Perceptions of prion disease

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The term prion disease was devised by Stan Prusiner¹ and refers to all the transmissible spongiform encephalopathies of animals (principally scrapie in sheep and bovine spongiform encephalopathy (BSE) in cows) and humans, together with those cases of prion disease which lack the diagnostic hall-

marks of spongiform encephalopathy (SE) and experimental transmissibility and which have, therefore, been termed "atypical prion dementia". Biochemical and immunohistological evidence of prion disease in atypical cases can sometimes be very scanty, and laboratory tests (some of which require fresh or frozen brain tissue) are often not available for individual cases, making diagnosis a matter of some controversy. In all prion diseases, however, a normal brain protein, prion protein (designated PrP^c), whose function remains unknown, is converted to an abnormal form called PrP^{sc}. PrP^c is encoded by a single copy gene on chromosome 20 in humans (the PrP gene). The mechanism by which this conversion occurs is currently the subject of much research and speculation.

The various presentations of prion disease are referred to by different names according to their clinical features, neuropathological picture, and mode of acquisition (table 1). It would be a mistake, however, to refer to these different presentations as if they were separate entities which have an identity independent of the circumstances of their occurrence. The nature of the disease necessarily depends on the individual in which it occurs and it therefore makes little sense to talk about "human mad cow disease" or "mouse scrapie".

Prion disease differs from other transmissible diseases in that no "organism" causing "infection" has been identified. What seems to be transmissible is the initiation of the physicochemical process whereby PrP^c is converted into PrP^{sc}. One supposition is that molecules of PrP^c act as a seed in the conversion of PrP^c to PrP^{sc}. As these newly modified molecules will also act as *agents provocateurs*, it follows that the formation of PrP^{sc} will progress exponentially. This will give the appearance, in the *acquired* cases, of a long "incubation" period, followed by a terminal phase in which the pathological process proceeds with increasing speed. The duration of the early "silent" phase will depend on the amount of abnormal protein which is introduced at the time of contamination and the similarity between the contaminating PrP^{sc} and the host PrP^c.

It is supposed that molecules of PrP^c with the normal, wild type amino acid sequence also have a very low spontaneous probability of converting into PrP^{sc}, such that prion disease will occur spontaneously, but very rarely, in people with a normal PrP gene. This is thought to account for the incidence of one in a million with which sporadic Creutzfeldt-Jakob disease (CJD) is observed in the general population. At least 19 differ-

Table 1 Presentation of prion disease

Kuru	Mode of acquisition Age at onset Incubation time Duration of symptoms Presenting symptom Neuropathology	Cannibalism Any age, often young 2-40 years < 3 years Ataxia Neuronal loss, astrocytosis sometimes SE sometimes PrP plaques
Acquired Creutzfeldt-Jakob disease (CJD) (a) Peripheral route	Mode of acquisition Age at onset Incubation time Duration of symptoms Presenting symptom Neuropathology	Human pituitary derived Hormone injections Young adult 2-> 30 years < 3 years Ataxia SE Neuronal loss, astrocytosis sometimes PrP plaques
(b) Central route	Mode of acquisition Age at onset Incubation time Duration of symptoms Presenting symptom Neuropathology	Neurosurgery, dura mater grafts, corneal graft Any age < 2 years < 3 years Dementia SE Neuronal loss, astrocytosis sometimes PrP plaques
Sporadic CJD	Mode of occurrence Age at onset Incubation time Duration of symptoms Presenting symptom Neuropathology	Idiopathic Late middle age — < 2 years Dementia SE Neuronal loss, astrocytosis sometimes PrP plaques
Familial CJD	Mode of acquisition Age at onset Incubation time Duration of symptoms Presenting symptom Neuropathology	Mutation in PrP gene usually at codon 200 Middle age — < 2 years Dementia SE Neuronal loss, astrocytosis sometimes PrP plaques
Gerstmann-Sträussler-Scheinker disease	Mode of occurrence Age at onset Incubation time Duration of symptoms Presenting symptom Neuropathology	PrP mutation Middle age — 3-15 years Ataxia or dementia PrP plaques Neuronal loss, astrocytosis sometimes NFTs sometimes SE
Fatal familial insomnia	Mode of occurrence Age at onset Incubation time Duration of symptoms Presenting symptom Neuropathology	Mutation in PrP gene at codons 178 plus 129 Middle age — ~ 15 months Insomnia, dysautonomia Neuronal loss, astrocytosis especially in thalamus
Atypical prion dementia	Mode of acquisition Age at onset Incubation time Duration of symptoms Presenting symptom Neuropathology	PrP mutation, often insertion Early middle age — 2-15 years Insidious dementia Neuronal loss, astrocytosis sometimes plaques sometimes SE

