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CASE REPORT

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# Sporadic motor neuron disease with severe sensory neuronopathy

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**Abstract** We report a 62-year-old man with sporadic motor neuron disease (MND) of 52 months' duration with progressive sensory disturbance and high cerebrospinal fluid protein content. Neuropathologically, both the upper and lower motor neuron systems were severely affected, and light and electron microscopy revealed Bunina bodies and skein-like inclusions, which are characteristic of amyotrophic lateral sclerosis, in the remaining anterior horn cells. Moreover, there was severe degeneration without inflammatory infiltrates in the spinal posterior columns, spinal ganglia, and peripheral sensory nerves. These findings suggest that this case may be an unusual variant of sporadic MND with severe somatic sensory system involvement.

**Key words** Motor neuron disease · Amyotrophic lateral sclerosis · Sensory neuronopathy · Bunina body · Skein-like inclusion

## Introduction

Sporadic amyotrophic lateral sclerosis (ALS) is a fatal motor neuron disease (MND) of unknown etiology in adults. Although an absence of sensory disturbances is a well-known negative neurological sign in ALS [19, 29], occasional reports describing sensory signs and symptoms have been published [5, 27]. In addition, morphometric studies have shown mild loss of large neurons in the spinal sensory ganglia and degeneration of large myelinated fibers in the posterior spinal nerve roots and sural nerves in ALS patients [2, 8, 11]. However, a number of large autopsy series of patients with ALS have revealed that involvement of the posterior columns of the spinal cord or spinal sensory ganglia is extremely rare [3, 10, 13].

Here we report a patient with sporadic MND in whom sensory dysfunction developed and progressively worsened; postmortem examination revealed involvement of the upper and lower motor neuron systems as well as the sensory systems, including the posterior columns, spinal ganglia, and peripheral sensory nerves.

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## Case report

A 57-year-old Japanese man developed dysesthesia in his shoulder, back and lower extremity on the right side in September 1991. Subsequently, he experienced difficulty in climbing stairs. He was admitted to our hospital in April 1992, when muscular weakness of the lower extremities, and dysesthesia and hyperesthesia in the trunk and upper and lower extremities on the right side were observed. A motor nerve conduction study showed slightly decreased conduction velocities (median nerve, 54.4 m/s; posterior tibial nerve, 39.0 m/s). No conduction block was seen. Sensory nerve action potentials of the median and sural nerves could not be elicited. Examination of the cerebrospinal fluid (CSF) showed elevated protein levels (67 mg/100 ml). An X-ray showed only minimal deformity of the lumbar spine. In April 1993, dysesthesia and impairment of the superficial sensations were observed in the right upper and bilateral lower extremities, but the deep sensations were preserved. Muscle atrophy developed in all four extremities and the chest, fasciculation was observed in the tongue and upper extremities, and he was unable to stand alone. He also complained of constipation and difficulty with urination. Tendon reflexes were slightly hyperactive in the biceps brachii muscles, and subsequently became hypoactive. Hoffmann and Babinski signs were absent. Electromyogram showed neuropathic changes in the biceps brachii and rectus femoris muscles. Serological tests for syphilis and anti-Yo and anti-Hu antibodies in the serum were negative. There was no elevation of anti-human T cell leukemia virus type-I (HTLV-I) antibody titer in the CSF. Chronic inflammatory demyelinating polyneuropathy was clinically suspected. He was

treated with steroid pulse therapy of 1000 mg methylprednisolone daily, and then double filtrated plasmapheresis was performed, but these treatments were not effective. By January 1994, the deep tendon reflexes in the extremities had disappeared. Serum antibodies to GM1, GM2, GD1a, GD1b, GT1b, GQ1b and sulfated glucuronyl paragloboside were negative. In May, the CSF protein content was 156 mg/100 ml (IgG 10.8 mg/100ml) with normal cellularity. Weakness of the extremities and dyspnea progressed, and he became bedridden and dependent on a respirator in July, 2 years and 10 months after the onset of neurological symptoms. Thereafter, dysphagia developed and muscle wasting and sensory impairment progressed. He died of ischemic colitis in January 1996. The total duration of this illness was 52 months. Neither ophthalmoparesis, dementia nor bedsore were noted during the course of disease. He had no family history of similar disorders.

