*Brain* (2001), **124,** 1989–1999

# Does primary lateral sclerosis exist?
## A study of 20 patients and a review of the literature

Nadine Le Forestier,[1] Thierry Maisonobe,[2] Ambre Piquard,[1] Sophie Rivaud,[3] Lise Crevier-Buchman,[4] François Salachas,[1] Pierre-François Pradat,[1] Lucette Lacomblez[1,5] and Vincent Meininger[1]

[1]*Fédération Mazarin de Neurologie Professeurs Delattre et Meininger,* [2]*Service de Neuro-anatomopathologie du Professeur Hauw, Laboratoire Escourolle,* [3]*Unité Inserm U 289,* [4]*Service de Pharmacologie, Hôpital de la Salpêtrière, AP-HP and* [5]*Service ORL 2 du Professeur Brasnu, Hôpital Georges Pompidou, Paris, France*

*Correspondence to: Professor Vincent Meininger, Fédération de Neurologie Mazarin, Hôpital de la Pitié-Salpêtrière, 47-83 Boulevard de l'Hôpital, 75013 Paris Cedex 13, France*
*E-mail: vincent.meininger@psl.hop-ap-paris.fr*

## Summary
**The question of whether primary lateral sclerosis (PLS) is a nosological entity distinct from amyotrophic lateral sclerosis (ALS) has been the subject of controversy since it was first described in the nineteenth century. PLS has been defined as a rare, non-hereditary disease characterized by progressive spinobulbar spasticity, related to the selective loss of precentral pyramidal neurones, with secondary pyramidal tract degeneration and preservation of anterior horn motor neurones. In the recent clinical literature, the frontier between ALS and neurodegenerative disease remains poorly defined. We studied 20 patients with a diagnosis of PLS. We carried out a variety of tests in order to determine the presence of a more diffuse neurodegenerative process. We also performed a longitudinal electrophysiological evaluation. Our clinical, electrophysiological and pathological investigations provide evidence that the disease has a heterogeneous clinical presentation and that degeneration is not restricted to the central motor system.**

**Keywords**: primary lateral sclerosis; amyotrophic lateral sclerosis; electromyography; neurodegenerative disease; motor cortex

**Abbreviations**: ALS = amyotrophic lateral sclerosis; CMCT = central motor conduction time; MEP = motor evoked potential; MUP = motor unit potential; PLS = primary lateral sclerosis; SEP = somatosensory evoked potential; VEP = visual evoked potential

## Introduction
In 1865, Charcot drew attention to the association in the spinal cord between involvement of the lateral tract and the disappearance of the motor neurones in the anterior horn, which led to the concept of amyotrophic lateral sclerosis (ALS). The concept of the exclusive involvement of the lateral tract of the spinal cord is due to Erb (Erb, 1875), who named this nosological entity 'primary lateral sclerosis'. However, the idea that primary lateral sclerosis (PLS) is a discrete entity has long been challenged. The initial clinical criteria were proposed by Stark and Moersch (Stark and Moersch, 1945) and in 1992 Pringle and colleagues supported the concept of an exclusive involvement of the lateral tract and, after a study of eight patients, proposed new diagnostic criteria (Pringle *et al.*, 1992). However, their interpretation of electromyographs—'absence of denervation potentials or, at most, occasional fibrillation and increased insertional activity in a few muscles (late and minor)'—implied that they accepted explicitly the presence of electrophysiological signs of denervation, i.e. pathology of the spinal motor neurones. In a preliminary study, we recently questioned the absence of involvement of lower motor neurones in PLS (Le Forestier *et al*., 2001). Here we reconsider the nosological classification of this disease with respect to two important questions. First, it is necessary to define the relationship between PLS and ALS, given that most authors describe PLS as involving clinical and electrophysiological signs of denervation, suggesting involvement of spinal motor neurones (Spiller, 1904; Mackay, 1963; Castaigne *et al.*, 1972; Ungar-Sargon *et al.*, 1980; Russo, 1982; Sotaniemi and Myllylä, 1985; Younger *et al.*, 1988; Pringle *et al.*, 1992; Le Forestier *et al*., 2001). Moreover, post-mortem studies have failed to demonstrate a clear distinction from ALS, since, in both conditions, degeneration of the lateral medullary tracts and macroscopic atrophy of the premotor region of the central

gyrus (Beal and Richardson, 1981; Greenfield, 1984; Pringle *et al.*, 1992; Norris *et al.*, 1993) as well as neuronal loss in the anterior horn have been widely reported (Spiller, 1904; Lawyer and Netsky, 1953; Mackay, 1963; Brownell *et al.*, 1970; Castaigne *et al.*, 1972; Fisher, 1977; Beal and Richardson, 1981; Younger *et al.*, 1988; Pringle *et al.*, 1992; Hudson *et al.*, 1993; Bruyn *et al.*, 1995; Hainfellner *et al.*, 1995).

Secondly, a potential relationship between PLS and other neurodegenerative diseases needs to be defined, since some publications describe neuropsychological impairment (Caselli *et al.*, 1995; Hainfellner *et al.*, 1995), abnormalities of ocular movements (Gascon *et al.*, 1995; Lerman-Sagie *et al.*, 1996), cortical atrophy (Bruyn *et al.*, 1995; Hainfellner *et al.*, 1995; Konagawa *et al.*, 1998) or dementia with diffusely distributed Lewy bodies (Hainfellner *et al.*, 1995) in PLS.

