INFECTIOUS DISEASES AND ZOONOSES

Cite as: Archiv EuroMedica. 2025. 15; 3. DOI 10.35630/2025/15/3.324

Received 16 June 2025;
Accepted 10 July 2025;
Published 15 July 2025

SPONGIFORM ENCEPHALOPATHIES - A THREAT TO HUMANS AND ANIMALS

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ABSTRACT

Introduction and Purpose: Prion diseases, or transmissible spongiform encephalopathies (TSEs), are rare but invariably fatal neurodegenerative disorders affecting humans and animals. These conditions are caused by misfolded prion proteins (PrP^Sc), which induce conformational changes in normal prion proteins (PrP^C), leading to protein aggregation and neuronal damage. This narrative review aims to present and compare major human and animal prion diseases, with particular focus on their etiology, clinical manifestations, diagnostic challenges, treatment limitations, and public health relevance.

Methods: A literature search was conducted in PubMed and Scopus databases using terms such as "prion diseases," "transmissible spongiform encephalopathies," "Creutzfeldt-Jakob disease," "kuru," "GSS," "FFI," "BSE," "scrapie," and "CWD." Publications between 2000 and 2024 were included, with priority given to clinical reviews, official guidelines, and epidemiological reports.

Results and State of Knowledge: The review synthesizes data on prion diseases in humans—such as sporadic and inherited Creutzfeldt-Jakob disease, kuru, Gerstmann-Sträussler-Scheinker syndrome, and fatal familial insomnia—as well as in animals (e.g., BSE, scrapie, CWD). All forms share a common pathogenesis involving pathological protein misfolding and accumulation in the central nervous system. Diagnosis remains difficult due to nonspecific symptoms and limited access to specialized tests such as RT-QuIC. Effective therapy is lacking. Resistance to conventional disinfection methods and the potential for zoonotic transmission present challenges for infection control and public health.

Conclusions: Although rare, prion diseases pose a serious challenge for neurology, epidemiology, and biosafety. Their study provides valuable insights into broader neurodegenerative processes, including Alzheimer's and Parkinson's diseases. Progress in diagnostics, surveillance, and molecular research may offer avenues for future therapeutic strategies.

Keywords: Prions, transmissible spongiform encephalopathies, Creutzfeldt-Jakob disease, kuru, GSS, FFI, BSE, scrapie, CWD, protein misfolding, neurodegeneration, zoonoses, RT-QuIC, PRNP.

1. INTRODUCTION

Spongiform encephalopathies, also known as transmissible spongiform encephalopathies (TSEs), are a group of rare, always fatal neurodegenerative diseases that affect the brain and nervous system of mammals include: Creutzfeldt-Jakob disease (CJD), Gerstmann-Sträussler-Scheinker syndrome (GSS), familial fatal insomnia (FFI), kuru and, in animals, bovine spongiform encephalopathy, scrapie and chronic wasting disease in deer [1].

These diseases are caused by prions - proteins with an abnormal structure that can induce a change in the structure of other normal prion proteins; they do not multiply in the classic way like bacteria or viruses. Prions cause disease by changing the shape of other proteins rather than by replicating genetic material. In the neurons of mammals, including humans, there is naturally present a protein called PrP^C, the exact function of which is not fully understood, but it is not in itself harmful. The PRNP gene, which encodes the PrP^C protein, is located on chromosome 20. The protein is made up of amino acids and its alpha-helix secondary structure is crucial for its proper function. Prions, such as PrPSc (the pathological form of the protein), have an identical primary structure (same amino acid sequence) to the normal PrP^C protein, but differ in spatial structure. PrP^Sc more often adopts a beta-harmonic form instead of an alpha-helix. When PrP^Sc encounters healthy PrP^C, it causes it to transform into an abnormal form, leading to the development of prion disease [1, 2, 4].

When it was first suggested that the infectious agent causing neurodegenerative disorders of the central nervous system in animals and humans might be simple protein molecules, this was met with much scepticism. In the 1960s, J.S. Griffith argued that some transmissible spongiform brain diseases, such as spongiform encephalopathies, are caused by infectious proteins.

In 1982, Stanley B. Prusiner of the University of California isolated infectious material from infected animals that consisted solely of proteins. Prusiner introduced the name “prions” (infectious protein molecules) for these molecules. For his research and formulation of the revolutionary theory that prion proteins are infectious in nature, Prusiner was awarded the Nobel Prize in Medicine in 1997. Despite this, many researchers could not accept that an infectious agent consisting solely of a protein could act without genetic material [3].

Research on prions has shown that these molecules are not only found in higher organisms. In 1997, it was discovered that prion-like proteins are also found in fungi, such as Podospora anserina [5].

Prion diseases fall into three categories depending on how they are acquired. Sporadic diseases (e.g. Creutzfeldt-Jakob disease) occur randomly. Genetic diseases (e.g. Gerstmann-Sträussler-Scheinker syndrome) result from mutations in the prion protein gene. Acquired diseases (e.g. kuru, a variant of Creutzfeldt-Jakob disease) are transmitted by infected biological material; fatal insomnia can occur both familially and spontaneously. Prion diseases are rare, the most common being Creutzfeldt-Jakob disease (CJD), with a prevalence of 1-1.5 per million people. The sporadic form occurs in 90% of cases. The familial form is rarer and accounts for up to several per cent of cases [4, 6].

Prions are extremely resistant infectious agents that require specialised procedures for effective inactivation. According to the According to the WHO Infection Control Guidelines for Transmissible Spongiform Encephalopathies (2003), standard disinfection methods such as formaldehyde or alcohol-based solutions are ineffective and may even stabilize prion proteins, increasing the risk of transmission. The CDC Infection Control Recommendations for Prion Diseases (2022) and European Food Safety Authority (EFSA) Panel on Biological Hazards Opinion (2017) recommend incineration of contaminated materials at ≥1000°C, autoclaving at 134°C for at least 18 minutes (or 60 minutes at 121°C) combined with 1N sodium hydroxide or sodium hypochlorite, and the use of strong protein-denaturing agents. WHO specifically warns against the use of glutaraldehyde and steam sterilization under standard hospital conditions. Alternative chemical treatments, such as 2N NaOH or 20,000 ppm available chlorine, may be used for immersion of reusable instruments under strictly controlled protocols. These recommendations aim to minimise the risk of iatrogenic transmission, particularly during neurosurgical procedures or handling of high-risk tissues.[7, 29, 44, 45, 46].

