endocytosis of PrP^c [52]. Sulphonated polyglycosides are not known to penetrate the CNS, and hence the first attempts to demonstrate their effects were made in peripheral organs [75].

Caughey and Raymond (1993) tested various polysulphonated glycosides (PG) and found PPS, carrageenan, and dextran sulphate 500 (DS500) to be highly active in the inhibition of PrP^{sc} production [73]. PPS was most active, showing half of its maximal activity at 1 ng/ml. Shyng et al. (1995) reported PPS and related compounds to cause a decrease of PrP^c on the surface of cultured chicken and mouse neuroblastoma cells. PPS caused a redistribution of PrP^c from the surface to the interior of the cell (intracellular late endosomes). The differences in the binding strength of PrP^c to PPS and to other PG were found to parallel their *in vivo* and *in vitro* anti-PrP^{sc} formation potency [52]. Ehlers and Diringer (1984) inoculated mice i.p. or i.c. with scrapie agent and treated them systemically with DS500 [76]. None of the i.c. inoculation experiments were affected by the treatment. With i.p. inoculations, however, it was seen that DS500 did decrease (by approximately one order of magnitude) the infectivity found in the spleen at various times after single injection of the drug, and significantly prolonged incubation times. Treated mice also showed a significant increase in the mean incubation period compared with controls. It was noted that DS500 remained in the body of an inoculated mouse for up to 7 months. A maximum effect was seen when the drug was given at the same time with the infection, and no effect was seen when it was given 35 days after infection [76].

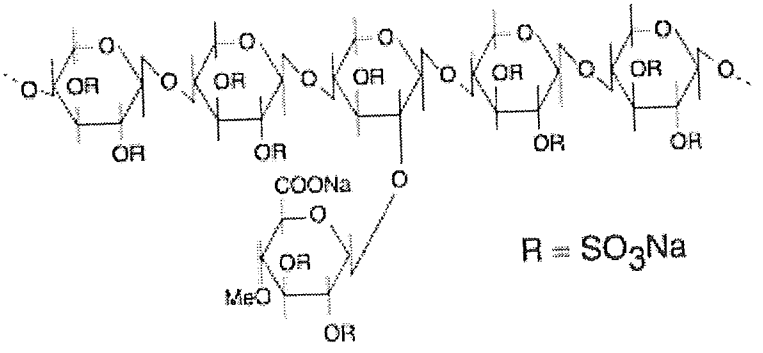

Figure 3. Chemical structure of pentosan polysulphate (PPS)

This work was followed by the study of Farquhar and Dickinson (1986), who carried out a series of murine experiments to inoculate i.p. scrapie [75]. This was associated, at various times before and after the scrapie inoculum, with various quantities of DS500 as a single i.p. injection. It was found that DS500 reliably increased the incubation period of the disease, and that this did not seem to depend on the strain of disease or the inbred strain of mouse

used. The effect seemed to be present when DS500 was given up to 4 weeks before and up to 3 weeks after the scrapie inoculum. The incubation period was extended by 5-19% at this dose, but if increased doses of DS500 were used, the incubation period could be prolonged by up to 62% [75]. Kimberlin and Walker (1986) gave various inocula of scrapie to mice either i.v. or i.p., and various drugs were tested before or after the scrapie infection [77]. DS500 proved effective in reducing the titre of the scrapie inoculum. Little effect was seen with heparin, dextran, or DEAE dextran. Diringer and Ehlers (1991) inoculated mice i.p. with scrapie and administered PPS i.p. on different days (84 to 50) before the PrP^{sc} infection. PPS increased the incubation period of mice by up to 75% [70]. Hamsters were also inoculated i.p. with various quantities of DS500 or PPS and with scrapie, separated by 2 to 24 hrs [78]. As the dose of DS500 increased, the incubation period also increased, but the maximum achieved with non-toxic doses of the drug was 21%. It was noted that a single i.p. administration of PPS increased the incubation period of i.c. inoculated scrapie by around 18% [78]. Farquhar et al. (1999) injected i.p. PPS immediately after scrapie infection of mice. Depending on mouse strain, a single PPS dose of 250 mg increased the scrapie incubation period by up to 66%. A single 1 mg i.p. dose of PPS protected mice completely from simultaneous scrapie infection. On the other hand, oral PPS was ineffective in delaying disease [79].

