Prion diseases

SIMON FLEMINGER and DAVID CURTIS

After being regarded for many years as intriguing curiosities (Harrison & Roberts, 1991), the prion diseases have entered the limelight and have had an impact on Britain's politics and economics in a fashion unparalleled at least since the arrival of AIDS. This has followed from the discovery of an apparently new variant of Creutzfeldt–Jakob disease (CJD; Will *et al*, 1996), with the worrying possibility that human prion disease might be acquired from exposure to beef products infected with bovine spongiform encephalopathy (BSE), a bovine prion disease. Of particular concern to psychiatrists is that patients with the new disease often present with psychiatric symptoms.

These diseases are invariably fatal and the only test that can confidently exclude the diagnosis is a brain biopsy. At present the disease is exceedingly rare; but because of its high media profile it now seems inevitable that, whether the new disease becomes common or not, British psychiatrists will be exposed to patients with hypochondriacal fears that they have the disease.

INTRODUCTION TO PRION DISEASES

Prion diseases occur when prion protein (PrP), a normal brain protein, undergoes a conformational change into an insoluble form (Prusiner & Hsiao, 1994). The insoluble form is poorly metabolised, accumulates and causes cell death, spongiform changes, and is sometimes deposited as amyloid. The normal, soluble form of the protein is denoted PrP^{C} (prion protein, cellular) and has unknown function; animals genetically engineered to lack prion protein seem entirely normal (Büeler *et al*, 1992), although it is possible to identify subtle changes in their synaptic function *in vitro* (Collinge *et al*, 1994). The insoluble form is termed PrP^{Sc} (prion protein, scrapie, as it was first identified as the agent which causes scrapie in sheep), even when it is responsible for causing CJD. It is resistant to proteases and indeed many of the agents which normally inactivate proteins, including moderately high temperatures. In the normal soluble form the protein molecule is arranged so that it contains about 40% α-helices and essentially no (3%) β-sheet, whereas in the insoluble conformation α-helices are decreased and the β-sheet content is about 40% (Cohen *et al*, 1994). The conformational change from PrP^{C} to PrP^{Sc} can occur in three different ways (Cohen *et al*, 1994):

(a) *Spontaneously* (Fig. 1*a*). Most often, at least in CJD, it appears that the conformational change from one form to the other occurs spontaneously. This causes sporadic disease, without any known risk factors, and currently accounts for at least 85% of British cases of CJD. It is possible that at least a proportion of these cases are due to some specific mechanism which goes undetected, such as somatic mutation of the PrP gene in cells in the brain, or exposure to an environmental pathogen.

(b) *Genetically* (Fig. 1*b*). An abnormality in the gene coding for PrP produces a protein which is unstable and undergoes a fatal conformational change into PrP^{Sc}. In these circumstances the disease displays an autosomal dominant pattern of transmission, and this currently accounts for about 10% of cases of CJD. Different mutations in the gene can produce different variants of human prion disease. For example, one form of Gerstmann–Sträussler syndrome (GSS), a disease which usually presents with cerebellar ataxia, is due to a mutation at codon 102 of the gene resulting in the substitution of a leucine for a proline residue in the prion protein (Hsiao *et al*, 1989).

(c) *Transmissibly* (Fig. 1*c*). It was the search for the transmissible agent which led Prusiner (1982) to coin the term prion (standing for proteinaceous infectious agent). Infection occurs because the abnormally conformed protein PrP^{Sc} can induce conformational change in the normal soluble protein, PrP^{C} to produce an additional copy of itself. The corrupt protein is able to pervert its innocent neighbours, probably by forming a transient PrP^{Sc}–PrP^{C} complex (Cohen *et al*, 1994). This means that prion disease can be induced in a normal host by exposure to abnormally conformed prion protein. Additionally, whenever a prion protein molecule changes conformation, spontaneously or because of genetically mediated instability, there is a potential to set off a chain reaction in which each new molecule of PrP^{Sc} will act as a template and produce further copies.

