Creutzfeldt-Jakob Disease With Amyotrophy and Demyelinating Polyneuropathy

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Objective: To report the clinical and neuropathological features in a patient with Creutzfeldt-Jakob disease with amyotrophy and demyelinating polyneuropathy.

Design: Case report.

Patient and Results: A 62-year-old man had progressive numbness of the left foot, unsteady gait, diminished deep reflexes, fasciculations, and tactile hypesthesia on the feet. Cerebrospinal fluid, electroneurography, and electromyography were suggestive of chronic inflammatory demyelinating polyneuropathy. He was treated with plasmapheresis, corticosteroids, and immunoglobulins, with minimal improvement. After 2 months, severe amyotrophy, polynuropathy, cerebellar signs, and dementia developed, and he died 8 months after onset of the disease. Autopsy and prion protein immunohistochemistry proved typical Creutzfeldt-Jakob disease. No mutation was found in the prion protein gene, and the codon 129 polymorphism was methionine-valine. In the ventral horn, the loss of the motoneurons was accompanied by prion protein immunoreactivity. The peripheral nerves were segmentally demyelinated but free of prion protein deposition.

Conclusions: The view that peripheral neuropathy and amyotrophy may occasionally be an integral part of Creutzfeldt-Jakob disease is supported by our case, which showed these abnormalities simultaneously. These symptoms, when prominent, may cause problems in differential diagnosis.

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was depressed. His score on the Mini-Mental State Examination was 27/30.

Magnetic resonance imaging of the brain showed mild atrophy with frontal dominance; single photon emission computed tomography detected right frontobasal hypoperfusion. Magnetic resonance images of the cervical and thoracic spine were normal. Electroencephalogram was normal during the course of the disease. Cerebrospinal fluid examination showed 4 cells/µL (lymphocytes) with protein content of 0.5 g/L and a normal electrophoretic pattern.

Motor nerve conduction studies (Table) showed mild to moderate slowing, with prominent temporal dispersion. F-wave minimal latencies were moderately increased in the upper limbs (33 milliseconds for the median nerve and 36 milliseconds for the ulnar nerve) and very much increased in the lower limbs (63 milliseconds for the peroneal nerve and 73 milliseconds for the tibial nerve). Sensory potentials were unobtainable in both upper and lower limbs (median, ulnar, sural). In addition, spinal or cortical responses were not identified on tibial somatosensory evoked potential examination. Needle electromyography of the left tibialis anterior muscle recorded a few fasciculation and fibrillation potentials, the interference pattern was full, and motor unit potentials showed a few motor units with increased amplitude (maximum, 5.6 mV), indicative of mild chronic neurogenic changes. In the left abductor digit minimi muscle, spontaneous activity was not recorded, the interference pattern was full, and motor unit potential analysis showed a few motor units with increased amplitude (maximum, 4.7 mV), suggesting mild chronic neurogenic changes.

These findings were consonant with the clinical picture, so at this stage an acquired polineuropathy with segmental demyelination and only little axonal involvement (such as CIDP) was diagnosed. The clinical symptoms and the cerebrospinal fluid findings ruled out Guillaumin-Barré syndrome. To exclude paraneoplastic origin, tumor was looked for with extensive imaging studies and tumor markers, which all proved to be negative. Viral serologic examinations were negative.

With the putative diagnosis of CIDP, the patient received 5 courses of plasmapheresis, with only minimal initial improvement; therefore, corticosteroids and immunoglobulins were administered. His condition quickly worsened, however, and he was hospitalized again in June 1999. Distal sensory deficit, fasciculation, diminished tendon reflexes, mild tetraparesis, and generalized muscle atrophy were observed. The ataxia of the limbs progressed to a degree that the patient was no longer able to walk. Cognitive deficit also became apparent at this time, with frontal lobe signs and slight short-term memory loss. The score on the Mini-Mental State Examination was 24/30 and decreased to 14/30 in just 2 weeks. The patient lost initiative and became apathetic. Nerve conduction studies suggested a slight increase in the degree of segmental demyelination. Needle electromyography of the left tibialis anterior, vastus lateralis, and abductor digit minimi muscles showed no increase of spontaneous activity or change in motor unit potentials, although interference patterns were slightly reduced. The lack of ongoing denervation and reinnervation spoke against significant acute axonal or motoneuron involvement. The patient died of bronchopneumonia at the end of July 1999, 8 months after the onset of symptoms.

