ELSEVIER

Clinical Neurology and Neurosurgery 110 (2008) 387–391

Clinical Neurology and Neurosurgery

www.elsevier.com/locate/clineuro

Case report

# Pure primary lateral sclerosis—Case reports

Barbara Tomik *, Kamila Anna Zur, Andrzej Szczudlik

*Department of Neurology, Jagiellonian University Medical College, 3 Botaniczna Street, Krakow, Poland*

Received 27 June 2007; received in revised form 26 November 2007; accepted 4 December 2007

**Abstract**

There is still a debate whether primary lateral sclerosis (PLS) is a distinct pathological entity or whether it represents one end of a continuous spectrum of motor neuron disease (MND).

In this report we present four PLS patients who have been observed from the time of symptom onset (1990–1999) through January 2007. All of them have had only upper motor neuron (UMN) signs and slow clinical progression. Three patients have been presented with spastic paraparesis. Spasticity was the main clinical feature in demonstrated cases with hyperactive deep tendon reflexes, clonus, and Babinski signs. One patient was presented with spastic dysarthria at the disease onset. Mean disease duration, measured from symptom onset to the present, was 11.5 years in our reported series. All four PLS patients had not developed lower motor neuron (LMN) signs during this time of observation.

This prospective analysis of our PLS series is in agreement with data from other studies suggesting that pure PLS cases have a prolonged course of disease with a high level of independence when compared to other MND.


*Keywords:* Primary lateral sclerosis; Spinobulbar spasticity; Slow progression

## 1. Introduction

Primary lateral sclerosis (PSL) is a rare, non-hereditary degenerative disorder of the upper motor neuron characterized by progressive spinobulbar spasticity, related to the selective loss of precentral pyramidal neurons, with secondary pyramidal tract degeneration and preservation of anterior horn motor neurons [1,2]. In 1874, Charcot described the exclusive involvement of the lateral corticospinal tract in PLS cases and named this nosological entity 'primary sclerosis of the lateral columns'. In 1992 Pringle et al. [3] proposed diagnostic criteria for PLS. The pathophysiologic basis of PLS remains unknown [4]. There is currently no defining test or disease marker; thus, PLS is still a clinical diagnosis and a variety of investigations are usually carried out to exclude other potentially reversible causes of such presentation [3,5,6]. Recently, Singer et al. [7] demonstrated the history of PLS from initial descriptions to present as well as the new diagnostic guidelines for PLS-spectrum disorders. This diagnostic criteria combining the clinical and laboratory features to classify patients as clinical PLS, suspected PLS, or complicated PLS ('PLS plus' with additional signs such as dementia, parkinsonism, or sensory abnormalities) [7].

PLS entity is not universally accepted. Debate continues over whether the disease constitutes a distinct clinical and pathological entity or whether it is a part of the spectrum of MNDs that presents an upper motor neuron (UMN) predominant form of MND [6,8–13].

In the present report we describe four PLS patients selected from the database of 350 sporadic MND patients at the Department of Neurology, Jagiellonian University Medical College in Krakow and diagnosed according to Pringle et al. criteria [3]. The patients were personally examined by one of us (BT). Clinical progression of the disease, electrophysiological examinations and neuroimaging were analyzed, respectively. An extensive serological screening and CSF examinations were carried out in all patients. The course of the disease and the details of the medical and diagnostic

* Corresponding author. Tel.: +48 12 424 86 00; fax: +48 12 424 8626.
*E-mail address:* tomik@neuro.cm-uj.krakow.pl (B. Tomik).

0303-8467/$ – see front matter © 2008 Elsevier B.V. All rights reserved.
doi:10.1016/j.clineuro.2007.12.002

history of the PLS patients were followed from the time of disease onset (1990–1999) up till January 2007. We excluded patients with other identifiable cause for corticospinal tract degeneration than MND.

## 2. Case reports

### 2.1. Patient 1

A 67-year-old man complained of stiffness and slight weakness of the right leg since 1990. A few months later he noticed stiffness in the left leg also. There was a period of sign stabilization lasting several months. He began using a walking stick in 1995. Stiffness of the legs and difficulty in walking gradually worsened. There was no history of fasciculation, cognitive decline, sensory or sphincter dysfunction. He had been previously healthy. The family history was negative. In 1970 he had an accident with a compressive fracture of spine (C3).