In order to address these two questions, following our preliminary study in nine patients, we carried out a prospective longitudinal study over a 5-year period in a new set of 20 patients initially classified as having PLS according to Pringle and colleagues (Pringle *et al.*, 1992). We analysed the incidence of involvement of spinal motor neurones using prospective longitudinal electrophysiological and morphological analyses. We also studied the involvement of other neuronal systems using somatosensory and visual evoked potentials, ocular movements and neuropsychological evaluation.

## Patients and methods

### *Patients*

The study was carried out at the ALS Centre at the Salpêtrière Hospital, Paris. From the 450 motor neurone disease patients followed up each year and referred with motor neurone disease, 20 patients were selected on the basis of the presence of Pringle and colleagues' diagnostic criteria for PLS (Pringle *et al.*, 1992) and the absence of diagnostic criteria for definite, probable or possible ALS (Brooks, 1994) from 1995 to 2000.

The diagnostic criteria proposed by Pringle and colleagues were the following: (i) adult onset and progressive insidious disease course of $>3$ years; (ii) absence of family history; (iii) nearly symmetrical, bilateral pyramidal involvement, including the face; (iv) normal serum chemistry; (v) CSF negative for oligoclonal bands, and negative tests for syphilis, Lyme disease, human T lymphocytic virus 1 and 2; (vi) absence of denervation potentials on electromyography; (vii) absence of compressive lesions of cervical spine or foramen magnum on spinal MRI; (viii) absence of high signal lesions outside the cortical tract on brain MRI.

An additional series of laboratory tests, specifically devised for the purposes of this study, was performed in order to ensure: (i) normal thoracic X-ray results; (ii) normal thoracic and abdominal CT scan; (iii) normal levels of serum folate, magnesium, manganese, copper and ceruloplasmin, serum and urine lead and serum iron; (iv) normal levels of angiotensin-converting enzyme, thyroxine and thyroid-stimulating hormone, carcinoembryonic antigen, α-foetoprotein, neurone-specific enolase, prostate-specific protein and carcinoma antigens 15-3, 125 and 19-9; (v) absence of hexaminidase A and vitamin B deficiency; (vi) negative serological tests for brucellosis and HIV1-2.

### *Methods*

#### *Tests of motor ability*

Analytical testing and grading of muscle strength and evaluation of spasticity using the Ashworth scale were carried out every 4–6 months over the 5-year period of the study, as described by Lacomblez and colleagues (Lacomblez *et al.*, 1996). During follow-up, we considered peripheral motor involvement to be distinct from the pyramidal deficit. This peripheral motor deficit was described as 'probable' if there were cramps or fasciculations and 'certain' if these symptoms were associated with amyotrophy.

#### *Electrophysiology*

The following electrophysiological parameters were evaluated: (i) motor nerve conduction in the median, ulnar and peroneal nerves; (ii) sensory nerve conduction in the median, ulnar and superficial branches of the musculocutaneous and sural nerves; and (iii) motor unit potentials (MUPs) and the presence of fibrillation and fasciculation potentials and giant MUPs ($>10$ mV), using concentric needle electrode EMG in both abductor pollicis brevis, extensor digitorum longus, extensor carpi ulnaris, deltoid, tibial anterior, rectus femoris, sternocleidomastoid and orbicularis lip muscles.

Motor evoked potentials (MEPs) and central motor conduction times (CMCTs) were recorded from the abductor pollicis brevis, hypothenar and tibial anterior muscles in response to magnetic stimulation delivered transcutaneously to the scalp and the cervical (C7) and lumbar (L4) spinal cord. Magnetic stimulation was performed with a MagStim 200 (MagStim Co. Ltd, Whitland, UK) discharging into a circular high-power coil. CMCTs were calculated by subtracting latencies obtained after nerve root stimulation from those after central stimulation. Peripheral latency was defined as the latency of the response obtained after anterior nerve root stimulation. CMCTs were calculated as described by Claus (Claus, 1990).

#### *Further functional tests*

The following functional tests were performed at least once during the study: (i) orofacial and velopharyngolaryngeal evaluation (unpublished); (ii) analysis of ocular movement according to Vidailhet and colleagues (Vidailhet *et al.*, 1994); (iii) neuropsychological evaluation, comprising (a) a standard evaluation of the global cognitive pattern to detect possible

