REVIEW

Creutzfeldt–Jakob disease and the eye. I. Background and patient management

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Background

The transmissible spongiform encephalopathies (TSEs), alternatively known as prion diseases, excite a fascination among both medical personnel and lay public for several reasons. They are the only known example of diseases which can be transmitted both genetically and by infection, though in most human examples the exact aetiology remains unknown. The nature of the infective agent is still not completely clear, the diseases are uniformly (and usually rapidly) fatal, and there is no known cure. Consequently, it is not surprising that there has been an enormous amount published on the subject. Indeed, if the number of publications on any disease is divided by the incidence of that disease, human TSEs reveal an 'interest factor' over 10 times that of any other condition, and over 100 times that of most.[1] This is reflected in the size of the reference lists at the end of this article and its companion![2]

The history of TSEs has involved the eye in a variety of ways. The first evidence that scrapie could be transmitted experimentally followed inoculation through the eye,[3] and the first evidence that Creutzfeldt–Jakob disease (CJD) could be transmitted directly from human to human by infection involved a corneal graft.[4] Visual symptoms are frequent, as are neuro-ophthalmological signs, and it is therefore likely that some patients will present to an ophthalmologist. This review and the companion article[2] set out to provide the reader with an update on the current understanding of human TSEs, and to discuss the management of patients, with particular reference to corneal transplantation. As yet, there is no effective treatment,[5] so this aspect will not be discussed further. In the companion article[2] we review the ophthalmic and neuro-ophthalmic features of these diseases in greater depth.

Methods

In preparing this review, MEDLINE and EMBASE were consulted using the following combination of keywords: *CJD, Creutzfeld, Creutzfeldt, Creutzfeldt–Jakob disease, Creutzfeldt–Jakob syndrome, eye, fatal familial insomnia, FFI, Gerstmann–Sträussler–Scheinker, Gerstmann–Sträussler–Scheinker disease, GSS, Heidenhain, Jacob, Jakob, kuru, ocular, ophthalmic, ophthalmological, optic, prion, prion disease, PrP, PrPSc, transmissible spongiform encephalopathy, TSE, vision, visual*, in addition to various permutations of *accommodation, evoked potentials, eye* and *eye diseases, ocular motility disorders,* and *vision.* Major neurological, ophthalmological and neuro-ophthalmological journals were also screened by hand over the last 10 years. Secondary referencing was carried out from the papers found by these procedures.

Transmissible spongiform encephalopathies

There are several different TSEs affecting animals and man, and a summary is given in Table 1. This article will deal with those diseases affecting man, i.e. CJD, Gerstmann–Sträussler–Scheinker disease (GSS), fatal familial insomnia (FFI) and kuru.

Neuropathologically, these conditions are recognised by the triad of spongiform change (affecting any part of the cerebral grey matter), neuronal loss, and proliferation and hypertrophy of astrocytes.[6–8] Neurons show loss of dendritic spines and intracytoplasmic vacuoles,[9] and there is accumulation in the brain of amyloid. The amyloid consists of an abnormal, 33–37 kDa degradation-resistant glycoprotein,[10] which is an isoform of a normally occurring protein known variously as prion protein (PrP), scrapie-associated protein, proteinase resistant protein, scrapie amyloid protein, or Sp33-37.[11,12] The normal, or wild-type, is known as PrP^{C} ('cellular', principally α-helical structure, detergent soluble) and the abnormal isoform as PrP^{Sc} ('Scrapie', principally β-sheet structure, insoluble in non-denaturing detergents).[13]

PrP^{C} is a normal constituent of the neuronal cell membrane,[14,15] but it is also widely expressed throughout the body.[12] It is transported along neurons[16] and accumulates at the neuromuscular junction.[17] Scrapie infection has been shown to alter receptor-mediated Ca^{2+},[18] and other reports suggest that PrP^{C} may be necessary for neuronal transmission[19,20] or

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Table 1. *Documented non-experimental animal TSEs*

Transmissible spongiform encephalopathy	First reported
Human TSE	
Creutzfeldt–Jakob disease	
Classical sporadic	1920
Familial	1924
Iatrogenic	1974
New variant	1996
Gerstmann–Sträussler–Scheinker disease	1936
Fatal familial insomnia	1986
Kuru	1957
Animal TSE	
Scrapie in:	
Sheep	1730
Goat	1942
Moufflon	1992
Transmissible mink encephalopathy	1965
Chronic wasting disease of deer and elk	1967
Bovine spongiform encephalopathy	1986
Captive primates	1999
Spongiform encephalopathy in captive Felidae:	
Domestic cat	1990
Puma	1992
Cheetah	1992
Ocelot	1994
Tiger	1996
Captive ruminants:	
Nyala	1986
Gemsbok	1988
Arabian oryx	1989
Eland	1989
Greater kudu	1989
Scimitar-horned oryx	1993
Ankole	1995
Bison	1996

that it may influence the activity of Cu/Zn superoxide dismutase,[21] but little else is known about its normal function. The fact that it is possible to rear transgenic mice totally devoid of the protein[22] implies that it is not essential for life, and adds to the confusion.

Pathogenesis

The transmissible nature of sporadic CJD was first demonstrated experimentally in 1968,[23] and it has subsequently been shown that it is possible to transmit familial CJD,[24,25] GSS[26] and other forms of familial prion disease to animals. However, the precise nature of the transmissible agent is still not clear. Three main hypotheses have been put forward.[11] One suggests that the infective agent is comprised of proteins surrounding a nucleic acid which encodes those proteins (i.e. a virus),[27] the second that it comprises proteins associated with a small polynucleotide (the 'virino' hypothesis[28]), and the third that it is entirely composed of protein and devoid of nucleic acid,[29] subsequently termed a *prion* ('proteinaceous particle').[30] It is now clear that the altered protein, PrP^{Sc}, is a major and necessary component of the infectious agent,[10,31,32] but exactly how it is pathogenic remains uncertain.

