NEUROPATHOLOGY

Neuropathology 2009; **29**, 632–636 doi:10.1111/j.1440-1789.2009.01058.x

Symposium: Prion diseases — Updated

Continuous intraventricular infusion of pentosan polysulfate: Clinical trial against prion diseases

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Prion diseases are progressive neurological disorders due to abnormal prion protein (PrP^{Sc}) deposition in the central nervous system. At present, there is no effective treatment available for any form of prion disease. Pentosan polysulfate (PPS) has been shown to prolong significantly the incubation period in mice with PrP^{Sc} infection when administered to the cerebral ventricles in preclinical trials. In human studies conducted in European countries and Japan, intraventricular PPS was administered to patients with different forms of prion disease and was well tolerated. We report 11 patients with prion disease treated with intraventricular PPS at Fukuoka University from 2004. Cases included three familial CJD (two with V180I mutation, one GSS with P102L mutation), two iatrogenic CJD, and six sporadic CJD cases. At present, average survival period after treatment was 24.2 months (range, 4–49). Seven cases died of sepsis and pneumonia. Subdural effusion with various degrees was seen on CT scan in most cases. Except for these, adverse effects did not occur in the treatment period. Although our preliminary study of the new treatment with PPS by continuous intraventricular infusion showed no apparent improvement of clinical features in patients with prion disease, the possibility of extended survival in some patients receiving long-term PPS was suggested.

Key words: clinical trial, continuous intraventricular infusion, Creutzfeldt-Jakob disease (CJD), prion disease, pentosan polysulfate (PPS).

INTRODUCTION

Prion diseases, also known as transmissible spongiform encephalopathies (TSEs), are adult-onset, relentlessly progressive neurodegenerative disorders. Human prion diseases are categorized as sporadic (or idiopathic), genetic (or familial), and acquired (or infectious) forms according to their etiology. All forms of prion diseases have abnormal prion protein (PrP^{Sc}) deposition in the central nervous system leading to neuronal dysfunction and death.[1] Human prion diseases include Creutzfeldt-Jakob disease (CJD), Gerstmann-Sträussler-Scheinker disease (GSS), kuru, and fatal familial insomnia. Recently, two acquired forms of human prion diseases have become widely known to the public: variant CJD (vCJD), which is reportedly caused by consuming animal products contaminated with prions that cause bovine spongiform encephalopathy,[2] and iatrogenic CJD transmitted by contaminated cadaveric dura mater grafts or growth hormones.[3]

At present, there is no proven specific or effective treatment available for any form of prion disease. However, sulfated polysaccharides may be effective in inhibiting PrP^{Sc} formation *in vitro*[4] and in prolonging disease incubation time in peripherally prion-infected animal models.[5–11] Pentosan polysulfate (PPS), a large polyglycoside molecule with weak heparin-like activity, is one of the most potent compounds among them. Even after the brain is affected with prion, PPS is remarkably effective in prolonging the incubation period and inhibiting PrP^{Sc} formation therein, when administered into the cerebral ventricle in cerebrally prion-infected animal models.[12] Therefore the introduction of intraventricular PPS infusion into humans has aroused new expectations of remedy for human prion diseases. Here, we review an ongoing clinical trial of long-term intraventricular PPS infusion in Japanese patients with prion diseases.

MATERIALS AND METHODS

Patients

This clinical trial of long-term intraventricular PPS infusion was approved by the ethics committee of Fukuoka

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Received 11 April 2009; revised 23 July 2009 and accepted 24 July 2009.

