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Prion Diseases in Focus: A Review of Diagnosis and Treatment

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Abstract

Prion diseases, or transmissible spongiform encephalopathies (TSEs), are rare and invariably fatal neurodegenerative disorders characterized by the misfolding of the cellular prion protein (PrP^{C}) into its pathogenic isoform (PrP^{Sc}). This protein transfiguration plays a central role in disease pathogenesis and leads to progressive neuronal dysfunction and neurodegeneration. Despite advances in understanding the molecular mechanisms underlying prion diseases, accurate diagnosis remains challenging because of their clinical and pathological resemblances to other neurodegenerative disorders.

This narrative review aims to recapitulate current diagnostic approaches and emerging therapeutic strategies for prion diseases. A comprehensive literature search was conducted using the PubMed database between the year 2024 and 2026 to identify recent studies on the diagnosis and treatment of prion diseases.

Diagnosis depends on clinical assessment, neuroimaging, CSF biomarkers, and detection of abnormal prion proteins. Protein amplification technologies, including protein misfolding cyclic amplification (PMCA), real-time quaking-induced conversion (RT-QuIC), and timed amyloid seeding assays (tASA), have demonstrated promising diagnostic sensitivity and specificity. The potential detection of prion proteins in blood represents an important emerging approach that may enable a rapid, minimally invasive technique and help reduce the risk of iatrogenic transmission from asymptomatic individuals.

Although no curative therapies currently exist, several experimental approaches targeting prion protein misfolding are under exploration. These include anti-PrP monoclonal antibodies, anti-PrP^{Sc} compounds, polyanionic molecules, Congo red derivatives, low-molecular-weight compounds, and recombinant prion proteins designed to inhibit pathogenic conversion.

Categories: Neurology, Public Health
Keywords: artificial intelligence (ai), biomarkers, creutzfeldt–jakob disease, early diagnosis, prion diseases, prion protein (prpsc), protein misfolding cyclic amplification (pmca), rt-quic, therapeutic strategies, transmissible spongiform encephalopathies

Introduction And Background

Prion diseases, or transmissible spongiform encephalopathies (TSEs), encompass a group of fatal neurodegenerative disorders affecting both humans and animals. In humans, these conditions include Creutzfeldt-Jakob disease (CJD), fatal familial insomnia (FFI), variant CJD (vCJD), Gerstmann-Sträussler-Scheinker disease (GSS), and kuru [1]. Animal TSEs comprise scrapie, chronic wasting disease (CWD), bovine spongiform encephalopathy (BSE), commonly known as mad cow disease, and transmissible mink encephalopathy (TME) [2-4].

Prion diseases are biologically unique and can be grouped etiologically into acquired, sporadic, and inherited forms [1]. Acquired prion diseases result from the transmission of infectious prions through exposure to contaminated biological materials, including infected tissues, medical instruments, or food products. In contrast, sporadic forms arise spontaneously without an identifiable infectious source or genetic predisposition. On the other hand, inherited prion diseases are caused by pathogenic germline mutations in the prion protein gene (PRNP), which are typically transmitted through an autosomal dominant pattern of inheritance [1]. Around 85% of human TSEs occur sporadically [5,6] and approximately 15% are linked to autosomal dominant pathogenic variants in PRNP [7]. In general, TSEs are very uncommon, and the incidence is nearly 1.5 cases/million people yearly [5]. It is believed that CJD is the most common human prion disease with an incidence of around 0.6 to 1.2 per million population annually [8].

Although the asymptomatic incubation period of TSEs is usually very long, especially for acquired prion diseases [9], the early symptoms of the disease are pain, sensory symptoms, poor memory, dysarthria, and unsteadiness of gait [10]. In late stages, patients with TSEs usually suffer from paranoid ideation,

confabulation, disorientation, impaired self-care, and hallucinations [10]. The most common neurological characteristics that occur in these late stages are chorea, dystonia, cerebellar signs, visual symptoms, myoclonus, and upper motor neuron signs [10]. These symptoms could vary from one prion disease to another.

