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CREUTZFELDT–JAKOB DISEASE: CURRENT ADVANCES IN DIAGNOSIS, MANAGEMENT AND ONE HEALTH IMPLICATIONS

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Abstract: Creutzfeldt–Jakob disease (CJD) is a rare, rapidly progressive and fatal neurodegenerative disorder caused by the conversion of the normal cellular prion protein (PrPC) into the pathogenic misfolded isoform (PrPSc). The accumulation of PrPSc within the central nervous system results in neuronal degeneration, spongiform change and progressive neurological dysfunction. Sporadic CJD accounts for most reported cases, while genetic, iatrogenic, and variant forms represent less common but clinically significant subtypes. The emergence of variant CJD linked to bovine spongiform encephalopathy highlighted the zoonotic importance of prion diseases and reinforced the need for coordinated surveillance under the One Health framework. Advances in prion biology have substantially improved understanding of disease mechanisms and enabled earlier diagnosis. Sensitive techniques such as real-time quaking-induced conversion (RT-QuIC), cerebrospinal fluid biomarkers, diffusion-weighted magnetic resonance imaging, electroencephalography and **PRNP** genetic testing have enhanced antemortem diagnostic accuracy. Despite these advances, no curative therapy is currently available and management remains primarily supportive. Ongoing research is exploring therapeutic strategies aimed at inhibiting prion propagation, reducing **PRNP** expression, stabilizing native prion protein, and developing immunotherapeutic approaches. This review summarizes current knowledge on the epidemiology, molecular pathogenesis, clinical features, diagnostic advances and emerging therapeutic strategies for CJD, while emphasizing the importance of integrating human and veterinary perspectives to strengthen surveillance, improve early diagnosis and guide future research on prion diseases.
Keywords: Creutzfeldt–Jakob disease, prion disease, Bovine spongiform encephalopathy, RT-QuIC, Surveillance.

1. Introduction

Creutzfeldt–Jakob disease (CJD) is an uncommon, rapidly progressive, and invariably fatal neurodegenerative disorder classified among the human transmissible spongiform encephalopathies (TSEs), a group of disorders caused by prions. Unlike conventional infectious diseases caused by microorganisms containing nucleic acids, prion diseases are uniquely

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mediated by the structural conversion of the normal cellular prion protein (PrPC) into an abnormal, β-sheet-rich, protease-resistant isoform (PrPSc). This pathogenic protein acts as a self-propagating template, inducing further misfolding of native prion proteins, ultimately leading to synaptic dysfunction, neuronal loss, astrocytic gliosis and the characteristic spongiform degeneration of the central nervous system (Prusiner, 1982; Prusiner, 1998; Collinge, 2001; Aguzzi & Calella, 2009). The identification of prions fundamentally transformed the concept of infectious diseases by demonstrating that a misfolded protein, independent of DNA or RNA, can serve as a transmissible infectious agent. This pioneering discovery was recognized with the Nobel Prize in Physiology or Medicine awarded to Stanley B. Prusiner in 1997.

Creutzfeldt–Jakob disease was initially documented by Hans Gerhard Creutzfeldt in 1920 and independently by Alfons Maria Jakob in 1921. The eponym *Creutzfeldt–Jakob disease* was later proposed by Walther Spielmeyer in 1922 (Will, 2003; Geschwind, 2015). Since its first description, CJD has progressed from being regarded as a rare neuropathological entity to becoming a cornerstone in prion research. Investigations into its unique mechanism of protein misfolding have provided valuable insights into the pathogenesis of neurodegenerative disorders and have significantly advanced the understanding of protein aggregation diseases.