The general examination was normal. There was asymmetrical spasticity in lower limbs, especially on the right side. The gait was spastic. The jaw-jerk and limb tendon reflexes were increased, with ankle and knee clonus and bilateral Babinski and Hoffman signs. There were no superficial abdominal reflexes. Ocular movements were normal. There was a small degree of wasting in the right leg. There was no fasciculation, sensory impairment, or cognitive dysfunction. Nerve conduction studies and EMG studies were normal. Hematology, serum biochemistry, B 12 level, CSF, autoantibody panel and chest X-ray were normal. Lyme serology was negative. MRI of the brain, cervical and thoracic spinal cord was normal.

### 2.2. Patient 2

A 77-year-old woman developed slurred speech in 1996, which gradually worsened. She described stiffness of the tongue and muscles of her face (spastic dysarthria), without features of fatigability (apocamnosis). She also complained of difficulty in swallowing especially of liquids. The swallowing problem remained moderate, with a long period of stabilization. There was no history of change in judgment or personality. Her past medical and family histories were negative.

The general examination was normal. Neurological examination showed spastic speech, brisk jaw-jerk tongue without atrophy and fasciculation but with slow movements and overshoot on right. Minor emotional lability was present. There were brisk reflexes in the upper limbs (more marked on the left side). There was no wasting or fasciculation in the limbs and trunk. Nerve conduction studies were normal and EMG examination did not show neurogenic abnormalities. Hematology, serum biochemistry, serum immunoelectrophoresis, autoantibody panel, B 12 level, CSF examination, chest X-ray, and brain as well as cervical spinal cord MRI were normal. Neuropsychological examination showed discreet cognitive impairment without features of dementia.

### 2.3. Patient 3

A 42-year-old man complained of stiffness, heaviness and pain in the legs which gradually worsened while walking, beginning in 1997. He found it difficult to walk quickly and it was increasingly difficult after an effort. There was a period of sign stabilization from 2000 to 2002. Since 2002, he also noticed stiffness of the fingers in both hands. There was no history of cognitive decline, sensory or sphincter dysfunction, change in judgment, personality, or memory but there was some tendency of emotional lability since 2005. There was no family history of neurological illness.

Physical examination revealed abnormalities restricted to the nervous system. There was asymmetrical spasticity in lower limbs, more prominent in the right leg .The jaw-jerk and limb tendon reflexes were increased, with ankle and knee clonus and bilateral Babinski signs. The gait was spastic. Cerebral examination was normal. Nerve conduction studies and EMG studies were normal. Hematology, serum biochemistry, B 12 level, antibody panel, CSF-examination, chest X-ray, and brain and thoracic spinal cord MRI were normal.

### 2.4. Patient 4

A 41-year-old woman complained of stiffness and heaviness in her legs since 1999. The symptoms gradually worsened during the years and she presented with a walking problem. In 2001, she also noticed stiffness in the left arm. She has used a walking stick since 2002. There was no history of wasting, fasciculation, cognitive decline, sensory or sphincter dysfunction. She had been previously healthy. There was no family history of MND or other neurological illness.

The general examination was normal. There was an asymmetric spastic paraparesis, more on the right side with a spastic gait. Power was graded 4/5 in the legs and 5/5 in the arms (MRC). The jaw-jerk and limb tendon reflexes were increased, with ankle and knee clonus and Babinski sign on the left side. We noticed the presence of cramps and slight amyotrophy proximally in the right leg. Ocular movements were normal. There were no other neurological abnormalities. There was no urination problem. Nerve conduction studies were normal and concentric needle EMG of the tongue and limbs did not reveal neurological changes. Hematology, ESR, serum biochemistry, B 12 level, CSF, serum immuno-electrophoresis, autoantibody panel, and chest X-ray were normal. Lyme serology was negative. MRI of the brain showed a single, small hyperintensive focus in white matter inferior to the precentral gyrus on the right side. MRI of cervical, thoracic, and lumbar spinal cord was normal.

## 3. Discussion

The question whether PLS has a nosological existence distinct from amyotrophic lateral sclerosis (ALS) has been the subject of controversy since it was described [3,4,14,15]. There are few clinical reports of PLS in the literature and it is suggested that the disease has a heterogeneous clinical presentation [1,5,15].

We studied 4 patients with PLS, diagnosed according to the criteria proposed by Pringle et al. [3]. None of them fulfilled the criteria for definite, probable or possible ALS [16]. The site of onset was the lower limbs and bulbar region. Three of them have had a relatively homogenous ascending pattern of slowly progressive course of symptoms, mainly spasticity, and the beginning of the disease in the leg. The disease gradually involved both legs before symptoms began in the arms [11,17]. During the years of observation, PLS degeneration progressed to debilitating and symmetrical spasticity in our patients. In all cases muscle strength never achieved 3/5 on the MRC scale (see Table 1); this has been pointed out as a characteristic sign for PLS cases [11,12]. One patient presented with pseudobulbar pattern of symptom onset and also had slow progression of the disease.