Transmissible spongiform encephalopathies (TSEs) are rare but invariably fatal disorders that continue to pose diagnostic and epidemiological challenges. Although several individual reviews have addressed specific forms such as CJD or BSE, few recent publications have provided a comprehensive comparison of major prion diseases in both humans and animals. Moreover, the incorporation of novel diagnostic methods such as RT-QuIC and current WHO recommendations has not yet been systematically integrated into a broad clinical overview. This review aims to fill this gap by summarizing current knowledge and highlighting developments in diagnosis, prevention, and classification.

AIMS

The aim of this article is to review and compare the most important human and animal prion diseases, with particular attention to their etiology, modes of transmission, clinical manifestations, diagnostic approaches, and current strategies for prevention. This narrative review also highlights recent developments such as the implementation of RT-QuIC and international biosafety recommendations, providing an integrated perspective for clinicians and

researchers.

2. METHODS

This article is a narrative review of the literature on transmissible spongiform encephalopathies in humans and animals. The authors searched PubMed and Scopus databases for English-language publications using keywords such as "prion diseases", "Creutzfeldt-Jakob disease", "kuru", "Gerstmann-Sträussler-Scheinker syndrome", "bovine spongiform encephalopathy", and "chronic wasting disease". Relevant studies, reviews, clinical guidelines, and official documents published between 2000 and 2024 were included. Particular attention was paid to epidemiology, clinical presentation, diagnostic tools, and preventive strategies. Articles not directly related to TSEs or without accessible full texts were excluded.

CONTENT OF THE REVIEW

3. OVERVIEW OF HUMAN TRANSMISSIBLE SPONGIFORM ENCEPHALOPATHIES (TSES)

3.1. CREUTZFELDT-JAKOB DISEASE (CJD)

3.2. KURU DISEASE

3.3. GERSTMANN-STRÄUSSLER-SCHEINKER SYNDROME (GSS)

3.4. FATAL FAMILIAL INSOMNIA (FFI)

3.1. CREUTZFELDT-JAKOB DISEASE (CJD)

Creutzfeldt-Jakob disease (CJD) is a fatal neurodegenerative disorder caused by the accumulation of an abnormal prion protein isoform (PrP^Sc) in the CNS. It is among the most common prion diseases, also known by the term spongiform encephalopathies. It inevitably leads to death within a few months of the appearance of the first clinical signs, which include neurological, psychiatric and cognitive symptoms. Due to the heterogeneous clinical picture, patients may present with motor deficits, visual disturbances, depressive disorders, as well as anxiety and dementia [8]. CJD is a kind of challenge in medicine due to the difficulty in diagnosis. Due to the non-specific clinical picture of CJD, the disease can be misdiagnosed or undiagnosed for a long time. Diagnosis is complicated and requires the exclusion of other neurological conditions with a similar course. These include subarachnoid haemorrhage, encephalitis, acute ischaemic stroke, multi-infarct dementia, brain tumours and paraneoplastic neurological syndromes. In addition, differentiation with other forms of dementia, including Alzheimer's disease, is necessary. Despite the fatal nature of the disease, its correct diagnosis is crucial to prevent iatrogenic transmission of pathogens, particularly through tissue grafts such as sclera and cornea and the use of inadequately sterilised neurosurgical instruments [9].

Classification

The pathogenesis of Creutzfeldt-Jakob disease is associated with the deposition of a pathological form of prion protein (PrP^Sc), which is a conformationally altered version of the physiological PrP^C protein, within the central nervous system. Nevertheless, the detailed mechanisms leading to neurodegeneration are still incompletely understood [8]. There are several forms of Creutzfeldt-Jakob disease (CJD), which differ in aetiology and mechanism of onset.

Table 1 shows the key differences between sporadic, hereditary and iatrogenic forms of Creutzfeldt-Jakob disease.

Table 1. Comparison of Creutzfeldt-Jakob Disease Forms

Form	Etiology / Transmission	Key Clinical Features	Survival	Diagnostic Clues
Sporadic CJD (sCJD)	Spontaneous misfolding of PrP^{Sc}	Rapidly progressive dementia, myoclonus, ataxia	~6 months	PSWC on EEG, DWI hyperintensities, RT-QuIC positive

Genetic CJD (fCJD)	PRNP mutation (autosomal dominant), codon 129	Younger onset, slower course; overlaps with sCJD or GSS	Variable	Family history, PRNP gene testing
Iatrogenic CJD	Medical procedures (e.g., dura mater grafts, hGH)	Similar to sCJD; latency months to decades	Variable	History of neurosurgery or hormone therapy
Variant CJD (vCJD)	Ingestion of BSE-infected beef	Early psychiatric symptoms, delayed neurological signs	~14 months	PrP^{Sc} in lymphoid tissue, MM at codon 129

Each of these forms leads to irreversible neurodegeneration, characterised by rapid progression and a fatal course [10, 11].

Clinical picture and course of disease

Creutzfeldt-Jakob disease (CJD) is characterised by a rapid and progressive course that can be divided into three main stages. Initially, non-specific symptoms such as mood, memory, vision or behavioural disturbances appear. In the next phase, there is rapid cognitive deterioration, myoclonus and typical EEG changes (PSWC), and DWI MRI often shows characteristic hyperintensities in the cortex and striatum. In the final stage, akinetic mutism develops and death usually follows complications such as infections or respiratory failure [10].

The clinical picture of sCJD varies, due in part to the polymorphism of the PRNP gene at codon 129 (MM, MV, VV) and the type of PrP protein deposited (type 1 or 2) [12]. The classic symptoms of sCJD (it occurs most frequently) include rapidly increasing dementia, ataxia and myoclonus. The disease has a very rapid course, with an average survival time of about six months and more than 90% of patients dying within a year of the onset of first symptoms. It most commonly presents in the seventh decade of life. Diagnosis is based on clinical characteristics supported by imaging studies, EEG and modern biochemical tests such as RT-QuIC [13].