Unlike Alzheimer's disease or Parkinson's disease, in which protein aggregation develops over years, CJD progresses rapidly, with most patients experiencing severe neurological deterioration and death within 6–12 months after symptom onset (Collinge, 2001; Geschwind, 2015). Although CJD affects only approximately 1–2 individuals per million population annually, its clinical importance is disproportionate to its incidence because of its devastating prognosis, diagnostic challenges, potential for iatrogenic transmission and public health implications (Will *et al.,* 1996; Mead, 2006; Zerr & Hermann, 2022). Sporadic CJD (sCJD) constitutes approximately 85–90% of all reported cases and occurs without an identifiable cause. The remaining cases comprise genetic CJD associated with pathogenic PRNP mutations, iatrogenic CJD resulting from accidental medical transmission, and variant CJD (vCJD), which emerged following human exposure to bovine spongiform encephalopathy (BSE)-infected cattle products (Collinge, 1999; Mead, 2006; Brown *et al.,* 2012). The global incidence of CJD has remained relatively stable, however, improvements in surveillance systems, physician awareness and advanced diagnostic techniques have contributed to increased recognition and more accurate reporting in many countries (Zerr & Hermann, 2022).

Clinically, CJD is characterized by rapidly progressive dementia accompanied by cerebellar ataxia, myoclonus, visual disturbances, pyramidal and extrapyramidal signs, behavioural abnormalities, and ultimately akinetic mutism. The early clinical manifestations are often subtle and overlap considerably with autoimmune encephalitis, Alzheimer's disease, dementia with Lewy bodies, frontotemporal dementia, metabolic encephalopathies and other causes of rapidly progressive dementia, making timely diagnosis particularly difficult (Geschwind, 2015; Hermann *et al.,* 2021). Consequently, early recognition requires a high index of clinical suspicion supported by characteristic neuroimaging, cerebrospinal fluid biomarkers, electrophysiological findings and molecular diagnostic assays.

From a veterinary and public health perspective, CJD gained unprecedented attention following the emergence of variant CJD during the bovine spongiform encephalopathy (BSE) epidemic in the United Kingdom in the 1990s. The demonstration that BSE could cross the species barrier and infect humans through contaminated beef products fundamentally changed global approaches to food safety, livestock management, feed regulations, disease surveillance, and zoonotic risk assessment (Will *et al.,* 1996; Bruce *et al.,* 1997; Brown & Bradley, 1998). This event remains one of the most compelling examples of the One Health concept, illustrating how animal health, human health, environmental management and food production are intrinsically interconnected. Continuous surveillance of animal prion diseases, including BSE in cattle, scrapie in sheep and goats, and chronic wasting disease in cervids, remains essential for minimizing the emergence of future zoonotic prion diseases (WOAH, 2023; WHO, 2024).

Significant advances during the past decade have transformed the diagnostic landscape of CJD. Recent advances in prion diagnostics have transformed the antemortem detection of CJD. Real-time quaking-induced conversion (RT-QuIC) enables highly sensitive and specific identification of misfolded prion protein, while diffusion-weighted MRI, FLAIR imaging, EEG, cerebrospinal fluid biomarkers (14-3-3 protein, total tau and neurofilament light chain), and **PRNP** genetic testing have collectively improved diagnostic confidence and reduced reliance on postmortem confirmation (Foutz *et al.,* 2017; Green, 2019; Rhoads *et al.,* 2020). Concurrent progress in prion biology has identified promising therapeutic targets, including gene-silencing approaches, antisense oligonucleotides, monoclonal antibodies, and small-molecule inhibitors (Minikel *et al.,* 2020; Vallabh *et al.,* 2020). However, no disease-modifying treatment has yet proven effective, and patient care remains largely supportive. This review provides an updated overview of the epidemiology, molecular pathogenesis, clinical manifestations, diagnostic advances and emerging therapeutic strategies for Creutzfeldt–Jakob

disease. It also revisits the lessons of the bovine spongiform encephalopathy (BSE) epidemic and emphasizes the importance of a One Health approach in strengthening surveillance, promoting early diagnosis, and advancing translational prion research.