The most compelling hypothesis to date is the third, the 'protein-only' hypothesis, which involves conformational change of PrP.[13,29,33–35] It has been shown that PrP^{C} and PrP^{Sc} are stereoisomers (or 'twisted' forms) of the same protein.[36] The former occurs normally, but can be caused to 'flip' into an altered shape, PrP^{Sc}. Once this has happened, the protein becomes resistant to proteases and so can build up in the cell membrane, eventually aggregating as amyloid. The reason PrP^{Sc} is pathogenic is not known, but recent work has suggested that small segments of some genetically abnormal PrP molecules may display a tendency to aggregate, and be pathogenic in cell culture.[37,38] Consistent with the suggestion that it is indeed the PrP^{Sc} itself which is pathogenic is the fact that those areas of the brain demonstrating the most marked spongiform change have the highest concentration of PrP^{Sc15}. Furthermore, transgenic mice reared without the PrP gene cannot be infected with scrapie, demonstrating that PrP is necessary for the disease.[39]

The suggestion is that the normal, or wild-type, PrP^{C} is converted into PrP^{Sc} by coming into direct contact with PrP^{Sc}, and that, once this starts, a cascading chain-reaction commences affecting Prp^{C} all over the brain. Thus, the normal brain is in a sort of 'metastable equilibrium', stable unless PrP^{Sc} is introduced, in which case normal PrP^{C} is gradually caused to 'flip' into the abnormal form (Fig. 1). An analogy might be that of crystals developing out of a supersaturated salt solution once it has been 'seeded' by a small salt crystal.[40] The abnormal PrP^{Sc} could be introduced by way of direct inoculation, as in transmitted CJD, or develop spontaneously if the normal host PrP is more unstable than usual due to genetic defects, or develop as a rare stochastic event in the sporadic form of the disease. Quite how the abnormal PrP is transmitted from cell to cell is not clear.

While the above hypothesis is compelling, it does not explain all aspects of TSE transmission, most notably the existence of different 'strains' of the diseases. These are discussed further below. Detailed reviews of the prion concept can be found elsewhere.[22,31–33,36,41–45]

Creutzfeldt–Jakob Disease

Creutzfeldt[46] and Jakob[47–49] are usually credited with having described the condition first,[50] though Fischer[51] described cases of spongiform cortical degeneration some 10 years earlier (none of which would meet the modern criteria for CJD). Interestingly, the original case described by Creutzfeldt probably did not have CJD on the basis of histology,[52] and, of Jakob's five patients, only the third and fifth definitely did.[52] The early literature (well reviewed by May[53] and Kirschbaum[54]) was similarly confused by the lack of standard criteria and a plethora of synonyms,[55] and it was not until full evaluation of the neuropathological changes in the brain were made in 1978,[6] and criteria generally agreed upon,[56]

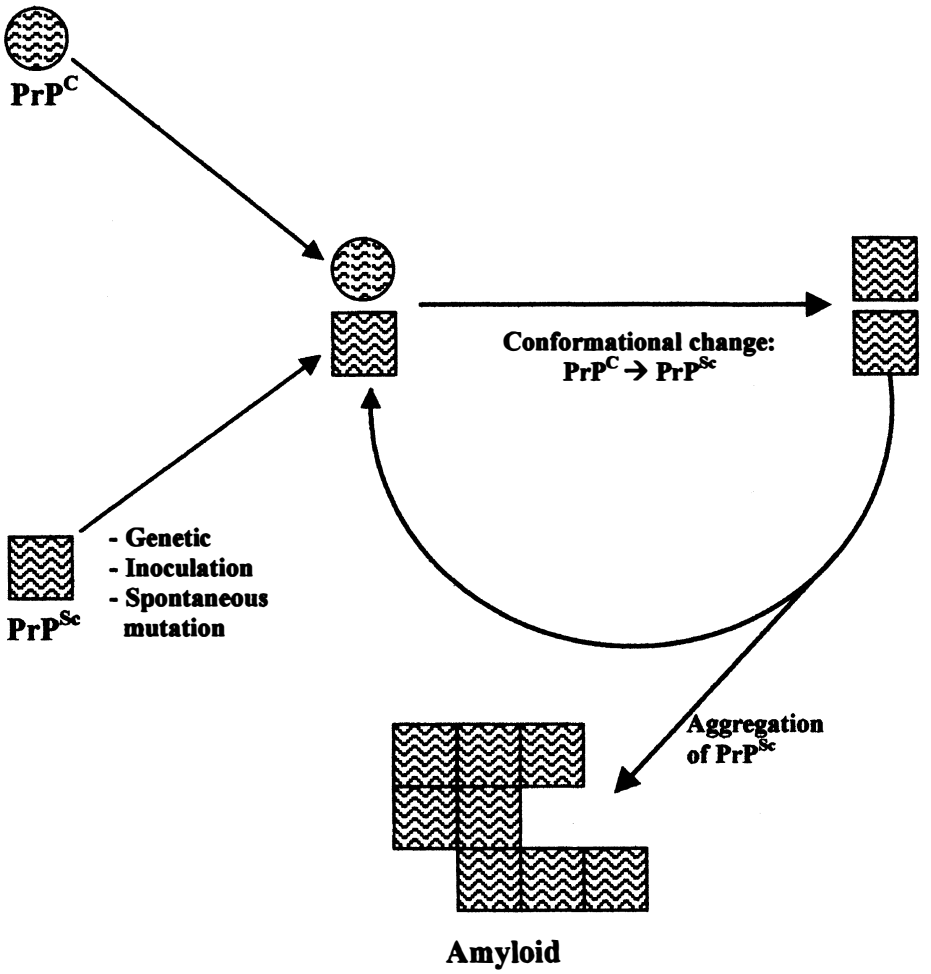

Fig. 1. *Pathogenesis. The presence of abnormal PrP^{Sc} somehow induces a conformational change in normal PrP^{C}, thereby converting it to PrP^{Sc}. PrP^{Sc} thus formed can convert more PrP^{C} into PrP^{Sc} or aggregate to form insoluble amyloid.*

that the picture began to become clearer. In particular, it was accepted that the 'gold standard' for diagnosis was histology (either brain biopsy or autopsy).[56,57]

