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CASE REPORT

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Upper motor neuron predominant degeneration with frontal and temporal lobe atrophy

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Abstract The autopsy findings of a 78-year-old man mimicking primary lateral sclerosis (PLS) are reported. He showed slowly progressive spasticity, pseudobulbar palsy and character change, and died 32 months after the onset of symptoms. Autopsy revealed severe atrophy of the frontal and temporal lobes, remarkable neuronal loss and gliosis in the precentral gyrus, left temporal lobe pole and amygdala, mild degeneration of the Ammon's horn, degeneration of the corticospinal tract, and very mild involvement of the lower motor neurons. The anterior horn cells only occasionally demonstrated Bunina body by cystatin-C staining, and skein-like inclusions by ubiquitin staining. This is a peculiar case with concomitant involvement in the motor cortex and temporal lobe in motor neuron disease predominantly affecting the upper motor neuron.

Key words Primary lateral sclerosis · Amyotrophic lateral sclerosis · Bunina body · Cortical atrophy · Amygdala

Introduction

Primary lateral sclerosis (PLS), which was reported by Erb in 1875 [4], is a condition affecting the upper motor neuron without lower motor neuron involvement. It has been discussed whether PLS is a variant of amyotrophic lateral sclerosis (ALS) with severe spasticity or a distinct disease entity. However, several cases in which the upper motor neuron has been predominantly affected have been reported recently, and PLS is now considered to be a disease entity [2, 5, 7, 8, 16, 20, 22]. Here we report autopsy findings mimicking PLS with neocortical and limbic system lesions.

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Case report

A 76-year-old man gradually developed dysarthria and character change in the summer of 1990. He had previously had no major illnesses and no family history of neurological disease. In September, he complained of clumsiness in his right hand, and bradykinesia in December. In March 1991, he visited our hospital, and was admitted in April of that year. Major neurological signs at admission were: clear consciousness, normal orientations, mild bradykinesia, slouching gait, mask-like face, anarthria, moderate facial weakness, dysphagia, clumsy tongue movement without atrophy or fasciculation, moderate contracture in four extremities with gegenhalten, no muscular atrophy, occasional fasciculations on the chest and forearms, generalized hyperreflexia with positive Babinski signs, brisk jaw jerk, mild muscular weakness and normal sensation.

Laboratory data showed normal routine examinations, negative anti-HTLV antibody, normal CSF and EEG. EMG revealed no denervation, giant motor unit potentials or decreased motor unit potential. Cranial computed tomography and magnetic resonance imaging disclosed bilateral fronto-temporal lobe atrophy.

Medication including anti-parkinson drugs resulted in no improvement. There was gradual progression of his motor disturbance. In May, tube feeding was initiated. After discharge in June, he could communicate by writing or using a computer. In September, he lost ambulation and was then readmitted in January, 1992. At that time, he had clear consciousness, but was completely anarthric, yet he could communicate via eye movements. Voluntary movements were only seen in eyes, face, neck and respiratory muscles. He showed decerebrated posture, and muscle tonus was marked rigo-spasticity. Reflexes were brisk, and there was mild muscular atrophy in the four extremities. Fasciculation was seldom seen in the lower extremities. In April 1993, he died of pneumonia.

Neuropathological findings

The general autopsy revealed pneumonia but was otherwise unremarkable. The brain weighed 1230 g, and there was remarkable bilateral atrophy of the frontal lobes and temporal lobes, predomi-