2. Epidemiology

Creutzfeldt–Jakob disease (CJD) is the most common form of human prion disease, yet it remains an exceptionally rare neurodegenerative disorder, affecting approximately 1–2 individuals per million population each year worldwide (Will *et al.,* 1996; Mead, 2006; Zerr & Hermann, 2022). Despite its low incidence, CJD is of major clinical and public health concern because of its rapid progression, inevitable fatality and the recognized risks of iatrogenic and in the case of variant CJD, zoonotic transmission.

The global epidemiology of CJD has remained largely consistent, with no marked geographic or sex-related differences in disease occurrence. The increase in reported cases over recent decades is mainly attributed to strengthened surveillance programs, greater clinical awareness, advances in neuroimaging and cerebrospinal fluid (CSF) biomarker analysis and the adoption of highly sensitive diagnostic assays such as real-time quaking-induced conversion (RT-QuIC), rather than a genuine increase in disease incidence (McGuire *et al.,* 2012; Green, 2019; Rhoads *et al.,* 2020). Sporadic CJD predominantly affects older adults between 60 and 70 years of age, whereas variant CJD (vCJD), associated with bovine spongiform encephalopathy (BSE), typically presents in younger individuals (Will *et al.,* 1996; Collinge, 1999). The BSE epidemic transformed the epidemiology of prion diseases by providing the first definitive evidence of food-borne zoonotic transmission, prompting major advances in livestock surveillance, feed regulation, food safety and international disease monitoring. Consequently, CJD is widely regarded as a model disease exemplifying the One Health approach, highlighting the interconnectedness of human, animal and environmental health (Brown & Bradley, 1998; WOAH, 2023; WHO, 2024).

Table 1. Global epidemiological profile of Creutzfeldt–Jakob disease

Parameter	**Description**
Global incidence	1–2 cases per million population annually
Geographic distribution	Worldwide
Most affected age	60–70 years (sporadic CJD)
Median age (variant CJD)	~28 years
Sex distribution	Nearly equal in males and females

Median survival	4–12 months after symptom onset
Predominant subtype	Sporadic CJD (85–90%)
Major zoonotic concern	Variant CJD linked to BSE

Table 2. Epidemiological distribution of human prion diseases

Subtype	**Approximate frequency**	**Epidemiological significance**
Sporadic CJD	85–90%	Most common form; unknown origin
Genetic (Familial) CJD	10–15%	Associated with inherited PRNP mutations
Iatrogenic CJD	<1%	Healthcare-associated transmission
Variant CJD	Rare	Food-borne zoonotic disease linked to BSE

3. Classification of Creutzfeldt–Jakob Disease

Creutzfeldt–Jakob disease is classified into four major clinicopathological forms based on the origin of prion propagation: sporadic, genetic (familial), iatrogenic, and variant CJD (Collinge, 2001; Mead, 2006).

Table 3. Classification of Creutzfeldt–Jakob disease

Subtype	**Frequency**	**Etiology**	**Typical age**	**Clinical significance**
Sporadic CJD (Scjd)	85–90%	Spontaneous PrP misfolding	60–70 years	Rapidly progressive dementia; most common subtype
Genetic CJD (Gcjd/Fcjd)	10–15%	Pathogenic PRNP mutations	40–60 years	Familial disease with variable phenotypes
Iatrogenic CJD (Icjd)	<1%	Medical or surgical transmission	Variable	Preventable through strict infection-control measures
Variant CJD (Vcjd)	Rare	Dietary exposure to BSE	Young adults	Only confirmed zoonotic form of human prion disease

Table 4. Comparative characteristics of CJD subtypes

Feature	**Sporadic**	**Genetic**	**Iatrogenic**	**Variant**
Cause	Spontaneous	**PRNP** mutation	Medical exposure	BSE-contaminated food
Inheritance	No	Autosomal dominant	No	No
Origin	Endogenous	Inherited	Healthcare-associated	Animal-to-human

Zoonotic	No	No	No	Yes
Age at onset	Older adults	Earlier onset	Variable	Younger adults
Public health impact	Moderate	Moderate	High	Very high

4. Clinical Manifestations

Creutzfeldt–Jakob disease (CJD) is a rapidly progressive neurodegenerative disorder characterized by widespread neuronal loss, spongiform degeneration and astrocytic gliosis resulting from the accumulation of misfolded prion protein (PrP^Sc^) (Collinge, 2001; Aguzzi & Calella, 2009). Clinical presentation is heterogeneous and depends on the molecular subtype and neuroanatomical distribution of prion pathology (Parchi *et al.,* 1999; Mead, 2006).

