Prion diseases

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Abstract

Prion diseases are transmissible and fatal neurodegenerative diseases affecting humans and animals, in which the infectious agent is composed of misfolded and multimeric forms of cellular prion protein. These conditions can be sporadic, inherited or acquired. Rapidly progressive dementia and ataxia are the common themes in the clinical presentation, but these can be accompanied by a wide variety of neurological or psychiatric syndromes. Neuropathological examination of brain tissue remains the only way of making a definite diagnosis, but major advances in magnetic resonance brain imaging, such as diffusion-weighted sequences, and cerebrospinal fluid prion amplification assays have proved to be reliable ante mortem diagnostic tools. Prion protein gene (*PRNP*) analysis is also recommended, to rule out Mendelian forms and provide the codon 129 genotype, which has profound effects on incubation period, susceptibility, duration of illness, clinical phenotype and neuropathology. At present, there is no effective treatment for prion disease.

Keywords Bovine spongiform encephalopathy; Creutzfeldt–Jakob disease (CJD); dementia; kuru; MRCP; nervous system infections; neurodegenerative; prion; protein-misfolding disorders; variant CJD

Key points

- The possibility of prion disease should be considered for every patient presenting with rapid cognitive decline and/or gait ataxia, particularly in those undergoing neuro-invasive procedures
- All patients suspected to have prion disease in the UK should be referred jointly to the National CJD Research & Surveillance Unit in Edinburgh, and the National Prion Clinic in London
- Diffusion-weighted magnetic resonance imaging of the brain and cerebrospinal fluid real-time quaking-induced conversion (RT-QuIC) assay have emerged as highly sensitive and specific tests for sporadic Creutzfeldt-Jakob disease (CJD).
- Prion protein gene analysis should be considered for all patients suspected to have prion disease, to determine the codon 129 genotype and exclude highly penetrant mutations in the prion protein gene
- Post-mortem examination of the brain remains the only method of making a definite diagnosis; post-mortem surveillance is now particularly important given the first reported case of variant CJD in a patient who is MV at codon 129 of the prion protein gene

Introduction

Prion diseases form a group of neurodegenerative disorders including sheep scrapie, bovine spongiform encephalopathy (BSE) and human Creutzfeldt–Jakob disease (CJD). Human prion diseases are classified as sporadic, inherited or acquired. Doctors should consider them in patients presenting with rapidly progressive dementia and/or ataxia, and in those with dementia and additional neurological or psychiatric features.

Molecular basis of prion diseases

The infectious agent comprises misfolded forms of the host cellular prion protein. In its normal form, the prion protein (PrP^{C}) is found on the cell surface and adopts a predominantly α-helical structure; the misfolded prion protein (PrP^{Sc}) forms amyloid assemblies rich in β-sheet structure that are resistant to protease degradation.[1] The basis of transmissibility between individuals (and different species) is the ability of PrP^{Sc} to act as a template that converts PrP^{C} to PrP^{Sc}. It is now becoming increasingly clear that misfolded proteins in other neurodegenerative diseases, such as amyloid β in Alzheimer's disease and α-synuclein in Parkinson's disease, can spread by a similar 'prion-like' mechanism.[1]

Sporadic Creutzfeldt–Jakob disease (sCJD)

Epidemiology: sCJD remains the most commonly encountered human prion disease, accounting for 85–90% of all cases. The incidence is about 1–2 per million worldwide. There is no gender difference. Peak incidence is in the seventh decade. No definite environmental risk factors have been found. Genetic risk factors have been identified; individuals who are heterozygous (methionine–valine) at codon 129 of the prion protein gene (*PRNP*) are less likely to develop disease.

Clinical features: sCJD is characterized by rapidly progressive dementia. Other key features include cerebellar ataxia, myoclonus, visual hallucinations and pyramidal and extrapyramidal signs. Less frequently, visual distortions and cortical blindness, or gait ataxia can predominate in the early phase of the illness, while cognition remains relatively intact. Patients eventually become akinetic and mute before death. Disease duration averages 4–6 months, but long-surviving patients with durations >1 year account for 10% of cases.

Investigations and diagnosis: investigations include electroencephalography (EEG), magnetic resonance imaging (MRI), cerebrospinal fluid (CSF) examination (proteins 14-3-3 and S100B) and real-time quaking-induced conversion (RT-QuIC).

The most useful and non-invasive supportive investigation is diffusion-weighted MRI of the brain,[2] which shows restricted

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diffusion in the basal ganglia, thalami or cortex (cortical ribboning); high signal can also be seen in these structures in fluid-attenuated inversion recovery (FLAIR) and T2-weighted sequences, but less frequently so.

The presence of protein 14-3-3 (rapid axonal degeneration) and raised concentrations of S100B (glial marker) in the CSF also support the diagnosis of sCJD, but RT-QuIC[3] (prion amplification assay) has recently emerged as a highly sensitive (≥90%) and specific (≥95%) test. The typical generalized periodic complexes on EEG are found in as few as 30% of sCJD patients, if done as a one-off, and are almost restricted to patients who are codon 129MM.

