SHORT REPORT

Long term survival in a patient with variant Creutzfeldt–Jakob disease treated with intraventricular pentosan polysulphate

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Variant Creutzfeldt–Jakob disease (vCJD) is a neurodegenerative disease that principally affects young people and has a median duration of illness of 13 (range 6–39) months. vCJD is incurable and there are currently no treatments that conclusively slow the rate of disease progression. However, recent animal studies and isolated case reports have suggested that treatment with intraventricular pentosan polysulphate (PPS) may be beneficial in the treatment of patients with vCJD.

We report a case of a 22-year-old male with vCJD treated 19 months after the onset of clinical symptoms with continuous intraventricular PPS (32 µg/kg/day) over a period of 31 months. Treatment with PPS appeared to be safe and well tolerated and was associated with prolonged survival (51 months) when compared to natural history studies. However, PPS treatment did not appear to arrest the progression of the disease.

Variant Creutzfeldt–Jakob disease (vCJD) is a devastating neurodegenerative disease which principally affects young adults.¹ There is currently no cure for vCJD and no treatment that conclusively slows the progression of the disease.

Treatment with intraventricular pentosan polysulphate (PPS) (a large polyglycoside molecule with antithrombotic and anti-inflammatory properties), infused relatively late after the intracerebral inoculation of 263K scrapie agent into transgenic mice, has been shown both to prolong the incubation period before the development of overt clinical signs and to reduce the extent of abnormal prion protein deposition in the brain.² The efficacy and safety of intraventricular PPS treatment in humans with vCJD, however, remains largely unknown.^{3,4} More research is needed both to describe the clinical outcome of treatment with intraventricular PPS in patients with vCJD and to define the therapeutic dose window for treatment in humans.

We report a case of a 22-year-old male with vCJD treated 19 months after the onset of clinical symptoms with continuous intraventricular PPS.

CASE REPORT

Clinical presentation

The patient presented in April 2003, aged 18 years, with a 12 month history of mood disturbance, a 6 month history of limb dysaesthesia and a 2 month history of ataxia, dysarthria and limb myoclonic jerks (fig 1). The patient had remained working as a decorator until March 2003. Clinical examination demonstrated brisk symmetrical limb reflexes, an independent but ataxic gait, dysarthria and jerky horizontal pursuit eye movements.

Assessment of intellectual function in May 2003 showed a global decline in scores from estimated premorbid levels (supplementary table 1; supplementary table 1 can be viewed

on the *JNNP* website at <http://www.jnnp.com/supplemental>). Although cooperative to assessment, he was abulic and volunteered little spontaneous speech. He was fully orientated in all spheres but formal assessment of long term verbal and visual memory produced severely impaired results. There was evidence of an acquired dyslexia and constructional dyspraxia. Assessment of executive function on a range of standard administered tasks consistently produced scores in the severely impaired range.

A T2 weighted MRI brain scan showed high signal in the pulvinar. The clinical diagnosis of vCJD was confirmed by a positive tonsil biopsy.

The parent's wish for us to consider treatment with intraventricular PPS was supported by a subsequent High Court hearing. Clinical reassessment in hospital immediately prior to starting treatment with intraventricular PPS in December 2003 showed that the patient had significantly deteriorated over the previous 8 months since diagnosis. There was no spontaneous speech although he was able occasionally to give appropriate simple one word answers. His parents had observed limited spontaneous speech at home. He was not orientated but did obey one stage commands and appeared to fix on the examiner's face during the examination. He was incontinent and dependent for all activities of daily living. A percutaneous gastrostomy tube provided nutrition although the patient could still swallow a soft diet. Tone was increased in all limbs with extensor plantars, the limb ataxia had worsened and the patient was no longer able to walk or transfer independently from bed to chair. Choreoathetoid movements were present intermittently in the upper limbs, and startle and spontaneous myoclonic jerks were observed in all four limbs.

