SHORT REPORT

Atypical form of dural graft associated Creutzfeldt-Jakob disease: report of a postmortem case with review of the literature

K Kimura, A Nonaka, H Tashiro, M Yaginuma, R Shimokawa, R Okeda, M Yamada

Abstract
A postmortem case of an atypical form of dural graft associated Creutzfeldt-Jakob disease (CJD) is described. A 42 year old man developed progressive spastic paresis 163 months after a cadaveric dural graft. He presented with no myoclonus and very late occurrence of periodic synchronous discharges on EEG. The prion protein (PrP) gene was homozygous for methionine at the polymorphic codon 129. Neuropathological examination disclosed plaque-like PrP deposits with atypical distribution of synaptic PrP accumulations in the brain. This patient represents an atypical form of dural graft associated CJD characterised by unusual clinicopathological features.

Keywords: cadaveric dura mater graft; Creutzfeldt-Jakob disease; prion protein; plaque

A considerable number of patients with Creutzfeldt-Jakob disease (CJD) have been reported to be associated with a cadaveric dura mater graft. The number of the dural graft associated cases was especially large in Japan; 67 such patients were reported in Japan during January 1985 to March 1999. In most of the dural graft associated cases, the clinical and neuropathological pictures were similar to those of sporadic (idiopathic) cases of CJD, although cerebellar signs were the most frequent early presentation in the dural cases. However, some patients with dural graft associated CJD have been reported to have atypical clinical features, with plaque formation in the brain. The plaque morphology in some patients has been reported to be identical with florid plaques, which have been described in the variant CJD (vCJD) recognised first in the United Kingdom. Here we describe a patient with an atypical form of dural graft associated CJD, showing unusual clinicopathological features.

Case report
A 42 year old man visited our hospital in February 1998 because of progressive right hemiparesis that had started 1 month before. In his medical history, he had had a pituitary adenoma with pituitary apoplexy and underwent an operation with a cadaveric dural graft in June 1984. The pituitary apoplexy was complicated by subarachnoid haemorrhage, which caused vasospasm resulting in infarction in the area of the left anterior cerebral artery. We have no further information about the dural graft. When he left the hospital, he had slight right hemiparesis; later he had no apparent paresis and no difficulty in activities of daily living. On neurological examination in February 1998, he was alert and oriented. The right upper and lower limbs were spastic. Although he had difficulty due to the right spastic hemiparesis, he could walk with help. There were no remarkable findings on cranial CT, MRI, or cerebral angiography, except for the old infarction in the area of the left anterior cerebral artery. Thereafter, dysarthria, dysphagia, and left spastic hemiparesis appeared. Then he became unable to walk and also showed urinary and bowel incontinence. On admission to our hospital in September 1998, he could answer to questions with only one or two words, but could respond to complicated commands. He could eat by himself and sit on a chair although he was unable to stand. He showed horizontal nystagmus, marked spasticity, and weakness in the bilateral upper and lower extremities with bilateral pyramidal signs. Ataxia was not evident. No involuntary movement was found. Laboratory tests were normal, except for low concentrations of serum sodium (125 mmol/l), which was compatible with the syndrome of inappropriate antidiuretic hormone secretion (SIADH), and low concentrations of some pituitary hormones that were related to the postoperative state of the pituitary tumour. Analysis of CSF was normal, except for increased concentrations of neuron specific enolase (NSE) (26 ng/ml) and the presence of 14–3–3 protein. Brain CT and MRI showed only the old infarction of the left anterior cerebral artery territory as found in February 1999; except for that, there was no atrophy or abnormal intensity even on MRI diffusion images. EEG showed slow activity without periodic synchronous discharges. Prion protein (PrP) gene analysis of the DNA extracted from the blood disclosed no mutation in the DNA of the DNA extracted from the blood.
open reading frame of the PrP gene. For the polymorphic codons, codon 129 was Met/Met, and codon 219 Glu/Glu. The diagnosis was possible CJD. After admission, he progressively deteriorated to the status of akinetic mutism after several weeks. He died of bronchopneumonia in February 1999, 13 months after the onset of the symptoms. The findings on CT and MRI were unchanged throughout his course. In repeated EEG studies, periodic synchronous discharges were first recorded 2 days before his death. At necropsy, a patch of the dural graft was found in the right frontal region. The brain weighed 1275 g. Macroscopically, the brain was slightly swollen and showed old cystic infarction scars in the territory of the left anterior cerebral artery with slight atrophy of the left cerebral hemisphere, and several, up to 10 mm sized, old infarction scars. Microscopically, there was mild to moderate spongiform change, neuronal loss, and astrocytosis in the cerebral cortex, especially in the paramedian cortical regions, subcortical grey matter, and brain stem (figure 1 A). Immunohistochemistry for PrP showed extensive accumulation of PrP in the brain; the PrP immunoreactivities, which were mainly granular (the synaptic type), were particularly intense in the cerebellar cortex and nuclei, brainstem nuclei (especially the inferior olivary nuclei), and cerebral deep grey matter (figure 1 B). In the cerebral cortex, the PrP distribution was not uniform showing accentuation in the paramedian cortical regions including the cingulate gyrus and parahippocampal gyrus; the PrP immunoreactivities were relatively weak in the cerebral convexity regions, where the deposits were mainly in the 5th and 6th layers (figure 1 C). In the cerebral cortex, especially in the deep layers, plaque-like PrP deposits were found in addition to the granular PrP immunoreactivities of the synaptic type (figure 1 D). The plaque-like PrP deposits were unicentric and
Table 1 Summary of patients with an atypical form of dural graft associated Creutzfeldt-Jakob disease (CJD)

