were used to obtain four slices with a  $32 \times 32$  array of spectra from voxels having a nominal volume of 0.84 mL ( $7.5 \text{ mm} \times 7.5 \text{ mm} \times 15 \text{ mm}$ ) within the selected sections that correlated to the anatomic regions of interest (ROI). For all subjects, the midline sagittal image was used to localize slice acquisition in the anterior-posterior commissure line with the lateral ventricles in the second slice. Anatomic images were coregistered with each slice. Each spectroscopy slice (15 mm) correlated with five anatomic slices (3 mm). ROI were placed in the hand<sup>21</sup> and leg region of the primary motor cortex on each side (figure 1), as well as in the posterior limb of internal capsule and the anterior pons on each side for an evaluation of the corticospinal tract. Metabolite levels were computed by measuring the area under the curves at the chemical shift corresponding to each metabolite, using in-house software.<sup>20</sup>

The anatomic MR images of patients and normal subjects were assessed qualitatively by a senior board-certified neuroradiologist (J.A.B.) in a randomized, blinded fashion. MRI were scored for the presence of primary motor cortex atrophy and abnormal signal on T2-weighted images using the following scale: 0 = normal, 1 = mild, 2 = moderate, 3 = severe abnormality.

**Statistical analysis.** Data are expressed as means  $\pm$  SD. Finger tapping, gait measures, and TMS thresholds of patients were compared to controls using Mann-Whitney nonparametric tests. In the MRS studies, Cr and Cho measurements were highly correlated, and NAA/Cr was the primary measure assessed. NAA/Cr ratios were compared using two-factor analysis of variance (by

**Table 1 Patient characteristics and tests performed**

Symptom pattern	Sex	Duration, y	Age at onset, y	Follow-up visit	TMS thresholds, R/L	MRS	Exaggerated startle	Gait aids	Baclofen or tizanidine	Benzo diazepines	Examination at initial visit
<b>Ascending</b>											
1	F	4	49	Y	>100/100	Y	Y	W	X		QP ± S
2	F	4	38	Y	—	Y	Y	W			QP + S
3	M	5	41	Y	>100/100	Y	Y	Cane			QP + S
4	M	5	35	Q	>100/100	—	Y	W		X	QP + S
5	M	6	39	Y	>100/100	Y	—	Cane	X		QP + S
6	M	6	59	Y	>100/100	Y	Y	W	X		QP
7	F	6	46	Y	>100/100	Y	Y	W	X		QP + S
8	M	8	56	Y	>100/100	—	Y	W-C	X		QP + S
9	M	9	38	Y	>100/100	Y	—	W-C	X		QP + S
10	M	9	49	Y	>100/100	Y	Y	W		X	QP + S
11	F	10	61	Y	>100/100	Y	Y	W	X		QP + S
12	M	11	40	Q	>100/100	—	N	W-C			QP + S
13	F	11	46	Y	>100/100	Y	—	Cane			QP + S
14	F	12	39	Q	>100/—	—	Y	W-C			QP + S
<b>Multifocal</b>											
1	F	3	57	NA	36/37	—	—	Cane			PP + S
2	F	4	40	Y	>100/100	—	N	None	X		S > QP
3	F	4	57	Q	—/52	—	—	None			PP ± A
4	M	4	46	Q	60/56	—	—	Cane	X	X	TP + S
5	F	4	48	Y	46/>100	—	Y	Cane	X		QP*
6	F	7	48	Q	>100/100	—	Y	None			S > QP
7	M	7	37	Y	47/47	—	N	Cane	X		PP
8	F	8	42	NA	67/82	—	—	Cane	X		TP
9	F	13	45	Q	62/64	—	Y	Cane		X	HP*
10	F	30	34	Q	>100/100	—	N	W			QP + S
<b>Unclassified</b>											
1	F	53	3	Y	48/48	—	N	None			PP

TMS = transcranial magnetic stimulation; W = walker; QP = quadriparesis; S = dysarthric speech/pseudobulbar symptoms; — = not done; Q = questionnaire follow-up only; W-C = wheelchair; NA = not applicable, less than 1 year since evaluation; PP = paraparesis; TP = tripareisis; HP = hemiparesis.