SE = spongiform encephalopathy; NFT = neurofibrillary tangles.

Part of a pedigree of fatal neurological disease associated with a mutation at codon 102 of the PrP gene.⁵ Although all three patients share the same primary mutation, one had an illness conforming to the definition of CJD, one had a disease characteristic of Gerstmann-Sträussler-Scheinker disease (GSS), and the disease and the neuropathology in the third was anomalous such that the patient was described as having atypical prion dementia (APD).

ent mutations within the PrP gene have been identified where the probability of the gene carrier developing prion disease by later middle age is nearly 100%. These constitute the inherited forms of prion disease. Some previously unsuspected cases of atypical prion dementia have been identified by genetic analysis.²³ It should be emphasised, however, that a mutation in the PrP gene does not, of itself, constitute a diagnosis of prion disease as such a mutation does not preclude other, much more common, neurological diseases, and there are some common mutations (polymorphisms) in the PrP gene which seem to be harmless. Genetic analysis is, in any case, only useful for the detection of inherited forms of prion disease, which probably constitute no more than 10–15% of all cases.

Different mutations in the PrP gene account for much of the clinical difference between separate pedigrees with inherited prion disease, although the common polymorphisms in both alleles of the PrP gene can also be important. Thus—for example, a mutation at codon 178 of the PrP gene in conjunction with a valine at codon 129 of the same allele results in a clinical picture of CJD while the same mutation at codon 178 in conjunction with a methionine at codon 129 results in fatal familial insomnia (FFI) (table 1).⁴ The figure shows a small part of a large pedigree in which prion disease is associated with a mutation at codon 102 of the PrP gene.⁵ The occurrence of the three main types of human prion disease within such a small familial group demonstrates the dependence of the clinical picture on individual host factors rather than the primary mutation.

As genetic analysis of the PrP gene has detected cases of prion disease which could not have been differentiated from other types of dementia on clinical grounds (because age at onset was late and the progression of dementia was slow and unremarkable), the question has been raised as to how many cases of sporadic atypical prion disease go undetected. Some such cases will inevitably be missed and a systematic search is impracticable. Because prion disease has an incidence of only 1 in 1 000 000, and Alzheimer type dementia has an incidence of, perhaps, 1 in 10 by extreme old age, a search for cases of prion disease by gene analysis or biochemical investigation in elderly demented patients who have none of the distinguishing features of prion disease (table 2) is unlikely to be worthwhile. On the other hand, Alzheimer's disease in people under 40 years of age is also so rare that the chance of a patient with very rapid, familial dementia of early middle age onset having prion disease may be as high as 10%.