The prion diseases are therefore quite unlike other infectious diseases which require genetic material, either viral or bacterial, to be transferred. The same disease is both heritable and transmissible. This is dramatically illustrated by the

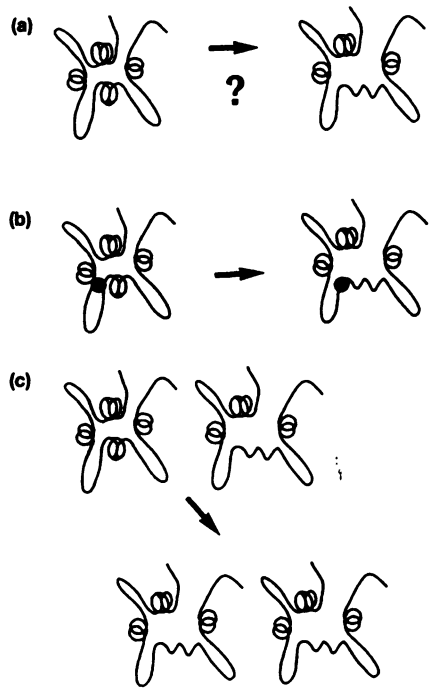

Fig. 1 Mechanisms of pathogenesis. Prion disease occurs when normal PrP^{C} with high α-helix content changes conformation to PrP^{Sc} with a substantial β-sheet content. (a) PrP^{C} to PrP^{Sc} conversion may occur spontaneously, resulting in sporadic cases. (b) A mutation in the gene encoding PrP results in an amino acid substitution, probably in an α-helix region which then becomes unstable leading to hereditary disease. (c) PrP^{Sc} can act as a template to induce conformational change in PrP^{C}, allowing transmission of the disease between different hosts.

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observation that brain material from several members of a family with autosomal dominant GSS (Hsiao *et al*, 1989) transmitted disease to animals.

Incubation times and the species barrier

Prion disease can be experimentally induced in one animal by directly inoculating its brain with PrP^{Sc} derived from another. This is the quickest and most reliable route but incubation takes months and occasionally years. 'Infection' can also follow ingestion of PrP^{Sc}, although transmission by this oral route is generally more difficult. In humans iatrogenic transmission of CJD has occurred through contaminated neurosurgical instruments and the use of cadaveric pituitary extracts. Kuru was maintained through cannibalistic rituals, demonstrating that the oral route can lead to disease in humans. The incubation time for kuru can be as long as two to three decades (Prusiner *et al*, 1982).

Although all animals have some form of prion protein there are variations between species which mean that it can be difficult for the PrP^{Sc} from one species to induce conformational change in the PrP^{C} of another species. Thus, epidemiological evidence demonstrates that sheep PrP^{Sc}, the cause of scrapie which is endemic in many sheep-rearing areas, is not capable of causing disease in man (Will, 1993). On the other hand, if there are sufficient similarities between the PrP of different species, then the species barrier can be crossed, although generally such transmission will be more difficult and result in a longer incubation time than is the case for transmission between members of the same species.

In experimental situations transmission between many different pairs of species has been shown to be possible, although usually by direct cerebral inoculation. Thus GSS PrP^{Sc} can induce disease in monkeys and rodents, while BSE PrP^{Sc} can induce disease in mice, sheep, goats and monkeys. It is possible that the BSE epidemic in cattle was due to exposure to sheep PrP^{Sc} in animal feed.

There are several amino acid sequence differences between human and bovine PrP and this might suggest that transmission of BSE to humans is unlikely. But there has been a drastic reappraisal of this risk recently because of the recognition of a few cases of an apparently novel type of human prion disease.

FROM CLINICAL SYNDROME TO PATHOGENESIS

What is the nosological relationship between CJD, the spongiform encephalopathies and the prion diseases?

CJD is rare; there are about 50 cases a year in the UK with a peak incidence between 50 and 70 years of age. It is characterised by a rapidly progressive dementing illness, often with severe cerebellar and/or extrapyramidal signs and myoclonus, causing death usually within a few months (Will & Mathews, 1984). Akinetic mutism and cortical blindness are recognised features. Characteristic triphasic complexes are found on EEG in about 80% of cases.

CJD is a spongiform encephalopathy; histopathology demonstrates spongiform change which consists of fine vacuolation of the neuropil of the grey matter. This is associated with astrocytosis and neuronal loss. Amyloid plaques, although common in two other human spongiform encephalopathies, kuru and GSS, are observed in only 5–10% of patients with CJD (Bell & Ironside, 1993). The spongiform encephalopathies all show similar spongiform change in the brain. The clinical picture across different species is similar; they produce a rapidly progressive and fatal degeneration of the central nervous system, often with prominent ataxia.

In humans immunohistochemistry demonstrates the presence of PrP^{Sc} in the brain of all cases with a histopathological diagnosis of a spongiform encephalopathy (Brown *et al*, 1986; Serban *et al*, 1990; Brown *et al*, 1993). However, PrP^{Sc} has been detected in the absence of spongiform change (Collinge *et al*, 1990), and some familial cases of atypical CJD or other degenerations of the CNS, with documented mutations of the prion protein gene, show little if any spongiform change. In general prion diseases can be reliably distinguished from other causes of neuronal degeneration provided that the brain is examined for PrP^{Sc}, or genetic analysis of the PrP gene is performed.