\* History of fluctuating symptoms.

diagnosis and region) with post hoc testing to determine significant comparisons, using a  $p < 0.05$  with Bonferroni correction. Significance of correlations was tested using Fisher's test, with  $p < 0.05$ .

**Results. Clinical evaluation.** All 25 patients had abnormalities on examination limited to corticospinal tract dysfunction, including spastic tone, hyperactive deep tendon reflexes, and extensor plantar responses. Pseudobulbar signs included spastic dysarthria and brisk jaw and gag reflexes. Despite marked spasticity, all patients but one had good strength to manual muscle testing (Appel motor score: 134 to 140). None had evident muscle atrophy. Although several patients reported fasciculations, few or none were observed during examination or during needle EMG studies. Sensory examination had normal results.

**Patterns of symptom progression.** Patients differed in the pattern of symptom progression, which was characterized as ascending, multifocal, or pure paraparesis (table 1).

**Ascending group.** Fourteen of the 25 patients reported that symptoms began in the legs and that there was a delay before

symptoms developed in the arms, with a temporary period of paraparesis. Both legs were affected before symptoms began in the arms. Loss of dexterity in the hands was quickly followed by changes in speech or swallowing. Although symptoms progressed at different rates in individuals, the duration of time between leg and arm symptom onset tended to be two to three times longer than the duration of time between arm and pseudobulbar symptom onset ( $p = 0.06$ ). On average, symptoms began in the second leg within 1.7 years after the first (range 1 to 4 years), and hands were affected 3.6 years later (range 1 to 6 years). Pseudobulbar symptoms began 1.5 years (range 0.5 to 5 years) after the arm symptoms, which averaged  $4.6 \pm 1.9$  years after the onset of the disease. Slow movements and stiffness were the predominant symptoms, rather than weakness. These symptoms worsened with cold. Symptoms of urinary urgency developed in 12 patients after 4.4 years (range 1.5 to 10 years). Emotional lability was a frequent later symptom. The age at the time of initial symptom onset was  $45.4 \pm 8.4$  years and symptoms had been present for  $7.6 \pm 2.8$  years at the time of evaluation.

Eleven of these patients were examined 1 or 2 years later, and

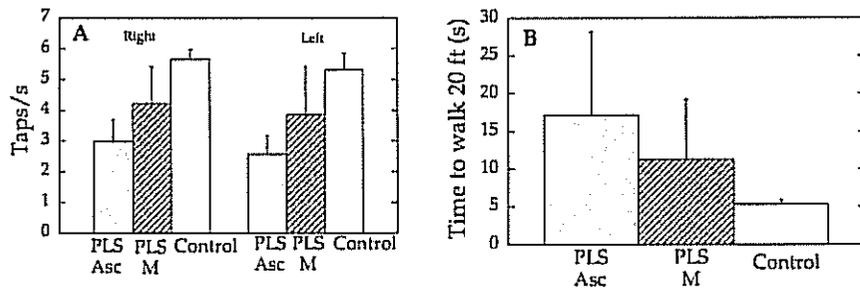


Figure 2. Differences in motor performance among patient and control groups (PLS asc = ascending primary lateral sclerosis subgroup; PLS M = multifocal subgroup). (A) Finger tapping speed. (B) Timed gait for 20 feet. Values are means  $\pm$  SD.

the three remaining patients in this group were assessed by written questionnaire, as noted in table 1. All but two reported worsening of symptoms, particularly pseudobulbar symptoms. Two patients had stopped working because of speech difficulties. One patient without pseudobulbar symptoms on first evaluation had developed slurred, slow speech. Two patients progressed from cane to walker; one progressed from walker to wheelchair. One had undergone placement of a baclofen pump.