Doh-ura et al. (2004) recently infected transgenic mice (Tg7) expressing hamster prion protein with i.c. scrapie, and different agents were infused cerebroventricularly starting on day 10 or day 35 after infection [80]. The infusion was continued for 4 weeks. Infused drugs included lysosomotropic chemicals, such as E-64d cysteine protease inhibitor, chloroquine, quinacrine, amphotericin B, and PPS. Lysosomotropic agents demonstrated marginal effects in prolonging the incubation time when administered on day 35 after infection, and either no effect or less effect at the earlier stage (day 10 after infection). Amphotericin B and PPS demonstrated remarkable effects either early or late in the disease course. Amphotericin B resulted in around 30% prolongation of the incubation time when administered at the early stage, and 12% prolongation at the late stage. PPS showed more beneficial effects than amphotericin B, and mice which received PPS at the early stage survived 173% longer, and at the late stage 92% longer. Maximal effects of PPS at a later stage (day 42 of infection) were obtained at 230 μg/kg/day. Analysis of detailed relationship between the initiation time of the infusion of PPS and the outcome revealed that the effects of PPS were quite dependent on the timing of infusion initiation, with earlier initiation of treatment rendering a better prognosis [80]. Analysis by either immunohistochemistry or immunoblotting demonstrated that PPS potently inhibited PrP^{sc} deposition in the brain. It also showed that amount or dis-

tribution of deposited PrP^{sc} in the brain of mice treated with PPS was modified and did not return to the same level observed in the control animals, even when they were at a terminal stage. Immunohistochemical analysis demonstrated that mice treated with PPS from the early stage did not show any PrP^{sc} deposits in the brain on day 52. On the other hand, control animals demonstrated PrP^{sc} deposits in the parahippocampal white matter on day 35, and later also in the thalamus. No notable adverse effects were observed in experimental mice treated with up to 230 μg/kg/day intraventricular PPS for two months. In a separate set of experiments in normal dogs, higher doses, such as 345 μg/kg/day and 460 μg/kg/day, did show adverse effects such as partial or generalized epileptic seizures, which began within 24 hours after PPS infusion at the above high doses was initiated [80].

Both heparin and PPS are rapidly taken up into RES cells by a saturatable pathway. Low doses are cleared quickly into the RES, whereas higher doses saturate the RES and are excreted in urine [81]. PPS is metabolised by cellular non-specific desulphation in many organs and tissues, including vascular endothelium [82]. Renal excretion of desulphated PPS from plasma takes place over 6 days following a single dose, which also involves partial polyxylose chain breakdown. PPS can be administered orally, but only a low proportion (0.5-4%) of the drug is detected in the blood circulation [83, 84]. When PPS is given orally, anti-inflammatory effects are seen in the bladder after long-term administration [85]. It is considered that this is due to accumulation of the drug in cells of the RES with slow break-down and excretion. When used for anticoagulation and given s.c. or i.v., PPS may cause an early, benign, reversible thrombocytopenia and a rise in lipoprotein lipase activity [83]. Similarly to heparin, a rare, immune, severe form of thrombocytopenia has been also reported [86]. No significant neurological symptoms or signs have been reported in humans or animals treated orally or parenterally with PPS.

There has been no penetration in the CNS demonstrated with peripherally administered PPS, which is not surprising with the hydrophilic nature of the drug. On the other hand, direct intracerebral administration of PPS may afford high compartmental concentrations of the drug in the CNS, but no pharmacokinetics is available for this specific mode of administration. Direct administration of PPS to the CNS would be expected to allow PPS to concentrate inside cells, entering them via ubiquitous heparan-binding sites, and to exert biological effects on those cells infected by PrP^{sc}. In analogy to other therapeutic molecules, e.g. recombinant proteins delivered directly into the primate and human brain [87, 88], it is considered likely that cerebroventricular infusion of PPS may have the highest ratio of local versus systemic drug concentration.

Rationale for local administration of drugs to the CSF

The clinical and late preclinical phase of PrD with PrP^{sc} formation in the brain requires drugs that can cross into brain parenchyma and be present in the brain in a biologically active concentration [32, 42, 43]. However, in the early stages of PrD, with an intact blood-brain barrier (BBB), there is severe limitation of the penetration of drugs from blood into brain interstitium, and from there into glial and neuronal cells. Even at late stages of the disease, tight junctions of the brain capillaries may remain at least partially intact and therefore selectively limiting the entry of most molecules.

Compounds that are highly lipid soluble, such as alcohol, barbiturates, and some anticonvulsants, may easily pass through the endothelial cells forming the inner layer of the BBB. Lipid solubility is measured by the oil/water (octanol/water) partition coefficient, and molecules with a high coefficient usually permeate efficiently the BBB (for review see [89]). Such highly lipid soluble compounds with a high partition coefficient are phenytoin and methadone, and they cross the BBB in large quantities under normal conditions. Not all lipid soluble molecules, however, easily traverse the BBB. Compounds highly bound to plasma proteins have restricted access to the brain. For these substances, the degree of dissociation of the protein complex in transit through the capillary bed determines the degree of penetration across the BBB. Furthermore, there are special transport systems responsible for enhanced passage of certain compounds with low lipid solubility across the BBB, such as the physiologically important molecules D-glucose and phenylalanine [90]. The BBB can be subjected to pharmacological or osmotic modifications aimed at temporarily increasing its permeability to certain therapeutic molecules. These approaches are however invasive and have the potential for serious side effects [91, 92].

