Prion diseases

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Abstract

The prion diseases, or transmissible spongiform encephalopathies (TSEs), are a group of neurodegenerative diseases. They are caused by an abnormal form of a naturally occurring cellular protein, known as prion protein. All prion diseases are fatal and without cure. Although all are rare, interest has increased over the last 20 years due to the appearance of a new prion disease called variant Creutzfeldt–Jakob disease. This disease is transmissible via medical devices and blood and therefore has implications for the anaesthetist, especially where blood transfusions and the use of airway devices and fibreoptic equipment are concerned.

Keywords Blood transfusions; Creutzfeldt–Jakob disease; endoscopes; prion disease; transmissible spongioform encephalopathies

Royal College of Anaesthetists CPD Matrix: 1E01, 3F00

Learning objectives

After reading this article, you should be able to:

- discuss the nature of prion diseases
- describe the differences between sporadic and variant Creutzfeldt–Jakob disease
- explain the implications of prion diseases for anaesthetists

Introduction

Prion diseases affect both humans and animals. Those affecting animals include transmissible mink encephalopathy, bovine spongioform encephalopathy (BSE or 'mad cow disease') and scrapie, seen in sheep. Scrapie was first described in the 1730s. Its name derives from the way infected sheep scrape their fleeces against hard surfaces to relieve itch. In the 1920s, Creutzfeldt and Jakob described the prion disease that affects humans and that became known as Creutzfeldt–Jakob disease (CJD). Recently, interest in prion diseases has burgeoned due to the emergence of a new form of CJD, known as variant Creutzfeldt–Jakob disease (variant CJD). Variant CJD arose from human ingestion of meat from BSE-infected cattle.

Pathophysiology

The unifying features of prion diseases are the neuropathological changes of neuronal loss, gliosis and spongioform change. These changes are caused by an abnormal form of the normal cellular prion protein (PrP^{C}), found on the surface of many cells and particularly neurons. This abnormal form is designated PrP^{SC} ('SC' for scrapie). PrP^{C} has a largely alpha-helical structure whereas PrP^{SC} has an increased number of beta-sheets. This conformational change in PrP^{SC} renders it resistant to proteolytic digestion and confers resistance to conventional methods of decontamination. PrP^{SC} is not significantly affected by disinfectants and is resistant to standard autoclaving methods.[1]

Infectivity of PrP^{SC} from cell to cell appears to occur by 'autocatalytic' conversion of PrP^{C} to PrP^{SC}. Human PrP^{C} is present in high concentrations in neural tissues and in low concentrations in cells of the immune system. No definite function of PrP^{C} has been confirmed, although it appears to have a role in synaptic transmission. PrP^{C} is encoded by a single gene, which is found on chromosome 20 and known as PRNP. Importantly, the gene is polymorphic at codon 129, encoding either methionine or valine. Homozygosity for methionine or valine seems to be a major risk factor for developing human prion disease.

The only definitive method for diagnosing prion disease is by biopsy and examination of affected tissue, with subsequent typing of PrP^{SC} using Western blotting techniques. However, the suspicion of disease on clinical grounds can be supported by MRI changes, electroencephalographic features, measurement of certain markers in cerebrospinal fluid (including 14-3-3 protein) and genetic sequencing of the PRNP gene. A more recent test, real-time quaking-induced conversion (RT-QUiC), has also been developed to aid diagnosis.

Human prion diseases

Human prion diseases may be classified into sporadic, inherited and acquired types.

Sporadic CJD

Sporadic CJD is the most common form of CJD (85%) with an annual incidence of one per million of the population. Sporadic CJD is found with similar incidence in all documented countries and usually affects people in late middle-age[2] with a typical onset age of 65 years. The trigger for sporadic CJD is unknown. It is characterized by a rapidly progressive dementia, often accompanied by behavioural and visual disturbances, ataxia, extrapyramidal features and myoclonus. There is frequently an insidious onset, then a rapid progressive phase and death within 1 year. Definitive diagnosis requires a brain biopsy. Genetic analysis of the PRPN gene reveals that 70% of confirmed cases are homozygous for methionine at codon 129. Elevation of 14-3-3 protein in CSF is a non-specific biomarker and may be a more sensitive test for sporadic CJD than for variant CJD.

Variably protease sensitive prionopathy, a relatively recently described form of prion disease, is considered a form of sporadic CJD. There have been 11 cases reported in the UK.[2]

Inherited human prion diseases

Inherited or familial prion diseases arise from mutations of the PRNP gene and are inherited on an autosomal dominant basis. More than 30 PRNP mutations have been identified, resulting in varied presentations. This group of diseases includes familial CJD, Gerstmann–Straussler–Scheinker syndrome and fatal familial insomnia. Once an initial diagnosis of inherited CJD has been made, family members must be considered for testing.

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Some may not wish to know whether they will develop an incurable disease later in life. The choice is personal and appropriate counselling should be available.

Acquired human prion diseases

There are several ways prion diseases may be acquired.

