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Rapidly progressive dementias and the treatment of human prion diseases

Brian S Appleby, MD[1] and **Constantine G Lyketsos, MD, MHS**[2]

Brian S Appleby: bappleb1@jhmi.edu

[1]Johns Hopkins University School of Medicine, Division of Geriatric Psychiatry and Neuropsychiatry, Department of Psychiatry and Behavioral Sciences, Meyer 279, 600 N. Wolfe St., Baltimore, MD 21287, USA, Tel: +1 410 955 3902; Fax: +1 443 769 1224

[2]5300 Alpha Commons Drive, Alpha Commons Building, 4th Floor, Baltimore, MD 21224, USA

Abstract

Importance of the field—Rapidly progressive dementia (RPD) has many possible etiologies and definitive treatment is reliant upon an accurate diagnosis from an appropriate diagnostic work-up. A large portion of the neurodegenerative causes of RPD are due to prion diseases (e.g., Creutzfeldt–Jakob disease). The study of prion diseases, for which there is no currently available treatment, has public health implications and is becoming increasingly more relevant to our understanding of other protein misfolding disorders including Alzheimer's disease, frontotemporal degeneration, and Parkinson's disease.

Areas covered in this review—This article begins with an overview of the etiologies and diagnostic work-up of RPD followed by a detailed review of the literature concerning the treatment of human prion diseases (1971 to present).

What the reader will gain—The reader will understand the differential diagnosis and work-up of RPD as it pertains to its treatment, as well as an in-depth understanding of treatments of human prion diseases.

Take home message—An accurate diagnosis of the cause of RPD is of paramount importance when determining appropriate treatment. Most studies of the treatment for human prion diseases are case reports or case series, and results from only one randomized, placebo-controlled study have been reported in the literature (flupirtine). Studies have been hindered by disease heterogeneity and lack of standardized outcome measures. Although no effective prion disease treatment has been revealed through these studies, they provide important considerations for future studies.

Keywords

Creutzfeldt–Jakob disease; diagnosis; doxycycline; pentosan polysulphate; prion disease; quinacrine; rapidly progressive dementia; treatment

Correspondence to: Brian S Appleby, bappleb1@jhmi.edu.

Declaration of interest

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1. Introduction

Rapidly progressive dementia (RPD) presents many clinical challenges including arriving at an accurate diagnosis and instituting available treatments in an expedited time frame. Demarcated by accelerated cognitive decline, RPD has a large differential diagnosis requiring a battery of diagnostic tests. Because of its broad differential diagnosis, RPD may respond to varied treatments such that achieving accurate diagnosis is essential to prescribing the correct treatment. Most dementia syndromes occur in the elderly and are often the result of neurodegenerative or vascular etiologies that are seldom responsive to disease-modifying treatments. However, disease-modifying treatments that can potentially halt or reverse the disease process are available for several RPDs. Hence the most important aspect of establishing treatment for RPD is establishing an accurate diagnosis, which will guide the clinician toward the appropriate treatment.

2. Diagnosis

The differential diagnosis of RPD is broad and is easiest to manage by classifying possible diagnoses according to etiologic category (Table 1). Whereas several causes of RPD may span diagnostic categories, such as paraneoplastic syndrome (oncologic and autoimmune) and prion disease (neurodegenerative and infectious), an organized classification system is a useful tool during diagnostic consideration. The differential diagnosis of RPD can then be reduced via history, clinical exam, diagnostic test results, and disease course.

2.1 History

Acquiring a thorough and accurate history is essential to assessing the differential diagnosis of RPD in an individual patient. The patient's clinical presentation, especially their symptoms at disease onset, is usually helpful in establishing a diagnosis. RPD may commence with cognitive symptoms, but may also present with various neurological findings including ataxia, weakness, movement disorders, sensory abnormalities, or vertigo. Signs of a systemic illness such as rash, heat or cold intolerance, anorexia, and fatigue may also be a prominent initial symptom and are more indicative of a systemic process. Non-cognitive psychiatric symptoms of mood disturbance, hallucinations, delusions, agitation, personality change, and apathy are also important to note. Finally, the characteristics of the initial cognitive disturbance can often be helpful (e.g., amnesia, aphasia, agnosia, apraxia, and executive dysfunction) in differentiating the disease etiology.

Having a systematic method to collect other historical information is useful in the evaluation of an individual with RPD. Family history components include age at onset of illnesses, cause of death, and the assessment of other primary medical, psychiatric, and neurological illnesses. If there is a family history of dementia, inquiring into the age at onset, presenting symptoms, and time course can aid in the identification of familial disorders (e.g., genetic prion diseases and familial forms of frontotemporal degeneration and Alzheimer's disease). A developmental history will indicate whether cognitive impairment has been lifelong or acquired. Past medical, surgical, and psychiatric histories can signal the exacerbation or recurrence of a prior illness. A medication and substance use history will establish the likelihood of possible toxicity. Obtaining the history from the patient as well as an informant (e.g., family member) is imperative, especially given that the patient may be cognitively impaired.

2.2 Clinical examination

The physical and mental status examinations are systematic observations of the patient, preferably made by a physician with experience in RPD. These observations are another critical tool in diagnostic assessment. All patients with RPD must receive a complete

physical exam to assess for systemic signs of illness. Additionally, a neurological exam must be performed to assess for neurological signs and symptoms that frequently accompany RPD. Finally, a systematic mental status exam is used to assess the type and severity of cognitive impairment and associated psychiatric symptoms.