The CSF-brain barrier (CBB) seems to be more permeable because of its anatomical structure lacking tight junctions between the neuroependymal cells lining the cerebral ventricles. Substances administered to the CSF have been shown to penetrate into brain tissue by diffusion. The physical process of diffusion is gradient-driven, and penetration of the CBB will be enhanced by higher concentration of a molecule in one compartment [93, 94]. This fact points at an important advantage of the local application of drugs to the CSF - high local concentration in the CNS compartments, as opposed to negligible systemic concentration due to low reabsorption in the blood stream.

Continuous CSF circulation is physiologic process which lends itself to dissemination of substances throughout the CNS. CSF is continuously produced and completely replaced in the brain approximately every 8 hours.

In normal adults, the rate of CSF removal by reabsorption is equal to the rate of CSF production by filtration of blood through the intraventricular choroid plexus. CSF circulates from the sites of production, the lateral ventricles and third ventricle, into the cerebral aqueduct and into the fourth ventricle. From there CSF escapes the internal ventricular system of the brain by the foramina of Luschka and Magendie into the subarachnoid space around the brain and the spinal cord. Arachnoid granulations and dural sinuses are the route for CSF reabsorption to the blood circulation [95].

Animal models support findings in humans. In a model of cerebroventricular infusion in rats, radioactive sucrose was infused into one lateral ventricle. Within minutes after infusion, sucrose moved into the third ventricle, the aqueduct, fourth ventricle, and the subarachnoid space of the quadrigeminal, ambient and interpeduncular cisterns. About 15% of the injected sucrose entered these large cisterns. In contrast to most other CSF-brain interfaces, little sucrose moved from CSF into the medulla next to the lateral recesses and tissues adjacent to the large CSF cisterns. A thick, multilayered *glia limitans* visible on electron micrographs seemed to form a CSF-brain barrier at these interfaces [96].

Evidence exists also for the bulk flow of brain interstitial fluid via preferential pathways through the brain, which is closely related to CSF. This bulk flow of interstitial fluid has implications for drug delivery, drug distribution, and drug clearance [97].

Preliminary results with continuous long-term cerebroventricular administration of PPS in human PrD

The first objective of cerebroventricular PPS administration in PrD patients was to evaluate the short and long term safety and tolerability of escalating doses of PPS administered by continuous long term infusion. A secondary objective was to assess efficacy of PPS in delaying disease progression and improving existing neurological deficits. Patients with probable sporadic, iatrogenic, or variant CJD, or with hereditary syndromes such as GSS or FFI were eligible to receive PPS infusion. Informed consent was obtained where possible. If patients were not fit and able to consent, a legally appointed representative signed the consent forms. The primary endpoint of PPS administration studies was maximum tolerated dose of PPS as assessed by occurrence of serious toxicity resulting from PPS administration. Dose-limiting toxicity (DLT) was defined as any one of the following occurring in two or more patients:

- Any grade 4 toxicity attributed to PPS

- Grade 3 toxicity for neurological symptoms or for symptoms in other organ systems lasting longer than 5 days and attributed to PPS

Patients considered for PPS administration had to have a probable diagnosis of one of the above PrD in accordance to WHO criteria. Normal haematological, renal, and liver function was also a requirement. Because of the surgical procedure for implantation of the ventricular catheter and subcutaneous pump and infusion system, ongoing treatment with anticoagulants such as warfarin, heparin, clopidogrel, or aspirin was not allowed. Also the presence of any active infection or any viral syndrome within two weeks prior to treatment was an exclusion criterion.

Patients undergoing surgery had standard ventricular catheters placed in the anterior horn of the right lateral ventricle or in a few cases in both frontal horns, unless clinical reasons dictated another point of access to the ventricular system. In the first case with PPS administration, the catheter was connected initially to an external pump for trial administration of PPS, and later attached to a subcutaneously programmable pump (Synchromed EL, 18 ml reservoir, with side port, Medtronic Inc.) (Figure 4) permanently implanted in the abdominal wall. Later cases had simultaneous implantation of the catheter system and the infusion pump in the same surgical session. After a period of time after the surgical procedure (3-14 days) in which the pump was not active and scar tissue formation was expected to occur, PPS infusion commenced at a low dose level. The decision to proceed to the next higher dose level was based on the absence of clinical side effects and on normal findings on non-enhanced CT scans (e.g. exclusion of hydrocephalus or intracranial blood).