CJD occurs throughout the world with an overall incidence of approximately 0.5–1.5 per million population per year as evidenced by epidemiological studies in Europe,[58–71] the USA,[56,72–74] Israel,[75] South America[76] and Japan.[77,78] Almost all these studies demonstrate an increased incidence in urban centres compared with the rural incidence, but this may be an artefact of case ascertainment. There are also a few areas of high incidence, such as among Libyan-born Israelis (40 per million per year),[79–81] due to genetic factors (see below).

The sex incidence is probably equal,[52,53,60,61,71,76] though some studies have found a slight male preponderance[56,59] and others the reverse.[58,64–66,70,74,78,82] For a sporadic CJD, the mean age of onset is in the range 55–65 years,[26,59–61,64,66,70,73,76,82] but it has occurred in a patient aged 92 years[83] and in one as young as 14 years.[84] The median and mean duration of illness are approximately 4 and 8 months, respectively,[60,64,65,73,76,83] but occasionally patients survive for much longer.

The disease typically evolves as a dementing illness with associated ataxia, myoclonus, and a wide variety of other neurological abnormalities.[11,85] World Health Organization (WHO) clinical criteria[86] are given in Table 2.

Several different clinical types have been delineated, of which the classic, or 'frontopyramidal' type, constitutes the triad of a rapidly progressive dementia with myoclonus and characteristic electrocephalogram (EEG) changes.[54,87] Of these, some 40% present with cognitive dysfunction alone, 30% with cerebellar dysfunction alone, and 10% with both.[88] An 'amaurotic' form (or 'Heidenhain variant'[89–91]) in which the initial symptoms are predominantly visual occurs in about 10%.[88] Rarer variants include a 'panencephalopathic' type showing major additional involvement of the white matter and occurring most frequently, but not universally, in Japan,[92–101] and an 'ataxic' form in which the initial symptoms are predominantly cerebellar.[102–105] More recently, a '(new) variant' has been described,[106,107] probably related to bovine spongiform encephalopathy (BSE). This is dealt with in detail below. More unusual phenotypes include a more slowly progressive illness[108,109] and presentation with a stroke-like onset.[110] Other cases have been reported with lower motor neuron

Table 2. *Revised WHO definition of CJD subtypes*[86]

Sporadic CJD

Definite
Diagnosed by standard neuropathological techniques *and/or*
Immunocytochemically and/or Western blot confirmed protease resistant PrP *and/or*
Presence of scrapie-associated fibrils

Probable
Progressive dementia *and*
At least two out the following four clinical features:
- myoclonus
- visual or cerebellar disturbance
- pyramidal/extrapyramidal dysfunction
- akinetic mutism

and
- A typical EEG during an illness of any duration *and/or*
  A positive 14-3-3 CSF assay and a clinical duration to death < 2 years
- Routine investigations should not suggest an alternative diagnosis

Possible
Progressive dementia *and*
At least two out the following four clinical features:
- myoclonus
- visual or cerebellar disturbance
- pyramidal/extrapyramidal dysfunction
- akinetic mutism

and
- No EEG or atypical EEG *and*
- Duration < 2 years

Iatrogenic CJD
Progressive cerebellar syndrome in a recipient of human cadaveric-derived pituitary hormone
or
Sporadic CJD with a recognised exposure risk, e.g. antecedent neurosurgery with dura mater graft

Familial CJD
Definite or probable CJD plus definite or probable CJD in a first degree relative *and/or*
Neuropsychiatric disorder plus disease-specific PrP gene mutation

involvement (these were probably frontal lobe dementia with motor neurone disease)[108,111] or a peripheral neuropathy (the significance of which is far from clear),[112,113] but these will not be dealt with further.

It should be noted that, while histology is the gold standard for diagnosis, genetic studies have now revealed that cases of dementia may occur due to genetic abnormalities of the PrP gene but without the characteristic spongiform changes.[114] This raises the possibility of under-ascertainment.[114]

Variant CJD (vCJD)

Most patients with sporadic CJD are in the 55–75 year age range. Previous reports of sporadic cases occurring in patients under 30 years are rare.[77,84,85,115–120] In 1995, two cases of young-onset CJD were reported in the UK in persons aged 18 and 16 years.[121,122] It subsequently became clear that these were the first of a series of cases with clearly different neuropathological features (in particular, 'florid plaques'),[106,123] and 'new variant' CJD was described in 1996.[106] The term 'new variant' has since been abandoned in favour of 'variant'. Compared with sporadic CJD, these patients have a much younger age of onset (mean 29, range 16–50 years) and a relatively distinct clinical course with early behavioural changes,[124] or sensory disturbance (or both), and a more prolonged duration of illness. In some, choreoathetosis or dystonia is a feature, and myoclonus develops late.[107,125,126] None of the cases reported had typical periodic EEG changes.[106,125] Imaging was reported to be normal in most cases,[107,125] though subsequent detailed analysis has suggested that signal change in the pulvinar on magnetic resonance imaging (MRI) is a frequent finding.[127,128] It is of interest that the pathological changes are particularly pronounced in the occiptal lobes.[123]

