

SHORT REPORT

Dura mater-associated Creutzfeldt–Jakob disease: experience from surveillance in the UK

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Between 1970 and 2003, seven cases of human dura mater-associated Creutzfeldt–Jakob disease (CJD) were identified in the UK. Furthermore, we identified a case of CJD in a porcine dura graft recipient. The mean incubation period of the human dura mater cases was 93 (range 45–177) months. The clinico-pathological features of the cases are described and compared with cases previously reported in the world literature.

Creutzfeldt–Jakob disease (CJD) exists in four clinical forms: sporadic, genetic, iatrogenic and variant. The cause of sporadic CJD, the most common form worldwide, is unknown and case–control studies have failed to identify any consistent risk factor, although two studies have implicated previous surgical interventions.^{1–2} Genetic forms of the disease are associated with underlying mutations of the prion protein gene (*PRNP*), which are generally considered to be directly causative. Mutations, however, possibly increase liability to some, as of yet unrecognised, source of infection. The two remaining forms of CJD are acquired. Variant CJD is considered to be caused by bovine spongiform encephalopathy through contaminated food products^{3–5}; iatrogenic CJD results from the inadvertent transmission of CJD during the course of medical or surgical treatment. The two most numerically significant instances of iatrogenic CJD resulted from treatment with cadaveric human growth hormone and the use of dura mater grafts in surgery. Corneal grafts, depth electrodes and neurosurgical instruments have also rarely been implicated.^{6–7}

The first report of dura mater-associated CJD was published in 1987,⁸ with a more detailed report appearing the following year;⁹ to date, 164 cases have been recognised worldwide (P Brown, personal communication, 2006). This paper reports and describes the seven cases of human dura mater graft-associated CJD identified during surveillance in the UK and, for the first time, reports a case of CJD in a porcine dura graft recipient.

METHODS

CJD surveillance in the UK has been undertaken in four phases.

- A retrospective review in England and Wales from 1970 to 1979.
- A prospective study in England and Wales from 1980 to 1984.
- A retrospective review in the UK to cover the period from 1985 to 1990.
- A prospective surveillance was instituted in the UK in 1990 and continues.

The methodology of the National CJD Surveillance Unit has been described in previous publications.^{10–11}

RESULTS

Human dura mater

During the period 1970 and 2003, seven cases of human dura mater-associated CJD were identified in the UK (table 1). The latent period between surgery and the onset of CJD ranged from 45 to 177 months* (mean 93). The mean age at surgery was 33 years, with a mean age at onset of 41 years.

Lyodura (B Braun Melsungen, Germany), a particular brand of human dura mater, was implicated in six of the seven cases (the manufacturer of the dura graft implicated in case I is unknown).

The six cases associated with Lyodura were exposed to the presumed source of “infection” between 1983 and 1987, with the first recognised case in the UK exposed to human dura mater in 1969.

A detailed account of both clinical and investigative features is available at <http://jnnp.bmjournals.com/supplemental>. In four cases, the clinical phenotype at onset appears to correlate with the site of graft placement or underlying parenchymal damage (cases II, III, V and VI). For example—in case II, the presenting clinical features included a right visual field defect in an individual with a tumour localised to the left hemisphere. The subsequent CJD began with a right visual field disturbance and progressed with signs indicating the involvement of the left hemisphere. Some of the cases were investigated before the widespread availability of MRI; therefore MRI was available in only four of the seven cases. None of the cases showed the characteristic radiological features of human prion disease¹⁴ with post-surgical change being the most commonly recognised abnormality. Despite all seven cases having at least one electroencephalogram during the course of investigation, only three of the seven cases showed the “typical” features.

Autopsy was carried out in five of the seven cases. In general, the neuropathology was characterised by widespread spongiform change accompanied by variable neuronal loss and gliosis. Western blot analysis for PrP^{res} was carried out in three cases (II, VI and VII). The mobility and glycoform ratio of the PrP^{res} is indistinguishable from those of type 1 PrP^{res} identified in cases of sporadic CJD, and is distinct from type 2B PrP^{res} identified in variant CJD.

Porcine dura mater

We believe the identification of CJD in a porcine graft recipient to be the first such report worldwide (table 1, case VIII). The recipient underwent excision of a right fronto-parietal meningioma in 1988 and a xenoderm graft was used to repair the dura. The recipient presented with

*Case V received two dura grafts, it is assumed that the first graft was responsible for transmission.

