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Creutzfeldt-Jakob disease as an example of Prion Disease: II. Prion Diseases

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Abstract

Transmissible spongiform encephalopathies (also known as prion diseases) are a group of progressive, incurable, and fatal conditions that affect the brain and nervous system of many mammals and impair brain function. They cause changes in memory, personality, and behavior; a decline in intellectual function (dementia); and abnormal movements, particularly difficulty with coordinating movements (ataxia). In this article, after a brief foray into the history and epidemiology of prion diseases, prions will appear to be the most infectious factors when in direct contact with affected tissues. Misfolded prion proteins carry the disease between individuals and cause deterioration of the brain. The diseases are unique in that their etiology may be genetic, sporadic, or infectious via ingestion of infected foodstuffs and via iatrogenic means. Transmission occurs when healthy animals consume tainted tissues from other animals with the disease. They cannot be transmitted through the air, through touching, or most other forms of casual contact. However, they may be transmitted through contact with infected tissue, body fluids, or contaminated medical instruments. Differences in shape between the different prion protein forms are poorly understood. Nonetheless, the known human spongiform encephalopathies can be classified according to the corresponding natural host and the prion name. The signs and symptoms as well as the etiology of prion diseases will be presented. Because of the associated progressive neurologic decline, the range of neurologic signs, and the heterogeneous presentation of genetic prion disease, the differential diagnosis is broad and needs to include other hereditary neurodegenerative disorders as well as a variety of acquired disorders. Further, because potential treatment options depend on identification of the underlying cause, autoimmune and paraneoplastic disorders will need to be considered. There are currently no known ways to cure or prevent prion diseases. While certain medications can slow

down the progression of the disease, ultimately, supportive care is currently the only option for infected individuals.

Abbreviations

ALS: Amyotrophic lateral sclerosis; BSE: Bovine spongiform encephalopathy; CDC&P: (U.S.) Centers for Disease Control & Prevention; CJD: Creutzfeldt-Jakob disease; CNS: Central nervous system; CWD: Chronic wasting disease; EOFAD: Early-onset familial Alzheimer's disease; fCJD: familial CJD; FFI: Fatal familial insomnia; FSE: Familial spongiform encephalopathy; FTD: Frontotemporal dementia; GSSS: Gerstmann- Sträussler -Sheinker syndrome; HIV: Human immunodeficiency virus; IBMPFD: Inclusion body myopathy associated with Paget's disease of bone and/or frontotemporal dementia; iCJD: iatrogenic CJD; KD: Krabbe's disease; MCD: Mad cow disease; PSL: Progressive spongiform leukoencephalopathy; sCJD: sporadic CJD; sFI: sporadic fatal insomnia; SOFIA: Surround optical fiber immunoassay; TSE: Transmissible spongiform encephalopathy; USDA: (U.S.) Department of Agriculture; vCJD: variant CJD; vPSPr: variable protease-sensitive prionopathy; WHO: World Health Organization.

Keywords

Bovine spongiform encephalopathy; Creutzfeldt-Jakob disease; chronic wasting disease; fatal familial insomnia; Gerstmann- Sträussler -Sheinker syndrome; Krabbe's disease; kuru; prion diseases; prionopathy; progressive spongiform leukoencephalopathy; scrapie; transmissible spongiform encephalopathy.

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Transmissible spongiform encephalopathies (TSEs), also known as prion diseases, are a group of progressive, incurable, and fatal conditions that affect the brain and nervous system of many mammals (including humans, cattle, and sheep). They impair brain functions causing changes in memory, personality, and behavior; a decline in intellectual function (dementia); and difficulty with coordinating movements (ataxia). After a brief foray into the history of prion diseases and their epidemiology, the so-called "prion hypothesis", whereby prion diseases are transmitted by prions, will be elaborated upon although some other data suggest an involvement of a Spiroplasma infection. Ways in which prions can be transmitted, and their etiological components will be discussed. The known human transmissible spongiform encephalopathies will be classified, and their signs, symptoms, and etiology will be summarized. Lastly, approaches to a differential diagnosis will be set forth. It will also be indicated that there are currently no known ways to cure or prevent prion diseases and while certain medications can slow down the progression of the disease, ultimately, supportive care is currently the only option for infected individuals.