BSE was first described in 1987[129] and has occurred vastly more frequently in the UK than elsewhere.[130] Current evidence suggests that the disease originated from the use of animal feed supplements containing meat and bonemeal (MBM) contaminated by a TSE agent. The stringency of the rendering procedure by which animal materials were processed to produce MBM changed during the 1970s and 1980s. Decreased use of hydrocarbon solvents and the adoption of lower temperatures probably resulted in increased survival of the infective agent. Epidemiological evidence suggests that sheep scrapie, endemic in Great Britain, was the likely source of the infective agent contaminating the MBM which initiated the BSE epidemic. However, a further hypothesis is that BSE may have been an

uncommon sporadic and/or hereditary disease of cattle which was dramatically amplified as a result of infected bovine material entering the modified rendering process. Whatever the origin of the agent responsible for BSE, it is clear that the recycling of infected cattle through the rendering process in the 1980s was responsible for fuelling the large and explosive epidemic.[131]

The peak incidence of BSE was in 1992–3, and the subsequent decline was largely due to a governmental ban on the feeding of ruminant-derived protein to cattle.[132] Granted that there had recently been an epidemic of BSE in Britain, much speculation arose as to whether this could be transmitted to humans in the form of CJD. An increased incidence of CJD among British farm workers was reported in the early to mid-1990s,[133–136] and most of these had worked on farms with cases of BSE. This led to much concern that BSE was the cause of occupationally acquired CJD in these farmers.[137] However, these cases did not exhibit an unusual clinicopathological phenotype, and a similarly high incidence of CJD in farm workers was seen in other countries without BSE.[68,69,130] This suggested that there was an increased incidence of CJD in farm workers for reasons unrelated to BSE or, more likely, ascertainment bias arising through more vigorous investigation of farmers because of the concern over a possible connection. Subsequent strain-typing studies have failed to identify the BSE strain type as the cause of any of the British cases of CJD in farm workers.[138,139]

At the time of publishing (June 2000) a total of 67 cases of vCJD have been identified in the UK along with a single case in France and one in Ireland. In contrast to the cases of CJD in British farm workers, there is now strong evidence that vCJD is causally related to BSE: first, the temporo-spatial association;[140] second, neuropathological features similar to those of vCJD are seen in macaque monkeys inoculated intracerebrally with BSE,[141] and, third, the 'strain' of the vCJD agent (see below) is identical to that of the BSE agent, but different from conventional CJD agents.[139,142–144]

Interestingly, all patients with vCJD have been homozygous for methionine (met/met) at codon 129,[106,121,122] a naturally occurring polymorphism in the human PrP gene (see below). Cattle do not show this polymorphism, all animals being met/met; humans with the met/met genotype may thus have increased susceptibility to BSE.[145] This is discussed further below.

The incubation period remains unknown, with estimates for the average period ranging from 10 to 30 years. The route of infection is also unknown, but epidemiological studies provide no evidence for parenteral inoculation and the most likely route is presumed to be oral.[146] The future number of cases is impossible to predict accurately.[147–150] There has been a recent increase in incidence of deaths due to vCJD, but the significance of this is unclear.[151,152]

Gerstmann–Sträussler–Scheinker (GSS) disease

GSS[153] is a very rare (1–10 cases per 100 million persons per year[154]) hereditary form of progressive ataxia associated with several different mutations of the PrP gene (see below). It is effectively a variant of familial CJD with a clinical course which may extend up to 5 or more years. The clinical phenotype can vary considerably in a single kindred and range from a picture indistinguishable from sporadic CJD with a rapidly progressive myoclonic dementia and typical periodic EEG to a slowly progressive spinocerebellar ataxia.[26,155] Pathologically, multicentric amyloid ('kuru') plaques are the hallmark of GSS.[156]

Three forms have been distinguished: the typical ataxic form, a telencephalic form (dementia, parkinsonism and pyramidal features)[157–159] and a variant with numerous neurofibrillary tangles pathologically.[160,161]

Fatal familial insomnia (FFI)

First described in 1986,[162] FFI is a rapidly progressive, autosomal dominantly inherited disease presenting in adult life (ages 40–60 years) and associated with a mutation at codon 178 of the PrP gene (and methionine 'downstream' on the same allele at codon 129 – if valine is present at codon 129 on the same allele, then the phenotype is similar to sporadic CJD)[162–168] (see below). It is characterised clinically by untreatable insomnia, endocrine disturbance, dysautonomia (hyperhidrosis, hyperthermia, tachycardia, hypertension and irregular breathing) and motor abnormalities (ataxia, myoclonus and pyramidal dysfunction). The pathological features include selective atrophy of the anterior ventral and mediodorsal thalamic nuclei with other changes such as cortical gliosis, cerebellar and inferior olivary atrophy. Interestingly, spongiform degeneration is not always present.[164] To date, only 24 kindreds have been described.[169]

To confuse matters, there are reported cases of codon 200 related CJD resulting in the clinical phenotype of FFI[170] and, more recently, a sporadic form of CJD clinically identical to FFI but not associated with the genetic mutation of the PrP gene has been described ('sporadic fatal insomnia' (SFI)).[171] Furthermore, most of the cases in Germany with the FFI mutation did not have insomnia,[172] and only about 50% of FFI cases have a family history of the disease!