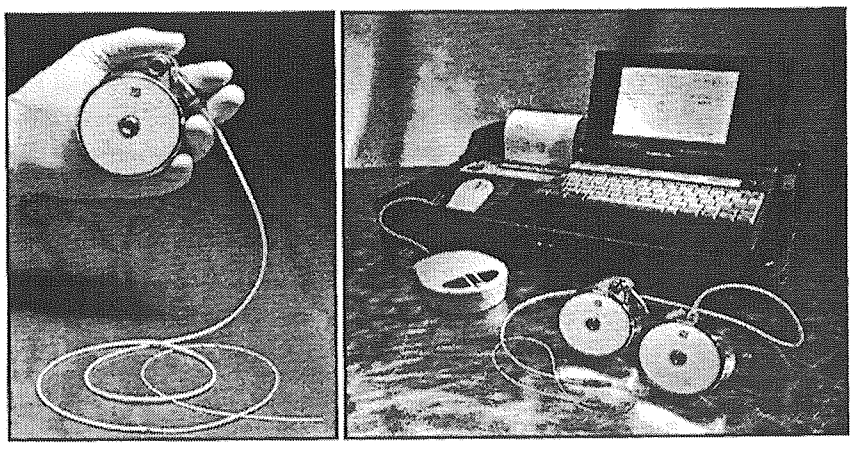

Figure 4. The implantable externally programmable pump (Synchromed EL with side port, Medtronic Inc., Minneapolis, MN) is shown with attached catheter (A). (B) shows a portable pump programming unit (telemetry unit) with printer.

There are no previously published data on a safe or potentially effective dose of cerebroventricularly infused PPS in human patients with PrD. Based on preclinical animal work, a dose escalation schedule was set up starting at 1 μg/kg/d and escalating on a daily basis until a target dose of 11 μg/kg/d was reached. This represented a 10-fold dose reduction, based on body surface area and weight differences, from the lowest effective PPS dose used in scrapie-infected mice in a preclinical study of intraventricular PPS [80]. The maximum daily dose of cerebroventricular PPS administered to the first 6 patients on a long term basis was 11 μg/kg/day. All further cases have received a maximum dose of 110 μg/kg/d in 10-20 μg/kg/d escalation steps, but long term follow up with this dose is still limited (Table 1).

The clinical source of PPS is *Pentosanpolysulfat SP54* in sterile 1 ml vials, supplied by the pharmaceutical company Bene Arzneimittel GmbH (Germany). Each vial contains 100 mg of Sodium-PPS (100 mg/ml) with 1% sodium-4-oxopentanate as a stabiliser. For filling of the pump reservoir, PPS SP54 100 mg/ml is diluted with 0.9% NaCl to a final concentration of 1-10 mg/ml. The pump is then programmed to deliver the total daily dose in a continuous simple infusion mode (constant volume and infusion rate over time).

There are no standardised or widely accepted criteria for assessment of treatment efficacy in PrD. Surrogate criteria for efficacy were thus adopted and included overall survival, speed of disease progression before PPS infusion compared with disease progression after start of PPS, neuroradiological imaging, and changes in the general and neurological condition of the patients.

The first patient to receive PPS infusion was a young man suffering from vCJD [98]. He presented initially with subjective signs of behavioural disturbance, followed a few months later by progressive ataxia, pyramidal signs and myoclonus, which led to the clinical diagnosis of possible vCJD. The clinical picture combined with abnormal MR findings in the FLAIR sequence (pulvinar sign) and positive tonsil biopsy allowed the diagnosis of probable vCJD 8 months after the occurrence of initial clinical symptoms. At the time of first administration of PPS, the patient had symptoms of advanced vCJD, such as ataxia, dementia, dysphagia, dysphasia, myoclonus, and was confined to bed and unable to care for himself. He was fed via percutaneous gastrostomy. The initial PPS dose of 1 μg/kg/d was escalated without drug-related complications to the target dose of 11 μg/kg/d. Continuous infusion of PPS for 23 months has not caused any drug-related side effects. Cerebroventricular PPS at the above dose did not have any measurable systemic anticoagulant activity in serum, as confirmed by unchanged INR (international normalised ratio) before and during PPS infu-

sion. Follow-up CT scans demonstrated no intracerebral haemorrhage, and there were no seizures. Subdural fluid collections first over the right hemisphere and subsequently over the left hemisphere necessitated surgical (burr hole) evacuation of fluid. Repeated surgical revisions of the fluid collections were necessary (Figure 5).

This first patient is currently alive and in a stable condition. Although there were no major improvements in the neurological and general condition, there were a few notable changes. The patient is now able to fix his eyes on persons, to obey simple one stage commands, and to make verbalization attempts in response to stimuli. The sleep/wake cycle and the reflex swallow are restored and the myoclonus is reduced. The patient has gained 5 kg of weight compared to pre-PPS baseline, while on the same nutritional regime. Regular follow-up CT scans have shown progressive brain atrophy during PPS administration, which could not be correlated to any worsening of the clinical condition (Figure 5).