The disease typically begins with subtle cognitive decline, behavioural changes, gait instability, or visual disturbances, followed by rapid progression to dementia, cerebellar ataxia, myoclonus, pyramidal and extrapyramidal signs and ultimately akinetic mutism. Most patients die within 4–12 months of symptom onset, although variant CJD generally follows a longer clinical course (Geschwind, 2015; Hermann *et al.,* 2021; Zerr & Hermann, 2022). Because the early manifestations overlap with several causes of rapidly progressive dementia, a combination of clinical assessment, MRI, EEG, CSF biomarkers, and RT-QuIC is essential for timely diagnosis (Green, 2019; Rhoads *et al.,* 2020).

Table 5. Clinical manifestations of Creutzfeldt–Jakob disease

Clinical domain	Major manifestations	Clinical relevance
Cognitive	Rapidly progressive dementia, memory impairment, executive dysfunction, confusion	Hallmark feature
Behavioural/Psychiatric	Depression, anxiety, apathy, irritability, hallucinations, psychosis	Early and prominent in variant CJD
Cerebellar	Ataxia, dysarthria, dysmetria, gait instability	Common early neurological sign
Visual	Blurred vision, diplopia, visual hallucinations, cortical blindness	Suggests occipital cortical involvement
Motor	Myoclonus, rigidity, bradykinesia, dystonia, tremor	Progressive basal ganglia involvement
Pyramidal	Hyperreflexia, spasticity, Babinski sign	Corticospinal tract dysfunction
Sensory	Paraesthesia, painful dysaesthesia	More frequent in variant CJD
Advanced disease	Dysphagia, akinetic mutism, coma	End-stage neurological deterioration

Table 6. Stage-wise clinical progression of CJD

Stage	Predominant manifestations
Early	Memory impairment, personality change, anxiety/depression, gait imbalance, visual symptoms
Intermediate	Rapid dementia, myoclonus, cerebellar ataxia, dysarthria, pyramidal and extrapyramidal signs
Advanced	Severe cognitive decline, dysphagia, incontinence, akinetic mutism, bedridden state
Terminal	Coma, secondary infections, respiratory complications, death

Table 7. Clinical differences among major CJD subtypes

Feature	Sporadic CJD	Genetic CJD	Iatrogenic CJD	Variant CJD
Typical age	60–70 years	40–60 years	Variable	Young adults
Initial presentation	Dementia	Variable	Cerebellar syndrome	Psychiatric symptoms
Myoclonus	Very common	Common	Common	Less prominent initially
Painful sensory symptoms	Rare	Rare	Rare	Characteristic
Disease duration	4–12 months	Variable	Months	Usually 12–24 months
Public health significance	Sporadic occurrence	Familial disease	Healthcare-associated	Food-borne zoonotic disease

5. Diagnosis

The diagnosis of Creutzfeldt–Jakob disease (CJD) is based on the integration of clinical findings, neuroimaging, cerebrospinal fluid (CSF) biomarkers, prion-specific assays, genetic testing and neuropathological examination. As the early manifestations frequently overlap with other causes of rapidly progressive dementia, diagnosis requires a multimodal approach while systematically excluding reversible neurological disorders (Collinge, 2001; Geschwind, 2015; Zerr & Hermann, 2022).