2.3 Diagnostic tests

Once a proper history and exam have been conducted, diagnostic tests can be ordered. Because of the multiple diagnoses that are possible in individuals with RPD, diagnostic testing is an inclusive and exclusive process. Several diagnostic investigations should be performed in all patients with RPD, but the history and exam helps the clinician focus on which diagnostic categories are more or less likely, hence influencing further diagnostic testing. Table 2 contains a suggested basic and expanded work-up for individuals with RPD.

2.4 Disease course

Although the clinical history, exam, and diagnostic results are important in assessing an individual with RPD, often the most valuable diagnostic tool is time. The characteristics of illness onset, whether gradual or acute, can be helpful, for example, in differentiating neurodegenerative from vascular etiologies. If the deterioration is stepwise as opposed to gradual, then a vascular etiology is more likely. Some illnesses fluctuate or even improve, ruling out most neurodegenerative causes. Finally, even though progression is accelerated in RPD, the rapidity itself varies by etiology. For example it is unusual, though possible, for patients with sporadic Creutzfeldt–Jakob disease (sCJD) to survive past 2 years. Illness durations of ≥ 3 years that are gradual in progression are most likely due to non-prion neurodegenerative brain diseases (e.g., frontotemporal degeneration, dementia with Lewy bodies, corticobasal degeneration).

2.5 Further guidance

Further information on the differential diagnosis, etiologies, and diagnostic work-up of RPD can be found in several reviews dedicated to this topic [1–3]. Further details are beyond the scope of this article. Once a diagnosis is made, treatment will be disease-specific, which is also beyond the scope of this article. The rest of this article will focus on the treatment for one of the most common forms of neurodegenerative RPD, prion diseases.

3. Human prion diseases

Although relatively rare, prion diseases represent a large portion of neurodegenerative causes of RPD. The reported prevalence of etiologic causes of RPD differs between studies and is probably representative of academic centers' areas of interest and/or expertise [1,4–6]. In a university study conducted in Athens over 3 years, the plurality of RPD cases were represented by secondary-cause dementias (n = 18, 26.5%) including normal-pressure hydrocephalus (n = 4, 6%) and neurosyphilis (n = 2, 3%) among other non-neurodegenerative causes [6]. The second largest cause of RPD in this study was Alzheimer's disease (n = 12, 17.6%). Other studies have found prion disease to be the most common neurodegenerative cause of RPD with reported prevalence rates of 54% [1], 36% [4], and 32% [5], respectively. In the study by Kelley and colleagues, non-prion disease causes of RPD presented similarly to Creutzfeldt–Jakob disease (CJD) and younger subjects, regardless of etiology, commonly exhibited psychiatric symptoms [5].

As previously stated, the prevalence of various etiologic causes of RPD are probably largely influenced by a center's academic and clinical interests. Over a 5-year period, for 2 years of which the center was conducting a clinical trial of quinacrine for the treatment of sCJD, the University of California in San Francisco (UCSF) received a total of 825 referrals for RPD

[1]. The majority of these cases were determined to be definite or probable prion diseases (54%), followed by cases of undetermined etiology due to insufficient records (28%), and non-prion disease causes (18%). Most of the cases of undetermined etiology met criteria for possible CJD. The non-prion disease cases were broken down into the following categories: neurodegenerative (26%), autoimmune (15%), infectious (11%), psychiatric (11%), and miscellaneous (9%). Thus, UCSF's quinacrine trial for the treatment of sCJD probably influenced their sample population.

Prion diseases are characterized by the presence of pathologic prion proteins or prions (PrP^{res}), abnormal conformations of the cellular prion protein (PrP^{c}). First postulated by Griffith [7] and later formulated by Prusiner [8], prions are widely thought to be the sole cause of prion diseases and there is strong support for the protein-only hypothesis [9]. Prions do not require nucleic acids or other co-factors to transmit disease [10,11]. PrP^{res} uses itself as a template to convert PrP^{c} into further PrP^{res} in an autocatalytic cycle that enables transmissibility. PrP^{c} is required for this process to occur and the disease does not manifest in animals devoid of PrP^{c} [12]. PrP^{res} is also characterized by resistance to nucleic acid destroying procedures [13] and protease K [14]. Also called transmissible spongiform encephalopathies (TSEs), prion diseases are associated with spongiform changes, neuronal loss, and gliosis on neuropathologic examination [15]. However, the method underlying neurotoxicity induced by PrP^{res} remains largely unknown [16].

Prion diseases can be divided into three etiologic categories: sporadic, genetic, and acquired. The majority of prion diseases are of sporadic origin (85%), followed in frequency by genetic (gCJD) (10 – 15%) and acquired (< 1%) forms. The latter includes iatrogenic CJD (iCJD) and variant CJD (vCJD) caused by the transmission of bovine spongiform encephalopathy to humans [17]. sCJD is the most common prion disease, with an estimated worldwide prevalence of one case per million individuals per year [17]. sCJD has a heterogeneous clinical presentation, often making it difficult to identify early in the disease course [18]. Most patients with sCJD develop dementia, cerebellar and/or visual impairment, motor impairment, extrapyramidal symptoms, myoclonus, and akinetic mutism [19].

Neuropathologic examination is the only way to achieve a definite diagnosis of prion disease. Nevertheless, three diagnostic tests are useful in determining a clinical diagnosis (Table 3). The classic electroencephalogram (EEG) finding of periodic sharp wave complexes (PSWCs) is observed in approximately two-thirds of patients, but findings vary depending upon the stage of illness [20]. The presence of the 14-3-3 protein in the cerebrospinal fluid (CSF) can be used diagnostically, but these results are also affected by illness duration, as evidenced by the finding that a positive 14-3-3 result in sCJD patients was associated with a shorter time from disease onset to lumbar puncture in one study [21]. However, this finding may depend upon other factors as well [18]. Brain MRI is increasingly useful in identifying cases of sCJD. High signal abnormalities in the basal ganglia and/or cortical ribbon on diffusion weighted imaging (DWI) and fluid attenuated inversion recovery (FLAIR) sequences have recently been added to the diagnostic criteria for probable sCJD (Table 3) [22].