## Materials and methods

The brain and spinal cord were fixed in 20% buffered formalin. Multiple tissue blocks were embedded in paraffin, sectioned at 4-μm thickness, and stained with hematoxylin and eosin (H&E) or by the Klüver-Barrera and Bodian's methods. Cryostat sections of the spinal cord were stained with oil-red O. The cranial, spinal and sural nerves were fixed in 2% glutaraldehyde, post-fixed in 1% osmium tetroxide and embedded in Epon 812. They were sectioned at 1-μm thickness. Selected H&E-stained sections of the spinal cord were reused for electron microscopy [30].

We also examined paraffin-embedded sections immunohistochemically, using rabbit polyclonal antibodies against cystatin C (Dakopatts, Glostrup, Denmark; diluted 1:800) and ubiquitin (Dakopatts; diluted 1:200) Immunolabeling was visualized using the avidin-biotin-peroxidase complex (ABC) method, with a Vectastain ABC kit (Vector, Burlingame, Calif.).

## Autopsy findings

The brain weighed 1380 g. The cerebrum, brain stem and cerebellum were unremarkable. The spinal cord was atrophic, and there was marked wasting of the anterior and posterior nerve roots.

In the motor cortex, there was severe loss of Betz cells and moderate loss of pyramidal neurons with gliosis. In the brain stem, moderate neuronal loss was observed in the facial and hypoglossal nuclei, and loss of myelinated fibers was evident in the trigeminal, facial and glossopharyngeal nerves. Slight atrophy with definite gliosis in the reticular formation of the medulla oblongata was also noted. The oculomotor nucleus and IIIrd, IVth and VIth cranial nerves were normal. In the spinal cord, the anterior and lateral funiculi, including the corticospinal and spinocerebellar tracts, showed severe degeneration with many macrophages (Fig. 1 a, b). The anterior horn showed almost complete loss of neurons with fibrillary gliosis (Fig. 1c). There was marked neuronal loss in Clarke's column and, to a lesser degree, in the intermediolateral nucleus. The anterior spinal nerve roots had undergone severe degeneration and neurogenic muscle atrophy was seen in the skeletal muscles. The neuronal population in Onuf's nuclei appeared normal.

In a few remaining neurons in the spinal anterior horn, and facial, hypoglossal and Onuf's nuclei, small eosinophilic intracytoplasmic inclusions, Bunina bodies, were observed (Fig. 2 a). Cystatin C immunohistochemistry revealed positive staining which

