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Prion Disease in Animals and Humans: Exploring, Pathogenesis, Transmission

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Abstract
Prion diseases are fatal neurodegenerative disorders affecting both humans and animals, caused by misfolded prion proteins that induce the conversion of normal cellular prion protein into pathogenic forms. This misfolded protein resist degradation, accumulates in the brain, and induces neuronal death, leading to rapid cognitive and motor decline. This project aims to investigate the mechanisms of pathogenesis, transmission pathways, and early detection methods for these transmissible spongiform encephalopathy (TSEs). Stanley Prusiner's team advanced this "protein-only hypothesis ", coining the term prion (1982) as a nucleic acid –resistant proteinaceous particle by 1985. A total of 27,872 cases of prion disease (PrD) and 24,623 cases of Creutzfeldt-Jakob disease (sCJD) have been reported across 34 countries with accessible annual data. Prion disease, including Creutzfeldt-Jakob disease (CJD), fatal insomnia and Kuru, can occur sporadically, be inherited, or result from exposure to infected material. Although rare, these disease are invariably fatal, with no current cure available. Recent advancement in diagnostic methods, such as Real-Time Quaking-Induces conversion (RT-QuIC) and Magnetic Resonance Imaging (MRI), offers hope for earlier diagnosis. Emerging treatment approaches, including antisense oligonucleotides (ASOs) and tetracyclic compound's, provide optimism for possible therapies. By synthesizing current knowledge and identifying gaps in research, this project seeks to contribute to a deeper understanding of prion diseases and inform future diagnostic and therapeutic developments.

Keywords: prion disease, neurodegenerative disorders, protein folding, Prpc, PrPSc, Creutzfeldt-Jakob disease, antisense oligonucleotides, tetracyclic compounds.

INTRODUCTION

The word prion means proteinaceous infectious particle, emphasizing that it is a protein that misfold its structure to cause sickness. Prion only cause disease by aberrant protein folding, as opposed to traditional infectious pathogens that rely on DNA or RNA[1.] The contagious nature of prion disease, which are fatal neurodegenerative conditions that impact both human and animals, sets them apart. Because it lacks certain nucleic acids the infectious agent that cause these illness known as PrPSc is distinct. Rather, it is Prpc[2, 3.] Dangerously misfolded and aggregated from of the regular cellular prion protein. Prion use an autocatalytic process to cause the hosts normal prion protein (Prpc) to misfold once they have been

transferred to an uninfected host. In the brain and spinal cord, this mechanism leads to a sharp rise in the misfolded form, PrPSc, which eventually culminates in neuronal death[4].

The host's Prpc, which is encoded by the prion gene PRPNP on human chromosome 20, determines the amino acid sequence of PrPSc[5]. Prions can accumulate in the central nervous system over a period of months to years and are extraordinarily stable. Prions are remarkably stable and can build up in the central nervous system over several months to years.

This accumulation ultimately results in widespread spongiform degradation and the loss of neurons, accompanied by the activation of astrocytes and microglia, while peripheral inflammatory cells are notably absent[6]. The prion protein (PrP) is an evolutionarily conserved glycoprotein existing in the two main isoform: cellular (PrP), found abundantly on neuronal surfaces and involved in various physiological process, and disease – associated PrPSc, linked to prion pathogies[7, 8, and 9]. Prpc plays roles in:

- Myelin regulation[10]
- Neuroprotection against stressors[11]
- Circadian rhythm modulation[12,13]
- Metal ion and mitochondrial homeostasis[14,15]
- Synaptic signalling via presynaptic/postsynaptic localization[16,17,18]

Historical Perspective and Significance

The history of human prion disease traces back to 1920, when Hans Gerhard Creutzfeldt and Alfons Maria Jakob independently described cases of a novel neurodegenerative disorder (later termed Creutzfeldt – Jakob disease CJD). Earlier observations included Creutzfeldt 913 documentation of a patient with speech impairments and myclonus[19]. In 1951, the tremor- associated "Kuru" disease emerged among Papua guineas for people [20]. Initially linked to "slow virus" due to similarities with scrapie in sheep, the field shifted when john Stanley Griffith proposed a protein based infection agent (1967)[21,22]. Stanley Prusiner's team advanced this "protein-only hypothesis ", coining the term prion (1982) as a nucleic acid –resistant proteinaceous particle[23, 24]. By 1985, Prusiner confirmed CJDs classification as a prion disease through scrapie agent comparisons, solidifying PrPSc role while leaving PrPC's physiological functions under ongoing investigation[25].