PLS usually is equally distributed between both sexes [3]. Median age of onset is 44.5 years [17], in our series it was 44.25 years (range 32–66). PLS occurs with frequency around 1–3% of all patients with MND [18]. In our study it represents 1.1% out of 350 patients with sporadic MND diagnosed in Department of Neurology in Krakow. The duration of the disease was 1–7 years before the patients were admitted to MND Clinic in Krakow. In all our patients the clinical course of disease was slowly progressive from 8 to 17 years. None of them died during the time of observation. Three patients have had difficulties in walking due to extreme spasticity, and two of them required a walking stick after a mean disease duration of 4.5 years (range from 3 to 6 years). One patient presented with pseudobulbar signs at onset and still differs significantly from the others by lack of pyramidal manifestation in the legs. None of our patients have had urinary incontinence as previously been reported in PLS patients, related to detrusor hyperreflexia and spastic internal sphincter [19]. Our patients have also had no clinical signs of cognitive deterioration. On detailed neuropsychological evaluation, minor cognitive impairment with marked emotional lability has been found in the patient manifesting a mainly pseudobulbar pattern of PLS.

Based on Gordon et al. criteria [18] (isolated UMN signs 4 years after symptom onset, with slow progression and high levels of function) we have classified our cases as having pure PLS (despite the occurrence of minor wasting and very limited amyotrophy in two of our cases, as described below).

The characteristic clinical signs of our PLS patients are shown in Table 1. The comparison between our PLS series and other studies is shown in Table 2.

Table 1
Clinical characteristics of presented patients

| Patient | Sex | Age at onset, years | Duration years | Site of disease onset | Pseudobulbar syndrome | Pyramidal syndrome in limbs | Gait aids | Urinary urgency | Sympt. pattern | Abnormal EMG/ENG findings | MRC scale legs |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | M | 60 | 17 | LLr | Yes | Yes | Cane | No | Ascend | No | 4/5 |
| 2 | F | 66 | 11 | PsB | Yes | Yes | None | No | Pseudobulbar | No | 5/5 |
| 3 | M | 35 | 10 | LLr | Yes | Yes | None | No | Ascend | No | 4/5 |
| 4 | F | 33 | 8 | LLs | Yes | Yes | Cane | No | Ascend | No | 4/5 |

LLs = both lower limbs, LLl = left lower limb, LLr = right lower limb, PsB = pseudobulbar, F = female, M = male, Symp = symptoms, Asced = ascending.

Table 2
PLS—the comparison of data

| | Le Forestier et al.[a] [5] | Zhai et al.[a] [11] | Tartaglia et al.[a] [12] | Kuipers-Upmeijer et al.[a] [17] | Gordon et al.[a] [18] | Singer et al.[a] [21] | Our study |
|---|---|---|---|---|---|---|---|
| Mean age of onset (years) | 53.4 (26–64) | 45.4 (37–53.8) | 54.6 (33–74) | 44.5 (23–57) | 51 | 53.7 (32–76) | 45.25 (32–66) |
| Mean duration of disease (years) | 8.5 (4–14) | 9.7 (3–53) | 11.2 | 12.7 (6–35) | 7.75 | 7.9 (3–15) | 11.5 (8–17) |
| Mean follow-up months | 43.4 (18–60) | More than 12 | 192 | 24–336 | 104.4 | 60 | 102 (96–204) |
| % of PLS cases out of all cases with MND | 4.4% | – | 6.5% | – | 1–3% | 3% | 1.1% |
| Male: female ratio | 15:5 | 10:15 | 49:51 | 9:1 | 7:4 | 14:11 | 2:2 |

[a] Reference number.

The lack of clinical presentation of LMN signs in PLS is considered a key feature distinguishing PLS from ALS [3]. However, Pringle et al. described diagnostic criteria broadened to also include those patients with limited electrophysiologic evidence of denervation ('occasional fibrillation and increased insertional activity in a few muscles (late and minor' [3])).

In our study we did not find any electrophysiological or strong clinical (i.e., fasciculation, amyotrophy) evidence suggesting LMN involvement. However, we noticed presence of cramps and very limited amyotrophy in the right leg (patient 4) and minor wasting in the right leg (patient 1). It could potentially be explained by extreme spasticity and a long period of under-use of lower limbs [20], especially in light of the fact that the patients still had normal results of EMG studies, which were performed four times during the clinical observation.