Kuru

Kuru was initially described in 1957.[173] It is characterised by cerebellar ataxia and a shivering-like tremor (*kuru*), progressing to complete motor incapacity and death in less than 1 year from onset. It is almost entirely confined to the Fore-speaking tribes in Papua New Guinea, affects all ages, but is rare in adult males, and is thought to have been transmitted by ritual cannibalism.[174] With the cessation of this practice, it has largely died out.[175]

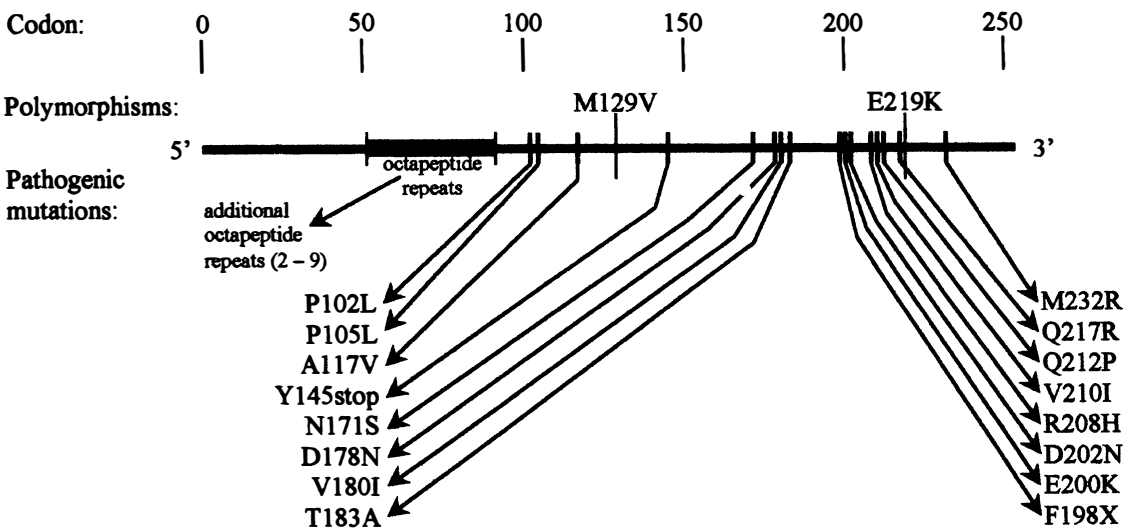

Fig. 2. *Schematic representation of the human prion protein gene to show sites of known polymorphisms and pathogenic mutations. 'M129V' implies methionine replaced by valine at codon 129. Amino acid abbreviations are: A, alanine; D, aspartic acid; E, glutamic acid; F, phenylalanine; H, histidine; I, isoleucine; K, lysine; L, leucine; M, methionine; N, asparagine; P, proline; Q, glutamine; R, arginine; S, serine; T, threonine; V, valine; Y, tyrosine.*

However, occasional cases of kuru still occur, and therefore, as cannibalism ceased in the late 1950s, the incubation period of kuru can extend beyond 30 years.[176]

Genetics

Familial prion disease

Worldwide, familial CJD represents some 10–15% of all cases of prion disease,[56,64] but the incidence does seem to vary somewhat in different countries, from 0 in Austria,[70] 6–12% in the UK,[108,177] 9% in France,[85] 35% in Libyan Jews,[79,178] to between 17.5% and 47% in Chile.[76,117] When familial, CJD is inherited as an autosomal dominant trait, but the percentage is age- and mutation-dependent,[179,180] and may also depend on the genotype at codon 129 (see below).

The gene coding for PrP is located on short arm of chromosome 20.[181] The first abnormality of the PrP gene was detected in 1989.[182] There have been subsequent reports of many other genetic abnormalities related to inherited prion diseases, and several new ones now appear in the literature each year (see Fig. 2). At the time of writing this review, the current list of detected abnormalities includes two basic types. The first is that of insertions into the open reading frame of the gene (between codons 51 and 91). These insertions take the form of octapeptide repeats in addition to the five which are normally present. There can be an additional two,[183] four,[170] five,[184] six (at least three types),[182,185–190] seven,[184,191] eight[25,184,192] or nine,[193,194] depending on the family involved.

The second type of abnormality is that of point mutations, which have been described at 16 different locations in the gene, in addition to the polymorphism at codon 129 (see below). There is an overall correlation between individual mutations and clinical patterns in each of the genetically different subsets.[195,196] Mutations have been described in CJD and GSS at codons 102 (P102L),[156,197–208] 105 (P105L),[209–211] 117 (A117V),[159,197,208,212,213] 145 (Y145stop),[214] 171 (N171S),[215] 178 (D178N),[166,216–222] 180 (V180I),[210,223] 183 (T183A),[224] 198 (F198S),[225,226] 200 (E200K),[81,112,178–180,199,204,227–238] 202 (D202N),[208] 208 (R208H),[239] 210 (V210I),[235,240] 212 (Q212P),[208] 217 (Q217R)[208,226] and 232 (M232R).[210,223,241,242] In FFI, the characteristic mutation is at codon 178 (D178N), with methionine at codon 129 of the affected allele.[163–166,168]

The age of onset in familial CJD shows an extremely wide range,[180,198,220,240] but the penetrance is probably 100%, at least in the D178N[220] and the E200K[179,180] mutations. In families with the latter mutation, an earlier age of onset is more likely if there is an increased load of abnormal PrP, suggesting that normal PrP may be somewhat protective, but there must also be an age-dependent factor since patients homozygous for E200K can remain well up to a certain age.[243]

Not all abnormalities of the PrP gene are pathogenic. Several deletions or silent mutations in the PrP gene have been found which seem not to confer genetic predisposition to prion disease.[235,244] Further reviews of the genetics of TSEs can be found elsewhere.[245]

Determinants of disease expression

It appears that there are three main determinants of disease expression in prion diseases. These are the agent strain, the route of inoculation and the host PrP genotype.[246] In animal studies an additional factor is that of the species barrier,[247] which may be relevant to man, particularly in the case of vCJD.