<table>
<thead>
<tr>
<th>No (authors)</th>
<th>Age/sex (y/origin)</th>
<th>Dural graft</th>
<th>Latency (y)</th>
<th>Initial symptom</th>
<th>Myoclonus</th>
<th>PSDs on EEG</th>
<th>Clinical course (months)</th>
<th>Brain weight (g)</th>
<th>Spongiform change</th>
<th>Plaques</th>
<th>Neuronal genotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (Lane et al)⁵</td>
<td>28/F</td>
<td>1984/Lyodura</td>
<td>6</td>
<td>Ataxia</td>
<td>–</td>
<td>18</td>
<td>1200</td>
<td>+</td>
<td>Kuru-type amyloid plaques</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>2 (Kopp et al)⁵</td>
<td>52/M</td>
<td>1984/unknown</td>
<td>11</td>
<td>Ataxia</td>
<td>–</td>
<td>5</td>
<td>NA</td>
<td>+</td>
<td>Florid-type PrP plaques</td>
<td>Met/Met</td>
<td>NA</td>
</tr>
<tr>
<td>3 (Takahshima et al)⁴</td>
<td>47/F</td>
<td>1985/Lyodura</td>
<td>9</td>
<td>Ataxia</td>
<td>+</td>
<td>17</td>
<td>1220</td>
<td>+</td>
<td>Florid-type PrP plaques</td>
<td>Met/Met</td>
<td>Glu/Glu</td>
</tr>
<tr>
<td>4 (Shimizu et al)⁵</td>
<td>68/M</td>
<td>1985/Lyodura</td>
<td>11</td>
<td>Ataxia</td>
<td>–</td>
<td>7</td>
<td>1260</td>
<td>+</td>
<td>Florid-type PrP plaques</td>
<td>Met/Met</td>
<td>Glu/Glu</td>
</tr>
<tr>
<td>5 (Shimizu et al, case 1)⁵</td>
<td>68/F</td>
<td>1986/Lyodura</td>
<td>10</td>
<td>Ataxia</td>
<td>–</td>
<td>4</td>
<td>1055</td>
<td>+</td>
<td>Florid-type PrP plaques</td>
<td>Met/Met</td>
<td>Glu/Glu</td>
</tr>
<tr>
<td>6 (this case)⁵</td>
<td>42/M</td>
<td>1984/unknown</td>
<td>14</td>
<td>Spastic paresis</td>
<td>–</td>
<td>4</td>
<td>13</td>
<td>1275</td>
<td>+</td>
<td>Plaque-like PrP deposits</td>
<td>Met/Met</td>
</tr>
</tbody>
</table>

*Very late occurrence of periodic synchronous discharges (PSDs) on EEG. NA=information not available.