Formal neuropsychological assessment was not feasible because of the level of disability. Informal assessment showed relatively preserved nominal abilities and that he was able to read simple text. He was able to give his name and date of birth but not his age. He could correctly identify colour and shape. He was unable to recall any of three items after a short delay and distraction.

In December 2003 the patient underwent stereotactic implantation of a right ventricular catheter and programmable subcutaneous infusion pump (Synchomed, Medtronic, Minneapolis, MN, USA). A CT brain scan 6 days postoperatively prior to treatment initiation with PPS showed that the ventricular catheter had become displaced from the right lateral ventricle requiring a further operation to re-site the catheter. The intraventricular PPS infusion was started 5 days later at an infusion rate of 1 µg/kg/day and the dose escalated over the following 15 days with serial CT brain imaging to the target dose of 11 µg/kg/day.³

Abbreviations: PPS, pentosan polysulphate; vCJD, variant Creutzfeldt–Jakob disease

Figure 1 A summary time course of the principal clinical events discussed in the text. ADL, activities of daily living; PPS, pentosan polysulphate; vCJD, variant Creutzfeldt-Jakob disease.

Subsequent clinical course

Since October 2004, the dose of intraventricular PPS has been slowly increased to 32 µg/kg/day (April 2005) and the patient monitored both clinically and with serial CT brain scans without adverse effect. An EEG performed in September 2004 showed more pronounced generalised slow wave activity compared with the EEG performed in April 2003.

Reassessment in July 2005 demonstrated that there had been further clinical deterioration since starting treatment with intraventricular PPS. The patient remained confined to either a chair or bed and fully dependent for all activities of daily living. His swallow had deteriorated although he was still able to take small amounts of soft diet orally. Discussion with the patient's family revealed that he was no longer able to say any family member's name and that recognising close family members was sometimes unreliable.

There was no verbal response to questions posed by the examiner although his family had occasionally heard him say "hello" spontaneously. He was unable to make a preference between two options or to clearly indicate his wishes prospectively. However, his parents felt that he expressed displeasure physically (eg, by forcibly ejecting food from his mouth if he had had enough to eat or by pushing people away).

Over the past 12 months, the patient has been seen with his parents in the outpatient clinic every 4 weeks. During this time, he has developed more myoclonic jerks of his limbs. His cognitive state and level of function, however, appears not to have changed significantly.

DISCUSSION

We have presented a patient with vCJD who was treated with intraventricular PPS over a period of 31 months. Our patient had survived for 51 months after the onset of his clinical illness, clearly exceeding the median duration of illness obtained from natural history studies (median 13 months; range 6–39).¹ A PPS dose of 32 µg/kg/day appears to have been safe and well tolerated with no adverse effects.

In contrast with a previous report, we found no trend for clinical improvement with intraventricular PPS, despite using doses nearly threefold higher.³ After treatment initiation, our patient showed slow progressive neurological deterioration over the following 18 months. The subsequent apparent stabilisation in his clinical state over the past 12 months is encouraging, however, although this also may reflect a reduced sensitivity for the detection of clinical change. The increased survival time of our patient is also in contrast with a previous report of a patient with vCJD treated with up to 110 µg/kg/day of intraventricular PPS.⁴

At the time of treatment initiation with PPS, our patient had already been symptomatic for 19 months. It is therefore possible that his natural survival without active treatment would have been prolonged. It is also possible that our patient's prolonged survival may be partially attributed both to good supportive care and to the active management of other related medical problems. However, good supportive care is unlikely to have been restricted only to patients also receiving "active" treatment and our patient was not admitted for the treatment of a secondary medical problem during the course of his illness reported here.

Since July 2006, the neurological status of our patient has remained stable. On 26 August 2006, our patient was admitted to his local hospital with pneumonia and was treated with intravenous antibiotics. He made a slow but complete respiratory recovery and was discharged home on 5 October 2006. There was no neurological deterioration during this admission and he remains stable (January 2007).

Supplementary table 1 can be viewed on the JNNP website at <http://www.jnnp.com/supplemental>.

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