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Prions and humans

(A brief review of human prion diseases)*

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Prion diseases, or transmissible spongiform encephalopathies are a group of neurodegenerative diseases that affect humans and animals. Prion diseases are manifest as infectious, genetic or sporadic disorders. They can be transmitted among different hosts by the infectious proteinaceous particles, called prions. Prions (PrP) are derived from a normal cellular isofrom PrPc after posttranslational conformational modification to PrPSc. New variant Creutzfeldt-Jakob disease (vCJD) is a novel human prion disorder with characteristic clinical and neuropathological features, which results from exposure to the prions causing bovine spongiform encephalopathy in cattle. Further studies are required to clarify risk factors and the possibility that the vCJD might spread from person to person by blood transfusion or by surgical procedures. Agricultura 1: 8-10 (2002)

Key words: prions; prion diseases; new variant Creutzfeldt-Jakob disease

INTRODUCTION

Prion diseases, also called transmissible spongiform encephalopathies are very rare slowly progressive and invariably fatal degenerative diseases of the central nervous system (CNS). They are caused by prions, special infectious proteins encoded in human or animal genomes that are able to replicate and by a yet unknown mechanism destroy neural cells. Prion diseases of humans include Creutzfeldt-Jacob disease (CJD), Gerstmann-Sträussler-Scheinker syndrome (GSS), fatal familial insomnia (FFI), and kuru.

All prion diseases have many common features, such as:
- long incubation period ranging from a couple of months to many years,
- progressive clinical course (weeks to years) with unavoidable fatal outcome,
- involvement of a single organ system (CNS) with chronic impairment of cognitive and motoric functions,
- characteristic histopathological changes in the form of spongiform degeneration (vacuolation and death of neurons), hypertrophy and proliferation of glial cells (reactive astrocytosis) and amyloid plaques (aggregates of prion proteins).

The emergence of the bovine spongiform encephalopathy (BSE) in the United Kingdom (UK) and the acknowledgement that bovine prions have been transmitted to human beings via contaminated beef resulting in a novel form of human prion disease, variant CJD (vCJD), has resulted in an extensive attention to these fatal neurodegenerative disorders. It is of particular interest to ask how many people will contract vCJD and whether blood and blood products from donors incubating vCJD may pose a risk for iatrogenic transmission of the disease.

PRION PROTEIN (PrP)

Prion is identical with a conformational isoform of PrPc (C=cell), a normal host cell protein, found predominantly on the surface of neurons (Prusiner 1989).

Human PrPc, consisting of 253 amino acids, is encoded by a gene on the chromosome 20. While the physiological function of PrPc remains largely unknown, several possible roles for the protein have been suggested, including that of a ligand, a receptor, a signal transducing element or a cell adhesion molecule (Harris 1999). During the course of prion disease a largely protease-resistant, aggregated form of PrPc, designated PrPSc (Sc=scrapie, a prion disease in sheep and goats), accumulates inside neurons mainly in brain. In the conversion to PrPSc, the protease-sensitive PrPc undergoes a posttranslational conformational change from a predominantly a-helical structure to one with a high b-sheet content.

The multiplication of prion proteins is an autocatalytic process in which a PrPSc molecule combines with one PrPc molecule giving rise to one heterodimer. This heterodimer is subsequently transformed into one homodimer (PrPSc/PrPSc) that dissociates to combine with two PrPc molecules creating an exponential process (Kitamoto and Tateishi 1996). The conversion of PrPc to PrPSc is most probably facilitated by an as yet unidentified chaperone protein x. PrPSc molecules which can be generated in multiple compartments inside the cell (lysosomes, endosomes, endoplasmic reticulum) accumulate and destroy neural cells.

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HUMAN PRION DISEASES

Four common forms of human prion diseases (CJD, GSS, FFI and kuru) may present as sporadic (arising spontaneously), inherited (linked to certain mutations), or infectious (acquired by transplantation, injection or ingestion of contaminated products) disorders (Prusiner 2000) (Table 1).

Kuru is a chronic degenerative disease of the CNS which was endemic in the tribal Fore group of Papua New Guinea. The affected individuals acquired kuru through cannibalistic ingestion of infectious brains of their own deceased relatives. With discontinuation of the practice of ritual cannibalism, kuru has completely disappeared. Incubation period of kuru ranged from 3 to more than 30 years. The major clinical features include cerebellar ataxia, action tremor, and involuntary movements. The patients become demented at an advanced stage of disease. In most cases the disease progressed to death within 12 months.

Creutzfeldt-Jakob disease (CJD) is found throughout the world. The incubation period varies from a few years to many decades. CJD typically presents as a rapidly progressive dementia with associated motoric and sensory disturbances (myoclonic jerking movements and visual problems), ataxia and memory loss. Most patients die within a year after onset.

Typical histopathological changes (neuronal vacuolation and astrogliosis) are predominant in the brain cortex. Amyloid plaques composed of extracellular deposits of polymerized prions have been found only in the minority of patients (in the case of kuru or GSS almost all patients have plaque deposits in the brains). Patients with CJD often have characteristic electroencephalogram (EEG), showing typical periodic sharp wave complexes.