Recent advances have significantly improved antemortem diagnosis. Real-time quaking-induced conversion (RT-QuIC) is now regarded as the most specific assay for detecting pathological prion protein (PrP^Sc^), whereas diffusion-weighted MRI (DWI) remains the most sensitive imaging modality. Electroencephalography (EEG), CSF biomarkers, and PRNP genetic testing provide valuable complementary evidence, while neuropathological examination with PrP immunohistochemistry remains the definitive diagnostic standard (McGuire *et al.,* 2012; Green, 2019; Rhoads *et al.,* 2020; Hermann *et al.,* 2021).

Table 8. Diagnostic modalities for Creutzfeldt–Jakob disease

Diagnostic test	Characteristic findings	Diagnostic significance
Clinical assessment	Rapidly progressive dementia, myoclonus, cerebellar and visual signs	Initial clinical suspicion
MRI (DWI/FLAIR)	Cortical ribboning; caudate, putamen or thalamic hyperintensity	Most sensitive neuroimaging test
EEG	Periodic sharp-wave complexes (PSWC)	Supportive, particularly in sporadic CJD
CSF biomarkers	Elevated 14-3-3 protein, total tau, NfL, S100B	Evidence of rapid neuronal injury
RT-QuIC	Detection of PrP^Sc^ seeding activity	Most specific antemortem assay
PRNP gene analysis	Pathogenic mutations; codon 129 polymorphism	Confirms inherited prion disease
Neuropathology	Spongiform change, neuronal loss, gliosis, PrP deposition	Gold standard for definitive diagnosis

Table 9. Diagnostic performance of major investigations

Investigation	Major advantage	Limitation
MRI (DWI/FLAIR)	Detects characteristic lesions early	Findings may overlap with other encephalopathies
EEG	Widely available	Lower sensitivity in early disease and variant CJD
CSF biomarkers	Rapid and minimally invasive	Supportive rather than disease-specific
RT-QuIC	Excellent sensitivity and near-perfect specificity	Limited availability in some centres
PRNP testing	Identifies hereditary disease	Limited role in sporadic CJD
Neuropathology	Definitive diagnosis	Usually postmortem or rarely by biopsy

6. Management

Creutzfeldt–Jakob disease (CJD) remains an incurable, rapidly progressive, and invariably fatal prion disorder. As no approved therapy has been shown to halt prion replication or reverse neurodegeneration, current management is centred on early diagnosis, multidisciplinary supportive care, symptom-directed treatment, infection prevention, and timely palliative care (Collinge, 2001; Geschwind, 2015; Zerr & Hermann, 2022).

Symptomatic management aims to improve patient comfort and preserve functional independence. Myoclonus is commonly controlled with clonazepam or sodium valproate, while behavioural and psychiatric manifestations may require carefully selected antidepressants or atypical antipsychotics. Nutritional support, physiotherapy, speech and swallowing rehabilitation, prevention of aspiration pneumonia and psychosocial support are integral components of comprehensive care (Mead, 2006; Green, 2019). As neurological

decline is inevitable, advance care planning and early palliative care should be incorporated soon after diagnosis.

Therapeutic research has shifted towards disease-modifying strategies targeting the underlying molecular pathology. Promising approaches include antisense oligonucleotides (ASOs), PRNP gene silencing, anti-prion monoclonal antibodies, small-molecule stabilizers, and protein misfolding inhibitors. Although these strategies have shown encouraging preclinical results, none has yet demonstrated proven clinical benefit, emphasizing the need for earlier diagnosis and well-designed translational studies (Minikel *et al.,* 2020; Vallabh *et al.,* 2020; Zerr & Hermann, 2022).