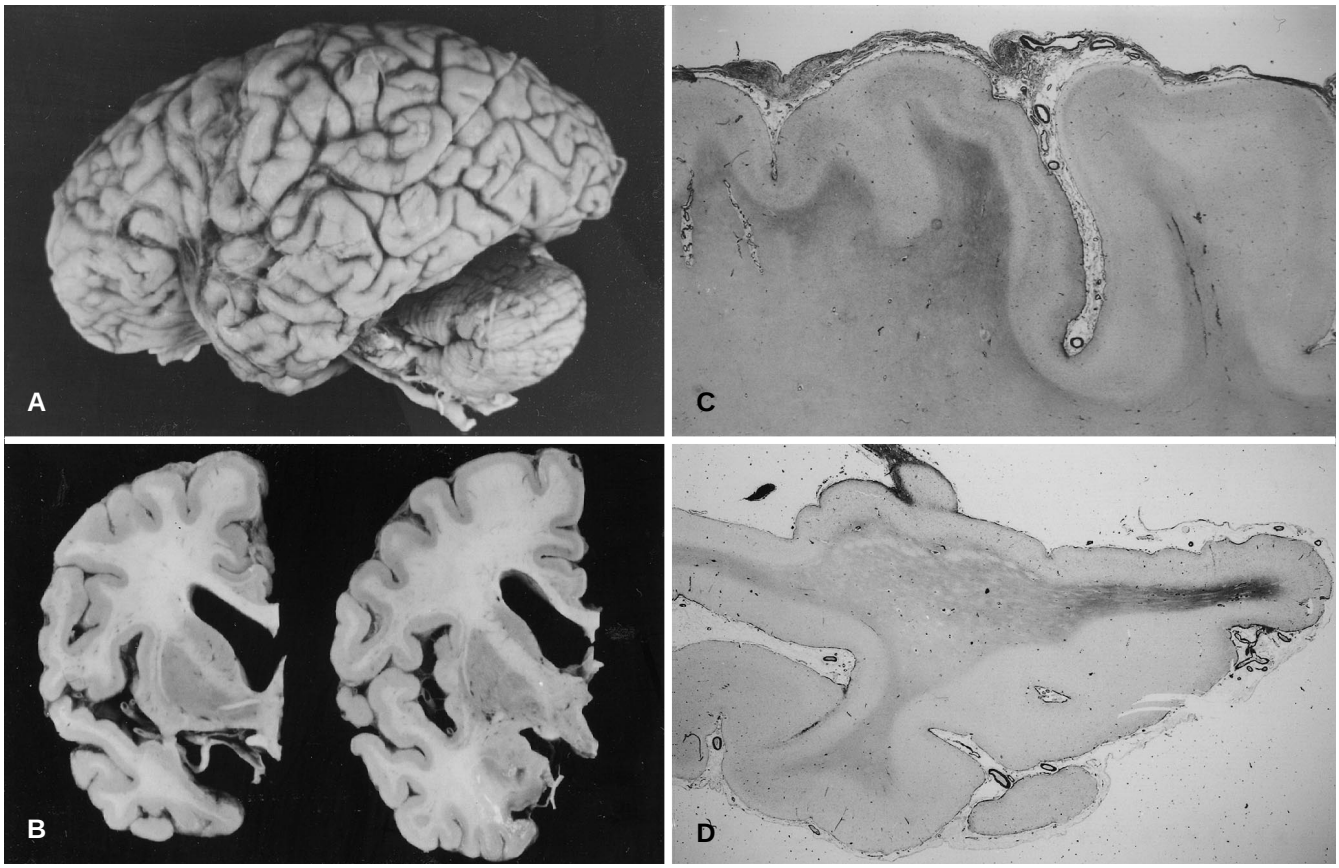

Fig. 1 **A** Brain showing remarkable fronto-temporal lobe atrophy. **B** Thin cortex of precentral gyrus. **C** Thin cortex and fibrous gliosis in the white matter in the precentral gyrus; Holzer staining. **D** Left temporal lobe; Holzer staining. **C** × 2.6, **D** × 1.8