Epidemiology

A total of 27,872 cases of prion disease (PrD) and 24,623 cases of Creutzfeldt-Jakob disease (sCJD) have been reported across 34 countries with accessible annual data. The United States leads in PrD cases with 5,156, followed by France (3,276), Germany (3,212), Italy (2,995), China (2,662), the United Kingdom (2,521), Spain (1,657) and Canada (1,311). Over the past 27 year, global and national PrD cases numbers and mortality rates have shown an upward trend. Genetic form of PrD represent 10.83% of all reported case of iatrogenic CJD (iCJD) and 232 cases of variant CJD (VCJD) documented worldwide[26].

Creutzfeldt- Jakob disease affects approximately one person per million annually worldwide, with around 350 cases diagnosed each year in the United States. Sporadic CJD (sCJD) in the most prevalent form of human prion disease, accounting for the majority of cases. The average age of onset for sCJD is 62 years, although it can occur in both younger and older individual. The disease affects males and female equally, with a 1:1 gender ratio. Globally, the incidence of sCJD is estimated at 1 to 2 cases per million people annually.

Nearly 70% of patients die within a year of symptom onset, with average survival ranging from 4 to 8 months; 90% of patient succumb to the disease within one year[27.] Genetic CJD (gCJD) is the second most common type and it's often linked to autosomal-dominant mutations in the PRNP gene, with many patient with family history of the condition. Acquired from the CJD, such as iatrogenic (iCJD), are rare, accounting for less than 1% of cases. These acquired cases typically occurs in younger adults and have an average onset age of 29years[28.]

Pathophysiology

The normal cellular prion protein (Prpc) can transform into its pathogenic form, PrP scrapie (PrPSc), either spontaneously or through exposure to PrPSc. Once formed, PrPSc propagates itself and accumulated in the brain. The chemically stable β-sheets aggregates of PrPSc disrupt intracellular processes such as protein folding, ubiquitination, and trafficking within neurons. Additionally, astrocytes may swell or degrade in response to prion-induced damage, contributing to neurodegeneration. These pathological changes ultimately lead to the progressive destruction of neural tissue[29.]

Prion protein

The Normal Prion Protein (Prpc)

Prions are made up of misfolded variant of the e major prion protein, which is a protein naturally present in humans and other animals. The structure of PrP found in infectious prions differs from the normal form, making it resist to proteases- enzymes that typically degraded proteins in the body. The standard form of this protein is referred to as Prpc. In humans the prion protein composed of 209 amino acids, contains a single disulphide bond, has a molecular weight of approximately 35-36kDa, and predominantly feature an alpha- helical structure[30.] Prpc is crucial for cell- cell adhesion and intracellular signalling in living organisms[31.] Suggesting that it may play role in facilitating communications between cells in the brain[32.]

The Misfolded Scrapie Prion Protein (PrPSc)

PrPSc is the scrapie form of the prion protein. PrPSc was the first prion, or infectious protein, to be identified and remains the definitive example of prion protein due to its historical significance and its connection to a specific group of lethal disease. PrPSc features a structure that is reach in beta sheets, with a core that is resist to proteases enzyme and has a tendency to aggregate[33.] PrPSc misfolded and aggregate form of Prpc its accumulation in the brain leads to neural death and neural dysfunction.