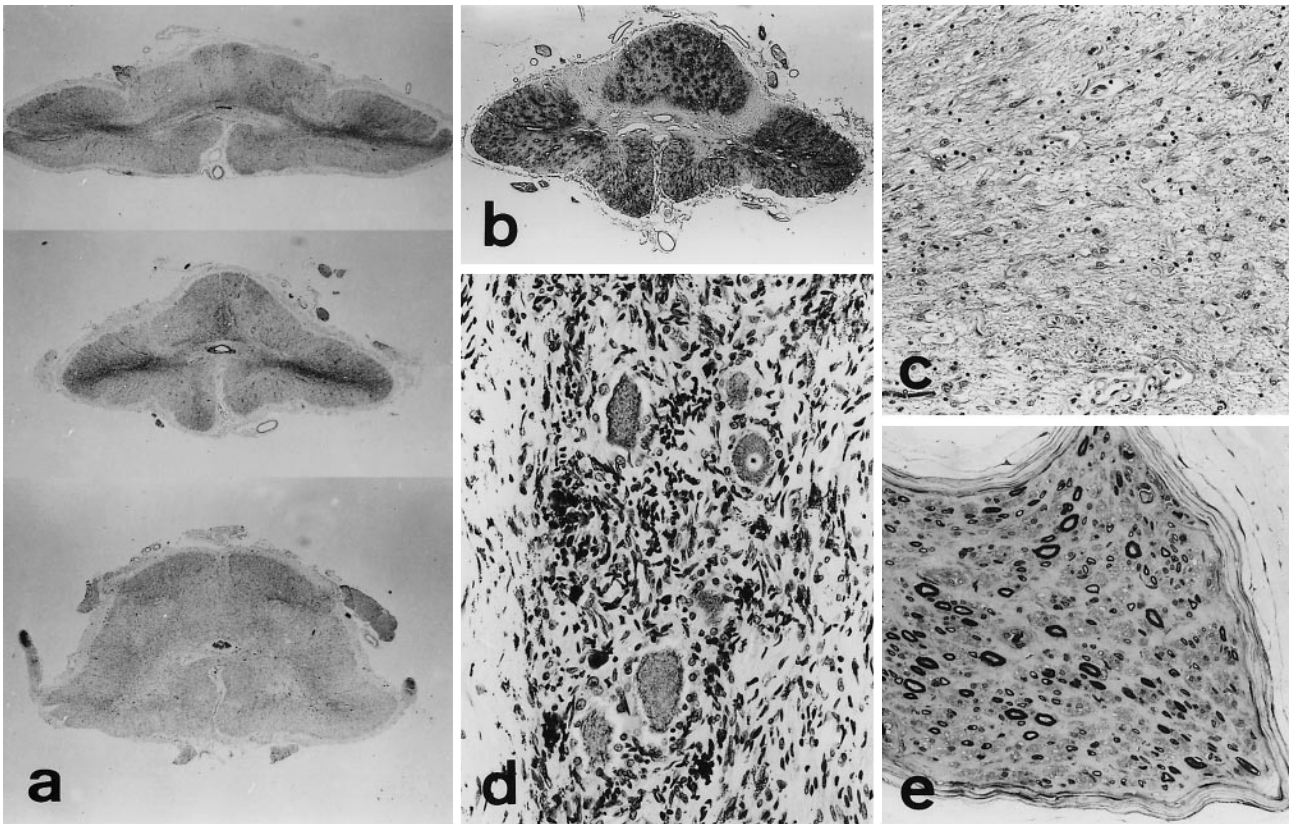



**Fig. 1** **a** Spinal cord at C7, T8, and L4 levels, showing severe degeneration of the white matter; Klüver-Barrera stain (K-B). **b** Many macrophages containing lipid granules in the white matter of the spinal cord are visible (T7); oil-red O stain. **c** Anterior horn at L4 level, showing almost complete loss of anterior horn cells with marked gliosis; K–B. **d** Spinal ganglion at L4 level, showing marked neuronal loss and many residual nodules; K–B. **e** Sural nerve showing marked loss of myelinated fibers and endoneurial fibrosis. Epon section, Toluidine blue and safranine stain. **a** × 5, **b** × 6, **c** × 125, **d** × 140, **e** × 250