Table 10. Contemporary management of Creutzfeldt–Jakob disease

Management domain	Current approach	Primary objective
Early diagnosis	MRI, RT-QuIC, CSF biomarkers, EEG	Prompt diagnosis and counselling
Symptom control	Clonazepam, sodium valproate, selected psychotropic drugs	Relieve neurological and behavioural symptoms
Multidisciplinary care	Nutritional, physical, occupational and speech therapy	Maintain function and quality of life
Supportive care	Dysphagia management, aspiration prevention, pressure sore care	Reduce disease-related complications
Palliative care	Pain control, psychological support, end-of-life planning	Maximize comfort and dignity
Emerging therapies	ASOs, immunotherapy, PRNP-targeted therapies	Disease modification (investigational)

7. One Health Implications

The emergence of variant Creutzfeldt–Jakob disease (vCJD) during the bovine spongiform encephalopathy (BSE) epidemic remains one of the most compelling demonstrations of the One Health paradigm, illustrating how diseases originating in animals can profoundly influence human health, food systems and global public health policies (Will *et al.,* 1996; Bruce *et al.,* 1997; Brown & Bradley, 1998).

The BSE crisis prompted major reforms in animal feed regulations, surveillance programmes, slaughterhouse practices, food-chain safety, and laboratory biosafety, substantially reducing the incidence of both BSE and vCJD (WHO, 2024; WOAH, 2023). Nevertheless, continued occurrence of atypical BSE, scrapie, chronic wasting disease (CWD), and camel prion disease (CPD) highlights the necessity for sustained surveillance and ongoing assessment of interspecies transmission risks (Benestad *et al.,* 2016; CDC, 2024).

Effective control of prion diseases requires coordinated collaboration among veterinarians, clinicians, neurologists, epidemiologists, food safety authorities, wildlife biologists, and public health agencies. Strengthening integrated surveillance, molecular diagnostics, safe tissue handling, wildlife monitoring, and international data sharing will be critical for early detection of emerging prion diseases and for mitigating future zoonotic threats. Consequently, CJD serves not only as a neurological disorder but also as a model for applying One Health principles to the prevention and control of protein-misfolding diseases at the human–animal interface (Collinge, 2001; WHO, 2024).

Table 12. One Health significance of Creutzfeldt–Jakob disease

Domain	Major implication
Veterinary health	Surveillance of BSE, scrapie, CWD and other animal prion diseases
Human health	Early diagnosis, infection control and prevention of iatrogenic transmission
Food safety	Feed regulations, removal of specified risk materials, meat inspection
Wildlife health	Monitoring and containment of chronic wasting disease
Public health	National surveillance, risk communication and international reporting
Research	Development of RT-QuIC, biomarkers and targeted anti-prion therapies
Policy	Integration of veterinary, medical and environmental surveillance under the One Health framework

8. Conclusion

Creutzfeldt–Jakob disease (CJD) remains one of the most devastating human neurodegenerative disorders, distinguished by its unique prion-mediated pathogenesis, rapid clinical progression, and uniformly fatal outcome. Although rare, its scientific significance extends far beyond its incidence, as the discovery of prions has fundamentally transformed our understanding of protein misfolding disorders and continues to shape research into a broad spectrum of neurodegenerative diseases. Over the past two decades, substantial advances in molecular diagnostics, particularly real-time quaking-induced conversion (RT-QuIC), advanced magnetic resonance imaging, cerebrospinal fluid biomarkers, and PRNP genetic analysis, have markedly improved the accuracy of antemortem diagnosis and strengthened global surveillance.

The emergence of variant Creutzfeldt–Jakob disease following the bovine spongiform encephalopathy epidemic demonstrated that prion diseases are not solely neurological disorders but also important One Health challenges at the interface of human health, veterinary medicine, food safety, and environmental surveillance. Sustained monitoring of animal prion

diseases, rigorous infection-control practices, and coordinated international surveillance remain essential to minimize the risk of future zoonotic transmission.

In conclusion, CJD continues to serve as a model disease linking molecular neuroscience, clinical neurology, veterinary science, and public health. Future progress will depend on integrating advances in molecular diagnostics, precision therapeutics, interdisciplinary research, and One Health surveillance. Such collaborative efforts will not only improve the diagnosis and management of CJD but also enhance preparedness against emerging prion diseases and provide valuable insights into the broader mechanisms underlying protein-misfolding neurodegenerative disorders.

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