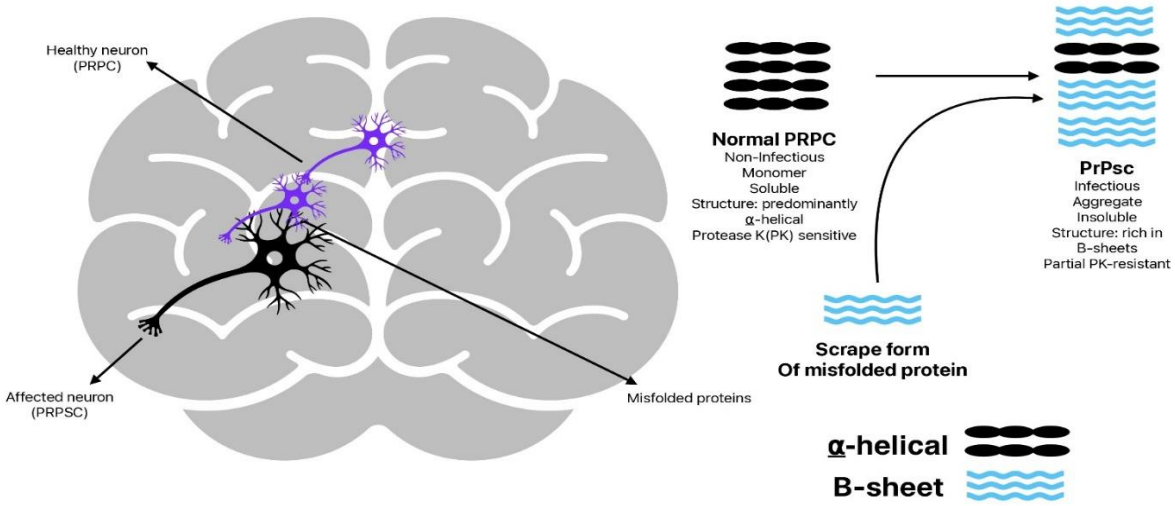

Fig 1: Conversion of Prpc (Normal form of protein) to PrPSc (Scrapie form of protein)

Symptoms of Prion disease

- Rapid developing dementia
- Ataxia
- Involuntary muscle jerks
- Visual disturbance
- Speech difficulties
- Personality changes
- Sleep disturbance
- Muscle stiffness
- Confusion
- Fatigue

Transformation

Its primary structure if protein and newly synthesized proteins rapidly attains the molten globule state. After that the folding continues and we have correctly folded proteins but during protein folding there are some errors proteins get miss shaped[34]. These misfolded proteins are sent for repairing and this repairing is done by chaperone molecules[35].

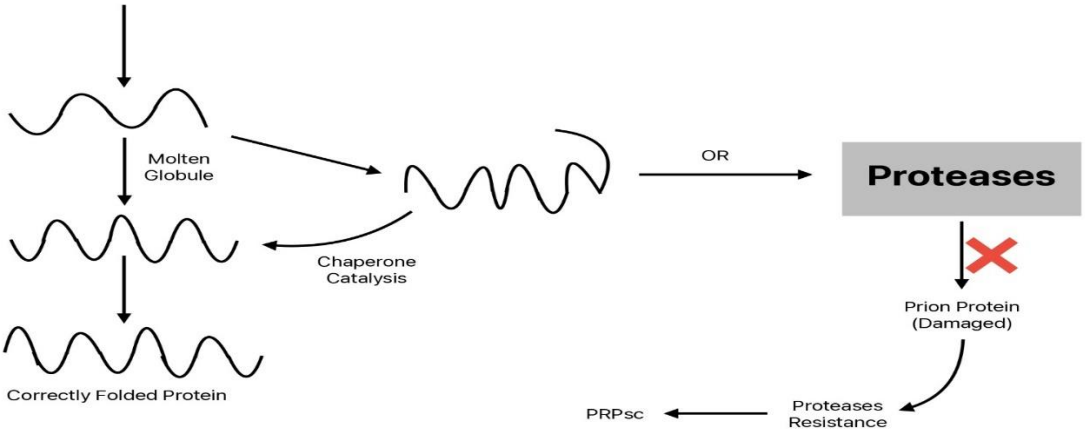

Fig 2: Transformation (Steps in Transformation of Prpc to PrPSc)

These chaperon molecules catalyze the misfolding protein and gets it corrected to the original form. If the misfolding protein does not get corrected it sent for proteolysis and is degraded eventually[36]. The misfolded protein is prion protein it has resistance for Proteolysis and remains undegraded in the body, so it evades the Proteolysis process so this misfolded protein are called prion protein these prions converts Prpc to PrPSc[37].