History

In the 5th century BCE: Hippocrates described a disease like TSE in cattle and sheep, which he believed also occurred in humans.

In the 4th and 5th centuries AD: Publius Flavius Vegetius Renatus recorded cases of a disease with similar characteristics.

In 1755: An outbreak of scrapie was discussed in the British House of Commons and may have been present in Britain for some time before that.

In 1759: There were unsupported claims that the disease was contagious. In general, it was thought to be due to inbreeding, and countermeasures appeared to be successful.

In early-20th-century: Experiments failed to show

transmission of scrapie between animals, until extraordinary measures were taken such as the intra-ocular injection of infected nervous tissue. No direct link between scrapie and human disease was suspected then or has been found since.

In 1921: TSE was first described in humans by Alfons Maria Jakob. Also, Daniel Carleton Gajdusek's discovery that kuru was transmitted by cannibalism accompanied by the finding of scrapie-like lesions in the brains of kuru victims strongly suggested an infectious basis to TSE. A paradigm shift to a non-nucleic infectious entity was required when the results were validated with an explanation of how a prion protein might transmit spongiform encephalopathy.

In 1988: The neuropathology of spongiform encephalopathy was properly described in cows. The alarming amplification of bovine spongiform encephalopathy (BSE) in the British cattle herd heightened fear of transmission to humans and reinforced the belief in the infectious nature of TSE. This was confirmed with the identification of a kuru-like disease, called new variant Creutzfeldt-Jakob disease (vCJD) in humans exposed to BSE.

As of 2007: Although the infectious disease model of TSE has been questioned in favor of a prion and a transplantation model that explains why cannibalism favors transmission, the search for a viral agent was being continued in some laboratories.

Epidemiology

TSEs are very rare but can reach epidemic proportions. It is very hard to map the spread of the disease due to the difficulty of identifying individual strains of the prions. This means that, if animals at one farm begin to show the disease after an outbreak on a nearby farm, it is very difficult to determine whether it is the same strain affecting both herds—suggesting transmission—or if the second outbreak came from a completely different source. Although the exact prevalence of prion diseases is unknown, studies suggest that this group of conditions affects about one person per million worldwide each year. In the United States, approximately 350 new cases are reported annually.

Classic Creutzfeldt-Jakob disease (CJD) was discovered in 1920. It occurs sporadically over the world but is very rare. It affects about one person per million each year. Typically, the cause is unknown for these cases. It has been found to be passed on genetically in some cases. 250 patients contracted the disease through iatrogenic transmission (from use of contaminated surgical equipment). This was before equipment sterilization was required in 1976, and there have been no other iatrogenic cases since then. To prevent the spread of infection, the World Health Organization (WHO) created a guide to tell health care workers what to do when CJD appears and how to dispose of contaminated equipment. The (U.S.) Centers for Disease Control & Prevention (CDC&P) have been keeping surveillance on CJD cases, particularly by looking at death certificate information.

Chronic wasting disease (CWD) is a prion disease found in North America in deer and elk. The first case was identified as a fatal wasting syndrome in the 1960s. It was then recognized as a TSE in 1978. Surveillance studies showed that CWD was endemic among free-ranging deer and elk in northeastern Colorado, southeastern Wyoming and western Nebraska. It was also discovered that CWD may have been present in a proportion of free-ranging animals' decades before the initial recognition. In the United States, the discovery of CWD raised concerns about the transmission of this prion disease to humans. It was suspected that many cases of CJD were transmitted by CWD, however, the evidence was minimal.

In the 1980s and 1990s, BSE or "mad cow disease" (MCD) spread in cattle at an epidemic rate. The total estimated number of cattle infected was approximately

750,000 between 1980 and 1996. This occurred because the cattle were fed processed remains of other cattle. Then, human consumption of these infected cattle caused an outbreak of the human form CJD. There was a dramatic decline in BSE when feeding bans were put in place. On May 20, 2003, the first case of BSE was confirmed in North America. The source could not be clearly identified, but researchers suspect it came from imported BSE-infected cow meat. In the United States, the (U.S.) Department of Agriculture (USDA) created safeguards to minimize the risk of BSE exposure to humans.

