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 immunglobulins, with minimal improvement. After 2 months, severe amyotrophy, polyneuropathy, 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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Creutzfeldt-Jakob disease (CJD) is a neurodegenerative disorder characterized by deposition of the abnormal isoform of prion protein (PrPSc), severe neuronal loss, and astrocytosis with spongiform change of the cortical and subcortical gray matter. The spinal cord is frequently involved but rarely examined. Here PrPSc is commonly deposited in the superficial layers of the dorsal horn. Although the main clinical symptoms are related to the damage of the brain, in some cases the spinal cord and the peripheral nervous system are preferentially involved. In a recent review of the literature by Worrall et al., 24 sporadic and 26 familial cases of prion disease were found to have amyotrophy (muscle atrophy and fasciculation). Demyelinating polyneuropathy is a rare consequence of CJD; only 7 patients have been described in the literature. Prominent fasciculation usually is a sign of the motor neuron damage, but it can be rarely caused by motor neuronpathy with conduction block. These atypical cases may cause problems in differential diagnosis. Herein we report a case of sporadic CJD with prominent muscle atrophy and fasciculation resembling chronic inflammatory demyelinating polyneuropathy (CIDP) and late dementia.

REPORT OF A CASE

A 62-year-old man with a history of tonsillectomy began having problems in November 1998 when numbness of the left foot and walking disability developed. These symptoms progressed within 5 months. When he was first seen in April 1999, he had bilateral hyposmia and hypacusis. There was no muscle atrophy, weakness, or hyperkinesia, but deep reflexes were symmetrically weak and fasciculations were seen in the calf muscles. Tactile hypesthesia was found on the left foot and calf with preserved deep sensation. He had mild dysdiadochokinesis and ataxia of the limbs and was barely able to stand in Romberg position. His gait was ataxic, especially with closed eyes. He had primitive reflexes and...
A tumor was looked for with extensive imaging studies and was negative. Therefore, multiple sclerosis (such as CIDP) was diagnosed. The clinical symptoms and the cerebrospinal fluid findings ruled out Guillain-Barré syndrome. To exclude paraneoplastic origin, tumor markers, which all proved to be negative. Viral serologic examinations were negative.

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 were increased (maximum, 5.6 mV), indicative of mild chronic neurogenic changes. In the left abductor digiti 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, 5.6 mV), indicative of mild chronic neurogenic changes.

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

Table

<table>
<thead>
<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>
</tr>
</thead>
<tbody>
<tr>
<td>L median</td>
<td>APB</td>
<td>4.2</td>
<td>8.8</td>
<td>5.6</td>
<td>Wrist-APB</td>
<td>45.4</td>
</tr>
<tr>
<td></td>
<td>Wrist</td>
<td>9.6</td>
<td>6.5</td>
<td>6.7</td>
<td>Elbow-wrist</td>
<td>47.1</td>
</tr>
<tr>
<td></td>
<td>Elbow</td>
<td>11.6</td>
<td>6.0</td>
<td>6.9</td>
<td>Axilla-Elbow</td>
<td>47.1</td>
</tr>
<tr>
<td>L ulnar</td>
<td>ADM</td>
<td>3.8</td>
<td>8.3</td>
<td>6.8</td>
<td>Wrist-ADM</td>
<td>41.9</td>
</tr>
<tr>
<td></td>
<td>Wrist</td>
<td>9.0</td>
<td>4.9</td>
<td>7.4</td>
<td>B elbow-wrist</td>
<td>64.0</td>
</tr>
<tr>
<td></td>
<td>A elbow</td>
<td>10.9</td>
<td>4.5</td>
<td>8.7</td>
<td>A elbow-B elbow</td>
<td>58.5</td>
</tr>
<tr>
<td></td>
<td>Axilla</td>
<td>12.3</td>
<td>4.3</td>
<td>9.2</td>
<td>Axilla-A elbow</td>
<td>58.5</td>
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<tr>
<td>L peroneal</td>
<td>EDB</td>
<td>Ankle</td>
<td>5.3</td>
<td>1.0</td>
<td>Ankle-EDB</td>
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<td>B fibula</td>
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<td>0.8</td>
<td>10.4</td>
<td>B fibula-ankle</td>
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<td></td>
<td>Popl</td>
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<td>0.7</td>
<td>10.6</td>
<td>Popl-B fibula</td>
<td>43.6</td>
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<tr>
<td>L posterior tibial</td>
<td>AbdHal</td>
<td>Ankle</td>
<td>4.8</td>
<td>1.2</td>
<td>Ankle-AbdHal</td>
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<tr>
<td></td>
<td>Popl</td>
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<td>0.9</td>
<td>13.6</td>
<td>Popl-ankle</td>
<td></td>
</tr>
</tbody>
</table>

*APB indicates abductor pollicis brevis muscle; ADM, abductor digiti minimi muscle; B, below; A, above; EDB, extensor digitorum brevis muscle; Popl, popliteal fossa; and AbdHal, abductor hallucis muscle.

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. Electroencephalograms were 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.

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 spongiiform 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. Hunsmann, 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...
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