The development of TSEs is primarily associated with the conformational conversion of the host-encoded cellular prion protein (PrP^{C}), a membrane-associated protein, into its abnormal, disease-associated, fibril-forming isoform (PrP^{Sc}). This abnormal protein was initially identified as the causative agent of scrapie in sheep [11]. Subsequent research established PrP^{Sc} as the infectious agent responsible for prion diseases in both humans and animals [1,4]. Although the precise molecular structure of PrP^{Sc} remains unresolved [12], substantial evidence indicates that its conformation is characterized by an increased proportion of β-sheet structures at the expense of the α-helical structures predominantly found in normal PrP^{C} [13]. Furthermore, PrP^{Sc} is believed to induce the conformational transformation of normal PrP^{C} into the infectious PrP^{Sc} isoform, supporting the self-replication hypothesis originally proposed by Griffith (1967) [11].

One of the earliest proposed mechanisms explaining prion self-replication is the heterodimer model described by Cohen et al. (1994) [14]. According to this model, the process is initiated when a single PrP^{Sc} molecule interacts with a normal PrP^{C} molecule, triggering its conversion into the abnormal infectious form. The resulting two PrP^{Sc} molecules subsequently dissociate, allowing each to interact with and convert additional PrP^{C} molecules, thereby propagating the conversion process [14].

An alternative explanation is provided by the fibril-based model, which proposes that PrP^{Sc} exists exclusively in fibrillar aggregates [15,16]. In this model, the conversion process occurs when normal PrP^{C} molecules bind to the ends of existing PrP^{Sc} fibrils, promoting their transformation into the abnormal isoform [15,16]. Although several studies have investigated the mechanisms underlying prion self-replication, the precise molecular events involved in this conformational conversion remain incompletely understood [17]. Similarly, the mechanisms through which PrP^{Sc} contributes to neuronal cell death have yet to be fully elucidated [17]. Understanding of such mechanisms could help to develop better diagnostic and therapeutic strategies. The aim of this review is to discuss current diagnostic and treatment methods for prion diseases.

Review

Diagnosis of prion diseases

Detection of Amyloid

Amyloid plaques are deposited in brain tissue in 100% of cases of GSS disease and kuru and in 15% of cases of sporadic CJD (sCJD) [18]. Congo red staining is used to detect amyloid [19]. Amyloid reveals red/green birefringence characteristics when stained with Congo red and exposed to polarized light [19]. The diagnosis of TSEs in humans and animals is usually confirmed by additional tests such as immunohistochemistry (IHC), enzyme-linked immunosorbent assay (ELISA), and Western blot [20-23]. Despite these diagnostic tests, there are still challenges in early diagnosis of TSEs because of nonspecific and variable clinical manifestations at early stages of the disease [24].

Detection of Changes in Cortical and Subcortical Grey Matter and 14-3-3 Protein in CSF

For instance, CJD, the most common human TSE, is distinguished from other poor-prognosis dementias via detection of changes in cortical and subcortical grey matter and 14-3-3 protein in CSF [25,26]. However, other neurological diseases such as intravascular lymphoma, vascular disorders and encephalitis could cause similar histological criteria to those found in CJD [27-29]. This may make it difficult to differentiate CJD from other neurological diseases using the previous method alone.

Detection of PrP

The unavailability of a reliable in vivo diagnostic test for CJD was a challenge for several years [24]. Previous studies noted that PrP deposition could be detected by IHC and immunoblotting in the muscle, spleen, and lymph nodes of patients with CJD, but it is difficult to collect biopsies from these tissues in living patients [24,30-32]. Although the specificity for detection of PrP by IHC and immunoblotting is high, the sensitivity is quite low [31,32]. The sensitivity is 27% to 33% in the muscle and 55% in the spleen [30-32].