Variant Creutzfeldt-Jakob disease (vCJD) was discovered in 1996 in England. There is strong evidence to suggest that vCJD was caused by the same prion as BSE. Since 1996, and as of August 2013, a total of 229 cases of variant CJD cases have been identified from 11 countries: 177 from the United Kingdom, 27 from France, 4 from Ireland, 4 from the United States, 5 from Spain, 3 in the Netherlands, 2 each from Portugal, Italy and Canada, and 1 each from Japan, Taiwan and Saudi Arabia.

Prions and the prion hypothesis

According to the most widespread "prion hypothesis", prion diseases are transmitted by prions, although some other data suggest an involvement of a Spiroplasma infection. Mental and physical abilities deteriorate, and many tiny holes appear in the cortex causing it to appear like a sponge when brain tissue obtained at autopsy was examined under a microscope. The disorders cause impairment of brain function which may result in memory loss, personality changes, and abnormal or impaired movement which worsen over time.

Human TSEs include CJD, GSSS, FFI, and kuru, as well as the recently discovered variably protease-sensitive prionopathy, and familial spongiform encephalopathy (FSE). CJD itself has four main forms: sporadic (sCJD), hereditary/ familial (fCJD), iatrogenic (iCJD), and the variant form (vCJD). These conditions form a spectrum of diseases with overlapping signs and symptoms.

Prions appear to be most infectious when in direct contact with affected tissues. For example, CJD has been transmitted to patients taking injections of growth hormone harvested from human pituitary glands, from cadaver *dura* allografts, and from instruments used for brain surgery. Prions can survive the "autoclave" sterilization process used for most surgical instruments. Dietary consumption of affected animals can cause prions to accumulate slowly, especially when cannibalism or similar practices allow the proteins to accumulate over more than one generation. An example is kuru, which reached epidemic proportions in the mid-20th century in the Fore people of Papua New Guinea, who used to consume their dead as a funerary ritual. Laws in developed countries now ban the use of rendered ruminant proteins in ruminant feed as a precaution against the spread of prion infection in cattle and other ruminants.

TSEs in non-human mammals include scrapie in sheep, BSE in cattle - popularly known as MCD – and chronic wasting disease (CWD) in deer and elk. The variant form of CJD in humans is caused by exposure to BSE prions.

Transmission agents

Unlike other kinds of infectious diseases, which are spread by agents with a DNA or RNA genome (such as viruses of bacteria), the infectious agent in TSEs is believed to be a prion, thus being composed solely of protein material. Misfolded prion proteins carry the disease between individuals and cause deterioration of the brain. TSEs are unique diseases in that their etiology may be genetic, sporadic, or infectious via ingestion of infected foodstuffs and via iatrogenic means (e.g., blood

transfusion). Most TSEs are sporadic and occur in an animal with no prion protein mutation. Inherited TSE occurs in animals carrying a rare mutant prion allele, which expresses prion proteins that contort by themselves into the disease-causing conformation. Transmission occurs when healthy animals consume tainted tissues from other animals with the disease. In the 1980s and 1990s, BSE spread in cattle in an epidemic fashion. This occurred because cattle were fed the processed remains of other cattle, a practice now banned in many countries. In turn, consumption (by humans) of bovine-derived foodstuff which contained prion-contaminated tissues resulted in an outbreak of vCJD in the 1990s and 2000s.

Prions cannot be transmitted through the air, through touching, or most other forms of casual contact. However, they may be transmitted through contact with infected tissue, body fluids, or contaminated medical instruments. Normal sterilization procedures such as boiling or irradiating materials fail to render prions non-infective. However, treatment with strong, almost undiluted bleach and/or sodium hydroxide, or heating to a minimum of 134 °C, does destroy prions.