Table 1 UK case details—human dura mater

Case	Surgical procedure	Dura	Year of surgery	Year of death	Incubation period (Months)	Duration of illness (Months)
I, Esmonde <i>et al</i> ²	Suboccipital craniotomy and C1/2 laminectomy for cerebellar ectopia and syringomyelia	?	1969	1979	104*	6
II, Esmonde <i>et al</i> ²	Excision of a left temporal cortex meningioma	L	1983	1991	93*	5*
III	Repair surgical leak after acoustic neuroma excision	L	1985	1989	51	2
IV, Willison <i>et al</i> ³	Posterior fossa decompression and cervical laminectomy for cerebellar ectopia or syringomyelia	L	1985	1989	45*	4
V	Excision of a left parietal cortex meningioma	1:L	1985	1993	1:86	11
VI	Excision of a cerebellar astrocytoma	L	1986	1997	2:79	33
VII	Excision of an eosinophilic granuloma right frontal region skull	L	1987	2003	103	5
Porcine dura graft: VIII	Excision of a right frontoparietal meningioma	P	1988	2000	177	3

*Revised from previously published figures.
L, Lyodura; P, Porcine dura.

headaches, ataxia and cognitive decline 134 months later. Investigative features, including an electroencephalogram, were supportive of the clinical diagnosis, and pathological confirmation was obtained. Autopsy showed spongiform change in the frontal and temporal cortex, with similar features identified in the basal ganglia, thalamus and cerebellum. Immunocytochemistry for PrP showed widespread accumulation and western blot analysis showed the type 1 isoform.

DISCUSSION

Human dura mater is a rare, but important source of transmission of human prion disease, with only seven cases recognised in a 33-year period. Surveillance systems worldwide have identified 164 cases of CJD in people previously exposed to human dura mater. Prevalence is particularly high in Japan and probably reflects neurosurgical practice, with an estimated 20 000 grafts used each year.¹⁵ The overall risk of CJD associated with human dura grafts in the UK is unknown because an accurate estimation of human dura graft use and thus a denominator for calculation of risk is not available. The estimated risk after exposure in Japan has been estimated to be approximately 1 per 2000 patients treated between 1979 and 2000 and approximately 1 per 1000 between 1983 and 1987.¹⁶ Neurosurgical practice in Japan, with widespread use of dura mater, may be different from other countries throughout the industrialised world and therefore it is unreasonable to extrapolate any estimated risk from these data. If neurosurgical practices in the UK were more akin to those in Australia, then a subsequent study by Brooke and co-workers would help provide additional information pertaining to estimated risk. By using information from the Australian CJD Surveillance system, Brooke and co-workers estimated the risk associated with exposure to human dura mater to be approximately 1 per 500 patients treated between 1978 and 2003.¹⁷ Clearly, the risk of developing CJD in this patient population is considerably higher than we would expect by chance.

The human dura mater implicated in the transmission of CJD was processed, almost exclusively, by B Braun Melsungen in Germany and traded under the name Lyodura. Over 100 Japanese cases, and all but one of the UK cases (the source of the first case identified in the UK is unknown), have been associated with this particular product and only rarely has dura processed by other manufacturers

been associated with transmission.^{18, 19} Although the first case in the UK was exposed to potentially infectious dura in 1969, a disproportionately large number of cases were exposed between 1983 and 1987 (80% of those identified worldwide and six of the seven cases in the UK). Interestingly, the apparent reduction in the number of cases post-1987 coincided with the introduction of stringent donor selection criteria and the introduction of sodium hydroxide immersion techniques in the manufacturing process.

We found no temporal or geographical association between any of the dura-associated cases, or any other case of CJD identified in the UK, despite potential contamination of neurosurgical instruments.

It has been proposed that clinical features at onset are dependent on the site of graft placement or underlying parenchymal damage²⁰⁻²² and our findings may support such a proposition. The explanation for this observation is unclear. We could speculate that the pathological process starts within a region adjacent to the graft and that this is reflected in the early clinical features. This proposition may also be supported by findings obtained at autopsy, with severe pathological changes identified adjacent to graft placement in three cases. Overall, the pathology is consistent for that previously described in dura mater-associated CJD.^{9, 18} We did not identify either "kuru-type" or florid PrP plaques. The florid PrP plaques were previously noted in limited distribution in a small number of dural graft-associated iatrogenic CJD cases in Japan.^{21, 23, 24}

We believe case VIII represents the first reported case of CJD in a person previously exposed to a graft from a non-human source. The age at onset, duration of illness, clinical and investigative features were similar to a typical case of sporadic CJD. Furthermore, the pathological features were also considered characteristic of sporadic CJD, with type 1 PrP^{res} identified. Neither finding can definitively exclude the possibility of transmission of a yet unidentified pathogen. As natural transmissible spongiform encephalopathies are, however, as yet unrecognised in pigs, despite experimental transmission in animal models,²⁵ a chance association seems the most plausible explanation.

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Additional data on the cases in this report are available at <http://jnnp.bmjournals.com/supplemental>

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