Sporadic CJD occurs worldwide with an incidence of approximately 1 case per million population per year. Etiology of this disease remains unknown. It has been hypothesized to involve a somatic mutation in the PrP gene, or a spontaneous, conformational change of prion protein.

Inherited CJD is a dominantly inherited familial disease caused by germline mutations in the PrP gene.

Infectious CJD is an inadvertent consequence of medical procedure. More than 200 iatrogenic infections have been recorded. Most of them have been acquired after transmission of prions present in human growth hormone preparations obtained from the pituitary glands of patients with sporadic CJD and after implantations of dura mater grafts contaminated with prions.

New variant CJD (vCJD) was first reported in 1996 in the UK (Will et al. 1996). It appeared about 10 years after the start of the BSE epidemic and it was soon proposed, that vCJD is the result of transmission of bovine prions to humans through the consumption of infectious beef meat or meat products (Table 2).

So far about 100 confirmed cases of vCJD have been identified in the UK. The epidemiologic, clinical, and pathologic features of these cases set them apart from other forms of CJD. Patients with vCJD are considerably younger, the duration of illness is longer, sensory disturbances and psychiatric manifestations present more often than in sporadic CJD. Most patients with vCJD have nonspecific EEG (absence of periodic high-voltage complexes) and unusual neuropathologic features in the form of large prion amyloid plaques located predominantly in the cerebellum.

Table 1. The human prion diseases.

Disease	Mechanisms of pathogenesis	Distribution
Creutzfeldt-Jakob disease (CJD)		worldwide
Sporadic CJD	unknown	1 person/million/year
Inherited (familial) CJD	germline mutations in PrP gene	about 100 families
Infectious CJD	iatrogenic infection (prion-contaminated human growth hormone, dura mater grafts, and so forth)	about 200 cases
New variant CJD	infection from bovine prions	about 100 cases
Gerstmann-Sträussler-Scheinker syndrome (GSS)	germline mutations in PrP gene	about 50 families
Fatal familial insomnia (FFI)	germline mutation in PrP gene	about 30 families
Kuru	infection through cannibalism	some 2600 cases in Papua New Guinea

A matter of concern is a slow but steady increase in the number of cases of vCJD in the UK. Andrews et al. (2000) assessed the incidence of vCJD in the UK from 1994 to 2000. They estimated that the number of onsets increased by 23% per year for 1994-2000 and that deaths increased by 33% for 1995-2000. There are however uncertainties about the future, because the magnitude of the epidemic of vCJD in the next years cannot be predicted with confidence yet.

It seems important, that pathogenic prions have been demonstrated in tonsillar tissue from patients with vCJD, which suggests a lymphoreticular phase in human infections with bovine prions (Hill et al. 1997). Involvement of the peripheral lymphoid system (also white blood cells) in v CJD raises the possibility of disease transmission from human to human through blood and blood products or by surgical procedures that involve contact with lymphoreticular tissue.

Despite the fact that at present no firm evidence exists for the presence of prions in blood or for infection via the

blood route regulatory agencies in several countries have been restricting blood donations from people thought to have been exposed to BSE.

Table 2. Evidence of a link between bovine spongiform encephalopathy (BSE) and new variant Creutzfeldt-Jakob disease (vCJD).

• First cases of vCJD were reported approximately 10 years after the emergence of BSE in the UK.
• Almost all (approximately 100) confirmed cases of vCJD have been diagnosed in the UK, where also the majority of BSE cases occured.
• Prions of vCJD and prions of BSE have the same glycosylation pattern, that differs from prions of sporadic or iatrogenic CJD forms (Collinge et al. 1996).
• Injection of brain homogenates from BSE-infected cattle into the brains of mice or macaque monkeys resulted in neuropathological lesions (large plaques in the cerebellum) strikingly similar to those found in the brains of patients with vCJD (Lasmezas et al. 1996).

Gerstmann-Sträussler-Scheinker syndrome (**GSS**) is an extremely rare familial and always genetic form of human prion diseases with different prion protein gene mutations. Main symptoms are cerebellar ataxia with tremor and late developing dementia. Patients complain of difficulty walking and accompanying impairment of speaking and swallowing. The duration of disease ranges from 2 to 10 years.

Fatal familial insomnia (FFI) is also an extremely uncommon neurodegenerative disorder. In the most characteristic presentation, the patients develop progressive, untreatable insomnia, sometimes lasting weeks or even months, motor disturbancies, and mental status abnormalities. Usually the average disease duration is one year.

CONCLUSION

Prions are a novel class of infectious pathogens responsible for transmission and development of a group of fatal neurodegenerative disorders, called spongiform encephalopathies or prion diseases (Prusiner 1998). Whereas human prion diseases provoked high interest in the biomedical science community, animal prion diseases, in particular BSE, influenced to a great extent also agricultural, economic and political issues. There is growing evidence that proteins with abnormal conformation which aggregate and form tissue deposits have a critical role not only in the rare prion diseases of CNS but also in the more common neurodegenerative disorders such as Alzheimer's and Parkinson's disease (Soto 1999).

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