Classification

Differences in shape between the different prion protein forms are poorly understood. Table 1 lists the known human spongiform encephalopathies, the corresponding natural host, and the prion name. (The corresponding encephalopathies in non-human mammals will not be or only rarely considered here.)

Disease	Disease variant	Prion name	Prion protein isoform
Creutzfeldt-Jakob disease (CJD)	o Original (CJD) o Familial (fCJD). o Iatrogenic (iCJD) o Sporadic (sCJD). o Variant (vCJD)	o CJD prion o fCJD prion o iCJD prion o sCHD prion o vCJD prion	o PrP(CJD) o PrP(fCJD) o PrP(iCJD) o PrP(sCJD) o PrP(vCJD)
Familial fatal insomnia (FFI)		FFI prion	PrP (FFI)
Gerstmann-Straussler-Sheinker syndrome (GSSS)		GSSS prion	PrP (GSSS)
Familial spongiform encephalopathy (FSE)		FSE prion	PrP (FSE)
Kuru		Kuru prion	PrP (Kuru)
Variable protease-sensitive prionopathy (VPSPr)		VPSPr prion	PrP (VPSPr)

Table 1: Classification of the known human spongiform encephalopathies

Signs and symptoms

The degenerative tissue damage caused by human prion diseases (kuru, CJD, and GSS) is characterized by four features:

1. Spongiform change (the presence of many small holes),
2. Death of neurons,
3. Astrocytosis (abnormal increase in the number of astr ocytes due to the destruction of nearby neurons), and
4. Amyloid plaque formation.

These features are shared with prion diseases in animals. The recognition of these similarities prompted the first attempts to transmit a human prion disease (kuru) to a primate in 1966, followed by CJD in 1968 and GSS in 1981. These neuropathological features have formed the basis of the histological diagnosis of human prion diseases for many years, although it was recognized that these changes are enormously variable both from case to case and within the central nervous system (CNS) in individual cases.

The clinical signs in humans vary, but commonly include:

- **Personality changes,**
- **Psychiatric problems** such as depression,
- **Lack of coordination,** and/or an
- **Unsteady gait (ataxia).**

Patients may also experience:

- **Involuntary jerking movements (myoclonus),**
- **Unusual sensations,**
- **Insomnia,**
- **Confusion, or**
- **Memory problems.**

In the later stages of the disease, patients have:

- **Severe mental impairment (dementia), and**
- **Loss of ability to move or speak.**

Early neuropathological reports on human prion diseases suffered from a confusion of nomenclature, in which the significance of the diagnostic feature of spongiform change was occasionally overlooked. The subsequent demonstration that human prion diseases were transmissible reinforced the importance of spongiform change as a diagnostic feature, reflected in the use of the term "spongiform encephalopathy" for this group of disorders.

Note that not all encephalopathies are caused by prions, as in the cases of PML (caused by the JC virus), CADASH (caused by abnormal NOTCH3 protein activity), and Krabbe's disease (KD) (caused by a deficiency of the enzyme galactosylceramidase). Progressive spongiform leukoencephalopathy (PSL), which is a spongiform encephalopathy—is also probably not caused by a prion, although the adulterant that causes it among heroin smokers has not yet been identified. This, combined with the highly variable nature of prion disease pathology, is why a prion disease cannot be diagnosed based solely on a patient's symptoms.

Etiology

Between 10% and 15% of all cases of prion disease are caused by mutations in the PRNP gene. Because they can run in families, these forms of prion disease are classified as familial.

Familial prion diseases, which have overlapping signs and symptoms, include familial Creutzfeldt-Jakob disease (CJD), Gerstmann-Sträussler-Scheinker syndrome (GSS), and fatal familial insomnia (FFI). The PRNP gene provides instructions for making a protein called prion protein (PrP). Although the precise function of this protein is unknown, researchers have proposed

roles in several important processes. These include the transport of copper into cells, protection of brain cells (neurons) from injury (neuroprotection), and communication between neurons. In familial forms of prion disease, PRNP gene mutations result in the production of an abnormally shaped protein from one copy of the gene known as PrPSc. In a process that is not fully understood, PrPSc can attach (bind) to the normal protein (PrPC) and promote its transformation into PrPSc. The abnormal protein builds up in the brain, forming clumps that damage or destroy neurons. The loss of these cells creates microscopic sponge-like holes (vacuoles) in the brain, which leads to the signs and symptoms of prion disease.

