Primary lateral sclerosis as a phenotypic manifestation of familial ALS

Abstract—Primary lateral sclerosis (PLS) is a diagnosis of exclusion in patients with progressive spinobulbar spasticity and could be part of the clinical spectrum of ALS. Unlike ALS, which is familial in 5 to 10% of the cases, PLS has been described as a sporadic disorder in adults. The authors report two patients with PLS from unrelated SOD1-negative familial ALS families. These observations provide further evidence that PLS can be linked pathophysiologically to ALS.

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F. Brugman, MD; J.H.J. Wokke, MD, PhD; J.M.B. Vianney de Jong, MD, PhD; H. Franssen, MD, PhD; C.G. Faber, MD, PhD; and L.H. Van den Berg, MD, PhD

Primary lateral sclerosis (PLS) is a diagnosis of exclusion in patients with slowly progressive spinobulbar spasticity.[1-4] PLS could be considered a clinical variant of ALS because PLS and ALS share a similar age at onset, male predominance, and both bulbar and spinal onset forms. Furthermore, transition of PLS to ALS can occur even after long-standing disease.[5]

Unlike ALS, which is familial in approximately 5 to 10% of the patients, PLS has been described as a sporadic disorder in adults.[1-4] A familial PLS-like disorder with infantile or juvenile onset has been reported and is sometimes associated with alsin (ALS2) mutations.[6,7] The diagnosis of PLS requires the absence of a positive family history according to proposed clinical diagnostic criteria.[1] The phenotype of patients with familial ALS (FALS) has been described as heterogeneous, also within families, including mixed upper and lower as well as pure lower motor neuron syndromes.[8] To further broaden the clinical spectrum of FALS, we report two patients with PLS who have a family history of FALS.

Case reports. The index patients were part of a cohort of 100 Dutch patients who were identified after a nationwide search for patients with PLS to participate in a natural history study. Other causes were excluded according to clinical diagnostic criteria.[1] Direct sequencing of the superoxide dismutase 1 gene revealed no mutations in either index patient. The pedigrees are shown in the figure. Clinical features of affected individuals are summarized in the table.

Family A. Patient II-8 (index patient). This 81-year-old man gradually developed slurring of speech during his 50s and gait unsteadiness and slowing of hand movements during his 60s. Neurologic examination at age 75 showed mild pseudobulbar dysarthria and a tetrapyramidal syndrome with slowed repetitive movements of tongue, fingers, and feet and a mildly spastic gait. Atrophy and fasciculations were absent. At the age of 79, needle EMG of bulbar, cervical, thoracic, and lumbosacral muscles was normal. Cortical magnetic stimulation showed abnormal central motor conduction to the arms and legs. He was diagnosed with PLS. At the last follow-up at age 80, the neurologic examination showed no signs of lower motor neuron involvement.

Patient II-7. This is the 82-year-old brother of the index patient. From the age of 50, he experienced difficulty with walking, which was slowly progressive. Slurring of speech developed since age 75. At age 80 he noticed weakness of the arms. Neurologic examination at the last follow-up at age 82 showed pseudobulbar dysarthria and a tetrapyramidal syndrome. Fasciculations and mild atrophy were seen in the upper arms but not in the tongue. Needle EMG at age 80 showed active denervation (fibrillations or positive sharp waves) and chronic denervation (polyphasic or large motor unit potentials) in the right abductor pollicis brevis muscle, chronic denervation in the left abductor digiti minimi muscle and in both anterior tibial muscles, but no abnormalities in the tongue. It was concluded that he had developed ALS, most likely following long-standing PLS.

Patient III-9. This is the son of the index patient. He was diagnosed with bulbar-onset ALS at age 35. He developed dysarthria from age 31. At age 33, he noticed weakness of the arms. Neurologic examination at age 35 showed pseudobulbar dysarthria. Fasciculations and atrophy of arm and hand muscles were noted; these were associated with brisk reflexes and a unilateral Babinski sign. He developed paralysis of the arms and severe weakness of the legs. By the time of his death, at age 40, he was anarthric and had to be fed through a percutaneous gastrostomy tube.

Family B. Patient III-14 (index patient). This 62-year-old man had stiffness in his legs and gait unsteadiness since the age of 50. During his 50s, arm movements became slower. Slurring of speech developed at age 60. Neurologic examination at age 62 showed a tetrapyramidal syndrome and mild pseudobulbar dysarthria, without atrophy or fasciculations. Cortical magnetic stimulation demonstrated impaired central motor conduction. Needle EMG at 53 and 55 years of age was normal. He was diagnosed with PLS. Repeated EMG at age 62 only showed chronic denervation in the right rectus femoris muscle.

Patient III-12. This man, an older brother of the index patient, never married and had no children. Family members recalled that he developed progressive speech and swallowing disturbances from the age of 22. By the time of his death, at age 28, he could not speak or swallow, had lost a lot of weight and had severe dyspnea. There were no symptoms in the arms or legs. No medical records could be traced. The most likely diagnosis was ALS.