Diagnostics

Definitive confirmation of CJD requires detection of pathological prion protein (PrP^Sc) in the brain, usually post-mortem or by biopsy, which makes diagnosis difficult during life. MRI, EEG and cerebrospinal fluid (CSF) examinations are used for supportive diagnosis, but do not provide a confident diagnosis on their own. A breakthrough has been made with RT-QuIC tests, which detect the presence of PrP^Sc in CSF and nasal mucosa with high sensitivity (96-97%) and specificity (100%), enabling the diagnosis of CJD while the patient is still alive [13].

The EEG often reveals characteristic periodic sharp wave complexes (PSWCs), which are present in the majority of sCJD patients and are rarely seen in other dementing diseases, making it a useful tool in differential diagnosis [14].

Treatment

Currently, no curative therapy exists for Creutzfeldt-Jakob disease (CJD). Management is primarily symptomatic and supportive. For example, clonazepam may be used to alleviate myoclonus. Although one clinical study reported cognitive improvement following flupirtine administration, subsequent trials have not confirmed its efficacy. Other investigational agents such as doxycycline, quinacrine, and pentosan polysulfate have also been explored, but none have demonstrated consistent clinical benefit.

Prevention

In the context of prion diseases such as CJD, rigorous preventive measures are essential to avoid accidental transmission of infectious material. This includes strict sterilisation protocols for surgical instruments, particularly in neurosurgery and ophthalmology, and careful screening of donor tissues and blood products. According to WHO and CDC guidelines, the use of disposable instruments and incineration is recommended when prion contamination is suspected. Adherence to established infection control procedures significantly reduces the risk of iatrogenic transmission.

3.2. KURU DISEASE

Medical history

Kuru is the first prion disease discovered in humans. It was described in 1957 by Daniel Carleton Gajdusek and Vincent Zigas, who were working in Papua New Guinea. In 1976, Gajdusek was awarded the Nobel Prize in Medicine for his findings [15].

The disease was mainly found among the Fore people, living in the Eastern Highlands region of Papua New Guinea. The word kuru in their language means "shivering due to cold or fever" [16, 17].

Kuru primarily affected women and children due to the local practice of endocannibalism — the ritual consumption of deceased family members. These groups were more likely to participate in such rites, often consuming brain tissue, which contained the highest concentrations of infectious prions. The epidemic began to decline after colonial authorities banned cannibalism in the 1950s. Epidemiological studies later provided definitive evidence linking kuru to this practice.

Initially, it was thought that the disease could be the result of hysteria, genetics or the action of witchcraft. In 1959, William Hadlow noted the similarities between scrapie and kuru and suggested that Gaidusek experiment with transmitting the disease to animals [17, 18].

In the 1960s, Gajdusek conducted an experiment in which he inoculated chimpanzees with infectious material from people who had died of kuru. The experiment aimed to understand the mechanism of transmission of this prion disease, which was prevalent in Papua New Guinea. The research showed that the prions responsible for kuru could be transmitted to animals, providing important evidence of the infectivity of prion diseases. The results helped to further investigate prions and their role in causing diseases such as kuru, Creutzfeldt-Jakob disease and bovine spongiform encephalopathy. It is noteworthy that animals of other species, such as sheep, goats, and pigs, were also experimentally inoculated, all of which proved to be completely resistant to infection [18,19].

Between 1957 and 1961, approximately 1,000 deaths from kuru were recorded, with a total of over 2,700 deaths by the early 21st century. Due to its exceptionally long incubation period — often exceeding 50 years — isolated cases continued to appear for decades. A study conducted between 1996 and 2004 identified 11 new cases, some with incubation periods longer than 50 years. The last known death occurred in 2005, and no new cases have been reported since [17, 47].

Symptoms

Kuru is an incurable and fatal neurodegenerative disease categorised as a transmissible spongiform encephalopathy (TSE), characterised by progressive damage to the nervous system, with only symptomatic treatment and palliative care possible. Typical symptoms include cerebellar ataxia (impaired motor coordination), tremor of the limbs, choreic and athetotic movements, and emotional changes - uncontrolled laughter has often been observed in patients, hence the disease has come to be known as the "laughter disease" [15, 17].

Kuru disease progresses in three main stages. In the initial gait (ambulatory) stage, the patient is still able to move independently, but the first neurological symptoms appear, such as gait instability, ataxia, tremors and impaired coordination of movements. These are accompanied by emotional changes - euphoria, anxiety, depression - and cerebellar symptoms, including nystagmus, dysarthria, intention tremor and clonus. In the sedentary stage, the patient loses the ability to walk and sit independently, and needs assistance with daily functioning. Neurological symptoms such as tremors, dystonia, jerky eye movements, hyperreflexia and markedly exaggerated reflexes increase. In the final stage, the patient is completely immobilised, unresponsive to his surroundings, although he may be conscious. Swallowing disorders, incontinence, muscle rigidity, contractures, athetosis and mild signs of dementia are present. Death usually occurs within 9-24 months of the onset of symptoms, usually as a result of complications such as pneumonia or wound infections [17,18, 19].

TABLE 2 ILLUSTRATES THE PROGRESSION OF KURU DISEASE, DIVIDING ITS COURSE INTO EARLY, MIDDLE AND ADVANCED PHASES.

Table 2. Stages of Kuru Disease

Stage	Functional Status	Symptoms
Ambulatory	Patient can walk independently	Ataxia, tremor, mood changes, dysarthria, nystagmus
Sedentary	Cannot walk/sit without help	Tremors, dystonia, hyperreflexia, exaggerated reflexes
Terminal	Immobile, unresponsive	Dysphagia, contractures, incontinence, infections, mild dementia

Macroscopic and microscopic changes in the brain

Macroscopically, the brain of a Kuru patient may not show obvious changes, but microscopic examination reveals a characteristic picture of spongiform degeneration. Neuronal atrophy and the presence of numerous vacuoles in nerve

cells are evident. Also typical are so-called kuru plaques - amyloid deposits 20-60 μm in diameter, particularly numerous in the cerebellum, basal ganglia and cerebral cortex. Astrogliosis, or proliferation and hypertrophy of the stellate glium in response to neural tissue damage, is also observed. Throughout the brain's gray matter, there are spongiform lesions - numerous tiny holes that give the tissue the appearance of a sponge. Immunohistochemical studies show the presence of a pathological form of the prion protein PrP^Sc in the form of deposits and within synapses and around neurons [15, 17 ,18].