3.1 Treatment of human prion diseases

3.1.1 Antiviral medications—Investigational disease-modifying treatments of human prion disease have varied over the years and have largely been influenced by the ever-changing state of knowledge within the field. The initial designation of prion diseases as 'slow viral illnesses' led to the early evaluation of several antiviral treatments. Two case reports have been published on the use of acyclovir for the treatment of CJD [23,24]. Both cases were from the UK, female, and diagnosed as definite CJD. Neither authors reported

changes in the clinical condition or EEG of their patients, and concluded that acyclovir was likely an unsuccessful treatment option. The antiviral, interferon, was also suggested as a treatment for CJD; but two cases of definite CJD, one sporadic and one genetic, were treated without beneficial effect [25]. The authors suggested that an intrathecal study using interferon may be warranted because of the blood–brain barrier's effect on drug concentration in the CSF. Three cases of definite CJD that had been treated with vidarabine were reported to have transient resolution of symptoms following its administration in two individuals and no response in a third [26].

Amantadine is an antiviral medication with dopaminergic activity that is sometimes used to treat Parkinson's disease. Two comparative studies of amantadine for the treatment of CJD have been published [27,28]. The first study comprised nine CJD patients (7 definite CJD and 2 probable CJD), four of whom were treated with amantadine 3.5 mg/kg/day [27]. There was no statistically significant prolongation of survival time from the onset of clinical care between those who were treated with amantadine (mean 45 days, range 30 – 60 days) versus those who were not (mean 28 days, range 18 – 70 days). Three of four patients experienced transiently increased alertness, but two developed worsened myoclonus. These results were replicated in another comparative study comprising eight patients [28] and one case report [29]. Another case report demonstrated some improvement in clinical status upon treatment with 600 mg daily of amantadine and a relapse of symptoms following its withdrawal [30]. Two published reports of three patients by Sanders and colleagues reported improvement with relapse, improvement with stabilization, and remission of symptoms, respectively [31,32]. However, a definite diagnosis of CJD during this time period was based upon spongiform changes on neuropathologic examination and not the presence of the abnormal prion protein, thus raising questions as to diagnostic accuracy.

There is one published case of a patient with probable CJD who was treated with methisoprinol [33]. The patient was given methisoprinol 7 g/day and although no improvement was noted, the authors did report a very prolonged terminal stage of the illness, suggesting that it might have had some effect on the disease process. Transient EEG improvements were noted, but the EEG eventually progressed as expected.

3.1.2 Amphotericin B—The polyene antibiotic, amphotericin B (AmB), was among one of the first compounds that demonstrated anti-prion activity *in vitro* and in animal models. A dose–response prolongation of the incubation period of hamsters that were intracerebrally inoculated with the 263K strain of scrapie was observed when they were administered intraperitoneal AmB [34]. However, no significant differences were noted when the infected animals were treated following the clinical onset of disease. The only reports of the use of AmB in human prion disease are two cases of definite CJD that were treated with 0.25 – 1 mg/kg/day i.v. 6 days per week, reaching the maximal dose at the eighth day of treatment [35]. No clinical improvement was noted and survival did not exceed that of historical controls (4 and 8 months from symptom onset, respectively). Serial electroencephalograms (EEGs) of the second case did not change following treatment. The authors concluded that the study could have been limited by the short duration of treatment in the first patient (20 days) and by the moderately advanced stage of illness at which the subjects began treatment.

3.1.3 Anticonvulsants—Although anticonvulsants are frequently used to treat myoclonus and seizures in human prion diseases, there are few published data on their effects. Myoclonus can be distressing to both patient and caregiver, warranting symptomatic treatment. Myoclonus and rigidity were adequately treated in a case of probable sCJD with phenytoin 750 mg i.v. followed by 300 mg/day p.o. and the addition of topiramate 50 – 100 mg p.o. twice daily [36]. EEG patterns transitioned from irregular epileptiform discharges to generalized dysrhythmia during treatment. Another case of probable sCJD was treated with

phenytoin, quinacrine, and chlorpromazine without noticeable clinical improvement, though hyperintensity on DWI decreased in the temporal and parietal lobes [37].

In another case of probable sCJD, myoclonus and seizures were not amenable to valproic acid 2000 mg/day, clonazepam 1 mg/day, or phenobarbital 100 mg/day [38]. Improvement in symptoms was only achieved with levetiracetam (LEV) 1000 – 3000 mg/day, with the return of symptoms when the medication was briefly stopped. The authors argued that LEV could be an ideal treatment for myoclonus in CJD, given its favorable safety profile and tolerability. However, a recent report describes continuous vomiting in a patient with probable sCJD whose myoclonus was adequately treated with intravenous LEV 500 mg twice daily [39]. Vomiting ceased upon discontinuation of the drug.

None of the above reports demonstrate any significant effects of any anticonvulsant on disease course or survival time. The presence of any adverse events is probably not medication-specific, as a comatose reaction to phenytoin has also been described in a case of definite sCJD [40].