Patient II-1. This woman was first seen by a local neurologist at age 71 for weakness of her left arm. At age 73, he documented the presence of bulbar paralysis, dysarthria, dysphagia, forced crying, reduced mobility of shoulder and hip joints, and weakness of the arms. There was severe weight loss, but fasciculations were absent. Reflexes were low and plantar responses were normal. ALS was diagnosed. She died at age 74.

Patient III-3. This man developed slurring of speech and swallowing difficulty at age 65. At age 68, he was anarthric and had arm weakness that was more prominent on the left side. He died at age 68 of respiratory insufficiency. Examination shortly before death revealed atrophy, fasciculations, weakness of the tongue and shoulder muscles, and hyperreflexia, including positive pseudobulbar reflexes. EMG at age 66 showed fasciculations and chronic denervation in the tongue, arms, and a lower leg muscle. Postmortem examination of

Table *Clinical characteristics of affected family members of Family A and Family B*

Family	Patient	Diagnosis	Onset site	Onset age, y	Disease duration, y
A	II-7	PLS/ALS	Spinal	50	32
A	II-8	PLS	Bulbar	50s	>20
A	III-9	ALS	Bulbar	31	9 (dead)
B	II-1	ALS	Spinal	71	3 (dead)
B	III-3	ALS	Bulbar	65	3 (dead)
B	III-12	ALS	Bulbar	22	6 (dead)
B	III-14	PLS	Spinal	50	12

PLS = primary lateral sclerosis.

the brain and spinal cord showed abnormalities consistent with ALS and also features of Alzheimer disease.

Discussion. We report two patients with PLS from unrelated families with a history of FALS. The phenotype of patients with FALS has been described as heterogeneous, also within families, but the occurrence of PLS and ALS within the same family has not been described before. Recognizing the PLS phenotype is important because it offers a much better prognosis than the ALS phenotype, which is also true for the patients described in this study.[1-5] Both pedigrees suggest autosomal-dominant inheritance, the most frequently observed pattern in FALS.[8] The presence of an obligate carrier in Family B (II-3) indicates incomplete penetrance, which is a feature of FALS.[8]

The affected brothers of Family A (II-7 and II-8) could represent the first reported cases of familial PLS in adults because both had a similar phenotype of spinobulbar spasticity for many years before lower motor neuron symptoms developed in the older

brother (II-7). Patient II-7 probably represents a case of transition to ALS after long-standing PLS, as has been described previously.[5] We believe that new diagnostic criteria for PLS should leave open the possibility of familial PLS, in contrast to the criteria proposed by Pringle et al.[1] in 1992, which require absence of family history.

The occurrence of ALS and PLS phenotypes in the same family suggests a common genetic defect leading to degeneration of motor neurons. Importantly, gene- or environment-modifying factors may protect lower motor neurons in the patients with PLS or, alternatively, promote their degeneration in the patients with ALS in these families. Identification of such modifying factors is a major challenge in ALS research.[9,10]

It is important to note that most cases of PLS appear to occur sporadically, as we found only these two patients among a cohort of 100 Dutch patients with PLS. These observations show that PLS can be part of the clinical spectrum of FALS, providing further evidence that PLS is linked pathophysiologically to ALS, at least in a proportion of patients.
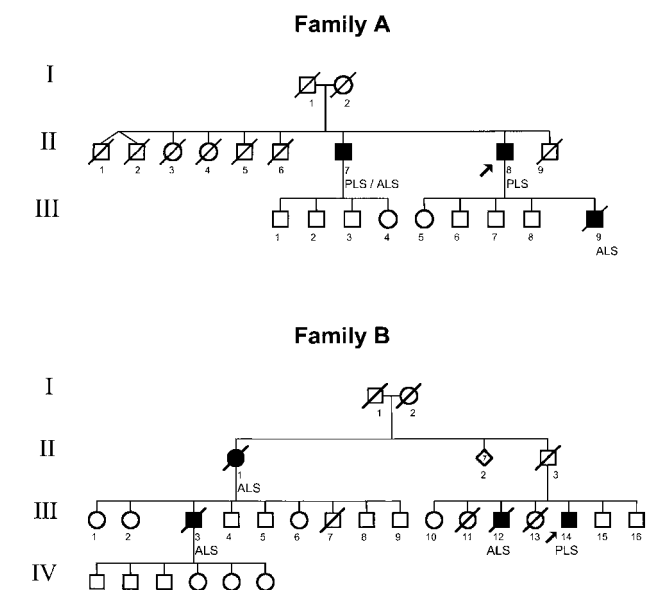

Figure. Pedigrees of Family A and Family B showing patients with primary lateral sclerosis (PLS) and ALS in the same family. Only offspring of affected family members are depicted if aged 18 or older.

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