Bruyn et al. [4] noted the development of LMN features after 7.5, 9, and 27 years in three men initially diagnosed as having PLS. Those patients were diagnosed as having ALS. Also Le Forestier et al. [5] found that 3 out of 20 of their patients initially diagnosed as PLS, satisfied criteria for probable ALS by developing LMN signs after 11–13 years. On the other hand, Tartaglia et al. [12] demonstrated the occurrence of limb wasting in patients with PLS but it was rare, only in 2% of his series as compared with 100% in patients with ALS [12]. The intensity and distribution of these symptoms always differed from those in ALS [1,5]. Singer et al. [21] reported a significantly decreased ability to ambulate independently in their patients with PLS and minimal EMG changes. Weber et al. [22] have found that PLS patients with EMG signs of active denervation remain stable, similar to those who have normal EMG. This may suggest that the demise of anterior horn cells in the course of PLS involves different mechanisms than that in ALS [22].

PLS tends to follow a very slow progressive course, a key distinctive clinical feature compared with ALS [7]. While the average life expectancy for patients with ALS is about 3 years [23], the longevity information for PLS cases is still incomplete [7]. In PLS patients with reported deaths, survival range from 1 to 15 years from disease onset [14,21,24]. Also, the urinary complaints appear more commonly in PLS than in ALS [7,19].

On the other hand, PLS could be considered a clinical variant of ALS because PLS and ALS share a similar age at onset (typically begin in the fifth to sixth decade) and both have bulbar and spinal onset forms [9]. As with ALS, sensory symptoms and signs in PLS patients should prompt continued investigations for an alternative diagnosis. Similar to ALS, there is no single diagnostic test for PLS [12]. Finally, pathological hallmarks of ALS, including ubiquitinated inclusions and Bunina bodies, have also been observed in patients with PLS [12].

There are some limitations of the present study. First of all we only observed a very small group of PLS patients; however, all of them are still being followed up on a rou-

tine basis. We did not perform the screening for presence of HTLV-1 antibodies in blood and CSF in our cases. We believe that we can exclude HTLV-1-associated myelopathy because HTLV-1 is an endemic disorder, and usually presents with bladder disturbances, constipation and some sensory symptoms [25]. None of these were observed in our cases. We also did not perform genetic screening for hereditary spastic paraparesis (HSP) as this disease usually displays strong patterns of familial incidence, and in a majority of cases presents at a much younger age [12].

We have observed that spasticity and stiffness were more common signs in our PLS cases with initial lower extremity presentation. The lack of limb wasting during the years of observation suggested the exclusion of ALS presentation throughout that time. However, the possibility that PLS could be a more benign form of ALS still cannot be excluded. It was pointed out that some patients with initial diagnosis of PLS can evolve into classical ALS [4,7,12], and require close follow-up to determine whether LMN develops [6,18].

Based on our long period of observation and literature review, we suggest that recognition of a characteristic phenotype of pure PLS is important because it offers much better prognosis than ALS. Pure PLS cases have a prolonged course of the disease with a high level of independence for years. This being said, those patients still need systematic clinical and electrophysiological observation.

## References


[1] Le Forestier N, Maisonobe T, Spelle L, Lesort A, Salachas F, Lacomblez L, Samason Y, Bouche P, Meninger V. Primary lateral sclerosis: further clarification. J Neurol Sci 2001;185:95–100.

[2] Short CL, Scott G, Blumbergs PC, Koblar SA. A case of presumptive primary lateral sclerosis with upper and lower motor neurone pathology. J Clin Neurosci 2005;12:706–9.

[3] Pringle CE, Hudson AJ, Munoz DG, Kiernan JA, Brown WF, Ebers GC. Primary lateral sclerosis. Clinical features, neuropathology and diagnostic criteria. Brain 1992;115:495–520.

[4] Bruyn RP, Koelman JH, Troost D, de Jong JM. Motor neuron disease (amyotrophic lateral sclerosis) arising from longstanding primary lateral sclerosis. J Neurol Neurosurg Psychiatry 1995;58: 742–4.

[5] Le Forestier N, Maisonobe T, Piquard A, Rivaud S, Crevier-Buchman L, Salachas F, Pradat PF, Lacomblez L, Meininger V. Does primary lateral sclerosis exist? A study of 20 patients and review of the literature. Brain 2001;124:1989–99.

