

Primary lateral sclerosis

Authors: Doctor Frans Brugman¹ and Professor John Wokke

Creation Date: December 2002

Update: April 2004

Scientific Editor: Professor Marianne de Visser

¹Rudolf Magnus Institute of Neuroscience, Department of Neurology section Neuromuscular Diseases, University Medical Center, HP G03.328, 3508 GA Utrecht, Netherlands. F.Brugman@neuro.azu.nl

[Abstract](#)

[Keywords](#)

[Name of disease and synonyms](#)

[Name of excluded diseases](#)

[Diagnostic criteria / definition](#)

[Differential diagnosis](#)

[Frequency](#)

[Clinical description](#)

[Management including treatment](#)

[Etiology](#)

[Diagnosis](#)

[Unresolved questions](#)

[References](#)

Abstract

Primary lateral sclerosis (PLS) is an idiopathic non-familial neurodegenerative disorder of upper motor neurons, presenting as a slowly progressive pyramidal tract syndrome. Disease onset is usually between 40 and 60 years with spasticity in the legs. Onset in the pseudobulbar region with speech and swallowing disturbance is also possible. Ultimately, a tetrapyramidal syndrome develops, sometimes with marked pseudobulbar features (forced laughing and crying). Life expectancy is normal. Pringle criteria for PLS consist of adult onset of symptoms, a negative family history, normal findings of blood, urine and CSF tests, no abnormalities on EMG, and on brain and spinal cord MRI. PLS is considered to be a benign variant of Amyotrophic lateral sclerosis (ALS). The etiology is not known. The annual incidence and the prevalence of PLS are estimated to 1 in 1.000.000 and 10-20 in 1.000.000, respectively. Treatment of PLS is symptomatic and can involve prescription of antispasticity medication and rehabilitation.

Keywords

Primary lateral sclerosis, PLS, amyotrophic lateral sclerosis, ALS, motor neuron disease, MND, hereditary spastic paraparesis, HSP

Name of disease and synonyms

Primary lateral sclerosis, PLS

progressive pyramidal tract syndrome, sometimes with marked pseudobulbar symptoms.

Name of excluded diseases

Other diseases that can present as progressive pyramidal tract syndromes and/or pseudobulbar syndromes. See "differential diagnosis".

The diagnosis is based on exclusion of other causes and requires normal findings of blood, urine and CSF tests, normal EMG findings and no abnormalities of brain and spinal cord MRI. In 1992, Pringle and colleagues proposed diagnostic criteria for PLS. These criteria are generally accepted and consist of adult onset of symptoms and a negative family history, in addition to normal findings of the above-

Diagnostic criteria / definition

PLS is an idiopathic non-familial neurodegenerative disorder of upper motor neurons. PLS presents clinically as a slowly

mentioned additional tests. The Pringle criteria require a disease duration of at least three years to exclude [Amyotrophic lateral sclerosis](#) (ALS), as the initial presentation of ALS can be a pure upper motor neuron syndrome.

Differential diagnosis

Other causes of a slowly progressive pyramidal and/or pseudobulbar syndrome include:

Structural disorders

- Cervical spondylotic myelopathy
- Arnold-Chiari malformation
- Spinal arteriovenous fistula
- Tumor
- Hydrocephalus

Uncomplicated forms of hereditary spastic paraparesis (pure HSP);

Leukodystrophies

- Adrenoleukodystrophy/adrenomyeloneuropathy
- Metachromatic leukodystrophy
- Globoid cell leukodystrophy/Krabbe's disease

Other metabolic and toxic disorders

- [Cerebro-tendinous xanthomatosis](#)
- Subacute combined degeneration of the cord
- Vitamin E deficiency
- Hexosaminidase deficiency
- Lathyrism
- Konzo

Infections

- Neurosyphilis
- Tropical spastic paraparesis (HTLV1)
- Neuroborreliosis
- Spinal sarcoidosis
- AIDS

Primary progressive multiple sclerosis (PPMS) can show a pure motor phenotype.