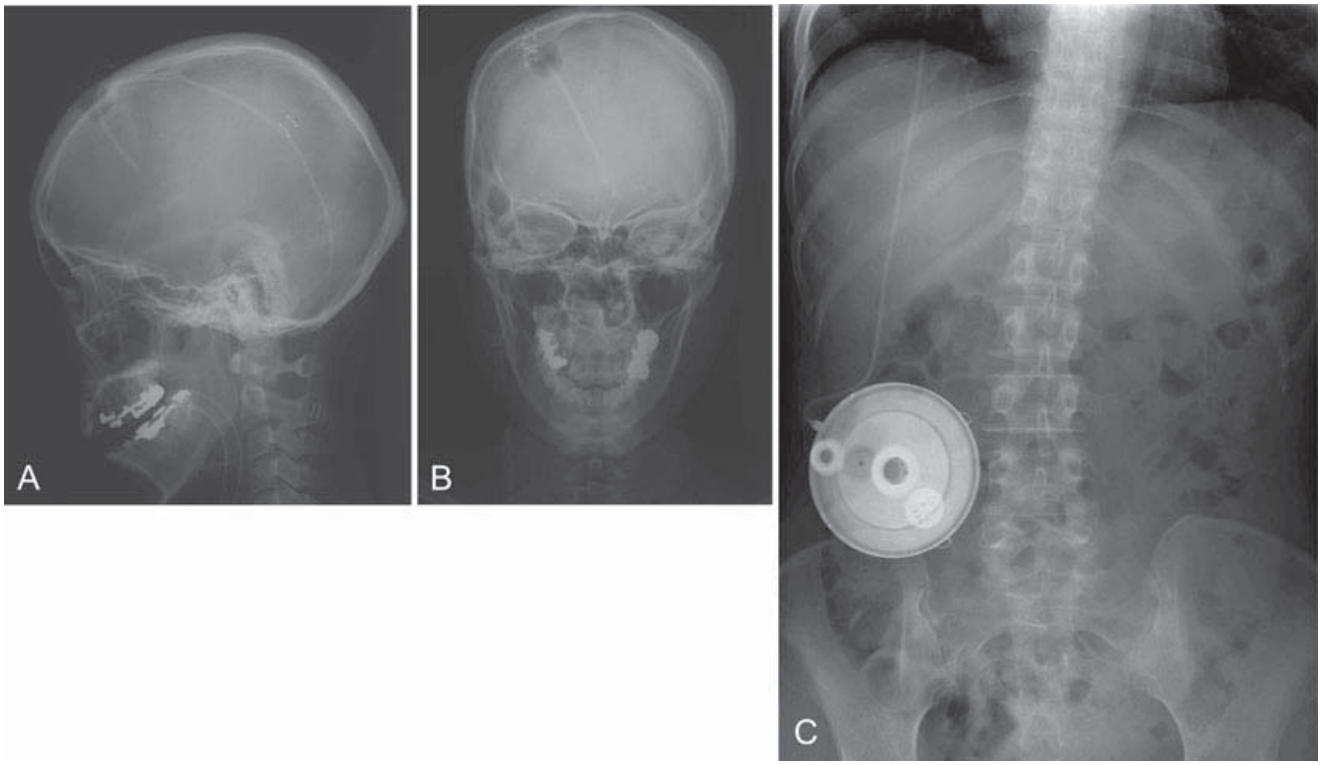

Fig. 1 (a,b) Skull X-ray shows a catheter inserted in the lateral ventricle. (c) Abdominal X-ray shows implanted pump on the abdominal wall and a catheter connected from the pump under the skin.

University. Written informed consent was obtained from the patients and/or family members after detailed explanation of the procedures was provided. Intraventricular PPS infusion was carried out in 11 patients with prion diseases, including four men and seven women with mean age of 64.9 years (range, 39–73) at Fukuoka University from 2004. Eligible patients had probable prion diseases according to WHO criteria,[13] normal hematology, and normal renal and hepatic function. Patients undergoing continuous treatment with anticoagulants such as warfarin, heparin, clopidogrel, or aspirin and those presenting with clinical symptoms caused by increased intracranial pressure and/or edema of the brain, active viral, bacterial, or fungal infection causative of either oral temperature > 38°C or clinically significant leukocytosis, and viral syndromes clinically diagnosed within 2 weeks prior to start of test therapy, were excluded.

Treatment

The patients had a single standard ventricular catheter placed in the anterior horn of the right lateral ventricle, unless clinical reasons dictated another point of access to the ventricular system. The catheter was connected to a subcutaneous infusion pump (Archimedes, 20 mL reservoir, flow rate 0.5 mL/24 h; Codman Inc., Raynham, MA US) implanted subcutaneously in the right upper abdominal wall (Fig. 1). Seven days after the surgical procedure, brain CT scan was performed (Fig. 2) to confirm no surgical complications. Then, PPS infusion was started via the implanted pump. PPS (pentosan polysulphate SP 54) was obtained from beneArzneimittel GmbH (Munich, Germany). Intraventricular PPS infusion started at a dosage of 1 μg/kg/day then was gradually escalated to the target dosage of 120 μg/kg/day; the dosage proceeded to the next higher level after the absence of adverse effects was confirmed. Pump refilling with PPS was performed every 4 weeks. Patients' conditions were checked thoroughly on a weekly basis in the first 4 weeks after commencement of PPS infusion, and on a monthly basis thereafter.