**Multifocal group.** Ten patients had a markedly asymmetric or patchy pattern of symptom spread. Region of symptom onset was variable: four began with arm symptoms or dysarthria, one began with hemiparesis, and five began with leg symptoms, but as symptoms progressed, one or more limbs remained unaffected. A few patients in this group reported transient improvement or long periods of stability, rather than a steadily progressive course. One patient had moderate leg weakness to manual muscle testing in addition to spasticity. A few patients had pain or paresthesias, although no objective sensory loss was present on examination. Half of the patients had urinary urgency, which began on average 7.25 years (range 3 to 16 years) after onset of disease. Age at onset was  $45.4 \pm 7.6$  years, with a duration  $8.4 \pm 8.1$  years (range 3 to 30 years).

Of the eight patients in this group followed more than a year, three returned for a follow-up examination and five were assessed

by questionnaire. All reported worsening of symptoms. In six, worsening occurred within previously affected body regions. In two, an additional limb became symptomatic. One of the patients had begun using a walker and one had undergone baclofen pump placement.

**Unclassified paraparesis.** One patient had symptoms limited to both legs, of 3 years' duration, and could not be confidently classified. Repeat evaluation 1 year later showed no progression.

**Measures of motor performance.** Finger tapping speed was slower in both groups of patients than in age-matched controls (figure 2). In the ascending group, finger-tapping speed tended to be inversely correlated with duration of symptoms ( $r = -0.59$  for right hand;  $r = -0.42$  for left hand;  $p = 0.055$ ). In patients re-evaluated a year or more later, finger tapping speed was unchanged or slightly slower (figure 3, ascending group). In the multifocal group, no correlation between disease duration and finger tapping speed was evident. Timed gait was slower in patients than control subjects. Gait speed was quite variable among patients with similar clinical examinations in both groups, perhaps because patients were allowed to use canes or walkers during testing.

**Transcranial magnetic stimulation.** TMS was performed in all but one patient who had a remote history of seizures. All patients in the ascending group examined (13 out of 14) had

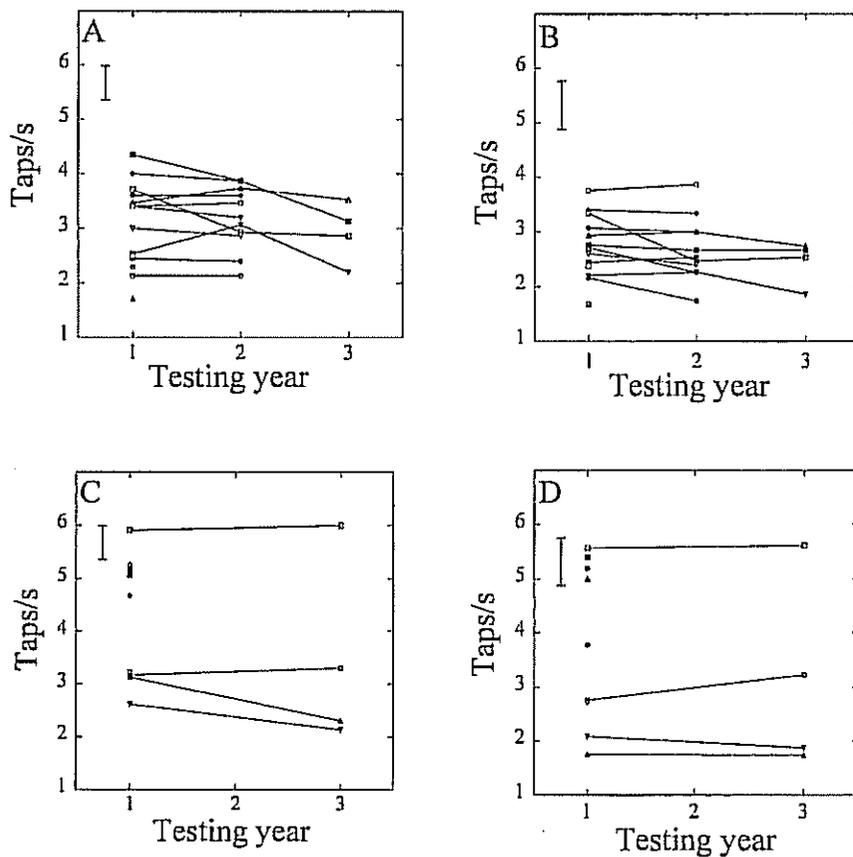


Figure 3. Changes occurring in motor performance on annual follow-up examinations in patients with primary lateral sclerosis. Each symbol represents an individual patient. Mean  $\pm$  SD for control subjects indicated by bar on left. Ascending subgroup, finger tapping, (A) right hand, (B) left hand. Multifocal and paraparesis subgroup, finger tapping, (C) right hand, (D) left hand.