Kuru and Alzheimer's

Both prion diseases, such as kuru, and neurodegenerative diseases, including Alzheimer's disease, share a common feature — the pathological aggregation of proteins in the form of amyloid. Although kuru is an infectious disease associated with prions (proteins capable of self-replication by inducing conformational changes in other proteins), and Alzheimer's disease is not, both are driven by a shared molecular mechanism: the misfolding of proteins leading to the formation of stable, toxic amyloid structures.

Protein misfolding diseases are characterized by long incubation periods, lack of immune response, resistance of deposits to degradation, and incurable progression [20]. The identification of amyloid as a unifying factor — initiated by studies of kuru and scrapie — has opened a new direction in the study of neurodegenerative conditions [20]. Despite differences in etiology, both prion and non-prion neurodegenerative diseases share this molecular basis, making them a common focus of research interest [20].

Recent findings suggest that in disorders such as Alzheimer's, amyloid aggregates may propagate through prion-like mechanisms, where misfolded proteins act as seeds that induce pathological folding in otherwise normal proteins [49].

This process, known as "templated misfolding" and initially described in prion diseases, is now also recognized in Alzheimer's, where the normal prion protein (PrP^C) is structurally transformed into its pathogenic isoform (PrP^Sc) [50].

For this reason, further research into the mechanisms of amyloid formation and potential strategies to inhibit it is essential, as it may pave the way for effective therapies against many devastating neurological diseases [20].

3.3. GERSTMANN-STRÄUSSLER-SCHEINKER DISEASE (GSS)

Etiology and pathogenesis

Gerstmann-Sträussler-Scheinker disease (GSS) is one of the rare prion encephalopathies inherited autosomal dominantly. The etiology of GSS is associated with a mutation in the PRNP gene located on the short arm of chromosome 20 encoding the prion protein. The most commonly described mutation is P102L (substitution of proline for leucine). Other mutations have been identified, such as A117V, which can also lead to the disease. Some cases may result from de novo mutations, but most are familial. GSS most often manifests between the ages of 50 and 60, with an estimated incidence of 1 to 10 cases per 100 million people [21, 22, 23].

Clinical picture

Gerstmann-Sträussler-Scheinker disease (GSS) exhibits a wide spectrum of clinical phenotypes. The early stage of the disease can manifest as numbness, seizures, deafness and psychiatric disorders in the form of depression. In the advanced stage, cerebellar and cognitive disorders appear [21].

Diagnosis

Gerstmann-Sträussler-Scheinker (GSS) disease presents a diagnostic challenge due to its clinical heterogeneity, lack of characteristic features on imaging studies and often equivocal family history. GSS should be considered in patients with unexplained ataxia, especially in cases of cognitive decline, even in the absence of a positive family history. The diagnosis of GSS cannot be made on the basis of laboratory and imaging studies. The presence of the PRNP gene mutation is a sensitive and highly specific test [22].

Additional tests have limited diagnostic value. EEG shows nonspecific slowing of bioelectrical brain function. Cerebrospinal fluid (CSF) examination results show no abnormalities; in some cases, there may be elevated levels of 14-3-3 protein or tau, but this marker is not characteristic of the disease. Magnetic resonance imaging (MRI) in some patients may reveal areas of reduced T2 signal in the striatum and midbrain. In contrast, it is not a suggestive test for the diagnosis of GSS [23].

Treatment and management

Currently, there is no effective causal treatment for Gerstmann-Sträussler-Scheinker disease. Therapeutic management is based on symptomatic treatment, as well as comprehensive care provided by a multidisciplinary team of specialists, including neurologists, psychiatrists, physiotherapists, occupational therapists, speech therapists and social workers.

Due to the rapidly progressive nature of the disease, it is necessary to regularly monitor the patient's condition, usually at two-week intervals. This assessment allows ongoing adjustment of symptomatic treatment and support, according to the patient's changing needs. It is also worthwhile to provide support to the patient's family.

Symptomatic treatment may include the administration of antidepressants for depression and psychosis. Clonazepam is used for myoclonus, dopaminergic drugs for muscle rigidity, and antispastic drugs for current spasticity [22, 23].

Prognosis

GSS is a slowly progressive disease that usually lasts from several months to 10 years. It eventually causes severe disability and eventually death [23]. The severity of symptoms shows considerable variability both between different families and within the same family. Differences in phenotype may be due to differences in the type of mutation of the PRNP gene. These factors can affect the rate of disease progression and patient prognosis. P102L mutation carriers homozygous for Met129 usually show an earlier onset of symptoms and a shorter survival time. In contrast, patients with the P102L mutation and Val129 configuration have a slower disease course, sometimes with dominant ataxia and later development of dementia [22].

Table 3 outlines the key clinical, genetic and diagnostic features of Gerstmann-Sträussler-Scheinker syndrome (GSS), allowing a comprehensive view of the characteristics of this rare neurodegenerative disease.

Table 3. Key Clinical, Genetic, and Diagnostic Features of Gerstmann-Sträussler-Scheinker Syndrome (GSS)

Category	Description
Inheritance	Autosomal dominant (rare de novo mutations reported)
PRNP Mutations	Most common: P102L; others include A117V and additional rare variants
Typical Age of Onset	50–60 years
Initial Symptoms	Paresthesias, depression, seizures, deafness (may precede ataxia)
Main Clinical Features	Cerebellar ataxia, progressive dementia, dysesthesias, proximal muscle weakness
Diagnostic Method	Genetic testing (PRNP sequencing); family history often inconclusive
EEG Findings	Non-specific slowing of brain electrical activity
CSF Findings	Usually normal
MRI Findings	Often inconclusive; may show T2 signal reduction in striatum or midbrain
Management	Symptomatic and supportive care by multidisciplinary team
Survival Time	Ranges from several months to 4 years; up to 10 years in rare cases

3.4. FATAL FAMILIAL INSOMNIA (FFI)

Fatal familial insomnia (FFI) is a rare, incurable prion disease with autosomal dominant inheritance. It is characterized by aggressively progressive insomnia accompanied by autonomic nervous system dysfunction, cognitive deficits, motor system symptoms and endocrine disorders [24]. To date, no therapeutic regimens have been developed beyond symptomatic treatment and palliative care [25].