ALS can initially present as a pure upper motor neuron syndrome, before the appearance of clinical or neurophysiological signs of lower motor neuron loss.

Disease duration of at least three years is required before the diagnosis of PLS can be made, according to the Pringle criteria. However, transition to ALS has been described in patients with longstanding PLS, even after a disease duration of as long as 18 years.

Frequency

PLS is very rare. Norris and colleagues reported a number of 26 PLS patients among their population of 708 motor neuron disease (MND)

patients (93.8% ALS, 3.7% PLS, 2.4% progressive muscular atrophy) between 1970 and 1986. In their database of 1200 patients with motor neuron disease, Haverkamp and co-workers reported 35 patients with upper motor neuron signs only (2.9 %). ALS has an annual incidence of 1-2 per 100.000, thus the incidence of PLS can be estimated at approximately a little less than 1 per 1.000.000 a year. The prevalence is probably around 10-20 per 1.000.000, since PLS has a chronic disease course.

Clinical description

PLS is characterized by a slowly progressive bilateral pure upper motor neuron syndrome. Disease onset is usually between 40 and 60 years with spasticity in the legs. Onset in the pseudobulbar region with speech and swallowing disturbance is also possible. Ultimately a tetrapyramidal syndrome develops, sometimes with marked pseudobulbar features (forced laughing and crying). Disease progression is usually very slow over many years. Life expectancy is normal. Considerable functional impairment can develop over time. Bladder involvement, in the form of urgency and frequency symptoms, occurs in approximately half of the patients, usually late in the disease course. Subclinical neuropsychological disturbances have been described in PLS patients in some studies, but dementia is exceptional.

Management including treatment

There is no cure for PLS. Treatment of PLS is symptomatic and can involve prescription of antispasticity medication and rehabilitation.

Etiology

The etiology of PLS is not known. Since the original description by Erb in 1875, it has long been debated whether PLS exists as a disease entity. PLS is now considered to be a benign variant of ALS, at the one end of the clinical spectrum where there are only upper motor neuron symptoms. The exact pathogenesis of ALS is unknown. Hypotheses include glutamate-excitotoxicity, oxidative stress and mitochondrial dysfunction. Similar mechanisms may play a role in the pathogenesis of PLS.

To our knowledge, a PLS-like phenotype has never been described in the families reported to have familial ALS (FALS) with *superoxide dismutase* (*SOD1*) mutations. However, a PLS-like phenotype has been described in a subset of patients of Tunesian autosomal recessive juvenile ALS (JALS) families. In the initial Tunesian family and three additional consanguineous families from the Arabic

peninsula, homozygous mutations have been found in a newly identified gene (*ALS2*) on chromosome 2q33, encoding a protein called alsin. Interestingly, it has recently been shown that the *alsin* gene is mutated in a subset of patients with infantile-onset ascending hereditary spastic paraparesis. It cannot be ruled out that some patients with PLS could actually be sporadic cases of uncomplicated hereditary spastic paraparesis (HSP). Some forms of HSP can now be ruled out with genetic testing.

Patients presenting with PLS in combination with small-cell carcinoma of the lung, HIV infection, multiple myeloma, IgM paraproteinemia and breast cancer have been reported. It is not clear whether this is based on causal relations or on chance associations.

Diagnosis

There is no positive marker for PLS. Additional tests should be performed to exclude other causes (see "differential diagnosis"). This may involve blood, urine and CSF examination and electromyography, as well as brain and spinal cord MRI.

Atrophy of the motor cortex, visible on brain MRI, was described as suggestive for the diagnosis of PLS, but was not a consistent finding in other studies. Motor evoked responses are usually delayed or absent.