**Table 1** *Clinical characteristics of the patients*

| Patient | Sex | Age at disease onset (years) | Duration of disease (years) | Follow-up period (months) | Site of disease onset | Pseudobulbar syndrome | Tetrapyramidal syndrome | Urinary urgency | Prefrontal and/or premotor dysfunction |
|---|---|---|---|---|---|---|---|---|---|
| 1 | M | 26 | 10 | 24 | B+LLs | Yes | Yes | No | Yes |
| 2 | M | 52 | 8 | 60 | B | Yes | Yes | No | Yes |
| 3 | M | 61 | 5 | 36 | LLr | Yes | Yes | Yes | Yes |
| 4 | M | 56 | 10 | 30 | B | Yes | Yes | Yes | Yes |
| 5 | M | 47 | 9 | 36 | LLl | Yes | Yes | Yes | Yes |
| 6 | F | 50 | 13 | 18 | LLs | Yes | Yes | Yes | Yes |
| 7 | M | 55 | 13 | 41 | LLs | Yes | Yes | No | Yes |
| 8 | M | 52 | 7 | 56 | LLs | Yes | Yes | Yes | Yes |
| 9 | M | 59 | 11 | 24 | LLl | Yes | Yes | No | Yes |
| 10 | M | 60 | 11 | 60 | B | Yes | Yes | No | Yes |
| 11 | M | 47 | 9 | 41 | B | Yes | Yes | Yes | Yes |
| 12 | F | 48 | 7 | 30 | B | Yes | Yes | Yes | Yes |
| 13 | F | 63 | 8 | 84 | LLs | Yes | Yes | Yes | Yes |
| 14 | F | 62 | 4 | 36 | LLl + B | Yes | Yes | Yes | No |
| 15 | M | 53 | 9 | 24 | LLl | No | Yes | Yes | Yes |
| 16 | M | 64 | 5 | 48 | B | No | Yes | Yes | Yes |
| 17 | M | 43 | 14 | 60 | LLl | Yes | Yes | No | No |
| 18 | M | 63 | 7 | 66 | B | Yes | Yes | Yes | No |
| 19 | F | 52 | 3 | 42 | LLr | No | Yes | Yes | No |
| 20 | M | 56 | 7 | 36 | LLr | Yes | Yes | Yes | Yes |

B = bulbar; LLr/l/s = right/left/both lower limbs.

frontal and frontotemporal dementia according to the Lund and Manchester criteria (Lund and Manchester Groups, 1994), (b) a study of global memory (Grober and Buschke and span tests), language (verbal fluency and Wechsler Adult Intelligence Scale—Revised) and attention (Stroop Test and Trail-Making Test), and gestural praxia and visual constructive tests (Rey's figure), and (c) more specific tests, including Luria's series and the Wisconsin Card-Sorting Test, for executive prefrontal and premotor functions [we diagnosed a premotor syndrome if the patient failed in at least two subtests (or failed badly in only one subtest, with performance that exceeded 2 SD below the normal mean) and a dysexecutive syndrome when all specific tests were failed (unpublished)]; (iv) a check-board study of visual evoked potentials (VEPs) and bilateral median and posterior tibial nerve somatosensory evoked potentials (SEPs); and (v) brain MRI with FLAIR (fluid attenuated inversion recovery) sequence.

### *Muscle histology*

A biopsy of the deltoid muscle was performed to look for evidence of denervation and reinnervation features. In this study, 'denervation' refers to small groups of three or more atrophic angular muscle fibres and 'reinnervation' to the coexistence of at least 10 adjacent muscle fibres of the same type. We also checked for histological mitochondrial dysfunction (as indicated by the presence of ragged red fibres) and biochemical mitochondrial dysfunction in frozen cross-sections for ATPase, NADH dehydrogenase, succinate dehydrogenase and cytochrome oxidase at various pHs (4.3, 4.6 and 9.4).

## Results

### *Clinical characteristics*

The study included five women and 15 men with a diagnosis of PLS (Table 1). Mean age at onset of symptoms was 53.4 years (range 26–64 years). Mean disease duration at first examination was 8.5 years (range 4–14 years). Mean follow-up duration was 43.4 months (range 18–60 months). One patient had an unaffected homozygous twin brother. The site of onset was the lower limbs in 11 patients, the bulbar region in seven patients and simultaneous onset in these two regions in two patients. In all cases, onset was insidious.

Disease progression was very slow and half of the patients experienced periods of stabilization lasting several months. Ten patients needed a wheelchair after a mean disease duration of 4 years, five patients used a walker and five patients could still walk unaided after a mean disease duration of 6 years. Age at onset was not related to a more rapidly progressive course of the disease.

In all cases, the main clinical feature was a tetrapyramidal syndrome (Table 1) with hyperactive deep tendon reflexes and bilateral Babinski and Hoffman signs. Six patients showed severe spasticity with clonus of the ankle and patella, which was frequently worsened by emotional stress and unexpected noise. This syndrome remained asymmetrical for

**Table 2** *Peripheral deficits*

| Patient | Cramps | Fasciculations | Amyotrophy | MRC scale | Bulbar Norris* | ALS FRS† |
|---|---|---|---|---|---|---|
| 1 | Yes | Yes | No | Normal | 17 | 30 |
| 2 | Yes | Yes | No | Normal | 13 | 35 |
| 3 | Yes | Yes | Yes | Normal | 17 | 21 |
| 4 | No | Yes | Yes | Abnormal | 17 | 25 |
| 5 | Yes | Yes | Yes | Abnormal | 15 | 25 |
| 6 | Yes | Yes | Yes | Abnormal | 9 | 18 |
| 7 | Yes | Yes | Yes | Abnormal | 20 | 23 |
| 8 | Yes | Yes | No | Normal | 19 | 28 |
| 9 | Yes | Yes | Yes | Abnormal | 9 | 19 |
| 10 | Yes | No | No | Abnormal | 14 | 25 |
| 11 | No | Yes | Yes | Normal | 5 | 18 |
| 12 | No | Yes | Yes | Normal | 10 | 27 |
| 13 | No | No | No | Normal | 19 | 30 |
| 14 | Yes | Yes | Yes | Abnormal | 13 | 25 |
| 15 | Yes | Yes | No | Normal | 27 | 30 |
| 16 | Yes | Yes | Yes | Abnormal | 17 | 35 |
| 17 | Yes | Yes | Yes | Abnormal | 8 | 21 |
| 18 | Yes | Yes | Yes | Abnormal | 11 | 14 |
| 19 | Yes | Yes | No | Normal | 19 | 30 |
| 20 | Yes | Yes | No | Normal | 18 | 33 |