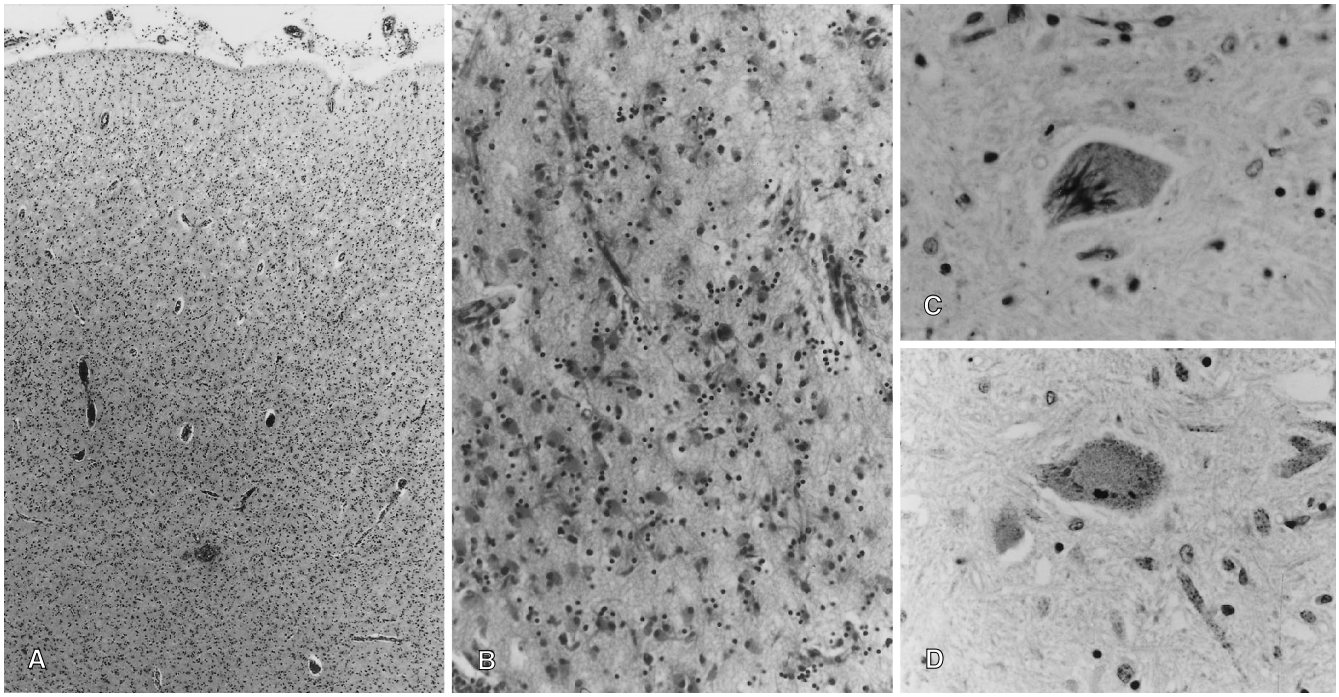

Fig. 2 **A** Precentral gyrus showing a severe spongy state, gliosis and complete absence of Betz cell; H&E staining. **B** Remarkable neuronal loss and gliosis in the amygdala; H&E staining. **C** Skein-like inclusion in the anterior horn cell of the thoracal cord; ubiquitin staining. **D** Bunina body in the anterior horn cell of the lumber cord; cystatin-C staining. **A** × 22.5, **B** × 112.5, **C**, **D** × 225