Discussion

Our patient was characterised clinically by progressive spastic ataxia (bilateral hemiparesis) which appeared 163 months after the neurological operation with cadaveric dural grafting, and pathologically by atypical distribution of the PrP accumulations with PrP plaques. Although some of the plaque-like PrP deposits were adjacent to spongiform changes, they were not surrounded by a distinct halo of spongiform change, and did not fulfil the criteria for florid plaques. In addition, there were PrP deposits surrounding neuronal cell bodies and processes in the cerebral cortex. A western blot analysis of protease resistant PrP with anti-PrP monoclonal antibody 3F4 disclosed a type 1 three band pattern showing no difference between this patient, dural graft associated patients without plaque-like PrP deposits, and patients with sporadic (idiopathic) CJD (data not shown).

faintly eosinophilic with no or slight congophilic, suggesting that most of the plaque-like deposits would represent a preamyloid (non-fibrillar) form of PrP. Although some of the plaque-like PrP deposits were adjacent to spongiform changes, they were not surrounded by a distinct halo of spongiform change, and did not fulfil the criteria for florid plaques. In addition, there were PrP deposits surrounding neuronal cell bodies and processes in the cerebral cortex. A western blot analysis of protease resistant PrP with anti-PrP monoclonal antibody 3F4 disclosed a type 1 three band pattern showing no difference between this patient, dural graft associated patients without plaque-like PrP deposits, and patients with sporadic (idiopathic) CJD (data not shown).

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Aphasia and Wernicke’s arc

Sextus Empiricus (about AD 200) is credited with being the first person to use the word “aphasia”, albeit in a philosophical sense. Carl Wernicke’s studies on aphasia, published from 1874, are among the classics of clinical neurology. However, Benton and Joynt suggest that Johann Schmidt in 1677 gave the first account of paraphasia and alexia. They also observed that: “Almost all the clinical forms of aphasia—complete motor aphasia, paraphasia, jargon aphasia, agraphia and alexia—had been described before 1800. The unawareness of defect which may accompany paraphasia and jargon aphasia had been noted, as well as the coincidence of apha sia and agraphia.”

After the studies of Gall in 1807, and Bouillaud, there were many exponents of a dynamic view of aphasia. Finkelburg (1870) regarded speech disorders as part of a wider disturbance, which he called lack of symbolic representation. Word blindness and word deafness, described by Bastian, were disorders of perception, independent of speech defects.

Critical to Wernicke’s concepts was his anatomical demonstration of an arc of cerebral matter, in which lesions would be associated with aphasia. He distinguished three varieties that still form the broad foundation of modern nosology.

Sensory aphasia, Wernicke attributed to a lesion of the auditory centre, which abolished “sound-images”, and so prevented the patient from understanding words and from recognising his own defects of speech.

Destruction of the third frontal convolution caused motor (Broca’s) aphasia, with loss of the images for articulated speech. A lesion that destroyed the pathway between the two centres caused conduction aphasia, leading to misuse of words but no defect of understanding. Moreover, a lesion destroying both centres caused loss of understanding both and expression of speech—total aphasia.

The anatomical substrate lay in an arc in the dominant temporal lobe with linked fibres in the left third frontal convolution with central connections (figure). This was known as Wernicke’s arc. He recognised that an auditory centre was in the first temporal convolution (Wernicke’s area), and the centre for articulated speech in Broca’s area.

Broca had described: “aphemia . . . the result of a profound, but accurately circumscribed lesion of the posterior third of the second and third frontal convolutions.”

Wernicke’s illustration of the arc, 1874

Wernicke’s arc has proved an invaluable guide to clinical localisation of focal lesions affecting language and speech.
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