*Normal value 27; †normal value 40.

several years in seven patients. Irrespective of the site of onset of the disease, 14 patients started to experience dysuria and urinary urgency after a mean disease duration of 4.5 years (Table 1).

In 17 patients, pseudobulbar involvement was experienced after a mean period of 5 years (range 1–7 years) from disease onset (Table 1). In 11 patients, this involvement was purely in relation to an upper motor neurone lesion with reduced amplitude and speed of lingual movements, the tongue remaining normal in appearance. In nine patients, of whom six had a bulbar onset, during the course of the follow-up the pseudobulbar involvement was associated with a few lingual fasciculations and/or incipient paresis and/or amyotrophy. In two patients, dysarthria progressed to aphemia. All patients presented emotional lability. Twelve patients experienced difficulty in swallowing, particularly of liquids. This difficulty remained generally less severe than in classical ALS and was not accompanied by increased salivation and weight loss. In five patients, examination showed facial hypokinesia and amimia. Strained and nasal voice was found in 19 patients and slow and monotone speech in 17 patients. Seventeen patients had mandible and lip stiffness and breathing was limited upon effort in 10 patients. The majority of patients presented a strained larynx with stiffness of the velum and pharynx.

Muscle strength remained normal in six patients. On repeated examination, loss of strength was found in 10 patients but all except two of these patients never reached 3/5 on the MRC scale (Table 2). This weakness was localized mainly to the proximal muscles of the lower limbs or to the upper limbs and/or the interosseous muscles of the hand. This loss of strength increased insidiously; most patients experienced periods of stabilization lasting several months or years, and mild improvement was noted in three patients. Nine patients reported fasciculations and/or cramps as one of the first symptoms of the disease. Sixteen patients had cramps during the course of the disease and 18 complained transiently or repeatedly of fasciculations. Cramps affected mainly the lower limbs, and fasciculations usually occurred in the quadriceps femoris and the small muscles of the hand but were observed sometimes in the forearm or arm. Twelve patients had mild asymmetrical amyotrophy involving the interosseous muscles of the hands in all cases. In the three patients with the longest disease duration (mean duration 11.6 years) the anterior tibial muscles were also mildly amyotrophic. Using our predefined criteria, a peripheral motor deficit was observed during the course of the disease in all patients except one. This deficit was probable in six patients with a mean disease duration of 8.6 years and certain in 13 patients with a mean disease duration of 8.5 years. With these different clinical findings, the bulbar Norris was between 8 and 27 (mean = 14.85) (27 is the normal score) and the ALS FRS (Amyotrophic Lateral Sclerosis Functional Rating Scale) was between 14 and 35 (mean = 25.6) (40 is the normal score).

There was never a dementia pattern in the standard evaluation of the global cognitive pattern. Sixteen patients had significantly more errors in the frontal lobe functions and/or the premotor functions tests than age- and education-matched controls (Table 1). In all cases, these abnormalities were always moderate. Four patients had an isolated premotor syndrome, seven had an isolated executive involvement and two had a premotor syndrome associated with dysexecutive abnormalities. There was no correlation between these

**Table 3** *Central pathways: clinical and laboratory results*

| Patient | VEPs | SEPs | | Ocular movements |
|---|---|---|---|---|
| | | Upper limb | Lower limb | |
| 1 | Normal | Normal | Normal | Abnormal |
| 2 | Normal | Normal/increased | Increased/normal | Normal |
| 3 | Normal | Normal | Increased | Normal |
| 4 | Abnormal | Increased | Increased | Abnormal |
| 5 | Normal | Normal | Normal | Normal |
| 6 | Abnormal | Increased | Increased | Abnormal |
| 7 | Abnormal | Normal | Increased | Normal |
| 8 | Abnormal | Normal | Normal | Abnormal |
| 9 | Normal | Increased | Increased | Abnormal |
| 10 | Normal | Normal | Increased | Abnormal |
| 11 | Normal | Normal/increased | Normal | Abnormal |
| 12 | Normal | Normal | Normal | Normal |
| 13 | Normal | Normal | Increased | Normal |
| 14 | Normal | Normal | Normal | Normal |
| 15 | Normal | Normal | Normal | Normal |
| 16 | Abnormal | Normal | Normal | Normal |
| 17 | Abnormal | Normal | Normal | Abnormal |
| 18 | Abnormal | Normal | Normal | Abnormal |
| 19 | Abnormal | Normal/increased | Normal | Normal |
| 20 | Abnormal | Increased/normal | Normal | Normal |

abnormalities and the clinical data. Nine patients had impaired ocular movement (Table 3). In two patients, the pattern showed features that suggested progressive supranuclear paralysis, according to the description of Vidailhet (Vidailhet *et al*., 1994), with decreased saccadic amplitude. In the five remaining patients, the features suggested frontal or prefrontal involvement, with errors in the antisaccade task. There was no correlation between these abnormalities and the clinical data, except in the two patients in whom ocular movement showed progressive supranuclear paralysis. These two patients had the earliest disease onset (26 and 43 years). None of them had postural instability or falls during the first year of the disease (the oldest patient began to fall only after 7 years of disease).