Since January 2003, a total of 13 patients with PrD have undergone surgery and continuous cerebroventricular administration of PPS. Anonymised clinical and follow-up data are presented in Table 1. The most important clinical finding is the safety of PPS administration to the cerebral ventricles. The maximum tolerated dose of PPS has not been reached. There were no cases with side effects attributable to PPS, even in patients receiving 110 μg/kg/d of PPS.

Focal seizures have been observed in one patient on 11 μg/kg/d, and generalised tonic-clonic seizures in one patient with 110 μg/kg/d. It remains to be clarified if these seizures were a side effect of PPS or of surgery, since in both cases they occurred months after start of PPS and during infusion with a stable dose of PPS.

It is currently unclear if a higher dose of PPS has a stronger effect, and if dose escalation should be continued above 110 μg/kg/d. In most cases it seems that PPS administration results in a temporary halt of disease progression, but this conclusion is not based on hard evidence or objective measurements. PPS administration seems not able to reverse the clinical course of advanced disease and to achieve functional recovery of established neurological deficits.

Furthermore, surgery in the brain affected by PrD may result in a higher rate of surgical complications than usually encountered in comparable non-PrD cases. Brain atrophy may progress while PPS is administered, and there is no apparent correlation between degree of atrophy and clinical status of the patients. Therefore, in accordance with results from the preclinical animal studies [80], cerebroventricular infusion of PPS should be commenced as early as possible after disease diagnosis and, if possible, before the occurrence of fixed neurological deficits.

In conclusion, despite the encouraging preliminary results in PrD patients receiving long term cerebroventricular PPS, further clinical, neuroradiological and laboratory investigations in the context of a prospective clinical study will be essential for the evaluation of genuine clinical benefits of PPS administration.

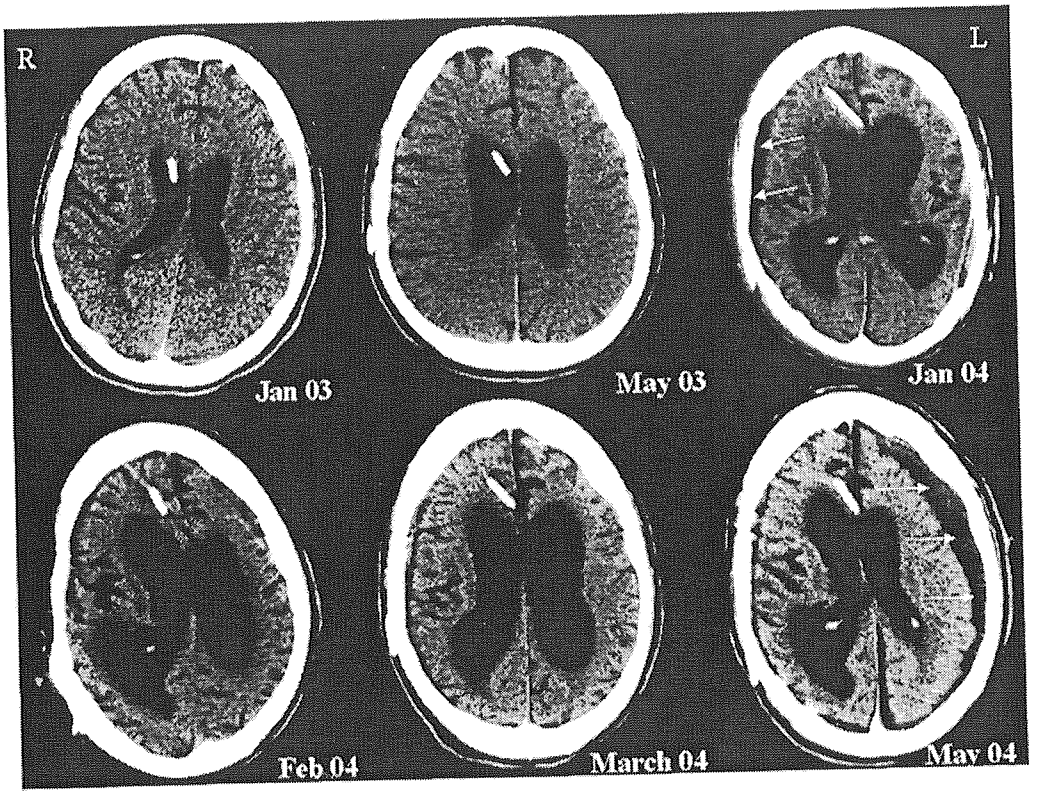

Figure 5. Serial CT scans of patient #1 demonstrating sequential occurrence of right parietal subdural fluid collection (upper right, arrows) and left parietal subdural collection (lower right, arrows). Note the progression of brain atrophy over time.