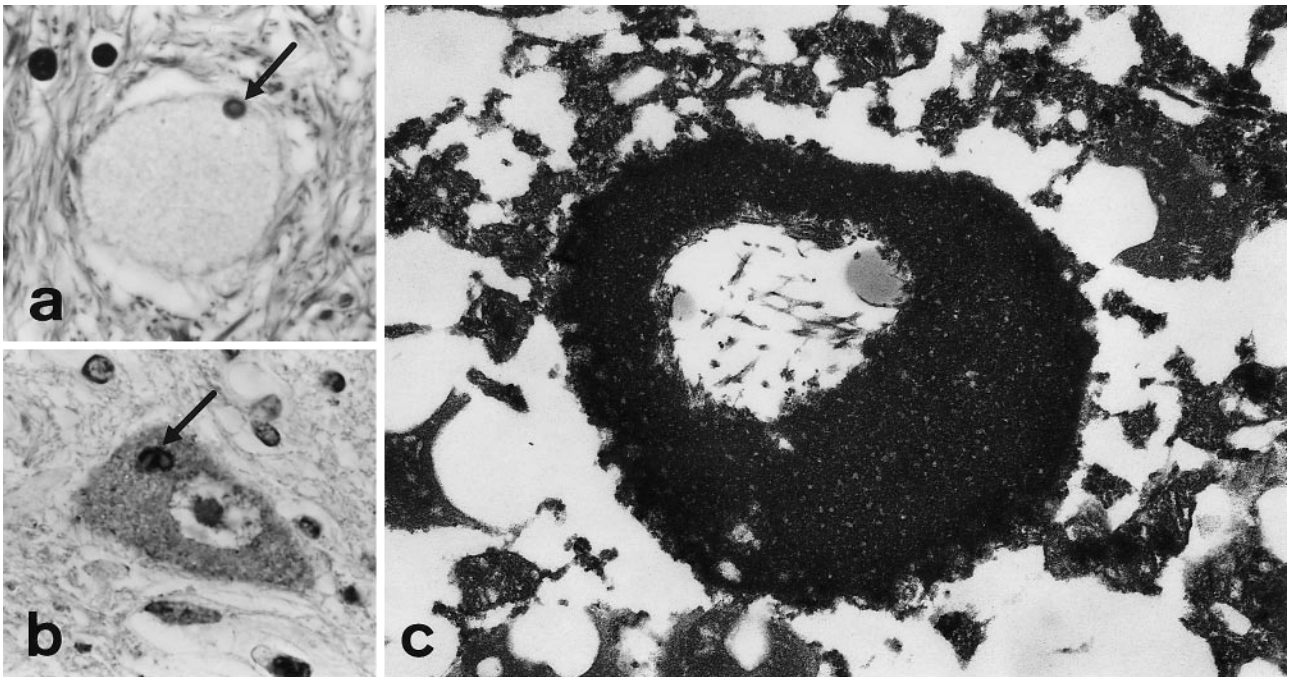
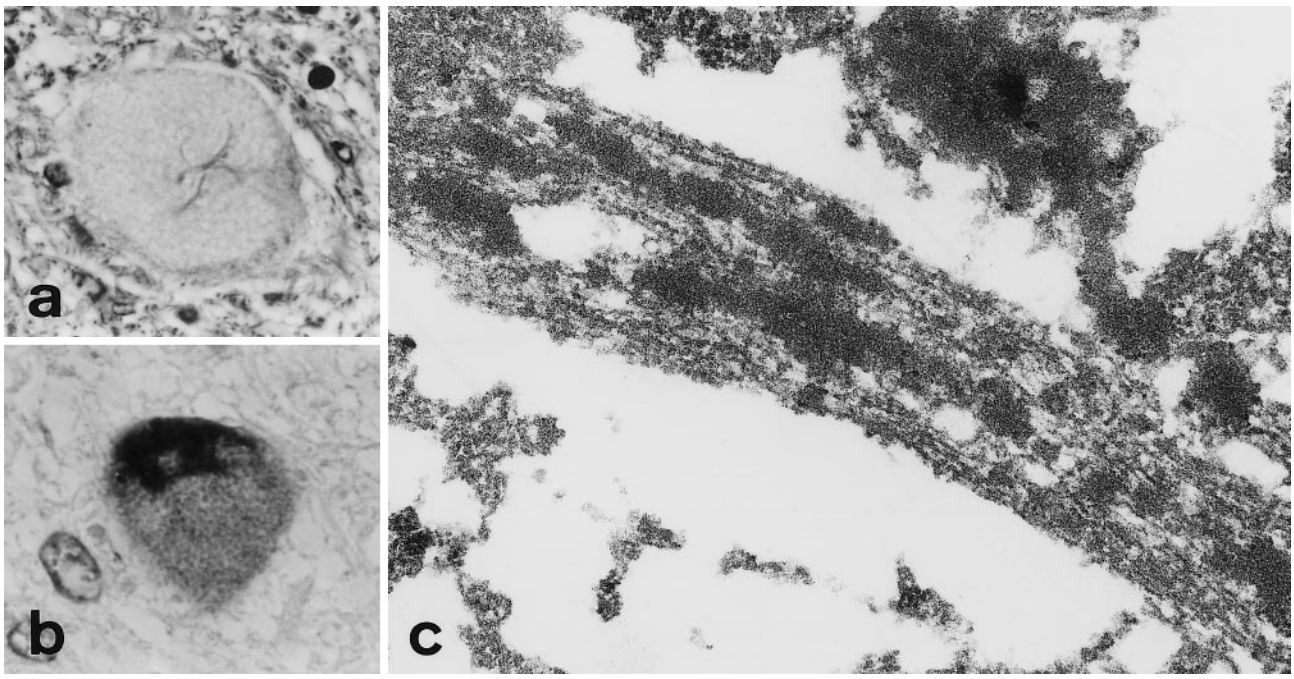



**Fig. 2** **a** A Bunina body *(arrow)* in a remaining anterior horn cell (L4); H & E. **b** Cystatin C-immunoreactive Bunina bodies *(arrow)* in another anterior horn cell (L4). **c** Electron micrograph of a section through the Bunina body seen in **a**, showing a round electron-dense, granular structure with filamentous structures in the translucent inner areas; lead and citrate stain. **a** × 1000, **b** × 750, **c** × 24 000

