SHORT REPORT

Postmortem findings in a case of variant Creutzfeldt-Jakob disease treated with intraventricular pentosan polysulfate

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ABSTRACT

Background A small number of patients with variant Creutzfeldt-Jakob disease (vCJD) have been treated with intraventricular pentosan polysulfate (iPPS) and extended survival has been reported in some cases. To date, there have been no reports on the findings of postmortem examination of the brain in treated patients and the reasons for the extended survival are uncertain. We report on the neuropathological findings in a case of vCJD treated with PPS.

Methods Data on survival in vCJD is available from information held at the National CJD Research and Surveillance Unit and includes the duration of illness in 176 cases of vCJD, five of which were treated with iPPS. One of these individuals, who received iPPS for 8 years and lived for 105 months, underwent postmortem examination, including neuropathological examination of the brain.

Results The mean survival in vCJD is 17 months, with 40 months the maximum survival in patients not treated with PPS. In the 5 patients treated with PPS survival was 16 months, 45 months, 84 months, 105 months and 114 months. The patient who survived 105 months underwent postmortem examination which confirmed the diagnosis of vCJD and showed severe, but typical, changes, including neuronal loss, astrocytic gliosis and extensive prion protein (PrP) deposition in the brain. The patient was also given PPS for a short period by peripheral infusion and there was limited PrP immunostaining in lymphoreticular tissues such as spleen and appendix.

Conclusions Treatment with iPPS did not reduce the overall neuropathological changes in the brain. The reduced peripheral immunostaining for PrP may reflect atrophy of these tissues in relation to chronic illness rather than a treatment effect. The reason for the long survival in patients treated with iPPS is unclear, but a treatment effect on the disease process cannot be excluded.
RESULTS
There have been 177 deaths from vCJD in the UK (as of August 2013) and the mean survival is 17 months from disease onset to death. Five of these cases received treatment with iPPS and the duration of illness in these cases is shown in figure 1, together with that of non-treated cases. The treated case that survived 105 months is described below.

Case report
An 18-year-old girl presented in September 2003 with a 9 month history of personality change, anxiety, tearfulness and withdrawal. She performed unexpectedly badly in school examinations and in July developed forgetfulness and unsteadiness walking. The cognitive problems progressed and were associated with fleeting delusions and auditory hallucinations. She developed unpleasant sensory symptoms in the feet, slurring of speech and fidgety movements of the hands and arms. On examination there was cognitive impairment, together with dysarthria, limb and gait ataxia and choreiform movements in the limbs.

There was a past history of vertigo in 2002, with normal MRI brain scan, but no history of treatment with human growth hormone or prior neurosurgery and no family history of a similar disorder. MRI brain scan in 2003 showed the ‘pulvinar’ sign and no other cause for the presentation was apparent on extensive investigation. The clinical diagnosis was probable vCJD. Testing for abnormal PrP in blood in August 2011, using the novel assay described by Edgeworth et al., was negative.

After careful and full consideration of ethical and legal issues in a patient who lacked capacity, the clinicians accepted the wishes of the patient’s family to begin treatment with iPPS which commenced in October 2003. Biventricular catheters were inserted using a stereotactic procedure and a programmable pump was implanted subcutaneously. Treatment with iPPS was given at a dosage of 11 μg/kg/day and following replacement of the catheters in 2011 the treatment was continued at 11 μg/kg/day up until the patient died. In 2007, additional systemic treatment with PPS was given by programmable pump via the external jugular vein in a dosage increasing from 1 μg/kg/day to 4 μg/kg/day. The treatment was stopped after 12 weeks because of persisting infection and haematoma at the pump site, and the pump was removed.

Despite the treatment there was neurological deterioration and by December 2003 the patient was unable to walk and needed assistance to dress, bathe, wash and feed. There was difficulty with swallowing and a percutaneous endoscopic gastrostomy tube was fitted in June 2005. Over subsequent years the patient’s condition was relatively static with only subtle further clinical deterioration. She was wheelchair bound and fully dependent for activities of daily living. There was no verbal or clear sentient response, but at times the parents reported transient responsiveness to outside stimuli such as the pet dog or family videos, contrary to clinical observations. The patient received excellent care from her family, with additional nursing support and regular treatment by a physiotherapist.

The patient died suddenly in November 2011 and postmortem was carried out at the request of the coroner. The patient’s family gave consent for detailed pathological investigation of the brain and peripheral tissues.