Table 1. Summary of clinical data of all current patients with PPS administration.

Patient number	Sex	Age at Dx[a] (years)	Diagnosis and clinical course after start of PPS	Survival (months after Tx[a])	Maximum PPS dose (μg/kg/d)
1	M	17	vCJD. Stable disease, swallowing and myoclonus improved, brain stem function improved. PPS started at very advanced stage of disease.	23	11
2	M	19	sCJD. Initially neurological improvement, later slow progression. Weight gain 10 kg. Reduction of myoclonus. Partial seizures occurring a few months after start of PPS, currently on phenytoin.	10	11
3	F	12	vCJD. Stable disease, wheelchair bound. Currently speech deficit, stable weight, swallowing remained intact.	13	11
4	M	15	vCJD. Stable after PPS, but disease progressed rapidly before PPS started.	9	11
5	F	34	GSS Stable disease, but surgical complications (brain haemorrhage) giving rise to neurological deficits.	10	11
6	F	32	GSS Stable disease. Initially only very mild neurological symptoms present.	3	11
7	M	37	Iatrogenic CJD (GH[b] administration) Cerebellar syndrome, initially stable condition. Rapid deterioration despite PPS.	6	110
8	F	27	Iatrogenic CJD (GH[b] administration) Stable disease, but rapid progression before start of PPS. Alive but in state of limited awareness.	9	110
9	F	39	vCJD. Presented with psychiatric syndrome. Continuous neurological deterioration while on PPS. Generalized seizures occurring 2 months after start of PPS. Died of disease progression.	4[c]	110
10	M	44	GSS Continued neurological deterioration. Increase in mental symptoms and disorientation while on PPS.	4	110
11	M	34	Iatrogenic CJD (GH[b] administration) Stable disease.	1	110
12	F	39	GSS Mild neurological deficits at start of PPS.	-[d]	110
13	F	66	sCJD	-[d]	110

[a] - Dx/Tx - Diagnosis/Therapy.

[b] - Growth hormone.

[c] - Patient deceased.

[d] - Follow-up period < 1 month.

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Cerebroventricular infusion of pentosan polysulphate in human variant Creutzfeldt-Jakob disease

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Brain;
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Abstract Variant Creutzfeldt-Jakob disease (CJD) is a transmissible spongiform encephalopathy believed to be caused by the bovine spongiform encephalopathy agent, an abnormal isoform of the prion protein (PrP^{sc}). At present there is no specific or effective treatment available for any form of CJD. Pentosan polysulphate (PPS), a large polyglycoside molecule with weak heparin-like activity, has been shown to prolong the incubation period of the intracerebral infection when administered to the cerebral ventricles in a rodent scrapie model. PPS also prevents the production of further PrP^{sc} in cell culture models.

These properties of PPS prompted its cerebroventricular administration in a young man with vCJD. Long-term continuous infusion of PPS at a dose of 11 μg/kg/day for 18 months did not cause drug-related side effects. Follow-up CT scans demonstrated progressive brain atrophy during PPS administration. Further basic and clinical research is needed in order to address the issue of efficacy of PPS in vCJD and in other prion diseases.

Introduction

Variant Creutzfeldt-Jakob disease (vCJD) is a form of CJD believed to be caused by the bovine spongiform encephalopathy agent.[1-3] Unlike the

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sporadic form, vCJD mostly becomes symptomatic in young adults and adolescents.[1] Pentosan polysulphate (PPS) is a large polyglycoside molecule with weak heparin-like activity. It has been shown to prevent the propagation of the abnormal isoform of the prion protein (PrP^{sc}) in cell culture models,[4] and to prolong the incubation period of intracerebral infection in rodent scrapie models when administered either systemically[5] or directly into the cerebral ventricles.[6] These properties of PPS prompted our use of cerebroventricular PPS in escalating doses in one patient with vCJD to assess the safety and tolerability of the drug when administered by this route.

Case report and discussion

The patient is a 20-year-old man who presented initially at the age of 16 years and 11 months with subjective signs of behavioural disturbance. A few months later this was followed by progressive ataxia, pyramidal signs and myoclonus, which led to the clinical diagnosis of possible vCJD. The clinical picture combined with abnormal MR findings in the FLAIR sequence (pulvinar sign) and positive tonsil biopsy allowed the diagnosis of probable vCJD 8 months after the initial clinical symptoms (Fig. 1). At the time of initial administration of PPS (Pentosan polysulphate SP54, Bene Arzneimittel GmbH, Munich, Germany) into the cerebral ventricular system, the patient had symptoms of advanced vCJD,[7] such as ataxia, dementia, dysphagia, dysphasia, myoclonus, and was confined to bed and unable to care for himself. He was fed via percutaneous gastrostomy.