Proteopathy Make this protease resistance

Prpc: Normal	PrPSc: Misfolded
Alpha helices: 43%	Alpha helices: 30%
Beta sheets: 03%	Beta sheets: 43% [38, 39]

Transmission pathway

Natural transmission pathway

Prion disease spread through ingestion or injection rather than direct contact. Outbreak like bovine spongiform encephalopathy (BSE) in cattle were linked to prion contamination fed, while Kuru in Papua guinea emerged from ritual cannibalism tied to sporadic Creutzfeldt-Jakob disease (CJD)[40.] Variant CJD in humans is associated with consuming BSE- infected products, a mechanism supported by oral transmission experiments in animals. After ingestion, prions resist digestive enzyme, potentially crossing the intestinal lining via M cells to access Peyer's patches and the enteric nervous system. In susceptible hosts, prions accumulate in lymphoid tissues (e.g.; spleen, lymph nodes) before migrating through peripheral nervous to the brain, utilizing pathway like the vague nerve[41.] Their spread relies on host prion protein (Prpc), as neural routes- not blood borne transmission is rare, low- level prion infectivity has been detected in some species, underscoring, the complexity of their propagation, which primarily involves neural and lymphoid systems rather than circulation.

Intragenic transmission of prion

Nearly 300 cases of CJD have been linked to medical procedure, primarily involving cadaveric human growth hormone and Dura mater transplant. A few cases have been associated with corneal transplant. Four instances of CJD transmission via neurosurgical instrument were reported, but causality was confirmed in only one case. In one incident an electrode used on undiagnosed CJD patient underwent cleaning with benzene, ethanol and formaldehyde vapor before reuse on two patients. Both developed

CJD within two years. Subsequent testing showed the electrode retained**.** Infectious prions, which cause fatal spongiform encephalopathy in a chimpanzee, highlighting the persistence of prion despite sterilization efforts[42.]

Classification

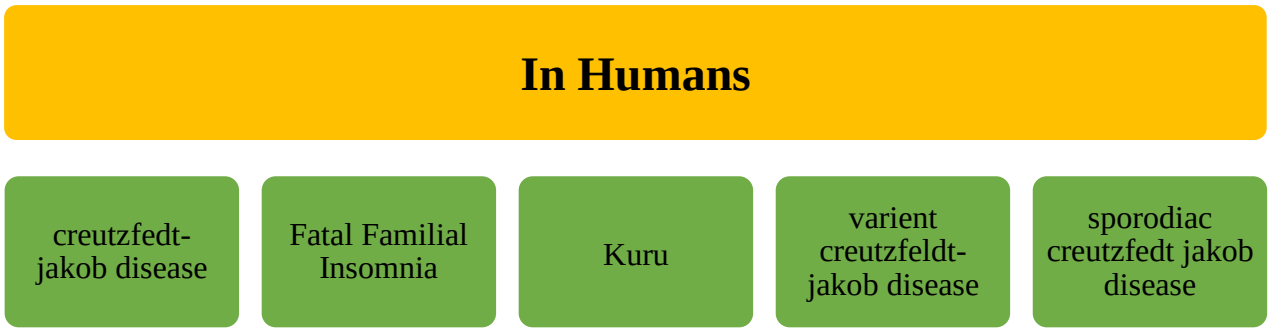

Fig 3: Classification of Prion disease in Humans caused by Prion

Creutzfeldt-Jakob disease (CJD)

Creutzfeldt-Jakob disease (CJD) is a transmissible, rapidly progressive, and universally fatal neurodegenerative disorder caused by prion proteins, although this is a rare disease. It is marked by a lengthy incubation period before symptoms develop[37, 38]. The first description of the disease was made by Hans Creutzfeldt in 1920 and by Alfons Jakob in 1921 and 1923. Later, Clearance J. Gibbs took on the term "Creutzfeldt-Jakob disease" because it matched neatly into his own initials — "CJD"[39, 40.] There are three main forms in which CJD appears — sporadic, familial and iatrogenic or acquired. Most cases are sporadic (sCJD; ~85%, including an atypical form called variant CJD), while about 10% to 15% are genetic (gCJD) and less than 5% are iatrogenic. A handful of cases are associated with exposure to Bovine Spongiform Encephalopathy (BSE). The incidence of acquired CJD has also reduced significantly over time as medical knowledge has improved and treatment errors have decreased[43, 44, 45.]