3.1.4 Flupirtine—Flupirtine is a non-opioid analgesic that has been shown to decrease neurotoxicity associated with prion disease [41]. In an *in vitro* study, co-incubation of flupirtine with $PrP^{106–126}$ resulted in decreased levels of glutathione and increased expression of the anti-apoptotic proto-oncogene *bcl-2* compared to untreated controls. These results, in combination with the already established favorable safety profile of flupirtine in humans, prompted the investigators to suggest its usefulness in the treatment of human prion diseases. A double-blind, placebo-controlled trial examining the cognitive effects of flupirtine in CJD patients was subsequently performed [42]. Twenty-eight patients meeting criteria for probable CJD (26 sCJD and 2 gCJD) were randomized to flupirtine 100 – 400 mg/day or placebo. Subjects underwent cognitive testing at intervals of 2, 4, 8, 12, 16, and 20 weeks. Comparisons were made between baseline and the best Alzheimer's Disease Assessment Scale (ADAS) scores while receiving treatment. There was a statistically significant difference in ADAS scores between the two groups ($+8.4 \pm 15.3$ vs $+ 20.6 \pm 15.1$, $p < 0.02$). There was less cognitive decline in the flupirtine group by Kessler-Cognitive (-13.8 ± 16.6 vs -34.6 ± 30.4, $p = 0.02$) and Kessler-Non-Cognitive (-16.8 ± 35 vs -46.9 ± 48.6, $p = 0.04$) scores. There was no significant difference in mean survival time between the groups. There were several limitations to this study, including younger subjects in the flupirtine group (median 58 years, range 35 – 68 years vs median 63 years, range 37 – 74 years) and an uncharacteristic representation of *PRNP* codon 129 genotypes compared with the average CJD population (Met–Met 14%, Met–Val 50%, Val–Val 36%), both of which are known to affect survival time [43].

3.1.5 Antioxidants—Several studies have found an association between prion diseases and inflammation [44]. Pro-inflammatory cytokines and chemokines may be responsible for, or contribute to, the neurodegenerative changes observed in prion disease, and several anti-inflammatory compounds have been shown to affect disease course [44]. A case report has been published that describes the use of numerous antioxidants in a case of definite sCJD (coenzyme-Q, alpha-lipoic acid, nicotinamide adenine dinucleotide (NADH), vitamins C, E, and B complex, multivitamin mineral mixture, L-glutamine, omega-3 fatty acids, magnesium, and a pureed mixture of fruits and vegetables in addition to parental glutathione and ascorbate) [40]. The author describes a reduction in apneic episodes, myoclonus, and rigidity; but the patient continued to decline overall, and had a disease duration of 22 months. Interpretation of this case is difficult, given the single case described and the numerous different compounds that were administered to the patient.

3.1.6 Quinacrine—In 2001, Korth and colleagues reported inhibition of PrP^{res} conversion in scrapie-infected neuroblastoma cells (ScN2a) with tricyclic compounds that have an aliphatic side chain at the middle ring moiety [45]. The antimalarial drug, quinacrine, demonstrated the greatest half-maximal inhibition of PrP^{res} formation at EC_{50} of 0.3 μM. Because of quinacrine's historical use in humans and its ability to cross the blood–brain barrier, the investigators suggested that it was an immediate candidate for the treatment of human prion diseases. This subsequently resulted in case reports, case series, and clinical trials examining the effects of quinacrine on individuals with prion disease, making it the most systematically studied pharmaceutical in human prion diseases to date.

Several case reports and case series on the use of quinacrine in human prion diseases have been published since Korth and colleagues' initial publication [37,46–52]. Subjects included those affected by sCJD [37,46–48], iCJD from dura mater grafts [47,49,50], fatal familial insomnia (FFI) [51], and gCJD [52]. Most patients received an oral loading dose of 1000 mg the first day of treatment, followed by 300 mg daily thereafter. Results ranged from no improvement in clinical status to transient symptomatic improvements. Adverse events were fairly common and included liver dysfunction [46–50,52], skin yellowing [47,50], psychosis [51], psoriasis [51], gastrointestinal symptoms [47], and urinary tract infection [47]. To counter quinacrine toxicity, Satoh and colleagues administered 120 mg of verapamil with 200 mg of quinacrine to two subjects and reported no adverse events and equal efficacy when compared with a control subject who received 300 – 600 mg of quinacrine without verapamil [48].

Three clinical trials have examined the effect of quinacrine on patients with prion disease [53–55]. An open-label trial conducted in France consisting of 32 patients (30 sCJD, 2 vCJD) who received a loading dose of 1000 mg quinacrine over 1 day followed by 300 mg daily failed to demonstrate a statistically significant difference in survival time compared with 125 untreated sCJD controls (8.8 ± 0.9 vs 7.0 ± 0.6 days) [54]. Non-statistically significant survival prolongation was observed in patients with homozygous *PRNP* codon 129 genotypes (Met–Met, 7.3 ± 1.4 vs 5.5 ± 0.6 months, Val–Val 7.9 ± 1.6 vs 6.0 ± 0.7 months) compared with heterozygotes (Met–Val 12.9 ± 2.0 vs 14.0 ± 2.1 months). Adverse effects included liver dysfunction, skin discoloration, gastrointestinal symptoms, and leukopenia. Overall, the authors concluded that quinacrine was not an effective treatment in this study.

The second quinacrine trial, PRION-1, was an open-label, patient-preference trial conducted in the UK that consisted of 107 patients with prion disease (45 sCJD, 42 inherited prion disease, 18 vCJD, and 2 iCJD) [53]. Although no significant difference in mortality was demonstrated between the treatment and control groups ($p = 0.62$), important lessons were learned from this study that will undoubtedly affect future trials in the field. Only two patients ultimately chose randomization. Similar to some case reports, 4/40 patients who received quinacrine demonstrated a transient improvement in symptoms and rating scales. Two serious adverse events were reported as a result of quinacrine (seizure and aspiration). The authors concluded that, although relatively well tolerated, quinacrine did not significantly affect the clinical course of prion disease in this study.