Definitive diagnosis is by brain biopsy or post mortem findings. Typical findings include spongiform change, neuronal loss and astrocytosis (Figure 1). PrP^{Sc} deposition can also be demonstrated by immunohistochemistry and western blotting of brain tissue homogenates (Figure 2). The most recently updated epidemiological diagnostic criteria are available online (http://www.cjd.ed.ac.uk/sites/default/files/diagnostic%20criteria.pdf).

sCJD is less likely when the dementia is of >2 years' duration, typical neurological signs are absent or there is evidence of inflammation on CSF examination. Patients in the UK should be referred to the National CJD Surveillance Unit, Edinburgh, and the National Prion Clinic, London, as soon as the diagnosis is suspected.

Differential diagnosis: alternative diagnoses include:

- neurodegenerative dementias (e.g. dementia with Lewy bodies, Alzheimer's disease)
- cerebral vasculopathies (ischaemic, amyloid, inflammatory, vascular, lymphoma)
- encephalitis (e.g. idiopathic, antibody-mediated, paraneoplastic)
- encephalopathy (e.g. hepatic, anoxic brain damage).

Management: there is no known treatment delaying disease progression. Drugs may alleviate symptoms, for example clonazepam or levetiracetam for myoclonus, donepezil for distressing visual hallucinations, and risperidone for agitation. CJD is not contagious through routine personal care. Guidelines to prevent transmission through blood transfusion and invasive procedures are available (https://www.gov.uk/government/publications/guidance-from-the-acdp-tse-risk-management-subgroup-formerly-tse-working-group).

Inherited prion disease

Many mutations have been described in the prion protein gene, which is located on the short arm of chromosome 20.[4] All display an autosomal dominant inheritance pattern, although some pedigrees exhibit reduced penetrance. The most commonly encountered clinical phenotypes in inherited prion disease

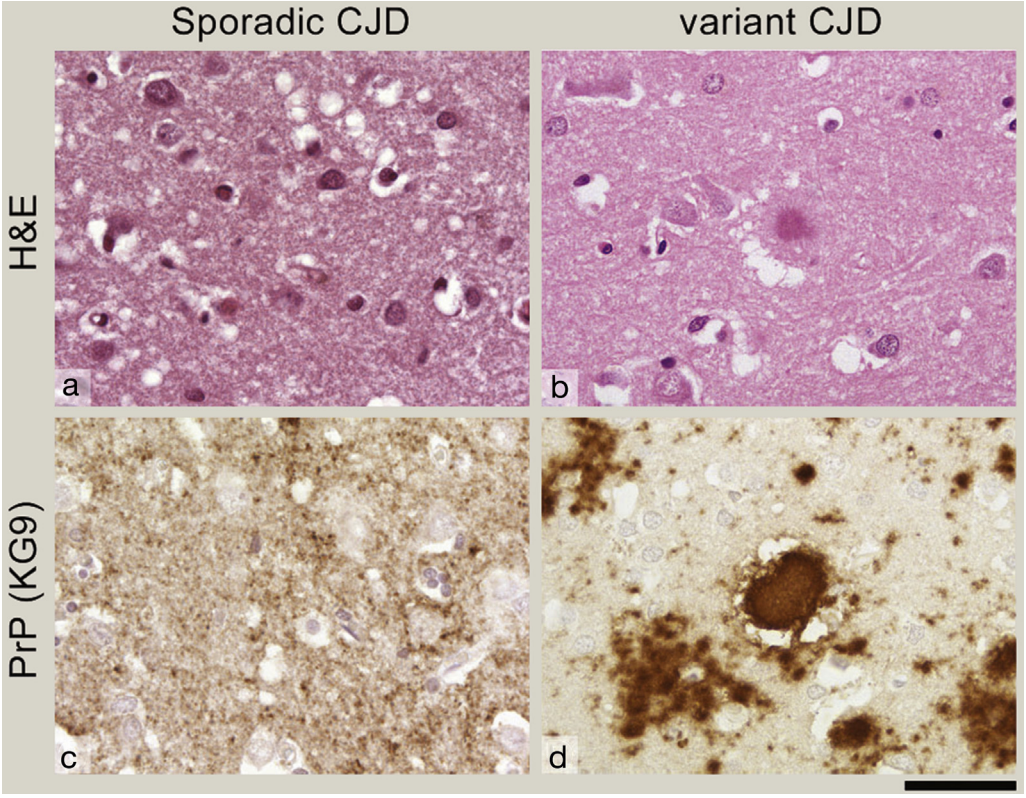

Figure 1 (**a**, **b**) Haematoxylin and eosin (H&E)-stained sections. (**a**) Fine vacuolization, commonly known as spongiform degeneration or spongiosis. The larger nuclei are neuronal and the smaller nuclei are astrocytic. (**b**) Florid plaque. A round amyloid plaque with a dense core is surrounded by multiple small vesicles. In addition, the cortex in variant CJD (vCJD) can also show variable degrees of spongiosis. (**c**, **d**) Detection of abnormal prion protein using antibody KG9. (**c**) Synaptic pattern of prion protein deposition in sporadic CJD. A fine granular distribution of prion protein and occasional intracellular, dendritic deposition are seen. (**d**) The plaques in vCJD are strongly positive for abnormal PrP, but synaptic deposits are also frequently found. Scale bar, 50 mm.

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