[6] Swash M, Desai J, Misra VP. What is primary lateral sclerosis? J Neurol Sci 1999;170:5–10.

[7] Singer MA, Statland JM, Wolfe GI, Barohn RJ. Primary lateral sclerosis. Muscle Nerve 2007;35:291–302.

[8] Georgesco M, Salerno A, Carlander B, Leger JJ, Camu W, Billiard M, Cadilhac J. Somatosensory evoked potentials in amyotrophic lateral sclerosis and primary lateral sclerosis. Revue Neurol (Paris) 1994;150(4):292–8.

[9] Brugman F, Wokke JH, Vianney de Jong JM, Franssen H, Faber CG, Van den Berg LH. Primary lateral sclerosis as a phenotypic manifestation of familial. ALS Neurol 2005;64:1778–9.

[10] Peretti-Viton P, Azulay JP, Trefouret S, Brunel H, Daniel C, Viton JM, Flori A, Salazard B, Pouget J, Serratrice G, Salamon G. MRI of the intracranial corticospinal tracts in amyotrophic and primary lateral sclerosis. Neuroradiology 1999;41:744–9.

[11] Zhai P, Pagan F, Statland J, Butman JA, Floeter MK. Primary lateral sclerosis A heterogeneous disorder composed of different subtypes? Neurology 2003;60:1258–65.

[12] Tartaglia MC, Rowe A, Findlater K, Orange JB, Grace G, Strong MJ. Differentiation between primary lateral sclerosis and amyotrophic lateral sclerosis: examination of symptoms and signs at disease onset and during follow-up. Archiv Neurol 2007;64:232–6.

[13] Sotaniemi KA, Myllyla VV. Primary lateral sclerosis; a debated entity. Acta Neurol Scandy 1985;71:334–46.

[14] Younger DS, Chou S, Hays AP, Lange DJ, Emerson R, Brin M, Thompson Jr H, Rowland LP. Primary lateral sclerosis A clinical diagnosis reemerges. Archiv Neurol 1988;45:1304–7.

[15] Hudson AJ, Kiernan JA, Munoz DG, Pringle CE, Brown WF, Ebers GC. Clinicopathological features of primary lateral sclerosis are different from amyotrophic lateral sclerosis. Brain Res Bull 1993;30:359–64.

[16] Brooks BR. El Escorial World Federation of Neurology criteria for the diagnosis of amyotrophic lateral sclerosis. Subcommittee on Motor Neuron Diseases/Amyotrophic Lateral Sclerosis of the World Federation of Neurology Research Group on Neuromuscular Diseases and the El Escorial "Clinical limits of amyotrophic lateral sclerosis" workshop contributors. J Neurol Sci 1994;124(Suppl.):96–107.

[17] Kuipers-Upmeijer J, de Jager AE, Hew JM, Snoek JW, van Weerden TW. Primary lateral sclerosis: clinical, neurophysiological, and magnetic resonance findings. J Neurol Neurosurg Psychiatry 2001;71:615–20.

[18] Gordon PH, Cheng B, Katz IB, Pinto M, Hays AP, Mitsumoto H, Rowland LP. The natural history of primary lateral sclerosis. Neurology 2006;66:647–53.

[19] Russo Jr LS. Clinical and electrophysiological studies in primary lateral sclerosis. Archiv Neurol 1982;39:662–4.

[20] Ungar-Sargon JY, Lovelace RE, Brust JC. Spastic paraplegia-paraparesis. A reappraisal. J Neurol Sci 1980;46:1–12.

[21] Singer MA, Kojan S, Baroh R, Herbelin L, Nations S, Trivedi J, Jackson C, Burns D, Boyer Ph, Wolfe G. Primary lateral sclerosis: clinical and laboratory features in 25 patients. J Clin Neuromusc Dis 2005;7:1–9.

[22] Weber M, Stewart H, Hirota N, Eisen A. Corticomotoneuronal connections in primary lateral sclerosis (PLS). Amyotrophic Lateral Scler Other Motor Neuron Discord 2002;3:190–8.

[23] Gastaut JL, Michel B, Figarella-Branger D, Somma-Mauvais H. Chronic progressive spinobulbar spasticity. A rare form of primary lateral sclerosis. Arch Neurol 1988;45:509–13.

[24] Fisher CM. Pure spastic paralysis of corticospinal origin. Can J Neurol Sci 1977;4:251–8.

[25] Araujo AQ, Silva MT. The HTLV-1 neurological complex. Lancet Neurol 2006;5:1068–76.