As a definitive diagnosis of prion disease can only be made using modern laboratory techniques to detect the presence of PrP^{sc}, it is clear that patients with prion disease must have received a different diagnosis in the past. Where large pedigrees of inherited prion disease have now been traced, it is possible to identify the obligate carriers of the PrP gene mutation in previous generations. While some of these gene carriers died prematurely of illnesses which were presumably unrelated to prion disease, there is documentary evidence for many of them from hospital notes, death certificates, or recorded place of death (for example, in an asylum) that they were demented at the time of death. Table 3 gives a brief indication of some of these diagnoses in a pedigree with a mutation in the PrP gene.⁶⁷ Interestingly, early diagnoses tended to be non-specific and therefore essentially correct (though sometimes quaint). These gave way to diagnoses which were specific, confident (and fashionable) but which were actually incorrect, before they were finally replaced by the current diagnosis of prion disease. Data on the evolution of clinical diagnoses before death are more scarce because they require a full set of clinical notes. It is discernible, however, that a neurological diagnosis was often preceded by a psychodynamic interpretation, unresolved grief on the premature death of a parent sometimes being cited.

An increasingly appreciated feature of the neuropathology of prion disease in a proportion of cases is the accumulation of deposits of PrP^{sc} in the form of insoluble plaques with the tinctorial properties of amyloid. PrP^c is rapidly broken down in vivo whereas PrP^{sc} does not break down. PrP^{sc} accumulates in neurones, particularly in dendrites, causing them to swell and form vacuoles and then to die. PrP^{sc} is then deposited extracellularly. In a pedigree with a mutation at codon 198, PrP amyloid is composed of a truncated form of PrP^{sc} with a molecular weight of about 11

Table 2 Pointers to prion disease

Non-obligatory, non-exclusive, clinical indicators of prion disease:

1 Very rapid progressive dementia

The median duration of CJD is about three months, although the maximum for prion disease is > 15 years. Most other dementias have a duration of several years

2 Ataxia, myoclonus, and other movement disorders superimposed on progressive dementia

3 Family history and very early onset

The ratio of Alzheimer's to prion disease decreases with age from about 10 000:1 in extreme old age to 10:1 in dementia cases aged under 45 years. Most cases aged under 45 years of either of these diseases are familial

Table 3 Historical diagnoses in a pedigree with inherited prion disease

Year at death	Diagnosis	Age at death
1864	Decay of dementia	47
~1866	General paralysis of the insane	~36
~1883	Brain disease and paralysis	~60
1891	Decay of epilepsy	39
1894	General paralysis of the insane	37
1896	<i>Trauma, exposure</i>	39
1897	Spinal sclerosis	39
1900	Hereditary dementia	44
1901	General paralysis of the insane	42
1912	Senile decay and dementia	62
1923	General paralysis of the insane	40
1927	Uraemia	47
1930	Cerebral thrombosis	42
1930	<i>Dementia praecox</i> dementia	39
1932	<i>Died in asylum</i>	54
1933	Exhaustion from dementia	46
1937	Cerebral softening	57
1942	<i>Died in asylum</i>	35
1944	Toxaemia, pressure sores	43
1948	Heidenham's syndrome	38
1950	? <i>Huntington's disease</i>	
	? CJD presenile dementia	46
1956	<i>Demented</i>	43
1960	? <i>Huntington's disease</i>	
	cerebral thrombosis	46
1961	Presenile atrophy	56
1963	Cerebral atrophy	37
1964	Cerebral atrophy	52
1964	Presenile dementia	40
1966	<i>Ataxic, demented, burns</i>	53
1968	Pick's disease	43
1968	Pick's disease	41
1971	<i>Demented</i>	44
1974	<i>Demented</i>	46
1974	Presenile dementia	57
1974	<i>Demented, choked</i>	41
1974	Marasmus, traumatic dementia	42
1981	<i>Demented, head injury</i>	45
1986	Huntington's disease	45
1987	<i>Demented, residential care</i>	48
1987	Alzheimer's disease, suicide	43
1988	Gerstmann-Sträussler syndrome ⁶	43
1988	<i>Alzheimer's disease?</i>	
	<i>Huntington's disease?</i> presenile dementia	36
1990	<i>Alzheimer's disease?</i>	
	Huntington's disease	53

In 1992 there were a further nine living affected family members.

Diagnosis: normal print refers to death certificate or medical notes at time of death.