**Table 2** MRS results for all motor areas assessed in patients and controls

	PLS (n = 9)		Control (n = 12)	
	L	R	L	R
Arm PMC				
NAA/Cr	2.30 ± 0.24	2.35 ± 0.37	3.02 ± 0.71	2.95 ± 0.52
NAA/Cho	2.45 ± 0.47	2.74 ± 0.80	3.44 ± 1.03	3.64 ± 0.95
Leg PMC				
NAA/Cr	2.15 ± 0.30	2.21 ± 0.42	2.51 ± 0.31	2.58 ± 0.28
NAA/Cho	1.98 ± 0.32	2.03 ± 0.30	2.58 ± 0.47	2.80 ± 0.44
Internal capsule				
NAA/Cr	2.67 ± 0.24	2.65 ± 0.46	2.96 ± 0.47	2.79 ± 0.26
NAA/Cho	2.33 ± 0.51	2.37 ± 0.71	2.38 ± 0.27	2.47 ± 0.46
Pons				
NAA/Cr	2.63 ± 0.61	2.43 ± 0.87	2.86 ± 0.75	2.84 ± 0.48
NAA/Cho	1.88 ± 0.37	2.00 ± 0.68	1.98 ± 0.34	1.99 ± 0.50

Values are mean ± SD.

PMC = primary motor cortex; NAA = N-acetylaspartate; cr = creatinine; PLS = primary lateral sclerosis; Cho = choline.

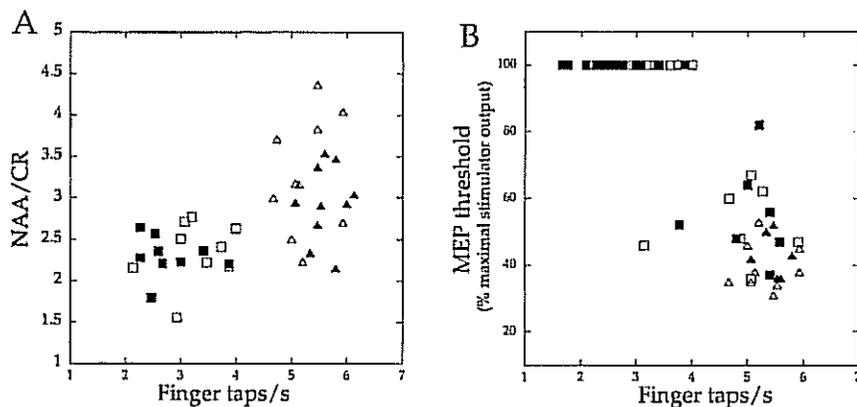
decreased cortical excitability such that MEP could not be evoked from hand muscles despite using the maximal output of the magnetic stimulator, a finding that indicates high thresholds for cortical activation. In these patients we were unable to calculate a CMCT. However, five patients had brief silent periods (20 to 56 msec) with maximal stimulator output. In these patients, paired maximal stimuli were delivered at short interstimulus intervals (1.3 to 2.5 msec) in an effort to facilitate MEP by I-wave superimposition.<sup>21</sup> However, even with this facilitation, MEP could not be elicited in these patients.

Seven of the patients in the multifocal group had relatively normal MEP thresholds for the hand muscles, including two patients with symptoms in their hands (thresholds as percent maximal stimulator output: patients, 53 ± 11 [right], 56 ± 15 [left]; controls, 43 ± 8, n = 22). In six of the seven patients, calculated CMCT were normal (patients, 6.8 ± 1.3 msec; controls, 6.7 ± 1.7 msec). The CMCT to the symptomatic hand was prolonged in only one patient (Patient 9, 15.6 msec). The single patient with paraparesis had normal hand MEP thresholds and CMCT.