Postmortem results
The general postmortem revealed pulmonary oedema and mild bronchopneumonia. The brain showed severe atrophy and weighed 775 g. Tubing for the delivery system for PPS passed through the brain into the lateral ventricles. The other main organs were unremarkable.

Examination of the fixed brain showed marked atrophy of the cerebral and cerebellar hemispheres, brainstem and midbrain.
On cross section, the hippocampus was relatively spared, but the deep grey matter nuclei of the cerebral hemispheres were atrophic and the subcortical white matter was firm and discoloured. No evidence of old or recent haemorrhage was identified. Microscopic examination confirmed marked atrophy of the major grey matter structures, accompanied by severe neuronal loss and widespread gliosis. The white matter was also markedly gliotic and showed secondary myelin loss as a consequence of axonal degeneration. Immunocytochemistry for PrP showed massive accumulation of abnormal PrP throughout the cerebral cortex and cerebellum, and also in the basal ganglia, thalamus and hypothalamus and to a lesser extent the brainstem. The pattern of deposition included florid plaques, small cluster plaques and some granular deposits (figure 2).

Sections of the appendix, lymph nodes, spleen and tonsil showed no evidence of abnormal PrP accumulation on routine immunohistochemistry. However, repeat immunohistochemical studies using an enhanced visualisation system showed PrP accumulation in follicular dendritic cells within the tonsil, lymph node, appendix and spleen. The spleen showed depletion of white pulp, with sparse follicular labelling (figure 3), which was confirmed on paraffin-embedded tissue blot studies for protease-resistant prion protein\textsuperscript{es}. Western blot analysis of frozen tissue samples from the cerebrum and cerebellum found high levels of PrP\textsuperscript{res} with a type 2B isoform characteristic of vCJD\textsuperscript{12} with highest levels in the occipital cortex and lowest levels in the thalamus. No specific signals for type 2B PrP\textsuperscript{res} were obtained using the centrifugal enrichment method on samples of appendix, tonsil, lymph node or spleen. The sodium phosphotungstic acid precipitation method allowed for detection of type 2B PrP\textsuperscript{res} in the spleen, but not in appendix, lymph node or tonsil samples (figure 4). The patient was a methionine homozygote at codon 129 in the PrP gene.

The pathological features confirmed the diagnosis of vCJD.

**DISCUSSION**

The data presented in this paper suggests that treatment with iPPS may extend survival in vCJD. Four out of five treated patients survived for periods significantly longer than untreated patients (figure 1) and this suggests that chance alone is an unlikely explanation. All the treated cases received excellent nursing care, assisted feeding and active treatment of intercurrent illness, but this was also true for many of the ‘untreated’ cases of vCJD. There is an inverse relationship between age and survival in human prion diseases\textsuperscript{13} and the three longest survivors treated with iPPS were aged less than 20 years at the time of starting treatment. However, there have been 31 other cases of vCJD in the UK with an onset age less than 20 years in which the mean survival was only 20 months. Many of these cases received active treatment (but not iPPS) from an early stage and case selection is unlikely to explain the extended survival in the iPPS group.

If iPPS influences the underlying disease process, the evidence from the postmortem examination of the brain in this case does not suggest that the treatment has reduced the extent or severity of the brain pathology. In fact the pathological changes were severe including the extent of abnormal PrP deposition and this perhaps parallels the observed neurological deterioration in the index case and the severe neurological deficits present in the latter stages of the illness. One potential explanation for the extended survival is that iPPS treatment resulted in relative preservation of the brainstem nuclei and the sudden death, without a clear cause on the general autopsy, may indicate that death may have been due to a combination of central and peripheral processes.

The relative paucity of abnormal PrP in lymphoreticular system (LRS) might be as a result of the systemic treatment with PPS. However, atrophy of LRS in chronic illness is well recognised\textsuperscript{14} and it may be that the depletion of white matter pulp, observed in this case, may reflect a more general atrophy of LRS as an epiphenomenon rather than an effect of PPS treatment on the levels of peripheral abnormal PrP. The blood-based assay for vCJD has a reported sensitivity of 71% in known cases of vCJD, therefore no clear conclusion can be drawn from this test being negative\textsuperscript{10}.

In conclusion the evidence suggests that iPPS treatment may have extended survival in vCJD and that this is likely related to an effect on the underlying disease process. Although iPPS is clearly not a cure for vCJD, the fact that such a treatment has had a significant biological effect provides encouragement for the future development of treatment for human prion diseases.

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