According to the present guidelines, a confirmed diagnosis of CJD requires neuropathology or using IHC or immunoblotting to detect PrP in brain tissue [24]. Brain tissue is usually obtained at autopsy, but it can also be collected from brain biopsies [24]. Because of the uncommonness of the latter method, most confirmed diagnoses are made postmortem. In addition, IHC lacks adequate sensitivity for detection of low

concentrations of PrP that are localized in tissues other than the brain, such as CSF [24]. This prompted scientists to develop the ultrasensitive ELISA, which can detect tiny amounts of PrP by a steel powder capture technique [33]. This method has a specificity of 100% and a sensitivity of 71% for diagnosis of vCJD from blood samples [34]. On the other hand, it could not detect PrP in the blood samples of patients with sCJD or other human TSEs [33].

Protein Misfolding Cyclic Amplification (PMCA) Assay

Several studies were carried out to improve the sensitivity of diagnostic tests for prion diseases by taking advantage of the PrP self-propagation activity [35-38]. Jones et al. (2007) developed the protein misfolding cyclic amplification (PMCA) assay, which is a highly sensitive method for PrP amplification [36]. This assay exploits the prion-induced seeded conversion of normal PrP into higher concentrations of PrP^{Sc} [39].

The sample tests could be tissue or cells from the brain. The analysis process includes sonication and rest cycles [37,38]. Immunoblotting or surround optical fiber immunoassay (SOFIA) is then used to detect the increased amount of PrP^{Sc} [40]. It is more sensitive for detection of vCJD and sCJD compared to ELISA [24].

From a practical diagnostic perspective, the PMCA assay has some disadvantages [37]. It requires tissue or cells from the brain as a source of PrP, which is difficult to obtain from living patients [24]. Moreover, sonication presents technical challenges. Reading the final result could take four to five days, which is time-consuming [24,37].

Real-Time Quaking-Induced Conversion (RT-QuIC) Assays

Scientists worked to overcome the disadvantages of PMCA by developing alternative techniques for detection of PrP-associated seeding activity [41-44]. The work ended in developing the RT-QuIC assays [41-44]. This new assay can be carried out in 96-well plates, and fluorescence plate readers are used to detect the products of prion seeding. The detection is done with the amyloid-sensitive dye thioflavin [24]. The RT-QuIC assays are highly sensitive, similar to PMCA assays; however, they have additional advantages in using a better substrate [24]. This bacterially expressed recombinant PrP^{C} substrate fluorescence as a read-out and easily replicable shaking improves the quality of the results [24]. Studies performed on CSF samples collected from sCJD found that the sensitivity of the RT-QuIC technique ranges from 77 to 97% and specificity ranges from 99 to 100% [41,42].

A previous study found that PrP is present in the olfactory neuroepithelium of patients with CJD [45]. In addition to the CSF samples, CJD can be diagnosed by analyzing samples collected from the olfactory mucosa brushings [43]. This sampling procedure can increase the specificity of RT-QuIC in diagnosing CJD to 100% [43]. Furthermore, RT-QuIC is able to detect all 28 different PrP strains seen in animals and humans [46]. These findings might mean that the RT-QuIC assay can be used to diagnose all TSEs [24].

Moreover, Bongianni et al. (2017) developed an algorithm for early and accurate diagnosis of CJD in CSF and olfactory mucosa samples using the RT-QuIC assay. In this study, the olfactory mucosa samples were collected using gentle flocked swabs instead of the traditional brush [47]. They found that the sensitivity for diagnosing sCJD was 100% and the specificity for the diagnosis of non-TSEs was 100% [47]. This proposed algorithm for diagnosing sCJD by analyzing CSF and olfactory mucosa could offer a more accurate diagnosis and could be a promising routine test. In addition, a recent meta-analysis identified RT-QuIC as the most accurate CSF biomarker assay for the diagnosis of sCJD [48].

Despite the promising discoveries, further assessment of the RT-QuIC assay and olfactory mucosa analysis is required to improve the accuracy for the diagnosis of CJD and other TSEs. Further investigation is needed to determine how early in the stages of prion diseases seeding activity can be identified.