**Imaging studies.** All patients had MRI scans of the brain from outside hospitals or at the NIH. Except for evidence of a remote cerebellar infarct in one patient with the multifocal clinical pattern, there were no structural abnormalities. In the blinded scoring by a neuroradiologist (J.A.B.) of the brain MRI for 10 patients and 12 age-matched controls, two patients and three controls had mild abnormalities of T2 signal intensity (scores = 1) and three patients and one control had mild precentral cortical atrophy (scores = 1).

MRS to assess for NAA, Cr, and Cho levels was technically satisfactory in 9 of the 10 patients in the ascending group and 12 age-matched controls. Figure 1 shows the ROI in the hand and foot areas of the motor cortex on both sides using the multislice technique. The means of the patient NAA/Cr and NAA/Cho ratios in the motor cortex were reduced compared to controls (table 2) (analysis of variance,  $F = 29.3$ ,  $p < 0.005$ ). NAA/Cr values had notable overlap between patient and control groups (figure 4), but post hoc comparisons showed a significant difference between patients and controls in the hand regions of the motor cortex, although not the leg regions. Single voxel measures of NAA/Cr or NAA/Cho in the internal capsule and pons were not significantly different.

**Correlation between measures of cortical function.** TMS thresholds, NAA/Cr ratios, and finger tapping are distinct ways of assessing the functioning of the motor cortex. Previous studies in patients with ALS have suggested a correlation between NAA/Cr ratios in MRS and finger tapping speed.<sup>23</sup> We compared finger tapping speed with MEP thresholds and NAA/Cr ratios in the hand area of the motor cortex. When all hemispheres of patients and controls were combined, the tapping speed was correlated with TMS threshold ( $r = -0.867$ ;  $p < 0.001$ ) and with NAA/Cr ratios ( $r = 0.58$ ;  $p < 0.001$ ) (see figure 4). TMS thresholds that were elevated beyond maximal stimulator output were deemed 100% for this analysis. Patients with the slowest rates of finger tapping typically had TMS thresholds elevated beyond maximal stimulator output (100%). NAA/Cr ratios had overlapping distributions in patients and age-matched controls, although the mean



**Figure 4.** Correlations between different measures of motor cortex function. (A) Finger tapping speed is plotted against N-acetylaspartate/creatinine ratios for the corresponding arm region of interest for each side in each subject. (B) Finger tapping speed is plotted against transcranial magnetic stimulation threshold for eliciting motor-evoked potential in hand muscles for each subject for each side. Squares = patients with primary lateral sclerosis; triangles = control subjects; open symbols = right side; filled symbols = left side.

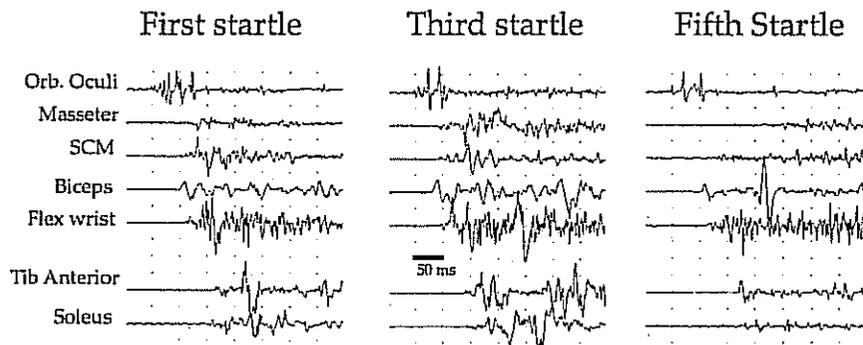


Figure 5. An example of the acoustic startle responses of a patient with primary lateral sclerosis for the first, third, and fifth presentations of the stimulus tone, which were given at intervals of 3 to 5 minutes. Multichannel EMG recording of muscles as labeled. Traces are triggered at the beginning of the tone. Only a small degree of habituation is present over the five trials.

was lower for patients. Gait speed was not well correlated with NAA/Cr ratios from the leg area.