Assessment

This was an open prospective study in newly diagnosed patients with prion diseases. The primary endpoint was overall survival; secondary endpoints were 6-month survival, neurological status, and activities of daily living (ADL) assessed at 6, 12, and 18 months after start of treatment. The patients were considered to be part of the study from the commencement of PPS administration until discontinuation of PPS because of adverse effects, death, or start of another treatment.

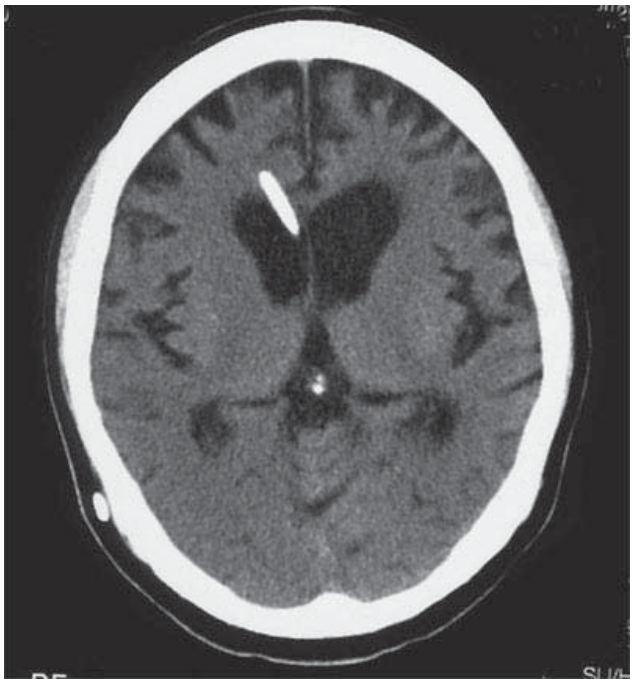

Fig. 2 CT scan 1 week after implantation shows that there are no complications such as bleeding.

Follow-up examinations included physical and neurological examinations, laboratory tests, electroencephalography, and head CT scans every 4 weeks. If applicable, head MRI scans with contrast were performed every 8 weeks. Evaluation of ADL including modified Rankin scaling was conducted every 6 months.

Adverse events

Adverse events related to PPS treatment were defined as all clinical abnormalities that appeared in patients during the study period. Abnormal laboratory results during the study period were considered as adverse events when the immediate relationship could be demonstrated.

RESULTS AND DISCUSSION

Eleven patients were enrolled in total: three cases of genetic prion diseases (familial CJD with V180I mutation, $n = 2$; GSS with P102L mutation, $n = 1$); two iatrogenic CJD; and six sporadic CJD (Table 1). Two cases with iatrogenic CJD were due to cadaver dura mater graft 18 and 24 years before the onset of the illness, respectively. Seven patients died, all due to sepsis or pneumonia. The four remaining patients continue to receive treatment with PPS 120 μg/kg/day infusions. These include sporadic CJD in two cases, including one MM2 cortical form diagnosed with biopsied specimen; and I180V mutation in the *PRNP* gene confirmed in another two cases. All the four cases have shown longer survival periods compared with previously reported cases. At the most recent estimate, mean survival after commencement of intraventricular PPS infusion was 24.2 months (range, 4–49). Mean modified Rankin score at start of treatment was 3.5 (range, 2–5); as of very recently this rose to 5.2 (range, 4–6). All cases treated with intraventricular PPS infusion have shown deterioration of brain function of various degrees. Subdural fluid collection was observed on CT scans in most (10 of 11) cases (Fig. 3). Phenitoin-controllable epileptic jerks were observed in one case. Except for these, no other adverse effects were observed during the treatment. No abnormalities in blood cell counts, serum chemistry, and coagulation tests were recognized.