The other 85% to 90% of cases of prion diseases are classified as either sporadic or acquired. People with sporadic prion disease have no family history of the disease and no identified mutation in the PRNP gene. Sporadic disease occurs when PrPC spontaneously, and for unknown reasons, is transformed into PrPSc. Sporadic forms of prion disease include sporadic Creutzfeldt-Jakob disease (sCJD), sporadic fatal insomnia (sFI), and variable protease-sensitive prionopathy (VPSPr).

Acquired prion disease results from exposure to PrPSc from an outside source. For example, variant Creutzfeldt-Jakob disease (vCJD) is a type of acquired prion disease in humans that results from eating beef products containing PrPSc from cattle with prion disease. In cows, this form of the disease is known as BSE) or, more commonly, MCD. Another example of an acquired human prion disease is kuru, which was identified in the South Fore population in Papua New Guinea. The disorder was transmitted when individuals ate affected human tissue during cannibalistic funeral rituals. Rarely, prion disease can be transmitted by accidental exposure to PrPSc-contaminated tissues during a medical procedure. This type of prion disease, which accounts for 1% to 2% of all cases, is classified as iatrogenic.

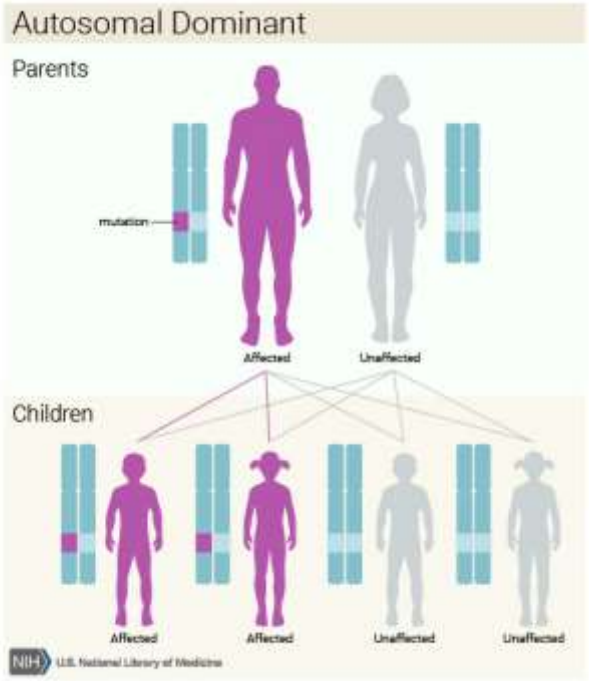

Figure 1: The autosomal dominant form of inheritance of prion diseases

The cause of TSEs may involve genetics or several other hypotheses (protein-only, multi-component, and viral) as further discussed below:

Genetics

Familial forms of prion disease are inherited in an autosomal dominant pattern, which means one copy of the altered PRNP gene in each cell is sufficient to cause the disorder. They are caused by inherited mutations in the PRNP gene (Figure 1).