Autopsy can provide evidence for the diagnosis PLS, by confirming the absence of another disease process and showing selective involvement of the central motor neurons, with degeneration of the Betz cells, and corticospinal and/or corticobulbar tract demyelination with sparing of the anterior horn cells.

Unresolved questions

Many questions are currently unresolved:

- Does PLS represent a single disease entity or a group of entities?
- Are there any prognostic factors and/or (genetic or other) susceptibility factors?
- What proportion of patients develops signs of anterior horn cell disease?
- What proportion of patients show progression to ALS, and how does this disease evolution affect the prognosis?
- Does riluzole, a drug with a small life-prolonging effect on the survival of ALS patients, have also an effect on the disease course in PLS?

References

Beal MF, Richardson EP, Jr. Primary lateral sclerosis: a case report. *Arch Neurol* 1981; 38:630-633.

Ben Hamida M, Hentati F, Ben Hamida C. Hereditary motor system diseases (chronic

juvenile amyotrophic lateral sclerosis). Conditions combining a bilateral pyramidal syndrome with limb and bulbar amyotrophy. *Brain* 1990; 113 :347-363.

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; 58:742-744.

Caselli RJ, Smith BE, Osborne D. Primary lateral sclerosis: a neuropsychological study. *Neurology* 1995; 45:2005-2009.

Desai J, Swash M. IgM paraproteinemia in a patient with primary lateral sclerosis. *Neuromuscul Disord* 1999; 9:38-40.

Donaghy M. Classification and clinical features of motor neuron diseases and motor neuropathies in adults. *J Neurol* 1999; 246:331-333.

Erb WH. Ueber einen wenig bekannten spinalen symptomenscomplex. *Berliner Klinische Wochenschrift* 1875; 12:357-359.

Eymard-Pierre E, Lesca G, Dollet S, Santorelli FM, di Capua M, Bertini E, et. al. Infantile-onset ascending hereditary spastic paralysis is associated with mutations in the alsin gene. *Am J Hum Genet.* 2002;7:518-27.

Forsyth PA, Dalmau J, Graus F, Cwik V, Rosenblum MK, Posner JB. Motor neuron syndromes in cancer patients. *Ann Neurol* 1997; 41:722-730.

Haverkamp LJ, Appel V, Appel SH. Natural history of amyotrophic lateral sclerosis in a database population. Validation of a scoring system and a model for survival prediction. *Brain* 1995; 118:707-719.

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; 71:615-620.

Lacomblez L, Bensimon G, Leigh PN, Guillet P, Meininger V. Dose-ranging study of riluzole in amyotrophic lateral sclerosis. Amyotrophic Lateral Sclerosis/Riluzole Study Group II. *Lancet* 1996; 347:1425-1431.

Le Forestier N, Maisonobe T, Piquard A, Rivaud S, Crevier-Buchman L, Salachas F *et al.* Does primary lateral sclerosis exist? A study of 20 patients and a review of the literature. *Brain* 2001; 124:1989-1999.

Leigh PN, Meldrum BS. Excitotoxicity in ALS. *Neurology* 1996; 47:S221-S227.

Norris F, Shepherd R, Denys E, U K, Mukai E, Elias L *et al.* Onset, natural history and outcome in idiopathic adult motor neuron disease. *J Neurol Sci* 1993; 118:48-55.

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.

Swash M, Desai J, Misra VP. What is primary lateral sclerosis? *J Neurol Sci* 1999; 170:5-10.

Thompson AJ, Polman CH, Miller DH, McDonald WI, Brochet B, Filippi MM, X *et al.* Primary progressive multiple sclerosis. *Brain* 1997; 120:1085-1096.

Wechsler I. The problem of primary lateral sclerosis. *JAMA* 1946;130:1195-1198.

Younger DS, Chou S, Hays AP, Lange DJ, Emerson R, Brin M *et al.* Primary lateral sclerosis. A clinical diagnosis reemerges. *Arch Neurol* 1988; 45:1304-1307.