A third randomized, placebo-controlled trial of quinacrine for sCJD started in February 2005 at UCSF and was completed May 2009 [55]. An estimated 54 patients with sCJD were enrolled in the study and the primary outcome measure was survival from time of randomization. Secondary outcome measures included scores on functional scales and testing and neurological exam at baseline, 2, 6, and 12 months [56]. Subjects were given 100 mg of quinacrine or placebo orally three times a day. Mean survival time from randomization was 6.1 months (SD 6, range 0.4 – 27.1 months) and mean survival time from

first symptom was 18.5 months (SD 11.3, range 2 – 50 months) [55]. The completed analyses of this study are pending. However, given the prior study results and side-effect profile, quinacrine is not generally considered a viable treatment option when considering risk–benefit and quality-of-life factors.

3.1.7 Chlorpromazine—Chlorpromazine is a conventional antipsychotic/neuroleptic that is used for the treatment of schizophrenia and other psychiatric disorders. Because of its long history of administration in humans and its anti-prion activity *in vitro*, chlorpromazine was one of the medications recommended by Korth and colleagues for the immediate treatment of human prion diseases [45]. Data on its use in humans are limited and confounded by multiple factors. Three case reports have been published in the literature, none of which have demonstrated any signs of clinical improvement [37,50,51]. A case of probable sCJD was partially successfully treated with chlorpromazine 25 mg/day in the treatment of choreoathetoid movements [37]. Despite the addition of quinacrine 100 mg/day and phenytoin, no clinical benefit in the overall disease course was noted in this case. Two cases of definite FFI were treated with a combination of quinacrine 600 mg/day plus chlorpromazine 225 – 600 mg/day [51]. No clinical improvement was noted, and one patient developed orthostatic hypotension that was likely caused by chlorpromazine. A final case of definite iCJD from a dura mater graft was treated with chlorpromazine 300 mg/day without clinical benefit or adverse events [50].

3.1.8 Antidepressants—Along with chlorpromazine and quinacrine, Korth and colleagues also demonstrated anti-prion activity among tricyclic antidepressants (TCAs) [45]. Earlier work in the field has also established abnormal serotonin regulation in prion diseases [57]. Clomipramine is a TCA with a tricyclic structure and an aliphatic side chain at the middle ring moiety that demonstrates strong serotonin reuptake inhibition. A case of definite vCJD was treated with clomipramine 125 mg/day for 3 weeks in addition to venlafaxine, a serotonin and norepinephrine reuptake inhibitor, at a dose of 200 mg/day for 7 weeks [58]. No clinical improvements were noted and the patient's disease duration was approximately 14 months.

Another patient with definite CJD was given a different TCA, dothiepin, 50 – 125 mg/day for the treatment of depression [59]. The medication had to be stopped after 11 days because of generalized choreic movements, orofacial dyskinesia, and mutism. All of these symptoms resolved 3 days following discontinuation of dothiepin. In order to further treat the patient's depression, fluvoxamine, a potent selective serotonin reuptake inhibitor, was given at a dose of 100 mg/day, which resulted in a resumption of orofacial dyskinesia and generalized myoclonic jerks that ceased when the medication was discontinued. No symptomatic benefit was reported from these medications and the patient's total disease duration was approximately 5 months. The authors concluded that clinicians should be suspicious of CJD in patients with a RPD who experience dyskinesia in response to TCA therapy.

3.1.9 Pentosan polysulphate—Pentosan polysulphate (PPS) is a polysulphonated polyglycoside and heparin mimetic currently administered in humans for the treatment of interstitial cystitis. PPS initially became a compound of interest in the field of prion disease when Ehlers and Diringer found that it and other polyanions impaired scrapie infection in mice [60]. Because it was administered peripherally and was subject to the blood–brain barrier, PPS was generally regarded as a possible preventative measure for those who were peripherally exposed to prion disease. However, the blood–brain barrier was bypassed in a later study by Doh-ura and colleagues [61]. The researchers infused PPS intraventricularly into transgenic mice that were intracerebrally inoculated with 263K scrapie and found a prolonged incubation period in early- and late-stage infected mice compared with controls. Cerebral hemispheres that were fitted with the intraventricular catheter demonstrated less

prion protein deposition, neurodegenerative changes, and infectivity compared with the contralateral hemispheres. Hematoma formation was observed at supratherapeutic doses. Results from this study, in combination with the prior enteral use of PPS in humans for the treatment of interstitial cystitis, prompted further clinical investigation regarding its use in the treatment of human prion diseases.

The use of PPS in the treatment of human prion disease sparked several concerns. Following the rejection of PPS as a possible treatment for CJD by Britain's Committee on Safety of Medicines and the CJD Therapy Advisory Group, a highly publicized court case ensued in which a family sought legal permission to treat a patient affected by vCJD with intraventricular PPS [62]. The two committees cited that they were unable to recommend its use due to a lack of *in vitro* and *in vivo* data that were relevant to human prion disease, specifically vCJD [63]. They encouraged further studies in animal models infected with prion diseases that are relevant to humans (e.g., BSE). Advisors also acknowledged the possible reluctance of clinicians to use such an invasive experimental treatment in a terminal illness such as CJD. There was also the risk of contamination, as treatment involved neurosurgery and exposure to highly infective tissues. Further controversy was wrought when the aforementioned patient started PPS treatment in 2003 and reportedly showed signs of slight neurological improvement that has since stabilized [64]. As of this writing, the patient remains alive in relatively stable, though severely compromised, condition.