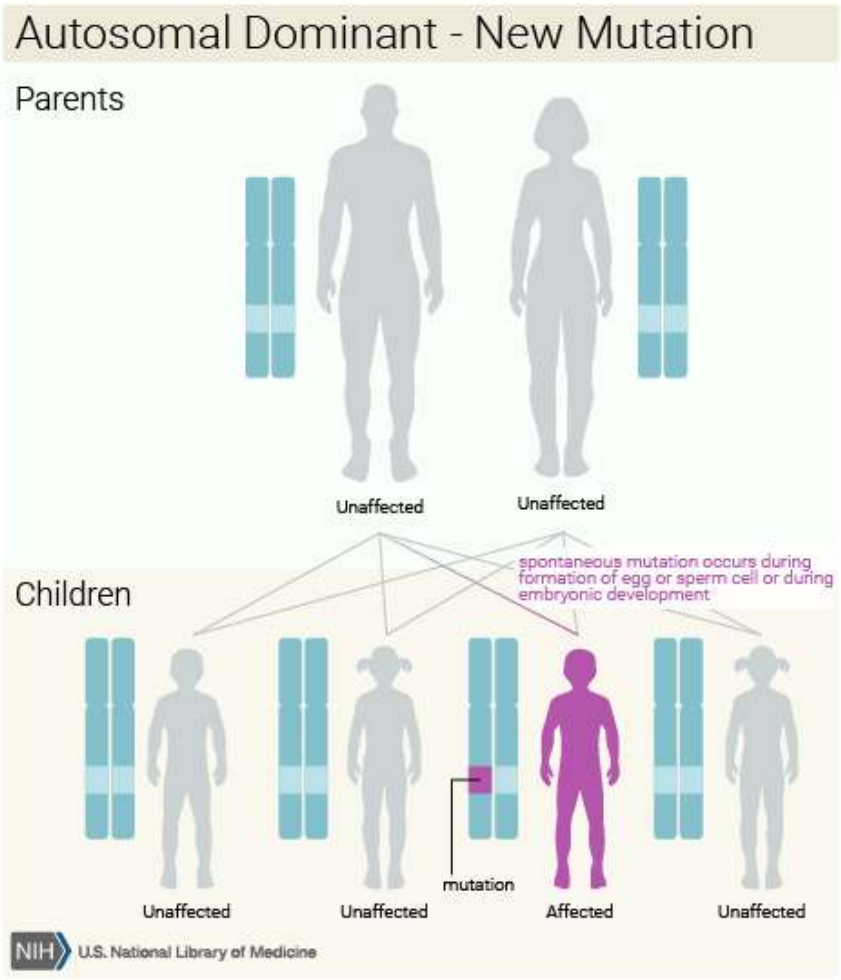

Figure 2: New mutation in the autosomal dominant form of inheritance of prion diseases

However, only a small percentage of prion disease cases are familial; most occur sporadically, without known genetic mutations or risk factors. In rare instances, prion diseases can be transmitted through exposure to prion-contaminated tissues or biological materials from affected individuals.

The PRNP gene encodes the prion protein (PrP) which, under normal conditions, may play a role in transporting copper into cells and protecting neurons. Misfolding of the prion protein leads to the accumulation of pathogenic PrPSc, the hallmark of prion diseases, causing progressive neurodegeneration.

In most cases, an affected person inherits the altered gene from one affected parent. In some people, the familial forms of prion disease are caused by a new mutation in the gene that occurs during the formation of a parent's reproductive cells (eggs or sperm) or in early embryonic development. Although such people do not have an affected parent, they can pass the genetic change to their children (Figure 2).

The sporadic, acquired, and iatrogenic forms of prion disease, including kuru and vCJD are not inherited.
Other names given for prion diseases include:

• Transmissible spongiform encephalopathies.
• Inherited human transmissible spongiform encephalopathies.
• Prion-associated disorders.
• Prion-induced disorders.
• Transmissible dementias.

Protein-only hypothesis

Protein could be the infectious agent, inducing its own replication by causing conformational change of normal cellular PrPC into PrPSc. The evidence for this hypothesis includes:

• **Infectivity titer correlates with PrPSc levels.** However, this is disputed.
• **PrP^{Sc} is an isomer of PrP^{C}**
• **Denaturing PrP removes infectivity.**
• **PrP-null mice cannot be infected.**
• **PrP^{C} depletion reverses early spongiosis and behavioral deficits:** In the neural system of mice with established neuroinvasive prion infection. PrPC depletion reverses early spongiosis and behavioral deficits, halts further disease progression, and increases lifespan.

Multi-component hypothesis

While not containing a nucleic acid genome, prions may be composed of more than just a protein. Purified PrPC appears unable to convert to the infectious PrPSc form, unless other components are added, such as RNA and lipids. These other components, termed “cofactors”, may form part of the infectious prion, or they may serve as catalysts for the replication of a protein-only prion.