To date in our clinical trial, PPS at a dosage of 120 μg/kg/day was well tolerated with no serious adverse effects observed. In most patients intraventricular PPS was associated with subdural fluid collection to various degrees, although this adverse effect did not influence their clinical conditions. Although thrombocytopenia and coagulation abnormality are known to occur occasionally with PPS,[14] such adverse effects were not observed in our patients.

Pentosan polysulfate, a large polyglycoside molecule with weak heparin-like activity, has been shown to prolong significantly the incubation period of PrP^{Sc} in a rodent scrapie model.[12] Clinically, the first treatment using intraventricular PPS was performed in a young man with vCJD.[15] At age 16 years, he developed behavioral disturbance followed by progressive ataxia, pyramidal signs and myoclonus, which led to the diagnosis of possible vCJD. At the time of first administration of PPS, the patient already had symptoms of advanced vCJD including ataxia, cognitive decline, dysphagia, and myoclonus, and was bedridden. A catheter was implanted in the anterior horn of the right lateral ventricle and connected to a programable pump implanted subcutaneously in the abdomen. Intraventricular administration of PPS did not elicit any systemic adverse effect. Follow-up CT scans demonstrated subdural fluid collections first over the right hemisphere and subsequently over the left hemisphere, necessitating surgical intervention.

This first patient is currently still alive and in stable neurological condition. PPS has been administered intraventricularly to the patient for 6 years. Although there were no major improvements in his neurological and general condition, there were a few notable changes in the brainstem function.

Since January 2003, more than 25 patients with different prion diseases have been treated with continuous intraventricular administration of PPS.[16–19] Although most reports have concluded that the treatment does not cause severe adverse effects, regrettably there are also no clear benefits

Table 1 Summary of clinical data of all 11 patients with intraventricular pentosan polysulfate (PPS) administration

No.	Age at surgery	Gender	Diagnosis	Date of surgery	PPS dose initial/final (μg/kg/day)	Duration from the onset (months)	Survival from the surgery (months)
1	67	F	sCJD	2004/11/16	1/120	9	17†
2	73	F	sCJD	2005/3/1	2/120	3	20†
3	68	F	sCJD (MM2)	2005/6/2	10/120	6	49
4	64	F	fCJD (V180I)	2005/6/21	10/120	4	49
5	64	F	sCJD	2005/11/14	10/120	3	25†
6	55	M	iCJD	2006/3/13	10/120	10	4†
7	66	M	iCJD	2006/6/12	20/120	3	9†
8	69	F	GSS (P102L)	2006/8/2	20/120	6	14†
9	73	F	fCJD (V180I)	2006/10/15	20/120	7	34
10	68	M	sCJD	2007/3/7	20/120	4	18†
11	39	F	sCJD	2007/4/3	20/120	20	27