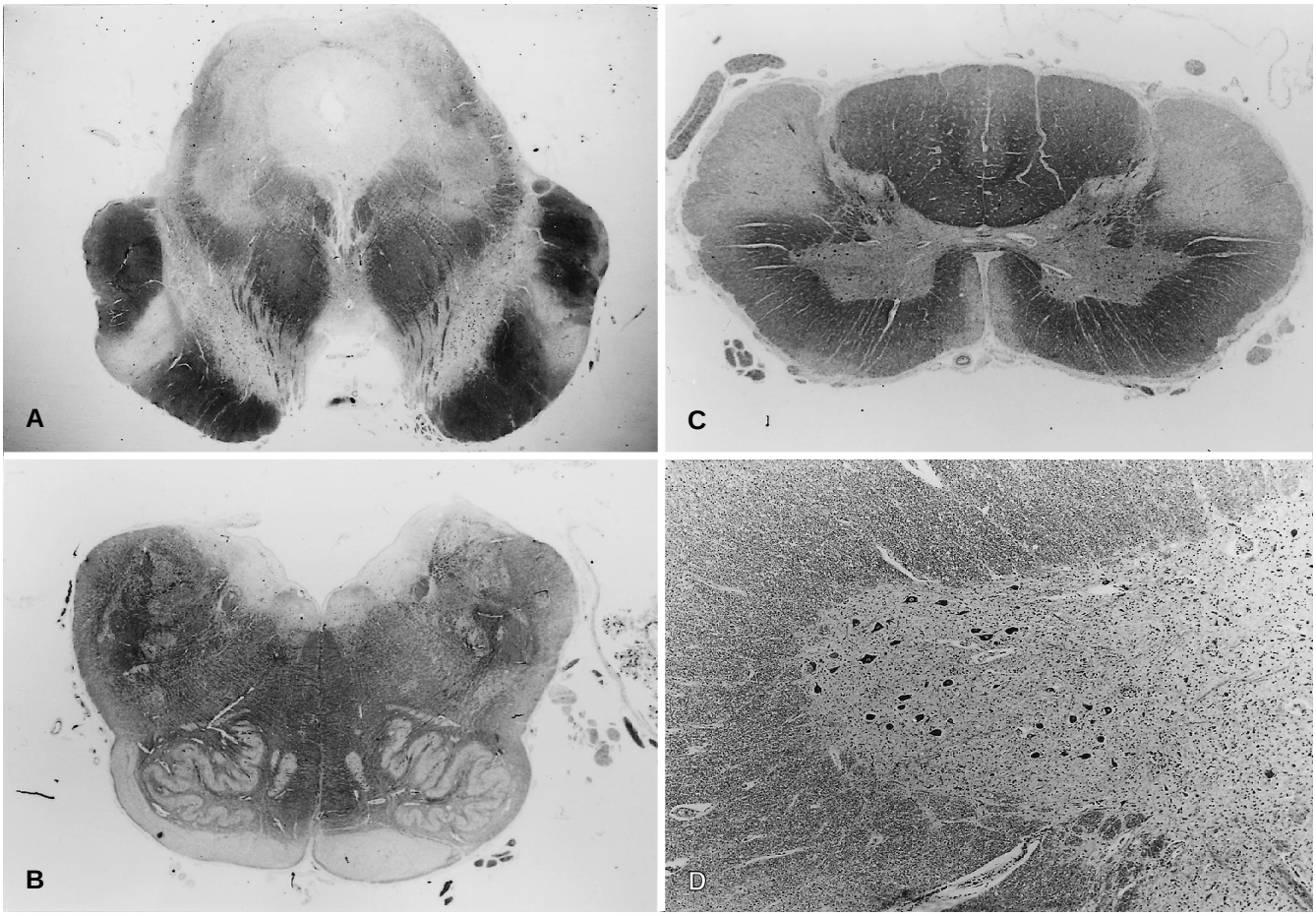

Fig. 3 Remarkable degeneration in the cerebral peduncle of midbrain (**A**), in the pyramidal tract of medulla oblongata (**B**), and in the anterior and lateral corticospinal tracts in cervical cord (**C**). **D** The lumber cord. The number of anterior horn cells was not significantly decreased in comparison to controls. **A**–**D** Klüver-Barrera staining; **D** × 9

nantly on the left side (Fig. 1 A, B). The anterior and lateral pyramidal tracts of the spinal cord showed pallor. The spinal nerve roots were intact. Other portions showed unremarkable changes upon macroscopic examination.

Microscopically, there were widespread neuronal loss and gliosis in the frontal, temporal and parietal cortices. These findings were particularly remarkable in the cortex of the bilateral precentral gyrus and left temporal lobe pole. Betz cells were completely absent in the precentral gyrus (Fig. 2 A). The white matter under the shrunken cortex revealed myelin pallor by myelin staining, and fibrillar gliosis by Holzer staining (Fig. 1 C, D). Neuronal loss and activated gliosis were observed in the sections from CA1 portion of hippocampus to pes hippocampi, and a small amount of neurofibrillary tangles in the CA1 portion. A few senile plaques were seen in the temporal lobe cortex, which were judged to be normal physiological changes for that age. No Pick body, Lewy body, balooned neuron or glial fibrillary tangle were detected.