**Startle reflexes.** An excessive ASR, defined as the spread of EMG activity to leg muscles and decreased habituation,<sup>19,24,25</sup> was present in 13 of the 17 successive patients tested (see table 1). Most showed some habituation over the testing period, with attenuation of the response amplitude or duration usually apparent by the fifth trial (figure 5). The onset of EMG in the orbicularis oculi was delayed ( $62 \pm 30$  msec) compared to normal,<sup>19</sup> and the duration of EMG bursts was prolonged, often exceeding 800 msec. Exaggerated ASRs occurred in patients with pseudobulbar symptoms more often than in patients with symptoms limited to the limbs. The tally of muscles activated in the eight trials, a rough measure of the spread and habituation of the ASR, was greatest in patients with PLS with recent onset of pseudobulbar symptoms (figure 6). Excessive startle was seen in patients with the ascending symptom pattern and in patients with the multifocal pattern, without obvious differences between the two groups.

**Discussion.** Clinical findings were heterogeneous among patients with PLS defined by current criteria,<sup>6,8</sup> even after excluding patients with clinical or

EMG evidence of lower motor neuron degeneration.<sup>11,12</sup> However, one subgroup of patients had a relatively homogenous ascending pattern of symptom progression. This pattern was smoothly progressive, with symptoms beginning in the legs and involvement of both legs before symptoms began in the arms. After a period of paraparesis, upper extremities became symptomatic. Quadriparesis was quickly followed by speech or swallowing difficulties. This pattern of progression would be compatible with a steady dying back of corticospinal axons. A similar length-dependent axonopathy has been proposed for some forms of hereditary spastic paraparesis.<sup>26</sup> Physiologic measurements of the corticospinal system in patients with PLS with the ascending pattern supported corticospinal dysfunction but did not allow further distinctions. All patients with PLS with the ascending pattern had elevated TMS thresholds with absent motor evoked potentials, a finding that can indicate either loss of cortical neurons or terminal axon degeneration. The loss of MEP is similar to findings late in ALS.<sup>27,28</sup> All patients with PLS had symptoms for at least 3 years, and it is unknown whether earlier TMS studies might show other abnormalities, such as hyperexcitability, which is seen in early ALS.<sup>29,30</sup> Of note, however, is that patients with PLS with a multifocal symptom course of similar duration were heterogeneous in TMS measures. We did not find prolonged CMCTs in patients with PLS<sup>11,31</sup> except for one patient in the multifocal group.

To explore whether patients with PLS in the ascending subgroup had a loss of cortical neurons, we assessed atrophy of the precentral gyrus in MRI scans,<sup>6,32,33</sup> and found no more than in age-matched controls. However, MRS showed reduced NAA/Cr ratios in the arm area of the motor cortex of these patients compared to age-matched controls, indicating neuronal atrophy, dysfunction, or loss. Similar reductions of NAA/Cr have been described in ALS.<sup>34-40</sup> NAA/Cr ratios of patients with PLS overlapped with age-matched controls, as reported in an earlier study that could confidently distinguish only half of the patients with PLS from controls.<sup>35</sup> Experimental models have shown that NAA/Cr ratios can decline following deafferentation, and may reflect neuronal inactivity rather than loss of neurons.<sup>41</sup>