Timed Prion Seeding Assay (tASA)

In the past 10 years, researchers have tended to find more accurate, sensitive, rapid, cheaper, and non-invasive tests to diagnose TSEs early in different body fluids [47,49,50]. Gray et al. (2016) developed a new technique to measure the time required by PrP^{C} to convert to PrP^{Sc}, called the timed prion seeding assay (tASA). This new method combines statistical analyses to get a prion-detecting amyloid seeding assay with an identified degree of confidence [49]. The tASA depends on using recombinant PrP as a substrate and on detecting prion conversion through fluorescence changes [49]. Compared with other techniques such as rodent bioassays and TSE rapid tests, tASA is more sensitive. The tASA can show clear cut-off values that allow the determination of negative and positive TSE states [49]. In addition, this test can detect and measure prion infection in different body fluids such as saliva, urine, and blood [49]. This in vitro test would offer a non-invasive technique to detect TSE infection in donor blood [49].

In addition, Luk et al. (2016) detected PrP^{Sc} in 40% of urine samples collected from patients with sCJD using

the PrP direct detection assay developed for blood screening [50]. The specificity of detecting PrP^{Sc} in urine of patients with TSEs was 100%, but the sensitivity to diagnose sCJD was 40% [50]. This assay could be improved to develop rapid, non-invasive molecular diagnostics for sCJD and other TSEs.

Detection of PrP in Blood Sample

Two studies were able to detect PrP in blood samples of patients with vCJD [51,52]. Both studies diagnosed vCJD using blood samples with specificity and sensitivity of 100% [51,52]. Both methods involved prion amplification via culturing PrP with normal proteins, and then they were subjected to sound waves [51,52]. This process simulates the environment for PrP replication. If the collected sample is infected, then the healthy proteins start to clump and stimulate infection of other proteins. This ends in the formation of a high concentration of abnormal proteins that are easy to identify and analyze. If the collected sample is not infected, then the healthy proteins present in the culture media remain normal [51,52].

Concha-Marambio et al. (2016) used the PMCA assay to analyze the blood samples, and they were able to detect PrP in very small amounts of blood [52]. On the other hand, Bougard et al. (2016) combined the PMCA technique with the plasminogen-bead capture assay, and they were able to detect PrP in the blood of asymptomatic patients [51]. Such studies could provide fundamental data to develop a method for accurate detection of vCJD and other TSEs in the future. Moreover, these methods could provide a non-invasive and rapid blood screening for donors, which may eliminate the transmission of prion diseases from asymptomatic patients to healthy humans and help in early diagnosis and treatment.

MRI, CT, and Electroencephalogram (EEG)

Clinical symptoms, neuroimaging techniques such as CT, MRI, and EEG, and CSF analysis are valuable diagnostic approaches for identifying neurological abnormalities associated with CJD [53]. Among these, EEG and MRI play particularly important roles in supporting the clinical diagnosis, while the detection of 14-3-3 protein in CSF provides additional supportive evidence of CJD [53]. Although MRI, CT, and other neuroimaging modalities can reveal characteristic pathological changes associated with CJD, including cerebral atrophy and increased signal intensity in the caudate nucleus, putamen, and cerebral cortex, these findings alone are insufficient to confirm the diagnosis [53]. Neuropathological examination of brain tissue, typically performed post-mortem, remains an important method for confirming CJD. However, the limited availability of such examinations highlights the need for further development of accurate and reliable ante-mortem diagnostic techniques [53].

Treatment of prion diseases

Effective therapeutic compounds for prion diseases must be delivered via intrathecal or intraventricular means or able to cross the blood-brain barrier (BBB) to reach the brain tissue [54]. The discovery of new treatments for prion diseases is based on three proposed mechanisms to reduce PrP^{Sc}: inhibit the formation of PrP^{Sc}, reduce the concentration of $PrP^{C,}$ or disaggregate the existing PrP^{Sc} [54]. Table *1* features a summary of the current detection strategies for prion diseases.