Table 3. *Summary of all proven or highly probable cases of iatrogenic CJD*

Mode of infection	No. of patients	Agent entry into brain	Mean incubation period (range)	Clinical presentation[a]
Stereotactic EEG	2	Intracerebral	18 months (16–20)	Dem/cereb
Neurosurgery	4	Intracerebral	20 months (15–28)	Vis/dem/cereb
Corneal transplant	3	Optic nerve	18 months[b] (16 months–30 years)	Dem/cereb[c]
Dura mater graft	83	Cerebral surface	6 years (1.5–16)[c]	Cereb (vis/dem)[c]
Gonadotrophin	4	Haematogenous	13[d] years (12–16)	Cerebellar
Growth hormone	98	Haematogenous	12 years[d] (5–30)[c]	Cerebellar[c]

[a]Dem, dementia; cereb, cerebellar; vis, visual.
[b]Median.
[c]Although clinical information not available for all cases.
[d]Calculated from the midpoint of hormone therapy to the onset of CJD symptoms.

Strain

Different 'strains' of the infective agent can be distinguished both on the grounds of reliable differences in incubation period and neuropathology following inoculation into panels of mice ('biological' strain),[139,248] and by the electrophoretic mobility of the PrP and the glycosylation pattern ('molecular' strain).[249,250] At least four different 'molecular' strains of human CJD have been reported to date. The first is associated with the typical CJD phenotype, the myoclonic variant and the Heidenhain variant, and is linked to the met/met genotype at codon 129 (see below).[250] The second is associated with atypical and rarer variants such as dementia of long duration, the ataxic variant and a variant with kuru plaques.[250] The third strain is associated with iatrogenic CJD where exposure has been by a peripheral route (e.g. human growth hormone).[251] The fourth is associated with vCJD,[249] and this strain is indistinguishable from that of BSE.

The existence of strains causes some difficulty with the 'protein only' prion hypothesis,[35,143] but some authors argue that different protein conformational changes can explain the phenomenon (see[44]).

Route of inoculation

In humans, when the infectious agent is introduced into, or near, the brain, the incubation period is measured in months, whereas peripheral inoculation (i.e. oral, intramuscular or intravenous) produces incubation period of years or decades[252] (see Table 3). Similarly, the route of infection may be a determinant of the clinical pattern of the disease.[7,252,253] In scrapie it has been shown that inoculation through non-neural, parenteral routes requires an obligatory phase of replication in the lymphoreticular system, and infection then spreads from spleen and visceral lymph nodes to the mid-thoracic cord via sympathetic nerves.[254] Similar pathways are involved after intragastric infection.[255,256]

PrP genotype

At codon 129 of the PrP gene, there is a methionine/valine (met/val) polymorphism. Seventy-one per cent of patients with sporadic CJD are homozygous for methionine compared with 39% of controls.[257] The codon 129 polymorphism has also been shown to have an influence on pathology: the presence of at least one valine allele is associated with the presence of PrP amyloid plaques.[258] Furthermore, patients with valine homozygosity tend to have a longer duration of illness, are more likely to present at a young age, and only rarely have periodic abnormalities on EEG.[257] This may vary geographically as similar findings have not been reported in Japan.[259] Codon 129 genotype is also an important component of the 'strain' of the CJD agent.[260]

In familial CJD and GSS, it appears that patients homozygous for met/met develop the disease earlier,[186,202,225,240,261] though this is not a universal finding.[207]

In transmitted CJD, there is a great excess of patients homozygous at codon 129. All three patients with CJD transmitted by corneal transplantation were met/met,[262–264] and most tested cases developing CJD transmitted by cadaveric dura mater grafts were met/met,[265–267] though one was met/val[268] and one val/val.[269] Val/val homozygosity is more common in patients developing CJD transmitted by human growth hormone,[270–274] and the codon 129 genotype appears to influence incubation period.[275] All patients with vCJD tested to date have been met/met homozygous.[106,121–123,125] This may relate to the fact that bovine PrP shows no polymorphism, all animals being met/met homozygous: met/met homozygous humans may have increased susceptibility to bovine prions.[145]

A similar effect of a naturally occurring polymorphism at codon 219 has been reported in P102L GSS patients. Those patients with lysine at codon 219 have clearly different clinicopathological features from those with the usual glutamine.[205]

Species barrier

When TSEs are transmitted experimentally from one species to another, the incubation period is usually longer than that seen on subsequent passage within the new species.[247,276] This effect is probably due to a combination of factors, including the efficiency of infection, agent strain selection,[277,278] and possibly the compatibility of PrP proteins between animals.[34] It has

also been postulated that a species-specific protein (a chaperone protein, or protein X) is required to facilitate the conformational change from PrP^{C} to PrP^{Sc},[279] though, as yet, there has been no direct identification of such a molecule.[245]

Summary

It appears that if an individual is exposed to CJD, whether or not that individual develops the disease may be influenced by their codon 129 genotype, with homozygosity somehow conferring increased susceptibility. The incubation period is likely to be determined by the mode of inoculation, as well as the strain type. The eventual clinical picture is probably determined by the strain type and route of inoculation. The effect of species barrier may be relevant to vCJD, as it may be that human-to-human transmission is more effective (by whatever means) than transmission from cow (BSE) to human. The implications of this are currently unknown, but much consideration is being given to possible modes of human-to-human transmission, such as surgical instruments,[280] blood transfusion,[281] contact lenses[282] or tonometry.