Symptoms

1. Personality changes
2. Memory loss
3. Impaired thinking
4. Trouble speaking
5. Trouble swallowing
6. Walking giant difficulties
7. Blurry vision

Pion Disease	**Host**	**Incubation Period**	**Life expectancy after symptom onset**
Kuru	Humans	10-13 year	12 months
Fatal Familial Insomnia	Humans	Up to 30 years	9.5-12 months
Variant Creutzfeldt-Jakob disease	Humans	Unknown	8 months

BSE	Cows	4.5 -5 years	2 weeks to 6 months
Scrapie	Sheep, goats	2- 5 years	1-6 months
Chronic wasting Disease	Cervids	13 - 32 months	5-12 months

Table 1: Prions in Animal and Humans: There Incubation period and life expectancy after symptoms

Evaluation

Creutzfeldt-Jakob disease (CJD) is typically difficult to diagnose, because of the way it can present similar to other diseases that can also lead to RPD. Initial screening tests that are recommended to evaluate RPD are as follows:

- Complete blood count
- Complete metabolic panel
- Blood magnesium
- Rapid plasma regain
- Erythrocytes sedimentation rate
- Antinuclear antibody
- C-reactive protein
- Thyroid function test
- Vitamin B12 level
- Autoimmune antibodies
- CSF 14-3-3 protein (a test of prion disease)

Magnetic resonance imaging (MRI), especially fluid-attenuated inversion recovery (FLAIR) and diffusion-weighted imaging (DWI), provides clear imaging findings of brain lesions in Creutzfeldt-Jakob disease (CJD). Diagnostic accuracy is improved by combining MRI with clinical, laboratory, and electroencephalogram (EEG) findings. The 1998 diagnostic criteria from the World Health Organization for CJD, which were based on clinical, EEG, and cerebrospinal fluid (CSF) findings, are now seen as outdated in the era of advanced MRI and genetic testing. MRI has higher sensitivity and specificity than CSF 14-3-3 protein testing, with roughly 90% accuracy. DWI demonstrates 98% sensitivity and 93% specificity; it usually demonstrates cortical ribboning and hyper intensities within the basal ganglia and thalamus. The hockey stick or pulvinar sign may be seen in variant or acquired CJD[46, 47, 48].

CSF biomarkers (for example, 14-3-3 protein, total tau [T-tau], neuron-specific enlace [NSE]) indicate fast neurodegeneration, but are not CJD-specific. Compared to 14-3-3 protein, elevated T-tau levels (>1150 pg/mL) are more accurate. But both tests can return false positives and false negatives. DWI provides better diagnostic accuracy than these biomarkers. Real-Time Quaking-Induced Conversion (RT-QuIC, 2015) enables direct detection of pathogenic prion proteins in cerebrospinal fluid (CSF) at high specificity (~98%), but moderate sensitivity (>80%). Not sensitive as MRI but often positive in genetic prion disease. _use olfactory epithelium brushings instead of CSF? _Sensitivity may be improved[49].

In sporadic CJD, MRI is more sensitive than EEG or CSF studies; however, EEG may identify periodic sharp wave complexes (PSWCs) in later stages. PSWCs are present in 67%-95% of sporadic cases, but

are rare in other prion diseases such as Gerstmann-Sträussler-Scheinker syndrome or fatal familial insomnia[50].

A definitive diagnosis can be made through biopsy or postmortem examination of the brain tissue. But this is uncommon, except when reversible conditions are suspected. Prions have also been found in the blood and urine of people with variant CJD and so there remains a short term risk from body fluids until prion infectivity has been excluded[51, 52.]