Way of diagnosis		Advantages	Disadvantages
Detection of amyloid		High specificity for GSS disease [18]	Not specific at early stages; needs brain tissue biopsy [18,24]
Detection of changes in cortical and subcortical grey matter and 14-3-3 protein in CSF		Can distinguish CJD from other dementias [25,26]	Not specific [27-29]
Detection of PrP	PMCA assay	High sensitivity [36]	Needs brain tissue or cells, time-consuming [24,37]
	RT-QuIC assays	High sensitivity, high specificity, use a better substrate, can detect all 28 different PrP strains seen in animals and humans [24,41,42,46]	More research is needed to establish sensitivity and specificity for the preclinical stage of disease [47]
	tASA	High specificity, non-invasive technique, can detect prion infection in different body fluids [49,50]	Low sensitivity [50]
	Detection of PrP in blood sample	High specificity and sensitivity for variant CJD; rapid, non-invasive technique [51,52]	More research is needed to establish sensitivity and specificity for other prion diseases [51,52]

TABLE 1: Advantages and disadvantages of current detection strategies for diagnosis of prion diseases

GSS: Gerstmann-Sträussler-Scheinker, CJD: Creutzfeldt-Jakob disease, PMCA: Protein misfolding cyclic amplification, PrP: Prion protein, RT-QuIC: Real-time quaking-induced conversion, tASA: Timed prion seeding assay

Use of Anti-PrP^C and Anti-PrP^{Sc} Monoclonal Antibodies

To date, no effective treatment has been found for TSEs [55]. Nevertheless, White et al. (2003) reported that the replication of PrP^C and PrP^{Sc} was inhibited and the disease was delayed by using specific anti-PrP^C and anti-PrP^{Sc} monoclonal antibodies in a murine scrapie model [56]. Perrier et al. (2004) found that the replication of PrP^{Sc} was suppressed via reducing the half-life and accelerating the degradation of the PrP^C [57].

Use of Large Polyanionic Compounds

To treat TSEs, early studies used various large polyanionic compounds such as sulfated glycans dextran sulfate 500 (DS500), pentosan polysulfate (PPS) [58], and polyoxometalate HPA-23 [59]. Such large compounds were not able to extend the survival time in intracerebrally inoculated mice [58,59]. Other studies that were carried out using PPS showed different findings with regard to prion strain, inoculum titer, and mouse background [60,61]. Nevertheless, in the following years, Doh-Ura et al. (2004) were able to introduce PPS to clinical use after the intraventricular delivery of PPS. They extended the survival time of the prion-infected mice to more than double [62].

Use of Congo Red Inhibitor

Although there was no significant improvement in the clinical prognosis of CJD in humans, the survival times for some patients were longer than expected [63]. However, this longer survival was only seen in patients with early stages of the disease [63]. In addition, Caughey and Race (1992) found that replication of PrP^C can be inhibited after binding to Congo red in cell culture [64]. In vivo, Congo red was found to increase the survival time for infected hamsters, but only in early stages of the disease [65].

Use of Low Molecular Weight Compound

Previous studies suggested that the use of low molecular weight compounds could be a possible treatment for TSEs [66, 67]. Examples of such compounds that were clinically investigated are various tricyclic derivatives of acridine and phenothiazine, mainly quinacrine and chlorpromazine [66,67]. This treatment was able to inhibit the conversion of PrP^C into PrP^{Sc} in the human ScN2a neuroblastoma cell line [66,67]. On the other hand, Barret et al. (2003) found that only treatment with higher doses of quinacrine and chlorpromazine reduced the formation of PrP^{Sc} in vitro and were not able to get similar results in vivo [68].

Use of Recombinant PrPs (rPrP)

The potential of rPrP to inhibit PrP^{C} and PrP^{Sc} in vitro was investigated by Workman et al. (2017) [69]. They used PMCA as a model for prion replication and Novablue (DE3) E. coli as a host for rPrP expression. The recombinant ovine PrP was able to inhibit the replication of VRQ/ARQ genotypes of PrP^{Sc} [69]. Although the mechanism of inhibition has not yet been explained, these findings suggested that rPrPs such as rVRQ and rARQ could be a promising therapy for prion diseases.