Investigations

Brain biopsy

CJD shares many clinical features with other diseases. Hence, the differential diagnosis is large. A detailed review of this is beyond the scope of this article, but the interested reader may care to consult other authors regarding wider and more specific differential diagnostic lists.[73,87,108,283–287] Short of autopsy, the gold standard for diagnosis remains histological examination of a brain biopsy.[56,57,177] Specific diagnostic criteria have been established[8] because spongiform change can occur in other conditions.[7,288,289] However, brain biopsy is an invasive procedure, with consequent risks, and it may be falsely negative in up to 5% of cases.[86,290,291] It is also costly in that it necessitates the destruction of surgical instruments (see below). Nevertheless, it remains the only way to diagnose CJD unequivocally during life; Western blot analysis of PrP in the brain biopsy allows identification of CJD strain, and this may have an important role in future assessment of CJD.[292] In the meantime, non-invasive tests are being sought, and the WHO recommends that antemortem brain biopsy should not be used to diagnose CJD unless a potentially treatable disorder is also considered a possibility.[86]

Electrophysiology

Electroencephalography (EEG)

Abnormalities of the EEG were first described in 1953,[293] and it is now accepted that the typical findings are of 1–2 Hz periodic sharp wave (simple biphasic or triphasic, or more complex polyspike) complexes (PSWCs) on a background of progressive increase in slow waves and loss of alpha rhythm.[53,294–309] This has now become part of the accepted criteria for clinical diagnosis.[56,86,310] Nevertheless, though these abnormalities are seen in approximately 75% of patients[60,82,87,108,311–314] (52% in the UK; R.G. Will, personal communication), particularly if recorded serially,[311,315–317] they are by no means diagnostic of CJD[86,289] and are absent in 25% of pathologically proven cases of CJD.[84,85,318–320] The changes are not seen in vCJD.[106,125] Sleep EEG[321] and brain mapping[322] do not appear to aid diagnosis. The source of the PSWCs is not clear, but both cortical and subcortical structures are thought to be involved.[300,303,306]

In the Heidenhain variant, the EEG may show occipital sharp and slow-wave complexes.[91,323,324] It is of interest that photic-induced responses have been shown to abolish the PSWCs, possibly in relation to involvement of the lateral geniculate nucleus.[325,326]

Other electrophysiology

Visual evoked responses (VERs) often show no significant abnormality,[9,84,105,116,327–330] but an exaggerated positive response has frequently been noted,[303,307,331–336] possibly due to an exaggerated GABAergic inhibitory influence.[337] Abnormally delayed VERs have occasionally been reported,[100,105,338,339] but in at least one case the patient had coexistent multiple sclerosis,[105] and in others the abnormalities may well have been due to poor fixation.[100,338] Abnormal somatosensory evoked potentials have occasionally been recorded,[9,121,340] and the blink reflex has also been reported to be abnormal.[341]

Electroretinography (ERG) has been reported to be abnormal in many cases of CJD transmitted by human growth hormone (hGH),[341–344] though this is not always the case.[331,333] A systematic study of ERG in CJD showed a significant decrease in amplitude of the B1 wave and the B/A ratio.[335] Interestingly, histological studies on the human retina have shown spongiform changes in the nerve fibre layer, with loss of ganglion and bipolar cells, but few changes in the photoreceptors;[331,335,345,346] photoreceptor abnormalities have, however, been detected in mice.[347]

Imaging

Computed tomography (CT)

CT imaging usually shows either no abnormality or just atrophy,[82,95,96,100,105,108,115,116,253,265,329,330,348–376] but minor abnormalities have been described in the basal ganglia,[377] the white matter[378–380] and in the occipital cortex,[370] and one case study demonstrated progressive enlargement of the fourth ventricle.[381] There is probably no consistent and reliable feature on CT.[382]

Magnetic resonance imaging (MRI)

A number of different but inconsistent MRI abnormalities have been reported in CJD, including minor abnormalities of the caudate and

putamen[91,236,323,362,364,369,374,376,377,383–391] (which may be asymmetric[392]), abnormalities of the thalamus,[107,125,362,393] occipital cortex (in the Heidenhain variant),[91,101,323,370,394,395] white matter[98,393,396] (particularly in the panencephalopathic type),[100,101] or simply an excessive rate of cerebral atrophy.[101,107,358] Careful retrospective analysis suggests that abnormalities of the basal ganglia may be found in 79% of patients if specifically sought.[390] Alternatively, there may be just atrophy or no significant abnormality.[84,101,272,273,358,365,372,375,376,390,396–402] Contrast enhancement has not been observed.[389,394]

The above changes on MRI are neither specific[390] nor sensitive,[382,401] but they may have a role in guiding biopsy.[390] However, in vCJD, a very large proportion of patients show abnormalities of the pulvinar on MRI,[127,128] and this may prove useful diagnostically. Also, newer sequences such as FLAIR[403] or diffusion-weighted MRI[324,404–407] are showing abnormalities where routine MRI does not, and these may be useful in the future.

Other imaging

Isotope brain scans are unhelpful,[82] as is magnetic resonance spectroscopy.[396] Single photon emission computed tomography (SPECT) has been shown to reveal widespread decrease in cortical perfusion,[190,236,242,372,373,397,405,408–414] and may be useful in suggesting the diagnosis.[415] Positron emission tomography (PET) using 2-[^{18}F]fluorodeoxyglucose has also shown diffuse cortical hypometabolism[355,366,367,375,416–418] or posterior cortical hypometabolism in the Heidenhain variant.[400,411,413] In FFI and SFI, PET scanning shows selective hypometabolism of the thalamus.[171,419] None of these observations has so far provided a clinically useful test.