**Fig. 3** **a** A remaining anterior horn cell (S2) containing skein-like inclusions; H&E. **b** Ubiquitin-immunoreactive skein-like inclusions in another anterior horn cell (S2). **c** Electron micrograph of a section through the skein-like inclusions seen in **a**, showing bundles of filaments (about 15–20 nm in diameter) associated with granular substances; lead and citrate stain. **a** × 1250, **b** × 1200, **c** × 39 000

might correspond to the Bunina bodies, as reported previously [24] (Fig. 2 b). Ultrastructural examination revealed that the inclusions were electron-dense, granular structures with entrapped filaments, one of the characteristic features of Bunina bodies [6, 21, 25, 28] (Fig. 2 c). In addition, loosely arranged bundles of filamentous material were also identified in the remaining anterior horn cells (Fig. 3 a) and were immunoreactive for ubiquitin (Fig. 3 b). The ultrastructural features were consistent with those of skein-like inclusions [17] (Fig. 3 c).

In addition to the above findings, posterior columns of the spinal cord showed severe loss of myelin and axons with macrophage infiltration (Fig. 1 a, b). Spinal ganglia showed marked loss of ganglion cells (Fig. 1 d). Posterior spinal nerve roots and sural nerves showed severe degeneration (Fig. 1 e), but neither inflammatory infiltrates nor onion bulbs were present. A detailed search



for a neoplasm in the visceral organs was carried out but no tumor was found.

## Discussion

Both the upper and lower motor neuron systems were severely affected in the present case. Moreover, light and electron microscopy revealed Bunina bodies and skein-like inclusions in the remaining anterior horn cells. The former are considered to be one of the hallmarks of sporadic ALS [6, 10, 21, 25, 28], and the latter are also considered to be significant structures in ALS [14, 17]. In addition, neuronal populations of the oculomotor and Onuf's nuclei were preserved. These findings are consistent with those of sporadic ALS [10, 15, 22, 23]. However, severe sensory system involvement, as found in our case, is quite unusual for ALS [10]. In our case, progressive sensory impairment was a salient clinical feature. Furthermore, our patient showed CSF protein concentrations above 100 mg/100 ml, which is also a rare phenomenon in ALS [31]. However, the clinical, laboratory and pathological features ruled out an overlap with either paraneoplastic sensory neuronopathy, HTLV-I-associated myelopathy, tabes dorsalis, subacute combined degeneration, or spondylotic myelopathy.

Several investigators have reported that posterior column lesions were observed in 5 of 45 cases [3] and in 1 of 53 cases of sporadic ALS [13]. In addition, rare instances of sporadic ALS with posterior column involvement have been recorded [4, 5, 12, 20]. However, the changes were usually less striking than those in the antero-lateral columns and were restricted to the fasciculus gracilis [4, 13] and/or middle root zone [3], or to several segments of the spinal cord [5]. Moreover, no sensory disturbance was noted during their clinical course [3, 4, 12] or, if present, was non-progressive [20]. Thus, some of these lesions have been considered to be an incidental complication, due to spondylotic myelopathy [10] or circulatory disturbance [3]. On the other hand, the results of an autopsy of patient with sporadic ALS reported by Manome et al. [16] showed dysesthesia and superficial sensory disturbance. In this case, loss of small-sized neurons in the spinal ganglia were evident, and small myelinated fibers in the posterior nerve roots and sural nerves were also decreased. However, no lesion was found in the posterior columns of the spinal cord. It is well known that a subgroup of familial ALS is characterized by posterior and spinocerebellar tract involvement and presence of Lewy body-like hyaline inclusions in the anterior horn cells [9]. However, our case had no positive family history of MND and lacked such inclusions.

Recent reports have described the autopsy findings of patients with sporadic MND presenting with subacute progression, ophthalmoplegia, sensori-autonomic dysfunctions, decubitus and high CSF protein content [1, 7, 18, 26], which revealed that multisystems other than the upper and lower motor neuron systems were involved: degeneration in the thalamus, pallido-luysian and dentato-rubral systems, substantia nigra, IIIrd, IVth and VIth cranial nerve nuclei, brainstem reticular formation and Clarke's column were common. Bunina bodies or skein-inclusions were not described in these cases [1, 18, 26]. Our patient showed neither ophthalmoparesis nor decubitus, the brain lesions were restricted to the motor neuron system except for slight gliosis of the medullary reticular formation, and both Bunina bodies and skein-like inclusions could be found in the remaining lower motor neurons.

In conclusion, at present, we classify this case as a peculiar type of sporadic MND with severe somatic sensory system involvement. Further clinicopathological studies of similar cases will be necessary to discuss the disease entity.

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