†Patient deceased. sCJD, sporadic CJD; fCJD, familial CJD; iCJD, iatrogenic CJD

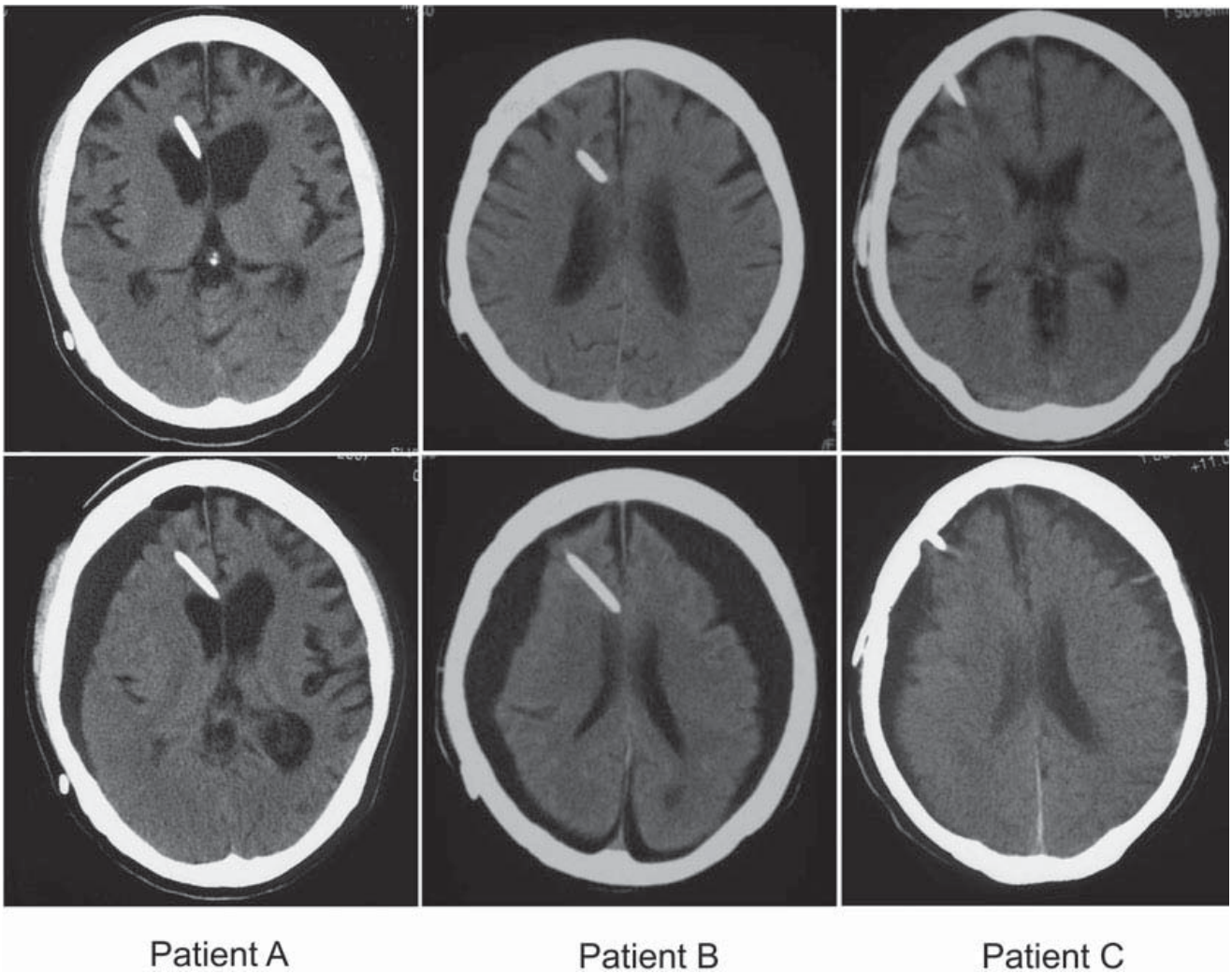

Fig. 3 Non-enhanced serial CT scans of three patients with treatment of pentosan polysulfate (PPS) administration. Upper panels show CT scans at start of PPS administration. Lower panels show CT scan of each patient at 4 months (patient A), 5 months (patient B), and 8 months (patient C) after the start of PPS administration. Note that subdural fluid collections over one or both hemispheres are observed on all lower panel CT scans.

against disease progression. PPS is neither able to reverse the clinical course of advanced disease, nor able to achieve functional recovery of established neurological deficits. Moreover, it remains unclear whether higher doses of the drug may exert better outcomes. Further experimental animal studies should be done to investigate optimal PPS dose and its effects on survival and to show the extent to which the drug penetrates and spreads throughout the brain.

Post mortem examination might support the efficacy of PPS for reducing abnormal prion deposit in the brain. In one sporadic CJD case treated with intraventricular PPS in the present study, quantitative Western blot analysis revealed that the level of abnormal protease-resistant PrP was reduced considerably compared with in individuals who had never been treated with intraventricular PPS (data not shown). Further formal, prospective, longitudinal, standardized studies, including post mortem investigation, are recommended.

ACKNOWLEDGEMENTS

The authors thank the patients and families who participated in the study. The authors also thank Drs Takeo Fukushima, Shinya Oshiro, Atsushi Yamauchi, Yasufumi Kataoka, Tetsuyuki Kitamoto, Toru Iwaki, Kensuke Sasaki, Shigeo Murakami, Imaharu Nakano, Tatsuhiro Terada, Muneto Ueda, Nobutaka Ishizu, Mitsuru Kawamura, Kenji Ishihara, Naoki Hattori, Keigo Nobukuni, Masanori Nakagawa, Kouichi Mizoguchi, Tomoko Saiko and Takuhiko Akatsu for contributions to this study. This clinical study of intraventricular PPS infusion was supported by a grant from the Japanese Ministry of Health, Labour and Welfare (H19-nanji-ippan-006).

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