History of discovery

FFI was first described in 1765, and then Lugaresi E et al. described it as a disease entity in 1986.Symptoms were observed in one family from the Veneto region of Italy. The disease manifested in members of this family usually in the 4th-5th decade of life, beginning with progressive insomnia. Sleep deprivation quickly led to mood and behavioral disorders and severe neurodegeneration [24, 26].

Epidemiology

Currently, it is estimated that there are about 30 families (about 100 individuals) worldwide diagnosed with Fatal Familial Insomnia (FFI) or who carry the mutation in the PRNP gene that leads to the disease. Cases of FFI have been documented in Europe, America, Japan, China and Australia, although the disease remains extremely rare and referred to as an "orphan disease" [26]. There has been an increase in cases in recent years, particularly in China. A total of 131 patients with FFI have been reported, including 57 females and 72 males, with a mean age of onset of 47.5 years, (age of symptom onset has been reported in the range of 17-76 years) [24]. Although the risk of FFI in the general population is estimated at about 1 in 30 million, in families with a history of the disease, where inheritance is autosomal dominant, the risk to the child is 50% [26].

Etiology and pathogenesis

Fatal familial insomnia (FFI) is inherited autosomal dominantly, caused by the D178N mutation in the PRNP gene, which encodes the PrP^C prion protein. The change is associated with the presence of methionine at codon 129, which affects the course of the disease. This mutation leads to a shorter disease course than the presence of valine at the same position [24, 25].

FFI is characterized by neuropathological changes such as neuronal and glial loss, especially in the thalamus, which is responsible for sleep regulation, sensory and motor functions. These changes spread to other areas of the brain, which explains the varied clinical manifestations, including sleep disturbances and autonomic dysfunction. The thalamus is most severely affected by the changes, and later extends to other brain regions, such as the parietal, temporal and frontal lobes. The pattern of prion protein deposition in the brain favors the initial involvement of the brainstem and thalamus, which may explain the specific symptoms of the disease [24].

Clinical picture

There are four clinical stages in the course of the disease, leading from mild symptoms to complete dependence and lack of contact with the environment [25]. Organic sleep disorders are characteristic, such as progressive, treatment-resistant insomnia, agrypnia excitata (sometimes with laryngeal stridor), sleep apnea and restless sleep with involuntary movements. Neurological and psychiatric symptoms are also present, including rapidly increasing dementia, ataxia, myoclonus, hallucinations, delusions and personality changes, as well as depression, anxiety, apathy and disorientation. The disease is also accompanied by increasing autonomic dysfunction, including hypertension, tachycardia, respiratory distress, hyperthermia, excessive sweating and significant weight loss (more than 10 kg in 6 months) [24].

The results are shown in Table 4 according to the clinical stages of fatal familial insomnia (FFI), showing the characteristic symptoms and changes occurring at each stage of the disease.

Table 4. Clinical Stages of Fatal Familial Insomnia (FFI)

Stage	Clinical Features
Stage I	Progressive insomnia, anxiety, panic attacks, phobias
Stage II	Worsening insomnia, hallucinations, agitation, weight loss
Stage III	Complete insomnia, autonomic dysfunction (tachycardia, hypertension, hyperthermia)
Stage IV	Profound dementia, mutism, complete dependence, coma-like state

Diagnostics

Diagnosis of FFI is made on the basis of clinical symptoms, but diagnostics are additionally performed to confirm the diagnosis and exclude other diseases

Instrumental methods

Polysomnography (PSG) shows disturbed sleep architecture in the form of: loss of slow-wave (N3) and REM sleep, absence of sleep spindles and presence of dreams in abnormal phases. Magnetic resonance imaging (MRI) and computed tomography (CT) scans are of limited value, but may show cerebellar atrophy and ventricular dilation. Flvorodeoxyglucose positron emission tomography (FDG-PET) reveals hypometabolism in the thalamus and cortex of the rostral cingulate, which is characteristic of FFI. Areas of hypometabolism overlap topographically with regions of PrP^Sc deposition. Electroencephalogram (EEG) usually reveals a generalized slowing of brain bioelectrical activity. Periodic sharp wave complexes, which are more commonly present in CJD, are not observed.

Biochemical markers

Investigations should begin with a baseline morphology, liver function tests, ammonia levels and blood cultures to rule out bacterial infection. Diagnosis of reversible causes of cognitive decline should include function tests, vitamin B12 levels, folic acid. In addition, tests for neuroblastoma and HIV. Cerebrospinal fluid testing for 14-3-3 protein is not specific, as it may be present in other diseases

Genetic analysis

Confirmation of the D178N mutation in the PRNP gene is important in the diagnosis of FFI.

Histology

Histopathologic examination, which is rarely used, can show severe lesions of the thalamic nucleus and inferior olivaries with associated astrogliosis, neuronal loss and metabolic brain abnormalities. It is also useful to exclude other neurological diseases [24, 26].

Treatment and Experimental Approaches

Currently, treatment of FFI is purely symptomatic and palliative, as there is no effective therapy to eliminate the pathological prion protein. Symptomatic treatment is focused on alleviating insomnia, psychotic symptoms and autonomic disorders. Patients usually respond poorly to classic sedative drugs, including barbiturates and benzodiazepines, which can even exacerbate symptoms of confusion, memory impairment and insomnia [25].

The literature describes a trial of gamma-hydroxybutyrate (GHB) that induced slow-wave sleep (SWS) in one patient. This is a single case report, so it does not allow this method to be considered effective.

The experimental treatment included the administration of pentosan polysulfate, quinacrine and amphotericin B. Unfortunately, clinical data are limited and inconclusive. They do not allow an assessment of efficacy.

In preclinical studies, immunotherapy has shown promise, especially approaches based on vaccines targeting the misfolded form of the prion protein (PrP^Sc), dendritic cell vaccines and adoptive transfer of PrP-specific CD4(+) T cells. Results in animal models are promising, but confirmation of efficacy and safety in humans is still lacking [24].