On autopsy, the brain weighed 1340 g and the brainstem with the cerebellum was 160 g. Slight frontopolar atrophy and enlarged ventricles were found on coronal slices. No focal changes were seen. On light microscopy, extensive spongiform change, neuronal loss, and astrocytosis were found in the cerebral cortex, the cerebellum, the basal ganglia, the thalamus, and the brainstem. There was astrocytosis also in the deep white matter. Immunohistochemistry for PrP (antibody 12F10 [courtesy of G. Hunsman, PhD, German Primate Centre, Gottingen, Germany]) in a dilution of 1:250 showed extensive PrP deposits appearing in diffuse, punctate, pericellular, and plaquelike forms (Figure, A). Diffuse staining of the spinal posterior horn was seen (Figure, B). The density of the

<table>
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<tr>
<th>Nerve</th>
<th>Site</th>
<th>Onset Latency, ms</th>
<th>Amplitude, mV</th>
<th>Duration, ms</th>
<th>Segment Name</th>
<th>Velocity, m/s</th>
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<tr>
<td>L median</td>
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<td>8.8</td>
<td>5.6</td>
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<td>45.4</td>
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<td>6.8</td>
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<tr>
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<td>4.9</td>
<td>7.4</td>
<td>B elbow-crease</td>
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</tr>
<tr>
<td></td>
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<td>4.5</td>
<td>8.7</td>
<td>A elbow-B elbow</td>
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<tr>
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<td>4.3</td>
<td>9.2</td>
<td>Axilla-A elbow</td>
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<tr>
<td>L peroneal</td>
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<tr>
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<tr>
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<td>L posterior tibial</td>
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motoneurons decreased in the ventral horn of the spinal cord, with degeneration of the Nissl substance. Immunoreactivity to PrP was detected around the motoneurons and in the neuropil of the ventral horn (Figure, C). The peripheral nerves were free of PrP. Demyelination was seen in the right C5 ventral root with Masson trichrome staining (Figure, D). The PrP gene was sequenced from frozen blood, and no mutation was found. The codon 129 polymorphism was methionine-valine.

**COMMENT**

The view that peripheral neuropathy may occasionally be an integral part of CJD is supported by our case. Few similar cases were published previously, none of them having early polyneuropathy, amyotrophy, and late dementia. Vallat et al reported a panencephalitic form of familial CJD with 5 years of history. Although the patient did not have clinical features of peripheral neuropathy, peripheral nerves showed evident demyelination. Two familial cases with a codon 200 mutation of the PrP gene were reported by Neufeld et al. Their first patient was a 60-year-old man with an 18-month history of CJD diagnosed by brain biopsy findings and by transmission of the spongiform encephalopathy to a chimpanzee with his brain tissue. He had clinical signs of polyneuropathy and no demyelination in the sural nerve biopsy specimen. The second patient was a 57-year-old man with prominent fasciculation and brisk deep tendon reflexes. His electroencephalogram showed triphasic waves, and severe demyelination was found in sural nerve biopsy. Antoine et al also published a report of a familial case of CJD with Glu200Lys mutation of the PrP gene with early dementia, cerebellar signs, and polyneuropathy. Three sporadic cases have been published in the literature. Esiri et al described a 63-year-old man with a 3-month disease history with early cerebellar signs and painful polyneuropathy. At autopsy, spongiform changes were seen in the subcortical gray matter and cerebellar cortex, with only slight involvement of the cortex. No spinal cord or peripheral tissue was available. A case reported by Sadeh et al had clinical signs of polyneuropathy and typical features of CJD with a duration of 20 months, while the case reported by Lope et al had acute ascending Guillain-Barre–like syndrome.

Neuropathological studies on spinal cords of patients with iatrogenic CJD (growth hormone recipients) have shown extensive PrP deposition in the ventral and dorsal horns, while patients with sporadic CJD had PrP deposition mainly in the dorsal horn. The peripheral nerves of patients with sporadic CJD were normal in a recent study by Hainfellner and Budka, although in experimental scrapie peripheral nerves contained PrP deposition. Our patient had a syndrome resembling CIDP as the initial sign with severe muscle atrophy and fasciculation, which is not typical in CIDP. The morphologic al-
terations of the spinal motoneurons might be the cause of the fasciculations, although electrophysiologic studies were not confirmatory.

The view that peripheral neuropathy and amyotrophy may be an integral part of CJD is supported by our case, which is the first described, to our knowledge, to show these abnormalities simultaneously. These symptoms, when prominent, may cause problems in differential diagnosis.

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Author contributions: Study concept and design (Dr Kovács); acquisition of data (Drs Kovács, Arányi, and Szirmai); analysis and interpretation of data (Drs Kovács, Arányi, Szirmai, and Lantos); drafting of the manuscript (Drs Kovács, Arányi, and Szirmai); critical revision of the manuscript for important intellectual content (Drs Kovács and Lantos); obtained funding (Drs Kovács and Lantos); administrative, technical, or material support (Drs Kovács, Arányi, and Szirmai); and study supervision (Drs Kovács and Szirmai).

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REFERENCES