Prevent Misfolding of PrP

A recent investigation has elucidated the molecular mechanism behind T183A huPrPC misfolding and aggregation under physiological conditions [70]. The study revealed that the C-terminal structured domain possesses intrinsic amyloid-forming capability independent of the traditionally recognized amyloidogenic region (residues 106-126) [70]. Furthermore, experiments utilizing POM antibodies demonstrated two key findings: first, they provided insights into the initial triggers of PrP misfolding; second, they suggested that stabilizing the structural dynamics of T183A huPrPC125-230 could effectively prevent the formation of huPrP* intermediates and subsequent pathogenic aggregation [70]. This stabilization approach emerges as a potential therapeutic strategy against PrP misfolding [70]. Table *2* features a summary of the treatment methods, mechanisms, and experimental models for prion diseases.

Treatment method	Mechanism	Experimental model
Anti-PrP^{C} and anti-PrP^{Sc} monoclonal antibodies	Inhibit formation of PrP^{Sc} [56]	Murine scrapie [56]
Large polyanionic compounds	Inhibit formation of PrP^{Sc} and disaggregate existing PrP^{Sc} [62]	Intracerebrally inoculated mice [58,59]
Congo red inhibitor	Reduce concentration of PrP^{C} [64]	Hamsters [65]
Low molecular weight compounds	Inhibit formation of PrP^{Sc} [66,67]	Human ScN2a neuroblastoma cell line [66,67]
Recombinant PrPs (rPrP)	Not yet explained [69]	Novablue (DE3) *Escherichia coli* [69]
Preventing PrP misfolding	Inhibit formation of PrP^{Sc} [70]	*E. coli* [70]

TABLE 2: Mechanisms and used experimental models of current prion diseases treatment methods

PrP^{C}: Cellular prion protein; PrP^{Sc}: Scrapie prion protein

Conclusions

Prions remain one of the most challenging diseases in neurology, representing a unique intersection of infectivity and neurodegeneration. As this review has highlighted, the field has made remarkable progress, particularly in diagnostic techniques. The advent of protein amplification technologies such as PMCA, RT-QuIC, and tASA has improved the detection of minute quantities of PrP^{C} and PrP^{Sc} present in biological fluids, offering unprecedented sensitivity and specificity. However, the persistent lack of curative or even disease-modifying therapies means that a diagnosis still carries a uniformly fatal prognosis, underscoring the urgent need for continued innovation.

Future research into prion disease management should focus on integrating earlier detection, a deeper understanding of disease mechanisms, and the development of targeted therapeutic interventions. One important priority is the advancement of preclinical diagnostic approaches, particularly the development and validation of reliable blood-based screening methods that may enable the detection of prion diseases before clinical symptoms appear. In parallel, therapeutic research should aim to move beyond palliative care towards disease-modifying treatments capable of slowing or preventing disease progression. Further investigations into immunotherapy and small-molecule therapeutics are essential to identify effective strategies for inhibiting prion conversion, propagation, and accumulation. Additionally, the potential of combination therapies should be explored, as targeting multiple pathways involved in prion pathogenesis may improve treatment efficacy. Another important research direction is elucidating the molecular mechanisms underlying prion strain diversity and understanding how different strains influence disease transmission, progression, and therapeutic responses. Such investigations may contribute to the

development of more targeted and effective treatment strategies.

In conclusion, while prion diseases continue to pose a significant and tragic challenge, the remarkable diagnostic breakthroughs of recent years provide a powerful foundation for the future. The leverage of these diagnostic advances enables early intervention and strengthens the search for effective therapies through diverse and innovative strategies. This could bridge the gap between our deep molecular understanding and tangible clinical benefit. The merging of these efforts offers genuine hope for transforming these universally fatal disorders into manageable, and perhaps one day, preventable conditions.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

Concept and design: Awf Al Khan, Salheen Salheen, Noora Al Balushi, Said Al Maawali

Acquisition, analysis, or interpretation of data: Awf Al Khan, Noora Al Balushi

Drafting of the manuscript: Awf Al Khan

Critical review of the manuscript for important intellectual content: Awf Al Khan, Salheen Salheen, Noora Al Balushi, Said Al Maawali

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