Prion related disorders

Human prion diseases are rare, progressive and fatal disorders of the central nervous system (CNS) which vary in clinical presentation, epidemiological characteristics and aetiology. The diseases are linked by the deposition in the CNS of a post-translationally modified host-encoded protein, prion protein, which is disease associated and may represent the causal transmissible agent. Scientific interest in prion diseases has been stimulated by increasing evidence in support of the prion hypothesis, paralleled by an extraordinary level of public interest following the identification of a novel form of human disease in the UK, new variant Creutzfeldt-Jakob disease (CJD), which may be causally linked to the epidemic of bovine spongiform encephalopathy (BSE).

Although all forms of human prion disease are currently rare, concern about the possibility of such a diagnosis is not uncommon. The clinical features and diagnosis of human prion diseases are described in this review, together with a description of some of the epidemiological characteristics.

Classification of human prion diseases

The different forms of human prion disease are listed in Table 1, classified according to aetiology.

Kuru occurred in the Fore region of Papua New Guinea, and was caused by transmission of the causal agent from person to person in the course of ritual cannibalism. The incidence has markedly declined since the cessation of cannibalism in the late 1950s, although cases are still occurring with incubation periods exceeding 40 years.

Sporadic CJD, which accounts for about 90% of all cases of human prion disease, occurs worldwide with an annual incidence of about one case per million population. Case-control studies have not identified any common environmental or medical risk factor for the development of disease and the cause of sporadic CJD is unknown.

Genetic analysis has demonstrated that the majority of cases are homozygous for methionine at the polymorphic site at codon 129 of the prion protein gene (PRNP) compared with about 40% of the normal population with this genotype.

Familial CJD accounts for about 10% of CJD cases, all of them associated with mutations of PRNP. More than 20 such mutations have been identified, including both point and insertional mutations.

Gerstmann-Straussler Scheinker syndrome (GSS) is associated with a point mutation at codon 102 of PRNP, while fatal familial insomnia (FFI) is linked to a mutation at codon 178. The importance of the codon 129 genotype in the expression of some prion diseases is underlined by the phenotypic variability in association with the mutation at codon 178. Cases expressing methionine in association with this mutation develop the FFI phenotype, while cases with valine have a phenotype similar to sporadic CJD.

CJD has been transmitted accidentally from person to person in the course of a range of medical procedures (Table 2). All iatrogenic transmissions have involved potential cross-contamination with high CNS titres of infectivity; transmission through blood or blood products has not been documented. Guidelines have been introduced to minimise the risks of iatrogenic transmission, for example the recommendation that all neurological or ophthalmological instruments be destroyed after use in patients with CJD.

The incubation period in sporadic CJD is unknown. In iatrogenic CJD with a CNS route of cross-contamination, the incubation period is 1.5–10 years; with a

Table 1. Human prion disease.

| Disease                                      | Distribution          | Aetiology    |
|----------------------------------------------|-----------------------|--------------|
| Kuru                                         | Papua New Guinea      | transmitted  |
| Creutzfeldt-Jakob disease:                   | worldwide             | unknown      |
| sporadic                                      | many countries        | genetic      |
| hereditary                                    | many countries        | transmitted  |
| iatrogenic                                    | many countries        | genetic      |
| Gerstmann-Straussler Scheinker syndrome       | many countries        | transmitted  |
| Fatal familial insomnia                      | UK (40 cases)         |              |
| New variant Creutzfeldt-Jakob disease        | France (1 case)       |              |

Table 2. Iatrogenic Creutzfeldt-Jakob disease worldwide.

| Mode of transmission | No. of cases | Mean incubation period (years) | Clinical |
|----------------------|--------------|-------------------------------|----------|
| Neurosurgery         | 4            | 1.6                           | Visual/cerebellar/dementia |
| Depth electrodes     | 2            | 1.5                           | Dementia |
| Corneal transplant   | 2            | 15.5**                        | Dementia |
| Dura mater           | 69           | 6**                           | Visual/cerebellar/dementia |
| Human growth hormone | >100         | 12**                          | Cerebellar |
| Human gonadotrophin  | 4            | 13                            | Cerebellar |

*range 1.5–30 years **estimated on incomplete data.
peripheral route, as in human growth hormone (HGH)-related CJD, the mean incubation period is about 12 years (range 4.5 to over 25 years). In contrast to sporadic CJD, homozygosity at codon 129 of PRNP, either methionine or valine, increases the risk of developing HGH-related CJD.