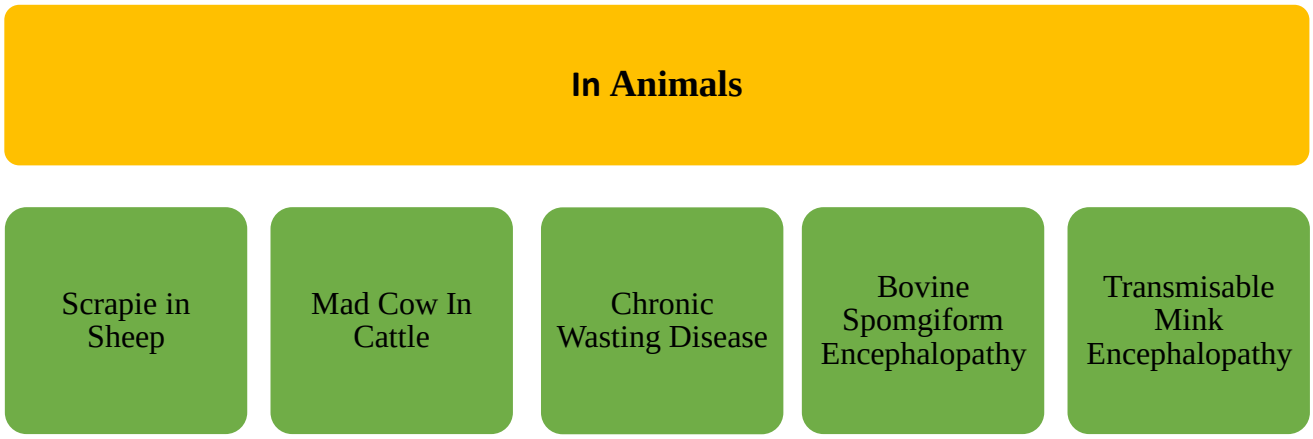

Fig 4: Classification of Prion disease in Animals caused by prion

Animal Prion disease are a group of disorder that effects humans and several species of animals. It occur in sheep, goats, cattle, elk, deer, minks, cats, and camels. Disease can be transmitted to one disease to another when an animal:

- Eats effected animal
- Comes in contact with an infected animals body fluids or waste
- In housed with infected animals[53]

Diagnosis

Prion disease may be difficult to diagnose, particularly early in its course, because its symptoms often overlap with other neurological conditions.

Traditional Diagnostic Approach

Clinical Assessment

Clinical neurological assessment is crucial in the diagnosis of prion diseases, with emphasis on clinical features like rapidly progressive dementia, sudden jerks of muscles (myoclonus), coordination problems (ataxia), visual disturbances, and behavioral alterations. These symptoms are not specific to prion diseases but can also be present in other neurological conditions[54].

Electroencephalogram (EEG)

Electroencephalogram (EEG) can measure electrical brain activity and could have typical periodic sharp wave complexes (PSWCs) on it in some prion conditions, including sporadic Creutzfeldt-Jakob disease (sCJD). EEG patterns, though, are not invariably found and also show in other illnesses, lowering EEG as an individual use tool.

Tau protein

Elevated levels of total tau protein (t-tau) in cerebrospinal fluid (CSF), especially when combined with a low phosphorylated tau (p-tau) to t-tau ratio, can contribute to the diagnosis of sporadic Creutzfeldt-Jakob disease (sCJD) [55].

Magnetic Resonance Imaging (MRI)

Magnetic Resonance Imaging (MRI), and more so diffusion-weighted imaging (DWI) and fluid-attenuated inversion recovery (FLAIR) sequences, has become an important diagnostic tool. It is able to identify characteristic high signal abnormalities in certain regions of the brain, including the basal ganglia (caudate and putamen) and the cortex, typically appearing as "cortical ribboning" in sporadic Creutzfeldt-Jakob disease (sCJD) and variant Creutzfeldt-Jakob disease (vCJD). With clinical presentation and other investigations, MRI has high sensitivity and specificity, making it highly diagnostic[56].

New Diagnostic Advancement

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

Principle

RT-QuIC is an in vitro assay designed to amplify misfolded prion proteins. It uses samples like cerebrospinal fluid (CSF), nasal brushings, or skin, which are combined with recombinant normal prion protein. Through cycles of shaking and incubation, any misfolded prion protein (PrPSc) in the sample acts as a "seed," inducing the misfolding and aggregation of the normal protein. These aggregates are detected in real-time using fluorescent dyes that bind to amyloid-like structures.

Advantages

High Sensitivity and Specificity: RT-QuIC offers sensitivity between 80-97% and specificity of 98-100% for sporadic Creutzfeldt-Jakob disease (sCJD) using CSF samples. Second-generation assays have further improved these metrics[57].

Early Detection

The method can identify PrPSc in the early stages of disease, enabling earlier diagnosis compared to traditional methods based on symptoms or non-specific biomarkers.

Minimally Invasive

CSF from lumbar punctures or olfactory mucosa samples is less invasive than brain biopsies, and skin sample analysis presents an even less invasive option[58].

Differentiation from Other Dementias

RT-QuIC helps distinguish prion diseases from other rapidly progressive dementias, such as autoimmune encephalopathy or Alzheimer's disease, aiding appropriate treatment planning.

Applications

RT-QuIC is now integral to the diagnostic criteria for prion diseases, particularly for "probable" sCJD diagnosis. It is also being explored for diagnosing other prion disorders and potential blood-based screening applications[59].