As in other experimental treatments, the literature contains primarily case reports and case series regarding the use of PPS for human prion diseases. This first published report noted prolonged survival in an adolescent with vCJD who was administered intraventricular PPS 11 μg/kg/day for 18 months [65]. Despite relative clinical stabilization, repeat CT scans of the brain depicted continued cerebral atrophy. No adverse events from the medication were noted, but the patient did experience recurrent subdural fluid collections related to the intraventricular catheter.

Two subsequent reports of two patients with vCJD treated with intraventricular PPS at doses of 1.1 – 110 [66] and 32 μg/kg/day [67] respectively demonstrated no clinical benefit in the former and possibly longer survival time in the latter. No adverse events were reported in either case. A recently reported case of sCJD treated with 120 μg/kg/day of intraventricular PPS had a survival time that was longer than the mean survival time of historical controls, but was within normal variation [68]. The subject also experienced subdural fluid collections and an intraventricular hemorrhage. Decreased cerebral PrP^{res} deposition compared with untreated controls at postmortem analysis suggested a possible disease-modifying effect of PPS. Intraventricular PPS has been administered to other types of human prion disease and a case series of 23 newly reported cases (8 sCJD, 7 iCJD, 5 Gerstmann–Sträussler–Scheinker disease (GSS), 2 gCJD and 1 vCJD) described varied responses ranging from improvement with relapse, stabilization, and slowed disease progression [69].

Two observational studies examining the use of intraventricular PPS for the treatment of human prion diseases have been conducted in the UK and Japan [70,71]. In a 6-month study, seven patients (3 vCJD, 2 GSS, and 2 iCJD) were administered 11 – 110 μg/kg/day of intraventricular PPS [70]. The patients were administered treatment at various degrees of disease severity (2 mild-moderate, 5 severe). The medication was well tolerated and mean and median survival times (range, 16 – 75 months) were longer than reported untreated historical cases, especially in the vCJD cases. Four cases were seen prospectively across the entire 6-month study period and displayed stability (n = 1), minimal deterioration (n = 2), and significant deterioration (n = 1). Surgical complications were common among the subjects. The authors concluded that the observed prolonged survival times compared with historical controls suggest a possible disease-modifying effect of PPS.

A Japanese observational study treated 11 patients (6 sCJD, 2 gCJD, 2 iCJD, and 1 GSS) with 1 – 120 μg/kg/day of intraventricular PPS [71]. Ten of the 11 subjects experienced complications from the intraventricular catheter, and although no improvements were noted in individual cases, mean survival times were longer than those of historical controls. The investigators concluded that although patients experienced prolonged survival, PPS did not reverse or ameliorate the underlying condition. They also argued for further prospective, longitudinal studies with post-mortem investigations, all of which should be standardized.

Both of these observational studies were hindered by gender discrepancies, with a preponderance of females enrolled in both studies (n = 6, 86% and n = 8, 73% respectively).

3.1.10 Doxycycline—The field of human prion diseases has recently focused on tetracyclines, particularly doxycycline, as a potential treatment option. Tetracyclines destabilize amyloid structures, reduce proteinase K resistance, and inhibit PrP^{res} conversion [72]. Decreased infectivity and prolonged survival times have also been demonstrated in animal models [72]. Preliminary results from two observational studies of doxycycline 100 mg/day in CJD patients have been reported [73,74]. In an Italian study, significantly longer survival times compared with historical controls were noted, though details are not available at this time [74]. A German study of 51 patients (44 sCJD and 7 gCJD) demonstrated significantly prolonged survival times compared with historical controls (median 292 days, range 162 – 635 days vs median 167 days, range 33 – 1448 days; p = 0.005) [73]. A recent report also noted a significant difference in mean survival times between *PRNP* codon 129 genotypes, Met–Met subjects appearing to receive the greatest benefit from the treatment [75]. Germany, Italy, and France have since commenced a multicenter double-blind, placebo-controlled trial of doxycycline in human prion diseases that is expected to be completed by the end of 2010 [73,74,76].

4. Conclusion

Prion diseases have been clouded by mystery since the description of scrapie, human TSEs and elucidation of the prion hypothesis. Despite tremendous advances in knowledge about these uncommon diseases, major questions remain. The most recent evidence supporting the prion hypothesis, the generation of prions in the absence of mammalian cofactors [10], will probably lead to increased research focused on the unascertained mechanism of neurotoxicity associated with prion diseases and/or treatments designed to inhibit or prevent the prion conversion process. In the field of human prion disease therapeutics, one can observe the transition from antivirals to prion conversion inhibitors.

Novel approaches to treatment such as vaccines [77], RNA interference [78], and anti-inflammatory agents [44], among others, are being examined in the laboratory setting in the hope that these therapies can be used in humans affected by prion disease. Perhaps one of the most popular approaches to treatment is to block neuronal PrP^{c}, which has been done successfully in animal models [79,80]. The exact function of PrP^{c} remains elusive and somewhat controversial, but an in-depth review of the literature suggests that PrP^{c} may be generally viewed as a platform for the assembly of signaling modules that affect basic physiology and behavior [81]. Although PrP^{c} knockout mice displayed normal development and behavior in one study [12], other studies have suggested that PrP^{c} is necessary for normal neuronal functioning [82]. Thus, what may apply to mice PrP^{c} may not apply to humans.