Kuru: a prion disease seen exclusively in the South Fore tribes of Papua New Guinea, kuru arises from the ingestion of infected brain tissue during cannibalistic mortuary rites. Its incidence is diminishing with the abolition of cannibalism and with better education. Women were historically infected more than men, probably because women were the primary participants in mortuary rites. Kuru victims were a highly regarded source of food, because the layer of fat on the victims, who died quickly, was felt to resemble pork.

Iatrogenic CJD arises from the transfer of PrP^{SC}-infected tissue to healthy individuals. Since 1990 there have been 84 deaths due to iatrogenic CJD.[2]

Transfer of infected tissue may occur in the following ways:

Implantation of cadaver-sourced dura mater or corneal grafts – prior to 1992, patients undergoing spinal or cranial operations that resulted in large dural defects would have the defect repaired using dural grafts. These were sourced from cadavers, a small percentage of which were infected with CJD. Dural grafts are no longer sourced from cadavers. They are now synthetically produced. A small number of people have been infected with CJD following corneal grafts.

Administration of growth hormone (GH) and gonadotrophin – prior to 1985, GH was given to children with restricted growth. The GH was extracted from pituitaries from cadavers, some of which were infected with CJD. Incubation periods may span many decades and presently 2–6 cases are diagnosed each year. Some women with fertility problems have received gonadotrophin supplements derived from cadavers infected with CJD. A very small number have developed CJD. Artificially synthesized GH and gonadotrophin are now available and in use.

Infected surgical instruments – there have been no documented cases of transmission via this route since 1976. The risk nonetheless still exists. The surgical instruments used on CJD patients having high-risk operations should be incinerated or quarantined for use on CJD patients only. Similarly, surgical instruments should be incinerated or quarantined for those patients at increased risk of having CJD, until such time as they are proved to be free of the disease. All instruments should be trackable.[3] Patients undergoing neurosurgical procedures who were born after 1997 should not be exposed to instruments that have previously been used on patients born before 1997. This is to protect the substantially lower variant CJD risk of patients born since 1997, when BSE-contaminated beef products were removed from the UK food chain.

Variant CJD: variant CJD was first reported in 1996. There have been 177 definitive and probable deaths from variant CJD in the UK.[2] Biochemical, neuropathological and transmission studies show conclusively that the agent responsible for prion disease in cows, BSE, is the same agent responsible for variant CJD.[4] Most people who have developed variant CJD have lived in the UK. Many of those who were diagnosed in other countries had previously resided in the UK and been exposed to BSE-infected meat. Exposure is mostly likely through consumption of bovine meat products contaminated with infected bovine brain or other central nervous system tissue.

Although the incidence of variant CJD cases peaked in 2000 and has since been declining, controversy remains about how many people carry the infectious prion protein and will eventually develop disease. A study of 63,000 pairs of tonsils failed to detect any abnormal prion protein, suggesting that the prevalence of variant CJD in the British population was zero.[5] Another study[6] of 12,674 tonsillar and appendix tissue samples found deposits of PrP^{SC} in three specimens suggesting a prevalence of 237 cases of asymptomatic variant CJD per million people. A further study[7] looking at 32,441 appendices found an incidence of between 412 and 733 per million. On balance, the published studies suggest a prevalence of between 1 per 4000 and 1 per 10,000 of the UK population. These rates far exceed those of proven variant CJD cases. This may be explained by the existence of a hypothetical long asymptomatic carrier state.

Before December 2009 all definite cases of variant CJD had been homozygous for methionine at the polymorphic codon 129 of PRNP. However, a possible case of variant CJD has now been reported in an individual heterozygous for the codon. This raises the question of whether such heterozygotes may develop disease with longer incubation periods. This patient did not have a post-mortem and consequently the diagnosis was not confirmed. Abnormal protein from appendiceal specimens in asymptomatic individuals was all homozygous for valine.[7]

Variant CJD differs from sporadic CJD in a number of ways.[8] It affects mainly young people (Table 1). In contrast to sporadic CJD, PrP^{SC} is not only present in CNS tissue but also in the tonsils and other lymph glands and in the appendix and other intestinal tissue. PrP^{SC} is also expressed in the cellular elements of blood. Diagnosis of variant CJD is supported by MRI findings of a characteristic abnormality seen in the posterior thalamic region, the so-called pulvinar sign. Diagnosis is confirmed by tonsillar biopsy, which is both sensitive and specific. Examination of the CSF may be unremarkable. The 14-3-3 test is not as sensitive for variant CJD as for sporadic CJD and is consequently not routinely used in clinical diagnosis.

A blood test has been developed to detect prion infection in variant CJD. This prototype blood test could facilitate a large screening programme for asymptomatic prion infection.[9] Given the absence of treatment options, the utility of a positive test remains unclear. Effective screening may enable cost reductions in sourcing blood products from overseas if the risks of variant CJD transmission can be eliminated.

No effective treatment for CJD has emerged. Various drugs have been studied, including intraventricular pentosan polysulphate, quinacrine, tetracycline compounds and flupirtine. No trial drug has shown either cure or definitive halting of disease progression.[2]

Anaesthetic implications

Contamination of airway devices

Laryngoscope blades come into contact with lymphoid tissue routinely during conventional laryngoscopy. Contamination with lymphoid tissue occurs even if a person has undergone a