Prognosis

The typical duration of FFI ranges from 7 to 36 months, with an average of 18 months. Population-based studies show a shorter mean survival time in Met-Met patients (12 ± 4 months) than in Met-Val patients, (21 ± 15 months) [25].

The differentiating features of the three main forms of human prion encephalopathies - SSE, sCJD and FFI - including clinical manifestations, genetic conditions and disease course characteristics are grouped in Table 5.

Table 5. Distinguishing Features of Gerstmann-Sträussler-Scheinker Syndrome, Sporadic Creutzfeldt-Jakob Disease, and Fatal Familial Insomnia

Feature	GSS	sCJD	FFI
Age of Onset	50–60	60–70	~50
Inheritance	Autosomal dominant	Sporadic	Autosomal dominant
Key Mutation	PRNP P102L	None	PRNP D178N + M129
Early Symptoms	Ataxia	Dementia	Insomnia, dysautonomia
EEG	Nonspecific	PSWC	Normal/slowing
MRI	Often unremarkable	Cortical hyperintensity	Thalamic changes
Course	Slowly progressive	Rapid	Subacute
Survival	1–10 years	~6 months	~12–18 months

The following data illustrate the comparative clinical and genetic features of Gerstmann-Sträussler-Scheinker syndrome (GSS), sporadic Creutzfeldt-Jakob disease (sCJD) and fatal familial insomnia (FFI), highlighting their similarities and diagnostic differences.

Table 6. Comparative Clinical and Genetic Features of GSS, sCJD, and FFI

Feature	Gerstmann-Sträussler-Scheinker Syndrome (GSS)	Sporadic Creutzfeldt-Jakob Disease (sCJD)	Fatal Familial Insomnia (FFI)
Inheritance	Autosomal dominant	Sporadic (rarely inherited)	Autosomal dominant
PRNP mutation	P102L (most common), A117V, others	None (in sporadic form)	D178N + M129M genotype
Typical age of onset	50–60 years	60–70 years	~50 years
Initial symptoms	Ataxia, paresthesias, deafness, depression	Rapidly progressive dementia, myoclonus	Insomnia, autonomic dysfunction
Clinical course	Slowly progressive	Rapidly progressive	Subacute
Survival	1–10 years	~6 months	7–36 months
EEG findings	Non-specific slowing	PSWCs (in ~70% of cases)	Often normal or mildly slowed
MRI findings	Often inconclusive	Cortical ribboning, basal ganglia hyperintensity	Thalamic hypometabolism (PET), subtle DWI changes
CSF findings	Usually normal	Positive 14-3-3, elevated tau	Usually normal

4. PRION DISEASES IN ANIMALS

The aforementioned prion diseases affecting humans are not the only spongiform encephalopathies we face. Animals of many species can also be attacked by prions, resulting in the formation of a spongiform brain structure and physical and functional degeneration of the central nervous system. This is accompanied by a range of symptoms, such as clumsiness of movement, tremors, dementia, insomnia, aggression or paralysis. In all cases, the disease ends in death.

Among the various animal prion diseases, bovine spongiform encephalopathy (BSE), scrapie, and chronic wasting disease (CWD) have received particular attention due to their historical impact, wide geographic spread, or potential implications for public health. These diseases also differ in their affected species, modes of transmission, and surveillance challenges, making them representative examples for illustrating the broader spectrum of animal transmissible spongiform encephalopathies (TSEs). By focusing on these three conditions, this section aims to highlight key epidemiological and diagnostic aspects relevant both to veterinary medicine and to One Health strategies [27].

Differences between the various disease entities include the length of the incubation period. Diseases such as fatal familial insomnia, Gerstmann-Sträussler-Scheinker syndrome and Kuru are very rare and, despite their tragic nature, have little social significance globally. The situation is different when prion diseases affect animals. They usually involve large livestock populations, leading to mass slaughter, a decline in consumer confidence in food producers and the closure of export markets. This was the situation in the UK in the 1990s with the BSE epidemic [27, 32].

Another problem, especially with chronic wasting disease in deer (CWD), is that there is very limited control over its spread. Prions can persist in the environment for years, and wild animals migrate long distances, spreading the disease to ever-widening areas. As a result, deer populations are being reduced, both as a result of the disease itself and sanitary culls being introduced [7, 28}.

Although the disease entities in question affect animals, their consequences are not limited to the livestock or conservation sectors. Due to the consumption of meat (e.g., beef) contaminated with prions, the health consequences can also affect humans, as was clearly demonstrated during the aforementioned outbreak of bovine spongiform encephalopathy [32].

BOVINE SPONGIFORM ENCEPHALOPATHY (BSE)

History and epidemiology

The epidemic of bovine spongiform encephalopathy (BSE), commonly known as mad cow disease, began in Britain in the 1980s. Although isolated cases may have occurred earlier, it was at this time that a surge in cases began to be observed. The peak of the epidemic was in 1992 and 1993, when record numbers of cases of the disease were reported [27, 29].

It has been established that the main mechanism for the spread of BSE was feeding cattle meat and bone meal made from the remains of other cows, including individuals already infected with BSE prions. However, it is not entirely clear where the prions in this meal originally came from. There are several theories attempting to explain the genesis of the outbreak. The most common assumes that the source was sheep sick with scrapie, a prion disease found in these animals. According to this hypothesis, the meat and bone meal was initially made from sheep leftovers, and the prions responsible for scrapie underwent interspecies transformation, adapting to the cattle body [29].

It is worth adding that, if this theory is true, there has been further diversification of prions from scrapie to BSE in the organisms of different species since the transition. Interestingly, scrapie samples from pre-1975 and post-1990 sheep given to cattle under experimental conditions produced different clinical signs, but none of these forms resembled classical BSE [30].

An alternative theory is that the prions responsible for BSE already existed in cattle, but in a very limited way, and it was only the use of tissues from infected animals to produce meal that caused the rapid spread of the disease [33].

After 1992, the number of new cases began a steady decline. This was directly related to the discovery of the mechanism of the spread of BSE and the introduction of strict regulations prohibiting the feeding of meat and bone meal to ruminants in the UK. Drastic measures were taken to combat the epidemic - more than two million cattle suspected of coming into contact with infected individuals or fed the banned meal were culled, even if the animals showed no signs of disease [32].