## *EMG studies*

The results of the repeated electrophysiological studies are shown in Table 4. Five patients had two EMGs, two patients had three, five patients had four, five patients had five, two patients had six and one patient had nine.

At the first evaluation, none of the patients fulfilled the electrophysiological criteria for definite, probable or possible ALS, but six patients (mean disease duration 10.6 years) presented either denervation activity at rest or denervation potentials with decreased recruitment of MUPs, compatible with the criteria of Pringle and colleagues (Pringle *et al*., 1992). During subsequent examinations, the EMG abnormalities persisted or worsened in two of these six patients, in three of them the EMG normalized and the remaining patient showed a normal EMG transiently. Among the remaining 14 patients, who initially had a normal EMG, six retained their normal electrophysiological pattern in subsequent evaluations, whereas five developed denervation activity at rest or denervation potentials with decreased MUP recruitment and three presented transient denervation features.

Fibrillation potentials and/or positive sharp waves in at least two muscles in different limbs were detected transiently or repeatedly in six patients. In two patients, they were recorded at regular intervals without any clinical evidence of disease progression. Transient fasciculation potentials were recorded in at least two muscles in different limbs in three patients. We also recorded transient pseudomyotonic salves in eight patients. During maximal effort, evidence of denervation with decreased MUP recruitment in at least two muscles in different limbs was found at least once in 19 patients. These recruitment abnormalities were stable in three patients without clinical evidence of disease progression. Denervation affected various muscles of the lower and upper limbs, the anterior tibialis being the most frequently affected. In 11 cases, denervation recruitment was observed in cervical and facial muscles. Evidence of reinnervation with increased MUP recruitment and polyphasic or giant potentials in at least two muscles in different limbs was found at some stage of the study in 16 patients. These abnormalities were stable in two patients, one of whom presented constant fibrillation potentials, constant fasciculation potentials, and constant denervation and reinnervation recruitment, which appeared 2 years after the beginning of the follow-up. This patient had a disease duration of 13 years and experienced periods of stabilization lasting for more than 3 years. Motor amplitude and conduction velocities were normal in 17 patients. In the three patients with abnormalities, the motor axonal loss was moderate and affected the peroneal nerves in all three patients

**Table 4** *Electrophysiological and histological motor results*

| Patient | Electrophysiology | | | Muscle biopsy | | MEPs | |
|---|---|---|---|---|---|---|---|
| | Denervation | No.* | Reinnervation | Denervation | Reinnervation | Upper limb | Lower limb |
| 1 | 1 | 2 | 1 | No | Yes | Absent | Absent |
| 2 | 9 | 9 | 3 | No | Yes | Increased/normal | Absent |
| 3 | 4 | 5 | 1 | No | No | Normal | Absent |
| 4 | 2 | 2 | 1 | No | No | Absent | Absent |
| 5 | 3 | 5 | 1 | No | No | Absent | Absent |
| 6 | 3 | 3 | 0 | Yes | No | Absent | Absent |
| 7 | 4 | 4 | 4 | Yes | Yes | Absent/increased | Absent |
| 8 | 1 | 4 | 0 | No | No | Increased | Increased |
| 9 | 1 | 5 | 0 | Yes | Yes | Increased | Increased |
| 10 | 2 | 3 | 1 | Yes | Yes | Normal | Absent |
| 11 | 2 | 5 | 1 | No | No | Increased | Absent/normal |
| 12 | 1 | 5 | 1 | Yes | Yes | Absent | Absent |
| 13 | 1 | 2 | 1 | Yes | Yes | Absent | Absent |
| 14 | 0 | 2 | 1 | Yes | Yes | Absent | Absent |
| 15 | 2 | 2 | 2 | Yes | Yes | Absent | Absent |
| 16 | 4 | 6 | 3 | Yes | Yes | Increased | Absent/normal |
| 17 | 2 | 6 | 1 | Yes | Yes | Absent | Absent |
| 18 | 1 | 4 | 0 | Yes | Yes | Absent | Absent |
| 19 | 3 | 4 | 2 | No | No | Absent | Absent |
| 20 | 4 | 4 | 1 | Yes | Yes | Absent | Absent |

*Number of electrophysiological studies carried out.

and the median nerve in one patient. In all patients, sensory nerve conduction was normal.

At the last evaluation, three patients fulfilled the electrophysiological criteria of probable ALS without clinical evidence of disease progression (Patients 6, 7 and 9), with mean disease progression of 11.6 years, nine patients conserved normal EMG and the remaining eight patients had either denervation activity at rest or denervation potentials with decreased MUPS recruitment.