**Aetiology of new variant Creutzfeldt-Jakob disease**

New variant CJD was identified in 1996. A causal link with BSE was proposed, as the evidence suggested that this was a new disease restricted to the UK, a country with a potentially novel risk factor in the form of BSE. Subsequent evidence has provided strong support for this hypothesis. Except for one case in France, new variant CJD has not been identified outside the UK despite review of archival clinical and pathological material in a number of countries. Analysis of prion protein subtypes and laboratory transmission studies in mice have demonstrated a remarkable similarity between new variant CJD and BSE, with findings distinct from similar studies in sporadic CJD. One hypothesis is that new variant CJD was caused by the oral transmission of the BSE agent through the consumption of bovine tissues containing significant infectivity, for example beef products containing bovine spinal cord. Future numbers of cases of new variant CJD cannot be predicted. To date, all cases of new variant CJD have been homozygous at codon 129 of PRNP, but cases of human BSE infection in other genotypes may occur in the future, perhaps with a different clinical or pathological phenotype.

**Clinical features of human prion disease (Table 3)**

**Kuru**

After a prodrome of headache and limb pain, kuru presents with a progressive cerebellar syndrome. Initial truncal ataxia, tremor and titubation are followed by gait ataxia and dysarthria. Myoclonus is not a feature, and dementia conspicuous by its absence. Total illness duration ranges from 12–18 months.

**Sporadic Creutzfeldt-Jakob disease**

The paradigm clinical features of sporadic CJD are rapidly progressive dementia and myoclonus, but other features, including cerebellar ataxia and rigidity, are common. The rapidity of progression of the neurological features may be dramatic, and the mean survival

**Table 3. Clinical features of human prion disease.**

| Disease                          | Presenting features                                      | Myoclonus | Terminal stages                  |
|---------------------------------|----------------------------------------------------------|-----------|----------------------------------|
| Kuru                            | Progressive cerebellar syndrome                         | −         | Immobility, no dementia          |
| Sporadic CJD                    | Progressive cognitive impairment + ataxia/rigidity       | +         | Akinetic mutism/dementia         |
| Familial CJD                    | Progressive cognitive impairment or ataxia or...         | ±         | Dementia                         |
| Iatrogenic CJD:                 | CNS route of infection                                  |           |                                  |
| Peripheral route of infection   | Progressive cognitive impairment + ataxia/rigidity       | +         | Akinetic mutism/dementia         |
| Gerstmann-Straussler-Scheinker syndrome | Progressive cerebellar syndrome                      | −         | Dementia                         |
| Fatal familial insomnia        | Dysautonomia, insomnia                                  | ±         | Dementia ±                       |
| New variant CJD                | Depression + forgetfulness, unsteadiness, painful sensory symptoms | +         | As sporadic CJD                  |

CJD = Creutzfeldt-Jakob disease; CNS = central nervous system.

**Table 4. Clinical features in familial prion disease.**

| Mutation                        | Clinical features                                      |
|---------------------------------|--------------------------------------------------------|
| Codon 178 (valine at codon 129) | Similar to sporadic CJD                               |
| Codon 200                       | Slowly progressive ataxia, pyramidal signs and dementia |
| Codon 210                       | Some cases similar to sporadic CJD                     |
| Codon 232                       | Dysautonomia, insomnia, progressive dementia           |
| Codon 102 (GSS)                 | Progressive spastic paraparesis                         |
| Codon 117                       | Variable-features of sporadic CJD or GSS               |
| Codon 198 (Indiana kindred)     | Slowly progressive dementia                            |
|Codon 217                        |                                                        |
| Codon 178 (methionine at codon 129) (FFI) |                                                        |

* There is heterogeneity in clinical features both within and between families. CJD = Creutzfeldt-Jakob disease; FFI = fatal familial insomnia; GSS = Gerstmann-Straussler-Scheinker syndrome.
is about four months from the first symptom. Sporadic CJD is largely a disease of late middle age, with a mean age at death of about 65 years.

The clinical presentation of sporadic CJD is usually relatively stereotyped, but there can be heterogeneity in the clinical presentation, for example cases of long duration or with a predominantly cerebellar onset. Recent evidence suggests that the clinico-pathological phenotype of sporadic CJD may be influenced by the type of prion protein deposited in the brain (identified by Western blot analysis) and the codon 129 genotype.