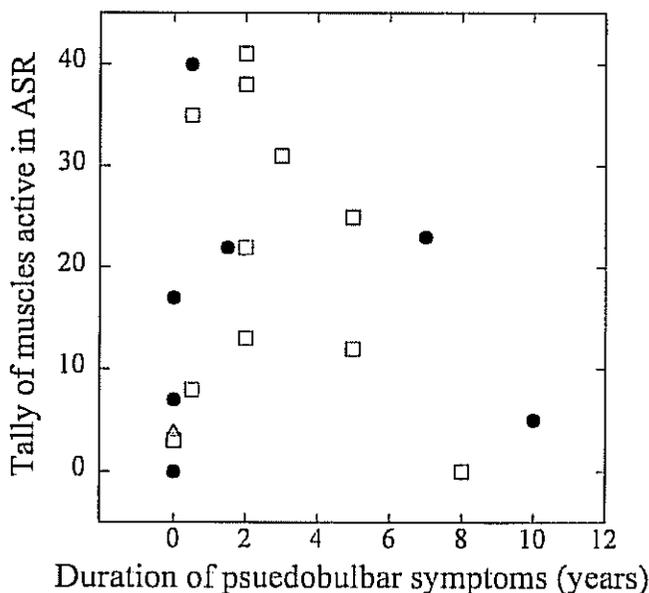


Figure 6. Exaggeration of acoustic startle responses (ASR) is more common in patients with primary lateral sclerosis with recent onset pseudobulbar symptoms. The tally of muscles activated in the eight trials, a rough measure of the spread and habituation of the ASR, is plotted for each patient according to the duration of their pseudobulbar symptoms. Squares = ascending pattern; circles = multifocal pattern; triangle = paraparesis.

Thus, it remains uncertain whether motor cortex neurons have been irreversibly lost in patients with ascending PLS. Future studies are needed to follow MRS serially among subgroups, and to provide pathologic correlation.

Startle reflexes were not only intact in patients with PLS, but often hyperactive. Exaggerated startle occurred mostly in patients with PLS with pseudobulbar symptoms of recent onset, regardless of clinical subgroup. Preservation of the startle reflex in PLS demonstrates the integrity of reticulospinal tracts, and supports the assertion that PLS selectively affects corticospinal and corticobulbar systems.<sup>6</sup> The loss of corticobulbar inputs probably leads to a hyperexcitability of brainstem reflexes in a manner analogous to the tendon reflex hyperreflexia that occurs in spastic limbs. Sparing of reticulospinal tract function in PLS has potential consequences for rehabilitative strategies. There is some evidence that the pathways mediating startle in man can access circuitry producing voluntary movement, not only advancing reaction times<sup>42</sup> but releasing intended movements waiting to be executed.<sup>43,44</sup> The strength of connections between rapidly conducting reticulospinal axons and motor neurons is modulated during locomotion in animals.<sup>45,46</sup> In humans, the startle response amplitude is likewise modulated during phases of the step cycle.<sup>47</sup> These findings suggest the possibility that, in certain circumstances, signals from descending reticulospinal pathways can be integrated into volitional movement. Further study will be needed to determine whether reticulospinal pathways can be used to enhance volitional movements in the setting of corticospinal dysfunction.

The goal of this study was to identify subsets of patients with common clinical, physiologic, and anatomic features, as a first step to investigate causes of PLS. Possible investigative approaches to the pathogenesis of complex, sporadic disorders such as PLS include analysis of the expression profile of large numbers of genes.<sup>48,49</sup> From a practical point of view, such experiments are limited to tissue samples from small numbers of patients. Patients with PLS with an ascending clinical course may offer a more homogeneous sample for such investigations than the overall population of patients fulfilling current diagnostic criteria for PLS.

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## Appendix: Inclusion and exclusion criteria

### Required for inclusion

#### Clinical

- Insidious onset in adulthood, progressive course
- No family history
- Duration >3 years without clinical lower motor neuron signs
- Clinical signs restricted to corticospinal ± corticobulbar tract dysfunction

#### Imaging studies

- Normal brain MRI (except for cortical atrophy results)
- Normal cervical spine MRI or myelogram results
- Normal chest X-ray results
- Normal mammogram results

## EMG

- No lower motor neuron findings
- EMG within 3 years

## Serologic studies

- Normal serum chemistry, vitamin B12, and vitamin E levels
- Negative serology for syphilis, Lyme disease, human T-cell lymphotropic virus 1 and 2, and HIV
- Normal serum levels of very long-chain fatty acids

## Causes for exclusion

- Implanted devices
- Prior neurologic surgeries
- Coexistent neurologic conditions
- Abnormal visual, auditory, or somatosensory evoked potentials
- Elevated CSF protein, cells, or oligoclonal bands
- Examination showing sensory loss, amyotrophy, or dementia
- Denervation on needle EMG studies
- Inadequate documentation or history
- Inability to travel

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