Treatment

Antisense oligonucleotides (ASOs)

Antisense oligonucleotides (ASOs) are artificially created nucleic acid sequence that specially attach to the messenger RNA (mRNA) of the prion protein (PrP). By doing so, they decrease the production of PrP in the brain. This strategy addresses the underlying cause of prion disease by reducing the levels of the

normal prion protein, which is essential for the development of harmful, misfolded protein forms that lead to nerve cell damage.

Mechanism of action

ASOs work by binding to PrP mRNA, either causing it to be degraded or inhibiting its translation, thereby resulting in decreased brain levels of prion protein. This reduction is critical since prion diseases depend on the intact prion protein to produce the pathogenic, aberrantly folded forms that propagate disease[60].

In animal models, particularly in prion-infected mice, ASO treatment has been reported to significantly prolong survival. Administered preventively, ASOs prolonged survival by 61% to 98%. Even with a single dose administered near the onset of clinical symptoms, survival was extended by approximately 55% (87 days) [61].

The efficacy of ASOs has been seen in several strains of prions and dosing regimens, with treatment initiated early or late after disease onset, suggesting their universal applicability across different scenarios. Crucially, ASO treatment was still effective even after extensive prion-induced brain damage had taken place, and a single dose was sufficient to reverse disease indicators in animal models, which implies that ASOs may even work when given long after the earliest phase of disease[62].

Delivery and Biomarkers

ASOs have been delivered effectively to mice by intracerebroventricular (i.e.) bolus injections, a route that has overcome previous challenges in drug delivery and tolerability[63]. Quantification of prion protein (PrP) in cerebrospinal fluid (CSF) is an effective pharmacodynamics biomarker for the assessment of ASO treatment efficacy, since reductions in CSF PrP indicate interaction with the therapeutic target.

Clinical Development and outlook

The robust genetic evidence in favor of PrP reduction, coupled with promising preclinical data, lays a strong basis for advancing ASO therapies to clinical trials for prion diseases[64, 65]. Researchers are hopeful that these genetically targeted ASO therapies may emerge as the first successful treatments for prion diseases, which are now untreatable and lethal.

Tetracyclic compounds

Tetracycline and Doxycycline in Prion Disease

Mechanism of Action

Tetracycline antibiotics, including tetracycline and doxycycline, have been found to bind directly to the misfolded, disease-associated conformation of the prion protein (PrPSc). In doing so, they reduce the protein's resistance to protease enzymes, thus increasing its degradation. This action has been shown in laboratory experiments as well as in animal models of prion disease[66, 67.]

Studies using Syrian hamsters inoculated with the 263K scrapie strain revealed that when infectious brain homogenate was pre-treated with tetracycline or doxycycline, there was significant delay in the onset of clinical signs and increase in survival over untreated controls. The delay in disease progression was correlated with reduced accumulation of PrPSc in the brain and delayed onset of neuropath logical changes and MRI-detectable abnormalities[68].

Tetracycline administered by peripheral routes (e.g., intramuscular or subcutaneous injection) or intracerebroventricular might also prolong survival in prion-infected animals. For instance, a single dose of doxycycline administered intramuscularly shortly after infection extended median survival by 64%, and repeated administration produced even more significant improvements[69].

Even in advanced disease stages, direct infusion of liposome-encapsulated tetracycline's into the brain at the time of symptom onset resulted in a modest but statistically significant prolongation of median survival, ranging from 8% to 10%[70].

Conclusion

Prion diseases are progressive, lethal neurodegenerative conditions that are particularly challenging due to their rapid nature, poor treatments, and multifaceted transmission mechanisms—ranging from sporadic, inherited, and acquired types, some of which have zoonotic potential. Diagnostic challenges occur because they mimic other dementias clinically, but technologies like RT-QuIC have radically enhanced early and accurate diagnosis by sensitively detecting misfolded prion proteins. Imaging modalities also aid in differentiating prion diseases from other associated conditions. Despite the lack of an approved therapy, promising experimental treatments such as antisense oligonucleotides (ASOs) and tetracycline's are under investigation for their potential to inhibit prion protein production and stability in preclinical models. Ongoing studies of disease mechanisms, transmission, and therapeutic targets are needed. Finally, the combination of new diagnostics and specific therapies has the potential to enhance the outcome for these catastrophic disorders, highlighting the importance of continued scientific and clinical progress.

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