## *Other electrophysiological results*

CMCTs were studied in all patients (Table 4). All patients had severe abnormalities. An absence of response was observed in both the upper and lower limbs in 12 patients, only in the lower limbs in two patients, and CMCTs were increased asymmetrically or absent in the remaining six patients. Peripheral conduction times were always normal.

We found nine patients with bilateral VEP abnormalities (Table 3). There was a significant increase in the latency of the P100 component (range 116–137 ms) with a difference between the sides of $<6$ ms. P55, N65, N130 and interpeak P55–P100 values were always altered. The P100–N130 amplitudes were normal except in one patient.

SEPs were abnormal symmetrically or asymmetrically in 11 patients (Table 3). In the upper limbs, the N9–N13 was not delayed significantly, although the N20 peak was altered bilaterally in seven patients and unilaterally in three patients. The N13–N20 interval was increased bilaterally in one patient and unilaterally in four patients. The amplitudes were variably decreased, independently from the other abnormalities. In the lower limbs, the P40 peak was altered bilaterally in three patients and unilaterally in three patients. The P40 peak was not measurable in four patients, in one of these in both legs. The P22–40 interval was increased in 10 patients, bilaterally in two, unilaterally in two and absent in six patients. The amplitudes were constantly decreased except in one patient.

## *MRI results*

Brain MRI was normal in six patients. None of the patients showed signs of multiple sclerosis. Mild diffuse cortical atrophy was observed in eight patients, bilateral temporobasal cortical atrophy in two patients, mild leucoaraiosis in three patients and mild cortical atrophy of the primary motor area in one patient. None of the patients had specific corticospinal tract hyperintensity.

## *Muscle histology*

Deltoid muscle biopsies showed no mitochondrial abnormalities or dysfunction (Table 4). Muscle biopsies were normal in seven patients. Signs of both denervation and reinnervation were seen in 11 patients, an isolated denervation pattern in one patient and an isolated reinnervation pattern in one patient. Of the seven patients for whom the biopsy was normal, only two had a normal EMG at the end of the study. However, both of them showed transiently either denervation activity at rest or denervation potentials with decreased MUP recruitment during the follow-up period.

## Discussion

We carried out a prospective study of 20 patients with PLS diagnosed according to the criteria proposed by Pringle and colleagues (Pringle *et al.*, 1992). Our patients were screened for systemic inflammatory disease and, in the light of the recent study by Forsyth and colleagues (Forsyth *et al.*, 1997), for cancer. In order to determine the relationship between PLS and ALS, we looked for evidence of involvement of lower motor neurones using electrophysiological examinations and muscle biopsy. We also analysed potential signs of other forms of neurodegenerative disease.

The mean age at onset of symptoms was nearly identical to the age of onset of ALS (Hudson *et al.*, 1993; Norris *et al.*, 1993; Preux *et al.*, 1996). One of our patients with a 7-year disease duration had an unaffected homozygotic twin. In all cases, disease onset was insidious with very slow progression, consistent with the other reports for PLS (Stark and Moersch, 1945; Pringle *et al.*, 1992). This contrasts with classical ALS, in which the survival period after onset is reported to be 2.5 years (Smith, 1992). Most of our patients reported long periods of stabilization, a feature also reported by Stark and Moersch (Stark and Moersch, 1945). The frequency of bulbar onset (a little less than half of our patients) was higher than that reported in the literature for either PLS or ALS (Pringle *et al.*, 1992; Smith, 1992). In all patients but four, the disease progressed to debilitating spasticity in all four limbs, irrespective of the site of onset. Spasticity was free from marked weakness and atrophy, in contrast to what is observed in classical ALS. Also in contrast to ALS, pseudobulbar swallowing difficulties generally remained moderate, with long periods of stabilization or even improvement, sometimes several years after the onset of symptoms. All patients presented emotional lability or, at a more advanced stage, inappropriate laughing and crying. Facial inexpressiveness, also noted by other authors (Gastaut *et al.*, 1988), was restricted to the lower half of the face and was probably related to supranuclear facial diplegia with automatico-voluntary dissociation. Urinary urgency, which is uncommon in ALS, has been reported in PLS patients, in whom it is probably related to detrusor hyperreflexia and a spastic internal sphincter (Russo, 1982). This dysfunction is not, however, a systematic feature of PLS. It was not mentioned by Stark and Moersch (Stark and Moersch, 1945) and was specifically excluded by Pringle and colleagues (Pringle *et al.*, 1992). Our patients, however, frequently presented this disturbance (14 out of 20).

The analysis of MEPs elicited by cortical, cervical and lumbar magnetic stimulation confirmed the pyramidal tract involvement. Central motor conduction times were affected in all patients. The increased central conduction latency or lack of response to cortical stimulation observed in patients with normal peripheral conduction latency implies direct involvement of the descending motor pathways (Eisen *et al.*, 1990). This feature does not discriminate PLS from ALS, since similar results have been reported in both diseases (Ingram and Swash, 1987; Eisen *et al.*, 1990). Brown and colleagues (Brown *et al.*, 1992) claimed that the intensity of the lengthening of MEP latencies within the first 2 years of the disease is probably the most specific diagnostic criteria of suspected cases of PLS. Our findings support this argument, especially in cases when prolonged MEP latencies in the lower limb are found at an early stage of the disease.