Viral hypothesis

This hypothesis postulates that an as yet undiscovered infectious viral agent is the cause of the disease. The strongest evidence for viral replication in TSE-infected brains is that long double stranded RNA is detected in 22L scrapie-infected mouse brains. Other evidence for this hypothesis is as follows:

• **Brain particle titers purified of PrP retain infectivity.**
• **Brain titers exposed to nucleases reduced infectivity by >=99%.**
• **Incubation time is comparable to a lentivirus.**
• **Strain variation of different isolates of PrPsc.**

Differential diagnosis

As stated earlier, prion disease cannot be diagnosed based solely on a patient's symptoms. Thus, there

continues to be a very practical problem with diagnosis of prion diseases, including BSE and CJD. They have an incubation period of months to decades during which there are no symptoms, even though the pathway of converting the normal brain PrP protein into the toxic, disease-related PrPSc form has started. At present, there is virtually no way to detect PrPSc reliably except by examining the brain using neuropathological and immunohistochemical methods after death. Accumulation of the abnormally folded PrPSc form of the PrP protein is a characteristic of the disease, but it is present at very low levels in easily accessible body fluids like blood or urine. Researchers have tried to develop methods to measure PrPSc, but there are still no fully accepted methods for use in materials such as blood.

In 2010, a team from New York described detection of PrPSc even when initially present at only one part in a hundred billion (10−11) in brain tissue. The method combines amplification with a novel technology called "surround optical fiber immunoassay" (SOFIA) and some specific antibodies against PrPSc. After amplifying and then concentrating any PrPSc, the samples are labelled with a fluorescent dye using an antibody for specificity and then finally loaded into a micro-capillary tube. This tube is placed in a specially constructed apparatus so that it is surrounded by optical fibers to capture all light emitted once the dye is excited using a laser. The technique allowed detection of PrPSc after many fewer cycles of conversion than others have achieved, substantially reducing the possibility of artefacts, as well as speeding up the assay. The researchers also tested their method on blood samples from apparently healthy sheep that went on to develop scrapie. The animals' brains were analyzed once any symptoms became apparent. The researchers could therefore compare results from brain tissue and blood taken once the animals exhibited symptoms of disease with blood obtained earlier in the animals' lives and from uninfected animals. The results showed very clearly that PrPSc could be detected in the blood of animals long before the symptoms appeared.

Because of the progressive neurologic decline, the range of neurologic signs, and the heterogeneous presentation of genetic prion disease, the differential diagnosis is broad and needs to include other hereditary neurodegenerative disorders as well as a variety of acquired disorders. Because potential treatment options depend on identification of the underlying cause, autoimmune and paraneoplastic disorders need to be considered (see Table 2).

Etiology	**Disorder/Comment**	**Gene(s)**
	CSF1R-related adult-onset leukoencephalopathy with axonal spheroids and pigmented glia	*CSF1R*
	Dementia with Lewy bodies (OMIM 127750)	*GBA1(GBA)* *SNCA* *SNCB*
	Familial Alzheimer's disease (1)	*APP* *PSEN1* *PSEN2*
Hereditary neurodegenerative disorders	Frontotemporal dementia (e.g., ALS/FTD, CHMP2B-FTD, GRN/FTD, IBMPFD)	*C9orf72* *CHMP2B* *FUS* *GRN* *HNRNPA1* *HNRNPA2B1* *TARDBP* *VCP*