CLINICAL AND PATHOLOGICAL SIGNS

BSE disease manifests with central nervous system problems that are often difficult to diagnose and are characterized by nonspecific symptoms, such as decreased milk yield, weight loss, anxiety, ataxia of the pelvic limbs and hypersensitivity to sensory stimuli (auditory, visual, tactile). Other symptoms may include bradycardia and decreased rumination, suggesting disturbances in autonomic innervation. The differential diagnosis should exclude other diseases of the central nervous system, such as rabies, which has a shorter clinical course. Cerebrospinal fluid analysis in cattle with BSE does not reveal abnormalities, and the diagnosis of the disease can only be confirmed post-mortem by examining brain tissue [29, 33].

Pathological examination of the brains of BSE cattle revealed characteristic changes such as vacuolization in the medulla oblongata, especially at the obex level, where spongy lesions were noticeable. Examination of brain tissue with anti-prion antibodies indicated the presence of prions, which coincided with the distribution of vacuolization in the brain. The details of these neuropathological changes were well described by veterinary pathologists during an epizootic in the UK [29].

DIAGNOSTICS

In the context of BSE (mad cow disease), the most infectious are the so-called specified risk materials (SRMs), or tissues with the highest accumulation of prions. These include the brain, spinal cord, eyes, tonsils, intestines (from the duodenum to the rectum), spleen and elements of the nervous system, such as the dorsal root ganglia and trigeminal nerve. In many countries, the spinal column (excluding the tail) in cattle over a certain age has also been included in SRM. Because of the risk of infection, all these tissues are systematically removed from the food and feed chain [34].

BSE diagnosis is mainly carried out post-mortem. Primary methods include microscopic examination of the brain and detection of the pathological form of prion protein (PrP^Sc) using techniques such as Western blot, immunohistochemistry, electron microscopy or ELISA tests. Surveillance also uses so-called Rapid tests, which are used on high-risk animals - especially cattle over 30 months of age, fallen or emergency slaughtered animals. In case of a positive result, the carcass and neighboring animals in the slaughter line are eliminated to prevent further spread of the disease [31, 34].

Promising ante-mortem diagnostic methods, such as in vitro PMCA and RT-QuIC techniques, have also been

developed in recent years. Although they show great potential, they have not yet been fully validated for routine use in BSE surveillance programs [31].

RISK OF INTERSPECIES TRANSMISSION

The BSE problem initially affected only cattle, but it turned out that the disease can transmit to other species. Infections have been reported in domestic cats and wild cats in zoos that have consumed contaminated feed, among others. Under laboratory conditions, it has also been possible to transmit the disease to pigs, sheep and primates, although the effectiveness of infection depended on the species and method of exposure. Of greatest concern was the possibility of transmission to humans. Cases of the new variant of Creutzfeldt-Jakob disease (vCJD) have appeared in people who are believed to have consumed infected beef products. The prions of BSE and vCJD show great similarity, confirming the link between the diseases. With the ban on the use of risky tissues in food, the risk of human infection is now considered very low. However, cases of vCJD have shown that prions can cross the species barrier, making BSE a serious zoonotic threat [33].

SCRAPIE

History and discovery

Scrapie was first described in the 18th century, around 1732, in Britain. It was named after its characteristic symptom, which was the persistent scratching of animals against various surfaces to the point of skin damage [35]. A breakthrough in research on the etiology came in the second half of the 20th century. In the 1960s, research by NIH scientists, followed by Stanley Prusiner, showed that the infectious agent was not a classical pathogen, but a protein – a prion. In 1982, Prusiner introduced the term "prion," and Scrapie was one of the key diseases on which this theory was proven [36].

There are two forms of the disease:

- Classical Scrapie, which has been known for centuries and is considered a contagious disease
- Atypical Scrapie (also called Nor98), first described in Norway in 1998

Atypical Scrapie occurs sporadically, mainly in older animals, and is believed to arise spontaneously rather than through transmission. It also differs in the distribution of prion deposits in the brain. Genetic selection of sheep with the ARR genotype has proven to be one of the most effective tools for limiting the spread of classical Scrapie [38, 39].

Disease areas and outbreaks

Classical Scrapie has been and continues to be an endemic disease in many European countries, especially in the UK, France and Germany, as well as in the United States [37]. In the US, cases of classical Scrapie were reported as early as the 1940s. In response to the problem, in 2003 the USDA launched a program to eliminate the disease – the National Scrapie Eradication Program. In contrast, atypical Scrapie is not considered to be contagious under natural conditions and has been detected sporadically in several European countries during active surveillance programs [38].

Clinical manifestations and course of the disease

Scrapie develops slowly, usually in adult sheep and goats after 2–3 years of age. The incubation period can last several years, making early detection difficult. In classical Scrapie, the first symptoms are behavioral changes – excessive skittishness, restlessness – followed by characteristic scratching against objects, leading to alopecia and wounds. As the disease progresses, ataxia, a shaky gait, muscle tremors and weight loss occur despite a preserved appetite. In the final stage, paralysis, seizures and death occur. Several weeks to several months usually pass between the onset of clinical symptoms and death. In atypical Scrapie, clinical signs may be absent or subtle, and the disease is usually detected post-mortem during routine testing of apparently healthy animals [37].

Spread of the disease

Classical Scrapie is spread by direct contact between animals and through the prion-contaminated environment (placenta, secretions, soil). Prions are extremely stable – they can survive in soil for many years. In contrast, atypical Scrapie does not appear to transmit between animals in natural settings and is considered to occur sporadically without evidence of environmental transmission [37].

Diagnosis and treatment

Traditionally, diagnosis was only possible post-mortem – by histopathological examination of the brain, immunohistochemical tests, ELISA or Western blot. In recent years, ante-mortem tests, such as amygdala or tonsillar biopsies, have been developed, but their effectiveness in the early stages of the disease is limited. There is no effective treatment for Scrapie. The disease is neurodegenerative and always results in the death of the animal [37, 39].