Paramount to the treatment of prion diseases is early diagnosis, enabling the administration of effective treatments prior to severe brain damage. This poses a particular problem in prion disease because of its low prevalence and rapid progression. As diagnosis currently stands,

individuals at risk of developing prion diseases (e.g., genetic and acquired prion diseases) are most likely to receive the greatest benefit from treatments. Treatments could be aimed at delaying disease onset in high-risk individuals or those who are presymptomatic or at early disease stages. Presymptomatic and early-stage treatment will become more practical through the use of biomarkers. An example of this is demonstrated in a brain 18FDG-PET scan study of FFI mutation carriers that demonstrated hypometabolism in the thalamus 13 – 21 months prior to clinical symptoms [83]. Serum prion detection tests, currently under development, will also enable researchers to identify individuals who are asymptomatically infected. Close clinical monitoring of these individuals and/or the development of biomarkers that signal presymptomatic disease states will ensure earlier diagnosis and thus earlier treatment.

5. Expert opinion

The treatment of human prion diseases is complicated by a variety of elements. First, the disease is characterized by rapid progression and short illness duration (mean survival time 5 months) that is variable and dependent upon several factors, including codon 129 genotype of the prion protein gene (*PRNP*), prion protein type, age at onset, and gender [43]. Human prion diseases are marked by heterogeneous clinical presentations that affect time to initial presentation, diagnostic work-up, and diagnosis [18,84]. Achieving an accurate diagnosis is often an iterative process as only 17% of all prion disease cases, including genetic forms, were initially diagnosed as such in a study that included several hospitals in the United States [84]. Diagnostic patterns probably vary by country and/or clinical center (e.g., community hospital vs university hospital). The rarity of the disease often delays diagnosis and complicates the recruitment and statistical power of clinical trials for prospective therapeutics. Finally, the rapid progression and severity of neurocognitive decline seen in prion diseases makes studying potential treatments difficult and may encourage some families to decline non-curative treatments.

For the above reasons, many therapeutic trials for human prion diseases have been hampered by study methodology (Table 4), leaving the interpretation of study results difficult. An example of the latter is the UK PRION-1 study of quinacrine for the treatment of prion disease, which was a patient-preference trial [53]. In this study, only two patients chose randomization and those who did choose to receive quinacrine at study enrollment were on average higher functioning (median Barthel index 14 vs 2, $p = 0.0007$), less cognitively impaired (Mini-Mental State Exam 22 vs 0, $p < 0.0001$), and less demented (Clinical Dementia Rating 7 vs 16, $p = 0.0007$). The reader is also referred to several other reviews concerning the treatment of prion disease [73,85–87].

At present, human trials have not been successful in determining effective treatments for prion diseases. These studies have contributed knowledge that will primarily be of value in helping to develop more successful treatments in the future. Small sample sizes will be improved through more sensitive and accurate diagnostic tools [22] and international consortiums such as Theraprion [88]. The development of bio-markers to ascertain presymptomatic and early disease stages will ensure that individuals are diagnosed and treated earlier, sparing as much brain damage as possible. Epidemiological studies regarding the natural history of prion diseases have established *PRNP* codon 129 polymorphisms and PrP^{res} protein types as important covariates that must be considered when performing survival analyses [43,89].

More practical and less invasive methods to cross the blood–brain barrier and administer anti-prion therapies are also under investigation [90]. Several novel experimental treatments are on the horizon, but they need to be translated into human treatments, which will take

some time. It is also unknown what possible deleterious consequences these treatments may have, necessitating further development of possibly effective compounds.

Finally, and perhaps most importantly, clinicians and researchers are well aware of the importance of achieving early diagnosis. Earlier diagnosis of human prion diseases will allow for a better quality of life for patients should future therapeutics be an option.

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Article highlights

- Having a systematic method to collect other historical information is useful in the evaluation of an individual with RPD.
- Because of the multiple diagnoses that are possible in individuals with RPD, diagnostic testing is an inclusive and exclusive process.
- Often the most valuable diagnostic tool is time.
- Paramount to the treatment of prion diseases is early diagnosis, enabling the administration of effective treatments prior to severe brain damage.
- As diagnosis stands now, individuals at risk of developing prion diseases (e.g., genetic and acquired prion diseases) are most likely to receive the greatest benefit from treatments.
- Earlier diagnosis of human prion diseases will allow for a better quality of life for patients should future therapeutics be an option.

This box summarizes key points contained in the article.

Table 1

Differential diagnosis of rapidly progressive dementia.

Etiologic Category	Examples
Neurodegenerative	Prion disease (e.g., Creutzfeldt-Jakob disease)
	Alzheimer's disease
	Frontotemporal degeneration
	Dementia with Lewy bodies
	Corticobasal degeneration
	Progressive supranuclear palsy
Oncologic	Primary CNS tumor
	Metastatic tumor
Autoimmune	Hashimoto's encephalopathy
	Paraneoplastic syndrome
	Lupus cerebritis
	Sjögren's syndrome
	Sarcoidosis
	Multiple sclerosis
	CNS vasculitis
	Isolated angiitis of the central nervous system (IACNS)
	Anti-VGKC antibodies
	Antineurophil antibodies
	Cerebral amyloid inflammatory vasculopathy
	Polyarteritis nodosa
	Celiac disease
	Behçet's disease
	Hypereosinophilic disease
Toxicity	Bismuth toxicity
	Lithium toxicity
	Mercury toxicity
	Arsenic toxicity
	Alcoholic dementia
Metabolic	Vitamin B_{12} deficiency
	Vitamin B_1 deficiency (e.g., Wernicke–Korsakoff syndrome)
	Niacin deficiency
	Folate deficiency
	Uremia
	Wilson's disease
	Portosystemic encephalopathy
	Acquired hepatocerebral degeneration
	Porphyria
	Electrolyte abnormalities
Infectious	Iatrogenic Creutzfeldt–Jakob disease

Etiologic Category	Examples
	Variant Creutzfeldt–Jakob disease
	AIDS dementia complex
	Syphilis
	Fungal/viral meningoencephalitis (e.g., aspergillosis, herpes encephalitis)
	Whipple's disease
	Progressive multifocal leukoencephalopathy
	Subacute sclerosing panencephalitis
	Parasitic infections
	Lyme disease
	Balamuthia
Vascular	Stroke
	Biswanger's disease
	Hyperviscosity syndromes
	CADASIL
Endocrine	Hypo-/Hyperthyroidism
	Hypo-/Hyperparathyroidism
	Adrenal insufficiency
Psychiatric	Depression
	Psychotic disorders (e.g., schizophrenia)
	Conversion disorder
	Malingering

CADASIL: Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy.