A NEW VARIANT OF CJD IN THE UK

The 10 cases described by Will *et al* (1996) differed from typical CJD in a number of ways. Onset was at an unusually young age, with most cases being in their 20s. The course of the illness was relatively prolonged with half of the cases surviving longer than a year. The subjects tended to present with anxiety, depression, withdrawal and other behavioural changes (Will, 1996, http://www.bmj.com/bmj/bse/clinical.htm). Four patients had dysaesthesiae in limbs or face as the first evidence of neurological involvement, which was generally followed, after a few weeks or months, by gait and limb ataxia. Cognitive impairment generally appeared relatively late. The majority of the patients developed myoclonus, but the typical EEG features of CJD, periodic triphasic complexes, were absent. Histopathology showed marked amyloid plaque formation, in addition to the spongiform changes, in eight cases.

When confronted with an apparently new disease it is worth considering whether there may be alternative explanations. For these new cases, the unusual clinical picture might be thought to reflect the early age of onset, which is known to be associated with longer duration of illness (Brown *et al*, 1984). Brown *et al* (1984) also found that long duration of the illness in CJD was associated with less evidence of myoclonus, neurological signs or characteristic EEG changes. However, analysis of six young-onset cases, all from outside of the UK (Packer *et al*, 1980; Monreal *et al*, 1981; Brown *et al*, 1985; Kulczycki *et al*, 1991), suggests that they bear little resemblance to the new British ones, either clinically or on histopathological grounds; none of them showed amyloid plaques.

It seems unlikely that the new cases are a result of ascertainment bias from doctors' increasing awareness of CJD; it does not seem likely that a dementing illness in a young adult would go uninvestigated. However, the pathological changes in patients with CJD are "not consistently present throughout the CNS and vary enormously from case to case" (Bell & Ironside, 1993). The main differential diagnosis on histopathological grounds is Alzheimer's disease. Given these observations it would be reassuring to have some measure of the reliability of the histopathological diagnosis of CJD among neuropathologists; a degree of inconsistency would suggest that neuropathologists might in the past have failed to make the diagnosis in specimens which would now be identified as possible cases of CJD.

Overall it seems reasonable to regard the new cases as representing a new form of human prion disease, although the relationship with BSE remains unclear.

It is perhaps worth emphasising that at the time of writing there is no direct evidence

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to link these cases with BSE, and suspicions are based entirely on the temporal and geographical coincidence of the BSE epidemic in Britain being followed a few years later by appearance of these cases. Another clue to the possible link comes from the concept that the source of infection of a prion disease may determine the expression of the disease. Since all prion diseases are based on a conformational change in a PrP it might seem surprising that different variants can occur at all. With the genetic cases (e.g. familial CJD and GSS) the different clinical patterns of disease could be due to subtle differences in the PrP^{C} molecule resulting in slightly different effects on the structure of the consequent PrP^{Sc} which might affect the pattern of neuronal degeneration in the central nervous system.

In animals different clinical pictures result from different transmitting PrP^{Sc} molecules (Bruce *et al*, 1994). Presumably the exact shape of the PrP^{Sc} has some effect on the nature of the conformational change induced in the host PrP^{C}, and this in turn can result in clinical and pathological differences. It is thus at least plausible that the new disease is a result of exposure to a novel PrP^{Sc}, that of BSE, and that this leads to a different clinicopathological picture from those of the other human prion diseases described to date.

The route of transmission could be another factor which determines the clinical picture, and could for example explain why the clinical picture of kuru, which is orally acquired, is rather different from that of CJD. In some respects the new variant of CJD resembles kuru rather more than classical CJD. This adds support to the notion that these new cases may have acquired the disease orally.

AN EPIDEMIC OF HYPOCHONDRIASIS?

If there is no increase in the prevalence of CJD, perhaps one in 100 psychiatrists will see a case of CJD over the next five years. However, many more may be asked to assess patients who have a fear that they have contracted the disease. Anxiety, depression and subjective cognitive symptoms may be a feature either of hypochondriasis or of CJD.

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At present no non-invasive investigation can confidently exclude CJD. If the illness does not progress after a period of several months to a year, to more definite cognitive impairment or neurological symptoms, then this effectively rules out the diagnosis. The management will be similar to that of AIDS or cancer hypochondriasis. It will require a thorough history and examination, appropriate education, avoidance of over-investigation, treatment of any underlying psychiatric condition and specific psychological treatment when appropriate.

Should a clinician suspect that a patient does have CJD they should contact the National Creutzfeldt–Jakob Disease Surveillance Centre at the Western General Hopital in Edinburgh for advice.

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