**Hereditary Creutzfeldt-Jakob disease**

The clinical features of hereditary CJD vary according to the underlying mutation (Table 4). As a group, hereditary cases have a mean age at death about 10 years younger than sporadic cases, often with a relatively prolonged clinical course. There may be variation in clinical presentation both within and between families. For example, pedigrees of GSS have been identified in which some family members present with the GSS phenotype and others with a phenotype similar to sporadic CJD.

**Iatrogenic Creutzfeldt-Jakob disease**

The clinical features of iatrogenic CJD vary according to the route of infection. When the infection has been introduced in or adjacent to the CNS, the clinical features resemble sporadic CJD. In HGH recipients with CJD, there is a progressive cerebellar syndrome and dementia occurs late in the clinical course, if at all. The mean duration of illness also varies, with survival of about 2–12 months with a CNS route and 8–18 months with a peripheral route.

**New variant Creutzfeldt-Jakob disease**

The clinical phenotype of new variant CJD is consistent and relatively distinct from other forms of CJD. There is initial psychiatric disturbance, commonly depression or withdrawal, without associated neurological symptoms. In some cases, there is early painful sensory disturbance, instability of gait or forgetfulness. After 6–8 months ataxia develops, followed by progressive cognitive impairment and involuntary movements, including myoclonus, chorea and dystonia. The terminal phase is similar to sporadic CJD. The mean age at death is 29 years (range 18–53 years) and the median illness duration is 14 months (range 13–38 months).

**Diagnosis of human prion disease**

Diagnostic criteria for both sporadic CJD (Table 5) and new variant CJD (Table 6) have been proposed and at least partially validated. Patients fulfilling Table 5. Diagnostic criteria for classical Creutzfeldt-Jakob disease.

| A – SPORADIC |
|--------------|
| 1 **Definite:** |
| 1. neuropathologically confirmed and/or |
| 2. immunocytochemically confirmed PrP positive (Western blot) and/or |
| 3. SAF |
| 2 **Probable:** |
| 1. progressive dementia |
| 2. typical EEG |
| 3. at least 2 of the following clinical features: |
| - myoclonus |
| - visual or cerebellar |
| - pyramidal/extrapyramidal |
| - akinetic mutism |
| 3 **Possible:** |
| 1. progressive dementia |
| 2. 2 of the clinical features listed above |
| 3. no EEG or atypical EEG |
| 4. duration <2 years |

| B Accidental transmission |
| 1. progressive cerebellar syndrome in a pituitary hormone recipient |
| 2. sporadic CJD with a recognised exposure risk |

| C Familial |
| 1. definite or probable CJD plus definite or probable CJD in a 1st degree relative |
| 2. neuropsychiatric disorder plus disease-specific PRNP mutation |

CJD = Creutzfeldt-Jakob disease; PNRP = prion protein; SAF = scrapie associated fibrils.
criteria for probable sporadic or new variant CJD have a high likelihood of suffering from a human prion disease.

- The diagnosis of sporadic CJD is often suspected because of the relatively characteristic combination of rapidly progressive dementia and myoclonus.
- Hereditary forms of human prion disease may be suspected because of the clinical features, particularly in the minority of cases with a family history of a similar disorder. PRNP analysis may be necessary to confirm the diagnosis.
- The possibility of iatrogenic CJD may be raised by the development of a progressive CNS disorder in an individual with a recognised medical risk factor.
- The clinical suspicion of new variant CJD depends on the identification of suggestive neurological features occurring in a patient of relatively young age. Distinction from more common psychiatric disorders may be impossible during the psychiatric prodrome of new variant CJD.

Diagnostic investigations

- In all forms of CJD, cerebrospinal fluid (CSF) examination may show an elevated protein content but there is no pleocytosis. The identification of an elevated CSF 14-3-3 protein has high sensitivity and specificity for the diagnosis of sporadic CJD. It is, however, only of use in an appropriate clinical context as this elevation occurs in other conditions including stroke and encephalitis.
- Generalised periodic complexes at one per second on an EEG are almost diagnostic of sporadic CJD, but this appearance is not found in 30–40% of cases, even with serial recordings.

Table 7. Investigations in human prion disease (percentage of cases with a positive investigation, where known, in parentheses).

| Disease                | 'Typical EEG' | 14-3-3 positive | High signal on MRI | Other                  |
|------------------------|---------------|-----------------|--------------------|------------------------|
| Sporadic CJD           | +             | + (60–70%)      | + (> 70%)          | prion protein          |
| (90%)                  |               | (caudate and putamen) | PRNP analysis      |
| Familial CJD           | ±             | ±               | ±                  | PRNP analysis          |
| Iatrogenic CJD:        | ±             | ±               | ±                  | PRNP analysis          |
| CNS route:             | ±             | ±               | ±                  | PRNP analysis          |
| peripheral route       | ±             | ± (50%)         | ±                  | PRNP analysis          |
| New variant CJD        | ±             | ± (50%)         | ±                  | Tonsil biopsy?         |
| (100%)                 |               | (> 70%)         |                    | (posterior thalamus)   |

CJD = Creutzfeldt-Jakob disease; MRI = magnetic resonance imaging; PRNP = prion protein.