A permanently implanted right frontal intraventricular catheter was connected to a subcutaneous programmable pump (Synchromed EL, Medtronic Inc.). The initial PPS dose of 1 μg/kg/d was escalated without significant problem to the target dose, extrapolated from animal studies, of 11 μg/kg/d. A possible therapeutic dose-effect relationship for intracerebroventricular PPS in humans with prion disease remains unknown, and therefore further dose escalation would only be limited by side effects. In mice, dose-response studies with PPS have shown that the most effective dose is 230 μg/kg/d.[6] In our current human dosing this would translate to 23 μg/kg/d, which is a little more than twice the current daily dose of PPS.

Continuous infusion of PPS for 18 months did not cause any drug-related side effects. Cerebroventricular PPS at the above dose did not have any measurable systemic anticoagulant activity in serum, as confirmed by unchanged INR (international normalised ratio) before and during PPS infusion.

Follow-up CT scans demonstrated no intracerebral haemorrhage (Fig. 2), and there were no seizures. A right parietal subdural fluid collection of increasing size was noted on CT scans 8 months after start of PPS infusion and necessitated surgical (burr hole) evacuation of fluid. PPS infusion was halted temporarily and restarted one week after the surgery. Due to recurrent subdural fluid collections, two further surgical revisions were necessary.

Clearly comments on efficacy are difficult in the setting of a single case, but after 18 months of continuous cerebroventricular PPS administration, the patient is still alive and there is some evidence of a change in the neurological condition. He is now able to fix his eyes on persons, to obey simple one stage commands, and to make verbalization attempts in response to stimuli. The sleep/wake cycle and the reflex swallow are restored and the

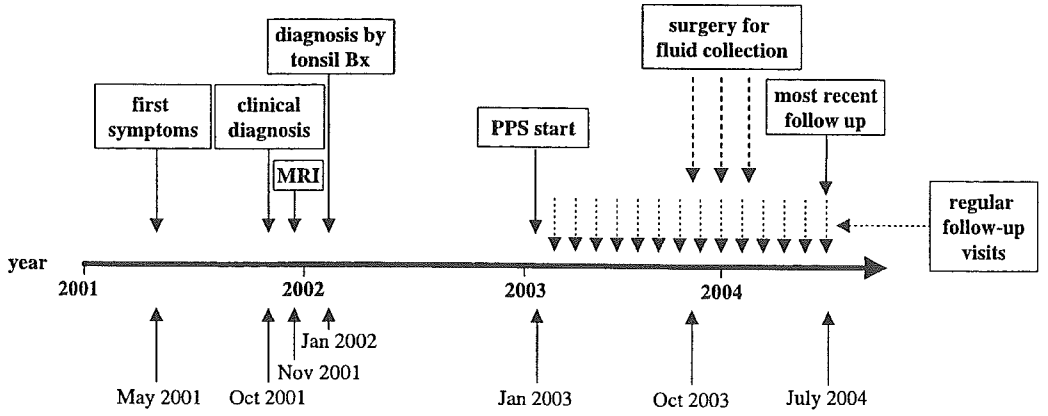

Figure 1 Schematic representation of the time course of disease presentation, diagnosis and management. Bx= biopsy.

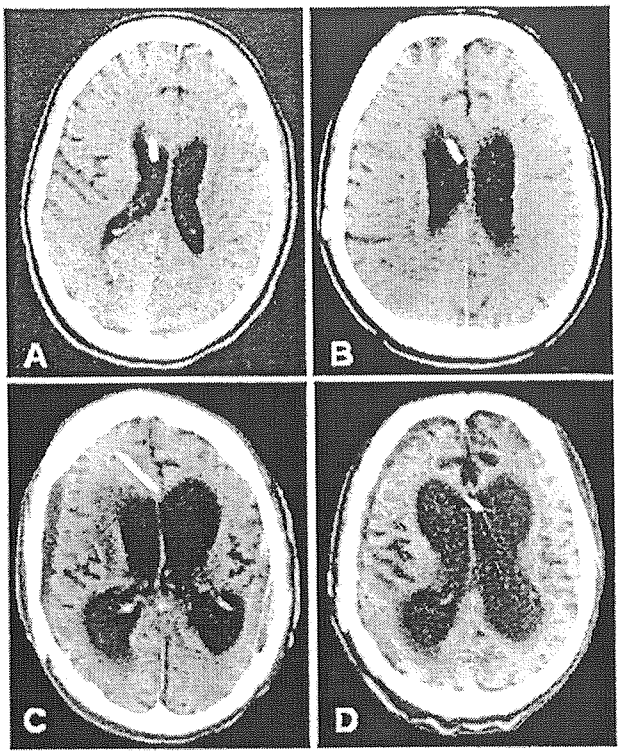

Figure 2 (A) Non-enhanced CT scan on day 6 after start of cerebroventricular PPS infusion. (B) Non-enhanced CT scan 3 months after start of PPS infusion. Note the slightly enlarged lateral ventricles compared to baseline (A). (C) Non-enhanced CT scan 1-year after start of PPS infusion. (D) Non-enhanced CT scan 15 months after start of PPS infusion. Note progressing cortical and subcortical atrophy with enlargement of the ventricular system on scans C and D.