Control measures and economic consequences

Scrapie causes serious economic losses – both through die-offs and decreased production, as well as export restrictions and loss of consumer confidence. In response, many countries have implemented eradication programs based on genetic selection (breeding sheep with the ARR/ARR genotype), active monitoring and elimination of infected individuals. In some cases, especially with classical Scrapie, mass culling of entire flocks has been used – including in the UK, Germany and France. In the US, a national Scrapie eradication program has been in place since 2003, which has significantly reduced its incidence [37, 38].

Interspecies transmission

Scrapie is not a zoonotic disease - there is no evidence that it can transmit to humans [36]. However, under experimental conditions, it has been possible to transmit Scrapie prions to other species, such as mice and hamsters. No cases of transmission to cattle or horses under natural conditions have been reported [39].

CHRONIC WASTING DISEASE (CWD)

History

Chronic wasting disease (CWD) is a prion encephalopathy affecting wild and farmed cervids. It was first identified in the 1960s in mule deer in Colorado (USA), and was recognized as a prion disease in the 1980s.

Epidemiology

CWD is now found in many states in the USA and Canada, as well as in several European countries, including Norway, Sweden, Finland and Poland The spread of the disease in North America has been extensive, with both wild and captive populations affected. In Europe, initial cases were reported in wild reindeer and moose. The expansion of CWD into new geographic regions highlights the importance of active surveillance and early detection [40, 41].

Clinical manifestations

CWD is characterized by a long incubation period and progressive cachexia in animals. Clinical symptoms include emaciation, behavioral changes (e.g. decreased fear, listlessness), excessive salivation, a shaky gait, and lethargy. As with other prion diseases, CWD is invariably fatal [40].

Diagnosis

Diagnosis of CWD is primarily post-mortem. Tissue samples (e.g. brain, retropharyngeal lymph nodes, tonsils) are tested using immunohistochemical staining or advanced methods such as RT-QuIC (real-time quaking-induced conversion). Research is ongoing to develop sensitive ante-mortem diagnostic tests, but their availability remains limited [40].

Risk to humans

Although transmission to humans has not been confirmed, experimental studies in animal models suggest a potential zoonotic risk. These findings have raised public health concerns, particularly regarding the consumption of venison from infected animals. Current public health recommendations advise against eating meat from animals known to be infected with CWD. As stated by the Centers for Disease Control and Prevention (CDC), "If your animal tests positive for CWD, do not eat meat from that animal" [43, 48].

Control measures

CWD poses a particular challenge for control because it affects free-ranging wildlife that are not subject to routine veterinary surveillance. Transmission occurs both directly (through contact between animals) and indirectly via environmental contamination. The prions responsible for CWD are highly resistant and can persist in soil and vegetation for many years. There is no effective treatment or vaccine. In affected countries, control measures include surveillance programs, transport restrictions, and in some regions, mass culling of infected populations. In endemic areas, hunter education and voluntary testing of harvested animals have also been implemented [41, 42].

Table 7 summarizes the key features of major prion diseases of animals, such as BSE, scrapie and chronic wasting disease (CWD), taking into account host species, clinical signs, disease course and transmission mechanisms.

Table 7. Comparative Summary of Major Animal Prion Diseases

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Feature	BSE (Cattle)	Scrapie (Sheep/ Goats)	CWD (Deer)

First Reported	UK, 1980s	UK, 1732	USA, 1960s
Main Transmission	MBM feeding	Contact, placenta, environment	Contact, environment
Incubation Period	2–8 years	2–5 years	>1.5 years
Clinical Symptoms	Ataxia, anxiety, weight loss	Itching, ataxia, tremors	Cachexia, drooling, lethargy
Diagnosis	Post-mortem brain exam	Post-mortem brain exam	Post-mortem (RT-QuIC, IHC)
Risk for Humans	Confirmed (vCJD)	None proven	Possible (based on animal studies)
Control Measures	MBM ban, culling, SRM removal	Genetic selection, culling	Monitoring, hunting bans, culling

CONCLUSIONS

1. **Prion diseases** are rare but clinically and epidemiologically significant neurodegenerative disorders, caused by the accumulation of abnormal prion proteins (PrP^Sc) in the central nervous system.
2. These diseases are characterized by:
    - a unique mechanism of transmission not involving nucleic acids,
    - pronounced resistance to conventional disinfection and sterilization methods,
    - absence of curative treatment options.
3. The clinical spectrum includes both **sporadic and inherited forms** in humans (e.g., CJD, kuru, GSS, FFI) as well as **zoonotic and non-zoonotic prion diseases in animals** (e.g., BSE, scrapie, CWD).
4. Accurate diagnosis remains challenging due to overlapping clinical features, the need for molecular confirmation, and often limited access to advanced diagnostic tools such as RT-QuIC.
5. Understanding prion biology has contributed to broader knowledge of **protein misfolding disorders**, with mechanistic parallels to Alzheimer's, Parkinson's, and other neurodegenerative diseases.
6. Despite the lack of effective therapies, recent advances in:
    - molecular diagnostics,
    - genotype-phenotype correlation studies,
    - public health surveillance,offer a framework for future research and potential therapeutic development.

PRACTICAL AND SCIENTIFIC RECOMMENDATIONS

1. **Strengthen diagnostic infrastructure** by improving access to validated molecular techniques such as RT-QuIC and PRNP gene testing, particularly in cases of rapidly progressive dementia or atypical cerebellar syndromes.
2. **Standardize infection control protocols**, especially in surgical, transplant, and post-mortem procedures. Medical institutions should adhere to WHO and CDC recommendations for prion decontamination and disposal of high-risk biological materials.
3. **Integrate prion diseases into medical education**, emphasizing their unique mechanisms and their relevance as models for understanding broader neurodegenerative disorders.
4. **Enhance public health surveillance**, particularly for atypical human cases and zoonotic reservoirs such as chronic wasting disease (CWD), to enable early identification and containment of potential outbreaks.
5. **Foster cross-disciplinary research** connecting prion pathophysiology with other protein misfolding diseases (e.g., Alzheimer's, Parkinson's), aiming to identify shared diagnostic markers and therapeutic targets.
6. **Promote international collaboration and data sharing** on rare prion diseases through registries, multicenter research networks, and harmonized reporting standards

DISCLOSURE

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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