	Hereditary ataxia (e.g., SCA1, 2, 3, 6,7,8) (2)	*ATXN1* *ATXN2* *ATXN3* *ATXN7* *ATXN8* *CACNA1A*
	Huntington's disease	*HTT*
	Pick's disease (OMIM 172700)	*MAPT* *PSEN1*
	Progressive supranuclear palsy (OMIM 601104)	*MAPT*
Autoimmune	e.g., Hashimoto's thyroiditis w/related encephalopathy, multiple sclerosis, antibody-mediated dementia/ encephalopathy, CNS lupus, acute disseminated encephalomyelitis	
Iatrogenic	e.g., medication toxicity (e.g., lithium, methotrexate, chemotherapy), illicit drug use	
Infectious	e.g., viral encephalitis (incl herpes simplex virus), HIV dementia, progressive multifocal leukoencephalopathy	
Metastases/ Neoplasm related	e.g., paraneoplastic diseases-limbic encephalopathy, metastases to CNS, primary CNS lymphoma	
Systemic/Seizures/ Structural	e.g., sarcoidosis, epilepsy, nonconvulsive status epilepticus	
Toxic-metabolic	e.g., heavy metals (incl bismuth), electrolyte disturbances (sodium, calcium, magnesium, phosphorus), endocrine abnormalities (thyroid, parathyroid, adrenal), extrapontine myelinolysis	
Vascular/Ischemia	e.g., multi-infarct, thalamic or callosum infarcts, cerebral amyloid angiopathy	

Table 2: Disorders potentially associated with rapid progression of interest in the differential diagnosis of genetic prion disease

Notes: (1) Listed genes are associated with early-onset familial AD (EOFAD): Alzheimer's disease (AD) that occurs in multiple members of a family with a mean onset usually before age 65 years. EOFAD represents fewer than 2% of AD cases. Late-onset familial AD (age >60-65 years), representing 15%-25% of AD cases, is thought to be a complex disorder possibly involving multiple susceptibility genes.

(2) The hereditary ataxias are a large group of autosomal dominant, autosomal recessive, and X-linked disorders characterized by slowly progressive incoordination of gait and often associated with poor coordination of hands, speech, and eye movements.

Symptoms management and treatment

There are currently no known ways to cure or prevent prion diseases. Certain medications can slow down the progression of the disease but, ultimately, supportive care is currently the only option for infected individuals.

Conclusions and take-aways

- Transmissible spongiform encephalopathies, also known as prion diseases, are a group of progressive, incurable, and fatal conditions that affect the brain and nervous system of many mammals, including humans, cattle, and sheep. They are very rare but can reach epidemic proportions.
- It is very hard to map the spread of the disease due to the difficulty of identifying individual strains of the prions.
- Chronic wasting disease is a prion disease found in North America in deer and elk.
- Bovine spongiform encephalopathy or "mad cow disease" spread in cattle at an epidemic rate. This occurred because the cattle were fed processed remains of other cattle. Then, human consumption of these infected cattle caused an outbreak of the human form.
- There is strong evidence to suggest that variant Creutzfeldt-Jakob disease was caused by the same prion as bovine spongiform encephalopathy.
- According to the most widespread "prion hypothesis", prion diseases are transmitted by prions, although some other data suggest an involvement of a Spiroplasma infection. Mental and physical abilities deteriorate, and many tiny holes appear in the cortex causing it to appear like a sponge when brain tissue obtained at autopsy is examined under a microscope. The disorders cause impairment of brain function which may result in memory loss, personality changes, and abnormal or impaired movement which worsen over time.
- Transmissible spongiform encephalopathies of humans include Creutzfeldt-Jakob disease, Gerstmann-Straussler-Sheinker syndrome, fatal familial insomnia, kuru, the variably protease-sensitive prionopathy, and familial spongiform encephalopathy. In non-human mammals, they include scrapie in sheep, bovine spongiform encephalopathy (or "mad cow disease"), and chronic wasting disease in deers and elks.
- The degenerative tissue damage caused by human prion diseases is characterized by four features: Spongiform change, death of neurons, astrocytosis, and amyloid plaque formation.
- The clinical signs in humans vary, but commonly include personality changes, psychiatric problems (such as depression), lack of coordination, and/or an unsteady gait (ataxia). Patients may also experience involuntary jerking movements (myoclonus), unusual sensations, insomnia, confusion, or memory problems. In the later stages of the disease, patients have severe mental impairment (dementia), and loss of ability to move or speak.
- The causes of prion diseases may involve genetics or several other hypotheses (protein-only, multi-component, and viral).

- A prion disease cannot be diagnosed based solely on a patient's symptoms.

- There are currently no known ways to cure or prevent prion diseases. Certain medications can slow down the progression of the disease but, ultimately, supportive care is currently the only option for infected individuals.

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