myoclonus is reduced. The patient has gained 5 kg of weight compared to pre-PPS baseline, while on the same nutritional regime. Regular follow-up observations and pump refills (every 6 weeks) were carried out by the same medical and nursing staff and physiotherapists involved with the patient's care from the early stages of his disease. Despite the apparent trend towards clinical improvement, brain atrophy, as seen on regular follow-up CT scans, continued to progress during the period of PPS administration and resulted in ventriculomegaly and grossly enlarged extracerebral CSF spaces (Fig. 2).

In conclusion, cerebroventricular infusion of PPS at 11 μg/kg/d appears safe and well tolerated for continuous long-term application. Our patient has survived for 37 months after initial symptoms and 30 months after diagnosis of probable vCJD, while the median duration of illness with vCJD is 13 months (range 6-39)[7].

Further lessons have also been learned from this first case. Firstly, surgery in a brain affected by vCJD may result in a higher rate of surgical complications than might be expected in a normal patient. We suggest that in order to allow the catheter track to organise, drug infusion should be delayed for at least 7-10 days after implantation of the pump system. Regular neuroradiological follow-up throughout the treatment period is strongly recommended. Secondly, if clinically significant benefits are to be expected, PPS administration should start as early as possible in the course of the disease and before irreversible loss of neurological function has occurred.

Further clinical, neuroradiological and laboratory investigations in the setting of a prospective clinical study with standardised follow-up protocol and data collection are essential in order to assess the efficacy of PPS administration in vCJD and in other prion diseases.

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Diffusion-weighted MRI in familial Creutzfeldt–Jakob disease with the codon 200 mutation in the prion protein gene

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Abstract

Magnetic resonance imaging (MRI) with diffusion-weighted imaging (DWI) has been reported to be a useful tool for early diagnosis of sporadic Creutzfeldt–Jakob disease (CJD). We report MRI findings with DWI, as well as with fluid-attenuated inversion recovery (FLAIR) and T1-weighted imaging (T1WI), in a case of familial CJD with a mutation at codon 200 of the prion protein gene. DWI in this patient showed high signal intensity in the basal ganglia and the cerebral cortex, similar to findings in sporadic CJD. In addition, T1WI showed areas of high signal intensity bilaterally in the globus pallidus. Despite the clinical diversity and atypical laboratory findings seen in familial CJD with the codon 200 mutation, these neuroimaging studies suggest that common regional distributions and a common pathogenesis might underlie the clinical progression both in sporadic CJD and in familial CJD with the codon 200 mutation in the prion protein gene. DWI abnormalities may be characteristic features that should be considered in the diagnosis of familial as well as of sporadic CJD.

Keywords: Creutzfeldt–Jakob disease; Diagnostic methods; Diffusion-weighted imaging; Familial; Magnetic resonance imaging; Prion disease; Prion gene mutation

1. Introduction

Creutzfeldt–Jakob disease (CJD) is a rare and fatal neurodegenerative disorder caused by abnormal prion protein accumulation in the brain [1–3]. CJD may occur in sporadic, infectious, or familial forms. The familial form is found in 10% to 15% of all cases of CJD [4]. The diagnosis of CJD is usually based on clinical features, characteristic electroencephalographic (EEG) activity, and laboratory values. The clinical features consist of rapidly progressive dementia, myoclonus, and ataxia and are typically fatal within 1 year from the onset of symptoms [1–3]. EEG activity in CJD is characterized by periodic sharp and slow wave complexes [5]. Laboratory criteria include an elevated concentration of neuron-specific enolase (NSE) and the presence of 14–3–3 protein in the cerebrospinal fluid (CSF) [5–8].

Diagnosis of familial CJD is often difficult because clinical presentation varies widely, and characteristic features are not always present [6,9]. Familial CJD can be caused by several different mutations in the prion protein gene [4]. Atypical clinical features may be related to different genotypes at codon 129 or 219 [10,11]. One mutation at codon 200 in the prion protein gene is known to present with diverse clinical characteristics ranging from features similar to those of sporadic CJD [12–15] to atypical features such as slow progression of symptoms, fatal insomnia, polyneuropathy, lack of characteristic EEG

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