Italics refers to early medical notes or other documentation.

Data adapted from Collinge *et al.*⁶

Cases include all except two known obligate carriers (cases with affected offspring) from the progenitor couple (who died before 1850) and 20 cases with as yet no affected offspring.

kilodaltons (PrP¹¹).⁸ Diffuse (non-amyloid) deposits of a larger component of PrP^{sc} are also seen in association with the amyloid deposits.⁹ Kitamoto *et al.*¹⁰ have presented evidence to suggest that in cases of Gerstmann-Sträussler-Scheinker (GSS) disease with a mutation at codon 102, the PrP^{sc} in amyloid plaques has a molecular weight of 25–30 or 15–20 kilodaltons and is composed of the product of the mutant allele. PrP^{sc} formed from the product of the normal allele in this pedigree may also be present in brain but does not aggregate to form amyloid. In another case of a very slowly progressive dementia in which a shortened form of PrP^{sc} is produced, only the short molecule was found in the amyloid plaques.¹¹ In vitro, PrP^{sc} (unlike PrP^c) is difficult to digest enzymatically beyond a partially truncated form which readily forms amyloid fibrils under certain conditions. Small, synthetic portions of PrP, especially those which have an amino acid sequence corresponding to the mutated sequence found in inherited cases, will also

readily form amyloid fibrils.^{12 13} All these results suggest that the partial breakdown of PrP^{sc} may produce protein products which spontaneously polymerise into amyloid fibrils which then aggregate to form plaques.

With the exception of cases of CJD associated with a mutation at codon 200, almost all cases of prion disease resulting from a mutation in the PrP gene have plaques or deposits of PrP amyloid. This may occur because almost all cases of inherited prion disease carry both a wide type and a mutant PrP allele and mixtures of mutant and wild type PrP peptides are particularly amyloidogenic.¹³ PrP amyloid deposits are usually only found in those sporadic cases which are heterozygotes for the methionine/valine polymorphism at codon 129 of the PrP gene.¹⁰ Because the deposition of PrP amyloid is associated with long duration of illness and an absence of SE¹⁴ and the long duration, non-SE cases are those from which it is the most difficult to transmit SE, it is possible that PrP amyloid may consist of an inactivated form of PrP^{sc} which is no longer infectious.

This brief review of prion disease should indicate that the core disease of CJD can be fairly readily diagnosed in life as a very rapidly progressive dementia with ataxia, myoclonus, and a characteristic electroencephalogram, and can be confirmed at post mortem examination by the presence of SE and, sometimes, PrP amyloid plaques. The more atypical forms, however, cannot be differentiated clinically from other forms of dementia and post mortem examination of the brain may not resolve the diagnosis without the use of immunohistological techniques. None the less prion disease is a distinct entity, all cases being related by the accumulation in brain of PrP^{sc}. Searching for these cases broadens the observed phenotype of prion disease and the identification of inherited cases is important for genetic counselling. Understanding prion disease is also important in relation to the production of amyloid. The recent demonstration that β amyloid plaques occur in the brains of middle-aged monkeys which have been injected intracerebrally with brain material containing β amyloid taken from a patient with Alzheimer's disease, but not in the brains of age-matched monkeys or those injected with brain which did not contain β amyloid,¹⁵ suggests that there may be close similarities in the mechanism of production of PrP amyloid and β amyloid. Although prion disease and Alzheimer's disease differ in that the former is very rare and the latter is relatively common, they are both neurodegenerative diseases of mature onset; the ratio of familial to sporadic cases is about 1:8 for each disease; familial cases have a mean earlier age at onset than sporadic cases, and mutations in the precursor protein are found in a large proportion of familial cases of each disease. The observation that transmission cannot be achieved from cases of atypical prion dementia and that β amyloidosis may be transmissible experimentally serves to remove transmissibil-

ity as a truly distinguishing feature of prion disease and allows us to perceive prion disease in a new light.

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