The cerebral cortices were examined by immunohistochemistry for cystatin-C and ubiquitin using the streptavidin-biotin method (LSAB kit, DAKO, USA) with rabbit anti-human cystatin-C and ubiquitin antibodies. Despite negative findings for the cystatin-C test, ubiquitin-immunoreactive neurons were observed transcortically in the precentral gyrus, cingulate gyrus and temporal lobe including granule cell of the dentate gyrus.

The amygdala showed marked neuronal loss and gliosis (Fig. 2 B), but the other basal ganglia and thalamus as well as the Meynert basal nucleus were normal. The posterior peduncle of the internal capsule, cerebral peduncle, pyramidal tract of the pons and medulla oblongata showed severe degeneration (Fig. 3 A, B). Activated astrocytes and macrophages were seen in these portions, and axonal swelling in the cerebral peduncle. There were no abnormal findings in the substantia nigra, red nucleus, oculomotor nucleus, pontine nuclei, locus coeruleus and cerebellum. Some neurons in the facial motor nucleus showed central chromatolysis, but the hypoglossal nucleus was normal. The inferior olivary nucleus showed mild gliosis, and the posterior funicular nucleus was intact.

In the spinal cord (Fig. 3 C, D), the lateral and anterior pyramidal tracts showed marked degeneration, loss of myelin and axon, and infiltration of macrophages. A quantitative study on cell number in the anterior horn [19] showed no significant reduction in comparison with three age- and sex-matched neurologically normal controls. The numbers of the motor neuron in ten slices of the present case were 140 in the cervical cord (control: 156.3 ± 28.0, mean ± SD; $P = 0.484$) and 167 in lumbar cord (197.7 ± 22.2; $P = 0.167$), respectively. Detailed examination revealed mild neuronal shrinkage and lipofuscin deposition. Ubiquitin staining showed occasional skein-like inclusions (Fig. 2 C). Only a few Bunina bodies with cystatic-C staining were noted in the anterior horn cells of the lumbar and sacral regions (Fig. 2 D). Clarke column, nucleus of Onufrowicz, intermediolateral nucleus, posterior funiculus and spinal roots were normal.

Microabcesses were observed throughout the central nervous system.

Discussion

This patient showed upper motor neuron predominant degeneration with degeneration in the frontal and temporal

Table 1 Reported PLS cases and the present case (*PLS* primary lateral sclerosis, *y* years, *m* months, – none, + mild, ++ moderate, +++ remarkable, *n.d.* not described, *EIB* eosinophilic inclusion body, *CC* central chromatolysis, *SLI* skein-like inclusion, *Vm* trigeminal nerve motor nucleus, *VII* facial nerve nucleus, *XI* hypoglossal nerve nucleus, *CT* computed tomography, *MRI* magnetic resonance imaging, *parahippo.gyr.* parahippocampal gyrus)

Reference	Sex	Age at death (years)	Duration of illness	Lower motor neuron sign	Motor cranial nerve nuclei	Spinal anterior horn	Frontal lobe atrophy	Betz cell loss	Tempora lobe atrophy	Limbic sytem degeneration	Others
[5]	M	72	5y	–	n.d.	–	–	Probably	–	n.d.	Old infarct in basis pontis
[2]	F	69	3y5m	–	EIB in XI	EIB	+++	yes	–	n.d.	
[8]	F	71	19y	–	EIB in XI	EIB	+++	yes	+++	–	
[22]	M	77	5y4m	–	n.d.	–	n.d.	no	n.d.	n.d.	Lung adenocarcinoma
[22]	M	61	1y1m	Fasciculation in EMG	n.d.	–	n.d.	no	n.d.	n.d.	Mild cerebral atrophy in CT and MRI
[22]	M	76	10y	–	n.d.	–	n.d.	n.d.	n.d.	n.d.	Cystic areas in right caudate, thalamus and frontal gyrus
[7]	M	77	6m	–	CC & EIB in Vm		++	yes	++	Amygdala Parahippo.gyr.	No examination of spinal cord
[16]	M	71	15y	Fibrillation in EMG	–	Gliosis CC	+++	yes	–		
[20]	M	64	3y3m	–		SLI, Gliosis Hyalin inclusion	+	yes	–		
Present case	M	78	2y8m	Fasciculation	CC in VII	Bunina body SLI	+++	yes	+++	Amygdala Hippocampus	

lobes. He presented severe spasticity and progressive pseudobulbar palsy. In spite of occasional fasciculation, absence of muscular atrophy and normal EMG suggested only minimum involvement of the lower motor neuron. He died of sepsis after 3-year course, but had been expected to live longer because of normal breathing. The character change before onset suggested a lesion of the limbic system.