The lack of lower motor neurone involvement in PLS is considered a key feature distinguishing PLS from ALS. However, clinical and electrophysiological evidence from the present study suggests that this is not necessarily the case; such involvement remained less marked than in ALS. The lower motor neurone involvement was suggested by the presence of cramps, fasciculations and/or mild amyotrophy. While these features are three classic symptoms of ALS, they have also been described occasionally in PLS (Spiller, 1904; Wilson, 1940; Mackay, 1963; Castaigne *et al.*, 1972; Ungar-Sargon *et al.*, 1980; Russo, 1982; Sotaniemi and Myllylä, 1985; Younger *et al.*, 1988; Norris *et al.*, 1993; Bruyn *et al.*, 1995). Although atrophy could potentially be explained by under-use atrophy of limbs due to spasticity (Ungar-Sargon *et al.*, 1980), it seems more probable that the high frequency and degree of association of all three symptoms reflects a transient or chronic dysfunction of lower motor neurones.

At least at the beginning of the study, the electrophysiological features of our patients never met the requirements for definite, probable or possible ALS (Brooks, 1994). Two patients presented persistent fibrillation potentials from the time of inclusion and went on to develop moderate axonal motor loss revealing motor denervation, without modification of the clinical picture. Overall, we found evidence of denervation at some point in the study in 14 patients, with fibrillations, positive sharp waves, abnormal recruitment and a reduction in the number of MUPs. These findings are consistent with a process consisting of periods of denervation followed by periods of reinnervation throughout the entire course of the disease. Chronic reinnervation was observed in EMG in 12 patients and in muscle biopsies in 11 patients. Some authors have suggested that fibrillation potentials and denervation activity may occur at later stages of PLS (Brown *et al.*, 1992; Pringle *et al.*, 1992; Norris *et al.*, 1993). The results of our prospective study, however, suggest that these potentials could imply active denervation not only in late stages but throughout the course of the disease. This conclusion is supported by the data from the muscle biopsies.

The physiopathological significance of these EMG findings remains controversial. Fibrillation potentials were considered by Brown and Snow to be a consequence of severe spasticity (Brown and Snow, 1990), whereas others have suggested an association of fibrillation and denervation potentials with lesions of cortical motor neurones (Ashby, 1987; Eidelberg *et al.*, 1989; Brown *et al.*, 1992). It has also been suggested that hyperexcitability of cortical motor neurones might produce a volley of fasciculations by synchronous stimulation

of multiple spinal motor neurones. (Kaji *et al.*, 1993; Mills, 1995; Kohara *et al.*, 1996). In our opinion, these signs actually reflect lower motor neurone involvement. This would be in agreement with a recent review by Swash and colleagues, who suggested that, in patients with an initial diagnosis of PLS, disease often evolves into classical ALS with lower motor neurone signs (Swash *et al*., 1999), and Rowland admitted 'the need to know what proportion of patients with PLS eventually prove to have symptoms and signs of ALS' (Rowland, 1999). In fact, anterior horn cell loss has been reported in PLS but appears to be much less extensive than in ALS (Mackay, 1963; Brownell *et al.*, 1970; Castaigne *et al.*, 1972; Pringle *et al.*, 1992). Rowland suggested that their patients could be divided into four groups: the first comprised patients with autopsy-proved PLS, the second living patients with normal EMG, the third patients with EMG signs of denervation and the fourth PLS patients who were HIV-positive. As no autopsy was performed during our longitudinal electrophysiological study, we could divide our patients in two groups. The first comprised three patients with normal EMG (Patients 9, 14 and 15); they would meet the criteria of Pringle and colleagues (Pringle *et al*., 1992) but they all presented cramps, fasciculation, a deficit on the MRC scale and denervation and reinnervation in biopsy. The second group comprised the 17 remaining patients, who showed EMG signs of denervation. To date, none of them has shown fatal progression to ALS. The three patients who fulfilled the electrophysiological criteria of probable ALS had no clinical evidence of disease progression even though they had the longest disease duration.

It appears from our study that the disease process in PLS extends beyond the motor system. In two patients, impaired ocular movements suggested a diagnosis of progressive supranuclear paralysis. However, none of them reached the criteria as defined by Litvan and colleagues (Litvan *et al*., 1996): the first patient was too young at the onset of the disease and had no falls during the first year of the disease course and the second patient began to fall only after 7 years of disease. We identified anomalies in VEPs upon at least one evaluation in eight patients. In 11 patients we also observed SEP abnormalities that were sufficiently stable to be seen on consecutive evaluations. Some studies have demonstrated that significant changes in SEPs can occur in spastic paraparesis without overt sensory impairment, and this has also been described in some patients with PLS (Bosch *et al.*, 1985; Dasheiff *et al.*, 1985; Matheson *et al.*, 1986; Aalfs *et al.*, 1993*a*, *b*; Georgesco *et al.*, 1994). There was no apparent correlation between the magnitudes of the VEP and SEP anomalies and the severity of spasticity. In PLS, Georgesco and colleagues claimed that the SEP abnormalities are related to involvement that is restricted to Brodmann area 4 (Georgesco *et al*., 1994), whereas others have implicated demyelinization and axonal degeneration of sensory fibres similar to that demonstrated in ALS (Bradley *et al.*, 1983). Post-mortem studies in PLS patients have demonstrated slight degeneration of both posterior columns, which accompanies the more severe degeneration of the lateral corticospinal tracts (Fisher 1977; Beal and Richardson, 1981; Younger *et al.*, 1988).