- Magnetic resonance imaging brain scan (particularly T2 weighted images) shows symmetrical high signal in the caudate and putamen in a high proportion of cases of sporadic CJD (Table 7). Similar changes in the posterior thalamus have been identified in the majority of cases of new variant CJD.
- Brain biopsy may allow diagnosis in life, but this procedure has risks to the patient and is mainly indicated for the exclusion of potentially treatable disorders.
- Tonsil biopsy has been advocated as a diagnostic procedure in new variant CJD, but this also has risks. Although it may be helpful in providing a diagnosis to clinicians and relatives, it is of no direct benefit to the patient.

Key Points

- Human prion diseases are rare and vary in clinical features, epidemiological characteristics and aetiology.
- The clinical features of new variant Creutzfeldt-Jakob disease (CJD) are relatively distinct from sporadic CJD, with a younger age at onset, a prolonged illness duration and different presenting symptoms.
- Cases of familial prion disease die, on average, at a younger age than sporadic cases and often have a protracted clinical course.
- The diagnosis of a human prion disease is often suspected on the basis of the history and clinical examination.
- Familial prion disease and new variant CJD are difficult to diagnose in the early stages.
- Investigations, including EEG, 14-3-3 cerebrospinal fluid immunoassay, prion protein gene analysis and magnetic resonance imaging brain scan are important aids to diagnosis.

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Multiple sclerosis and its treatment

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Summary

Multiple sclerosis (MS) is a common neurological disorder responsible for substantial neurological morbidity. Although it is considered to be an autoimmune demyelinating disease of the central nervous system (CNS), mediated by antigen-specific CD4+ T helper (Th1) T-cells, therapeutic strategies aimed at generalised immunosuppression have been disappointing. Recently, immunomodulatory therapies like interferon (IFN)–β and glatiramer acetate have proved more effective. They reduce the rate and severity of clinical relapses and, in the case of IFN–β, delay the rate of disease progression. Symptomatic therapies and rehabilitation, however, remain the mainstay of treatment for the majority of patients with MS. The immunopathogenesis of MS and its treatments, both disease modifying and symptomatic, are reviewed below.

Background

MS is the most common debilitating neurological illness to afflict young adults. The average prevalence across the UK is approximately 130 per 100,000, with an annual incidence of 0.2%. MS is more common in women and Caucasians on a genetic background associated with specific major histocompatibility complex (MHC) haplotypes (DR15/DQ6) and possibly other genetic loci. Epidemiological studies support an environmental aetiological factor. The disease usually manifests clinically in the third and fourth decades, typically presenting with a relapsing-remitting course which, after a period of time (average 5–15 years), enters the secondary progressive phase. Secondary progression can occur in the presence or absence of superimposed relapses. Approximately 10% of patients have a primary progressive course from the outset, without clinical relapses. About 25% have a benign course, with little or no disability after 15 or more years. Rarely, patients have malignant MS with a rapidly progressive course. Favourable prognostic features include young age of onset, a long duration between the first and second clinical events, initial symptoms limited to visual and sensory pathways, and a low lesion load on magnetic resonance imaging (MRI) during the first clinical episode. However, an accurate prognosis is not possible for individual cases.

The belief, although unproven, that MS is an organ-specific autoimmune disease has dominated most therapeutic strategies, which are aimed at either generalised immunosuppression or more targeted immunomodulation to reduce or switch off the specific autoimmune reaction. Following a brief summary of the immunopathogenesis of MS, this review will concentrate on recent developments in therapies aimed at modifying the underlying disease process, as well as symptomatic therapies which are still the mainstay of treatment for most patients with MS.

Immunopathogenesis of multiple sclerosis

MS is considered to be an organ-specific autoimmune disease orchestrated by autoreactive CD4+ T-cells (Fig 1 and 2)1. Genetic factors interact with an environmental factor to establish or maintain pathological autoreactive T-cells which, after a long and variable latency period (10–20 years), are activated, possibly by a systemic trigger.