Pathologically, there was severe loss of Betz cells in the precentral gyrus with remarkable degeneration throughout the pyramidal tract. The axonal swelling in the pyramidal tract of the cerebral peduncle seems to be related to Betz cell damage [15]. On the other hand, the involvement of the anterior horn cells in the spinal cord was quite minimal.

These findings mimicked the pathological features of PLS, in which lower motor neuron damage is rare. However, Bunina bodies or skein-like inclusions in the anterior horn cells and the findings of facial nucleus suggested scanty lower motor neuron involvement. Marked degeneration was also found in the frontal and temporal lobes and amygdala.

Nine cases with or without minimum involvement in the lower neuron have been reported as PLS since 1977 (Table 1) [2, 5, 7, 8, 16, 20, 22]. All but three cases reported by Younger et al. [22] showed shrinkage of the precentral gyrus or loss of Betz cells, which suggested degeneration throughout the upper motor neuron.

One case [22] had EMG evidence of anterior horn cell disorder. Pathological changes in the lower motor neuron were described in four cases despite the absence of clinical signs. Eosinophilic inclusion bodies were observed in the cells of the anterior horn [2] and hypoglossal nucleus [9]. Central chromatolysis was seen in the trigeminal motor nucleus [7] and the spinal anterior horn cell [16]. Immunohistochemical examinations have not been performed in most of these cases reported as PLS, and are necessary to disclose lower motor neuron involvement. Watanabe et al. [20] reported a case of PLS with ubiquitin-positive inclusion body in the anterior horn cell. However, they did not perform an immunohistochemical study for cyctatin-C, which is sensitive for Bunina body [14]. In the present case, despite the paucity of pathological findings in the anterior horn cell, immunohistochemical staining for cyctatin-C and ubiquitin [9, 11] revealed Bunina bodies and skein-like inclusions.

Explanations for the lower motor neuron involvement in PLS may reflect phenomena of the aging process, secondary changes related to the marked degeneration of upper motor neuron [16, 20], or ALS before affecting the lower motor neuron [3].

Extensive extra-motor system involvement was revealed in the present case. The patient showed frontotemporal lobe atrophy mimicking Pick's disease, but no Pick bodies were demonstrated. This kind of neocortical atrophy was also observed in two cases of PLS [7, 8], and in cases with ALS [13, 17]. The frontal cortex atrophy with ubiquitin-immunoreactive neurons indicated frontal lobe dementia [6, 18], but we could not estimate exact intel-

lectual function because of severe anarthria and motor disorders.

The marked atrophy and degeneration of the temporal cortex, amygdala and Ammon's horn were noteworthy in the present case. His obstinacy might be related with these lesions. Severe degeneration in the amygdala may have contributed to the character change. The involvement of this nucleus is not rare in motor neuron disease both in ALS [1, 12] and PLS [7].

The present case showed ubiquitin-immunoreactive neurons in the fronto-temporal cortex; this is a characteristic finding in ALS with dementia [9]. The distinctive pathological features of this type of ALS are involvement of the temporal lobe, degeneration in Ammon's horn, loss of neurons in the substantia nigra and mild degeneration of the upper motor neuron [10, 21]. Normal substantia nigra and marked degeneration of upper motor neuron in the present case thus represent features different from those of ALS with dementia.

There may be a subgroup of motor neuron disease which predominantly affect the upper motor neuron with concomitant involvement in the motor cortex and temporal lobe. To clarify the nosological entity of PLS, collection and study of further cases are needed.

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