In ALS, it has been largely demonstrated that the degeneration process extends to tracts other than the pyramidal tract. Numerous publications have described degeneration of Clark's column, the accessory cuneate nucleus, the middle root zone of the posterior column and the spinocerebellar, rubrospinal, vestibulospinal and tectospinal tracts (Charcot and Marie, 1885; Bertrand and van Bogaert, 1925; Engel *et al.*, 1959; Hirano *et al.*, 1967; Brownell *et al.*, 1970; Castaigne *et al*., 1972; Averback and Crocker, 1982; Sasaki *et al.*, 1992; Kato *et al.*, 1993; Katayama *et al.*, 1999). This is supported by several recent studies of multimodality-evoked potentials in ALS. Münte and colleagues provided evidence of alteration of early components of the VEPs in ALS and suggested that these were related to involvement of the inferior occipitotemporal areas (Münte *et al*., 1998). SEP abnormalities have been reported in sporadic or familial ALS (Laxer and Spence, 1980; Cosi *et al.*, 1984; Yamada *et al.*, 1984; Dasheiff *et al.*, 1985; Matheson *et al.*, 1986; Radtke *et al.*, 1986; Ghezzi *et al.*, 1989; Zanette *et al.*, 1996). In these series, SEPs were abnormal in 2–75% of patients, and they appeared to be more common in patients with a pyramidal tract dysfunction, as patients with progressive muscular atrophy had normal SEPs. Zanette and colleagues suggested that the frequent impairment of the early SEPs could reflect the activation of the prerolandic cortex in response to sensory input and thus be related to upper motor neurone involvement in this disease (Zanette *et al*., 1996). A similar hypothesis may be applicable to PLS, in which there is involvement of the pyramidal cells of the precentral gyrus.

Using MRI, we found discrete cortical atrophy in 11 patients, but the primary motor area was involved in only one patient. Pringle and colleagues considered atrophy of the motor cortex to be suggestive of a diagnosis of PLS (Pringle *et al*., 1990, 1992). However, this is not a consistent feature for other authors and so it cannot be considered as critical for the diagnosis of PLS (Gastaut *et al.*, 1988; Younger *et al.*, 1988). In a previous clinical, radiological and PET study of nine patients with PLS, we found four patients with discrete cortical atrophy, mainly in the primary motor cortex, and five patients with [$^{11}$C]flumazenil-PET abnormalities in both the density of benzodiazepine receptors and the regional distribution of cerebral blood flow (rCBF), localized in the fronto-opercular (precentral gyrus) and anterior cingulate cortex (Le Forestier *et al.*, 2001). Similar abnormalities have been reported in ALS (Kew *et al.*, 1993*a*, *b*; Abrahams *et al.*, 1996), suggesting that the abnormality in rCBF in PLS has features in common with that in ALS (Garnett *et al.*, 1990).

Although we did not observe any clinical evidence of dementia, at least one premotor syndrome was identified in nine patients (unpublished results). Five publications have reported normal intellectual function in PLS (Beal and Richardson, 1981; Russo, 1982; Sotaniemi and Myllylä, 1985; Gastaut *et al.*, 1988; Pringle *et al.*, 1992). Caselli

and colleagues observed mild cognitive impairment in nine patients (Caselli *et al*., 1995) and dementia has been reported in one atypical case of PLS, presenting diffusely distributed Lewy bodies (Hainfellner *et al.*, 1995). Alzheimer's disease, diffuse Lewy body disease and motor neurone disease are all distinguishable clinical entities, although individual patients may present various features of these conditions simultaneously (Appel, 1981; Calne *et al.*, 1986; Delisle *et al.*, 1987; Frecker *et al.*, 1990; Sadovnick, 1990; Eisen and Calne, 1992; Tranchant *et al.*, 1992; Hedera *et al.*, 1995). Recently, a variant of Alzheimer's disease with spastic paraparesis has been reported (Verkkoniemi *et al*., 2000).

This longitudinal study evaluated the evolution of a wide variety of clinical, laboratory and functional parameters in 20 PLS patients. It is the most extensive prospective study of this disease to have been reported. Our results, taken in conjunction with those reported in clinical and post-mortem studies, lead us to conclude that PLS is not a discrete nosological entity but represents one end of a continuous spectrum of motor neurone disease. To take this concept one stage further, the idea that motor neurone disease itself should be considered as a member of a family of neurodegenerative diseases with no absolute boundaries between them has emerged in recent publications (Burrow and Blumbergs, 1992; Ince *et al.*, 1998). Further longitudinal studies of PLS, as well as more systematic electrophysiological and morphological studies (neuroimaging and post-mortem studies), could help us to understand its commonalities with and differences from other neurodegenerative diseases and contribute to the further elucidation of their underlying physiopathology.

## Acknowledgements

We wish to thank the Association pour la Recherche sur la Sclérose Latérale Amyotrophique (ARS) for technical and financial assistance.

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*Received December 31, 2000. Revised May 23, 2001.*
*Accepted May 31, 2001*