Table 2

Diagnostic studies in the investigation of rapidly progressive dementia.

Level of Investigation	Suggested Studies
Preliminary/Basic	Serology: CMP, Mg, PO_4, CBC with differential, coagulation studies, TSH, RPR, vitamin B_{12}, folate, ESR Urine: urinalysis, urine toxicology screen 12-lead ECG Chest X-ray Brain MRI with and without gadolinium (include FLAIR and DWI sequences)
Expanded	Serology: CA-19 – 9, CEA, CRP, ANA, Anti-Ro Ab, Anti-La Ab, Anti-Hu Ab, Anti-smooth muscle Ab, Anti-Smith Ab, Anti-thyroglobulin Ab, Anti-thyroperoxidase Ab, Anti-endomyseal Ab, Anti-gliaden Ab, Whipple's PCR, SPEP/UPEP, homocysteine, MMA, full thyroid function tests, fasting lipid panel, Lyme Ab, HIV, genetic testing (e.g., *PRNP*, *PS-1*, *PS-2*, *APP*, *PGRN*, *MAPT*), paraneoplastic Ab panel, Anti-neurophil Ab, Anti-VGKC Ab Lumbar puncture: cell count, glucose, protein, bacterial/fungal cultures, India ink, HSV, JC virus, Lyme Ab, Whipple's Ab, oligoclonal bands, 14 – 3 – 3, tau, NSE, VDRL EEG Mammogram Brain FDG-PET scan Whole body PET scan

Diagnostic work-up will vary depending on clinical suspicions.

Ab: Antibody; ANA: Antinuclear antibody; *APP:* Amyloid precursor protein gene; CBC: Complete blood count; CEA: Carcinoembryonic antigen; CMP: Complete metabolic panel; CRP: C-reactive protein; DWI: Diffusion weighted imaging; ECG: Electrocardiogram; EEG: Electroencephalogram; ESR: Erythrocyte sedimentation rate; FDG: Fluorodeoxyglucose; FLAIR: Fluid attenuation inversion recovery; HIV: Human immunodeficiency virus; HSV: Herpes simplex virus; *MAPT:* Microtubule-associated protein tau gene; Mg: Magnesium; MMA: Methylmalonic acid; MRI: Magnetic resonance imaging; NSE: Neuron-specific enolase; PCR: Polymerase chain reaction; PET: Positron emission tomography; *PGRN:* Progranulin gene; PO_4: Phosphate; *PRNP:* Prion protein gene; *PS*-1: Presenilin 1 gene; *PS-2:* Presenilin 2 gene; RPR: Rapid plasma reagin; SPEP/UPEP: Serum protein electrophoresis/urine protein electrophoresis; TSH: Thyroid-stimulating hormone; VDRL: Venereal disease research laboratory; VGKC: Voltage gated potassium channels.

Table 3

Diagnostic criteria for sporadic Creutzfeldt–Jakob disease.

Definite sCJD [17]

- **I.** Spongiform encephalopathy in cerebral and/or cerebellar cortex and/or subcortical grey matter; and/or
- **II.** Encephalopathy with prion protein immunoreactivity (plaque and/or diffuse synaptic and/or patchy/perivacuolar types)

Probable sCJD [17,22]

- **I.** At least two clinical signs:
  - **a.** Dementia
  - **b.** Cerebellar or visual symptoms
  - **c.** Pyramidal or extrapyramidal symptoms
  - **d.** Akinetic mutism
  - **e.** Myoclonus (omitted in 2009 criteria)
- **II.** At least one of the following:
  - **a.** PSWC on EEG
  - **b.** 14 – 3 – 3 detection in CSF (in patients with disease duration < 2 years)
  - **c.** High signal abnormalities in caudate nucleus and putamen or at least two cortical regions (temporal, parietal, or occipital) on DWI or FLAIR sequences on brain MRI

Possible sCJD [17,22]

- **I.** At least two clinical signs:
  - **a.** Dementia
  - **b.** Cerebellar or visual symptoms
  - **c.** Pyramidal or extrapyramidal symptoms
  - **d.** Akinetic mutism
  - **e.** Myoclonus (omitted in 2009 criteria)
- **II.** Illness duration < 2 years

CSF: Cerebrospinal fluid; DWI: Diffusion weighted imaging; EEG: Electroencephalogram; FLAIR: Fluid attenuated inversion recovery; MRI: Magnetic resonance imaging; PSWC: Periodic sharp wave complexes; sCJD: Sporadic Creutzfeldt–Jakob disease.

Table 4

Clinical trials of treatments for human prion disease.

Study design	Drug	Ref.
Randomized, double-blind	Flupirtine	[42]
	Quinacrine (results pending)	[55,56]
	Doxycycline (ongoing)	[73,74,76]
Case-control	Amantadine	[27,28]
	Quinacrine	[54]
Observational	Quinacrine	[53]
	Pentosan polysulphate	[69–71]
	Doxycycline	[73,74]