Cerebrospinal fluid (CSF)

Early reports on routine CSF examination in CJD found either no abnormality or just a slight elevation of CSF protein.[53,77,82,87,102,103,108,115,116,302,329,350,420,421] Similar findings have been found in FFI[162] and vCJD.[125] Oligoclonal bands have occasionally been reported,[339] probably coincidentally. Several potential markers have been looked at, including neuron-specific enolase,[91,372,422–425] ubiquitin,[426] lactic acid,[427] τ-protein,[428] S-100 protein[423,429–432] and inflammatory cytokines (TNF-α and IL-1β),[433] but none has been reported to show abnormalities sufficient to be the basis of a useful clinical test.

A different marker, originally described as proteins 130 and 131[434] but subsequently termed 14-3-3 protein, has shown more promise. It is found in patients with sporadic[290,425,435,436] and codon 200-related familial CJD[437] with a high degree of specificity and sensitivity, though there can be false positives, in particular in patients with recent stroke, subarachnoid haemorrhage and viral encephalitis, and occasionally in a range of other conditions.[86,151,438,439] There can also be false negatives,[440] and the degree of sensitivity is not as high for vCJD.[124,125] The exact role of 14-3-3 in normal brain is not clear, but it may have a role in signal transduction.[441] It is not normally present in CSF, and seems to appear as a result of massive neuronal destruction.[438]

Blood tests

Elevated hepatic enzymes have been noted in some cases,[442–444] but these abnormalities can be transient, or absent.[445] Serum neopterin levels have been shown to be elevated in CJD, implying some cell-mediated immune system activation, but this test is not in any way specific.[446] It has been suggested that the fact that PrP is present in blood monocytes[447] might provide a useful test.[444] However, if the abnormal form of PrP is expressed in the blood of affected individuals, the titre of infectivity is extremely low (see below). Much work is in progress to try to develop highly sensitive assays capable of detecting such extremely low levels of abnormal PrP.

Other tests

As in scrapie,[448] abnormal PrP can be detected in the tonsils of patients with vCJD,[449] but not in sporadic CJD or GSS.[450] It has been suggested that tonsillar biopsy could be a useful diagnostic test,[451] and even that it might obviate the need for brain biopsy,[393] but this is by no means certain.[452]

In sheep, biopsy of the nictitating membrane ('third eyelid') has been advocated for the purpose of diagnosing scrapie,[453] but this is not applicable to man.

An appendix removed 8 months before initial symptoms of vCJD was found to show abnormal PrP. This raises possibilities for assessing prevalence, as well as possible infectivity issues.[454] A study of the prevalence of vCJD based on appendicectomy specimens is currently in progress.

Transmission

Transmission of TSEs has been documented to occur in man by various routes, and suggested to occur in others. A summary of the documented routes has been presented in Table 3, above.

Neurological and hormonal transmission

Neurosurgery

Following the first clear demonstration of human-to-human transmission via corneal transplantation (see below),[4] the next method of transmission to be firmly implicated was neurosurgery. Two patients developed CJD following a procedure using stereotactic EEG electrodes previously used on a patient who had CJD.[455] The electrodes in question were subsequently shown to transmit the disease to a chimpanzee.[456] Neurosurgical instruments have subsequently also been strongly

implicated in several case reports,[56,457,458] and there have been a few weaker associations with neurosurgery in general, e.g. in surgery for trigeminal neuralgia,[58] resection of meningioma,[459,460] cerebral abscess[459] or leukotomy.[459] An increased risk associated with general surgical operations has also been reported in a recent epidemiological study.[280] However, the strongest association in neurosurgical practice has been with the use of cadaveric dura mater grafts (see below).

Cadaveric dura mater homografts

The first report that grafting of cadaveric dura mater might be responsible for the subsequent development of CJD was in 1987.[461] Since that time there have been over 80 reports of CJD developing following the neurosurgical use of cadaveric dura mater (P. Brown, personal communication),[253,265,266,269,368,462–473] some 26 cases having been recently reviewed.[264] Dura mater has been shown in animal studies to transmit hamster scrapie,[474] and several different types of CJD have developed, for example the panencephalopathic type[267] and the Heidenhain variant,[253,472] presumably depending somewhat on the site of the graft.

Interestingly, cadaveric dura mater has been implicated in the development of CJD in other circumstances, including using it to embolise a nasopharyngeal carcinoma[268] or even an aspergilloma in the chest.[402] Closely related is the development of CJD following the use of a pericardial membrane homograft to repair an eardrum.[475]

Pituitary hormone therapy

Cadaveric pituitary glands can be harvested to obtain pituitary hormones in high concentration. This technique has been used principally in treating short stature in children with human growth hormone (hGH) and infertility in women with human pituitary gonadotrophin (hPG).

The fact that hGH was implicated in the subsequent development of CJD first came to light in 1985,[476] since which time there have been over 100 reports (P. Brown, personal communication),[132,272–274,330,338,343,344,378,409,477–486] including an asymptomatic case which was found incidentally following death from pneumonia.[487] The incidence of CJD has been suggested to be as high as 1/300 patients treated.[484] These cases have been reviewed elsewhere.[252,488–492] There are four reported cases due to hPG.[365,398] As with cadaveric dura mater, it is possible to harvest pituitaries from patients who are asymptomatic but nevertheless incubating the disease, and, in the absence of a test for 'carrier' status, the possibility of infection is therefore never negligible.[493] Pituitary-derived hGH is no longer used[488] (except, perhaps, illicitly by bodybuilders[494,495]), genetically engineered sources being used instead.[496]

Blood and other routes of transmission

Blood

CJD has been transmitted to animals from human whole blood or buffy coat,[212,251,497,498] a finding consistent with the observations that blood monocytes contain PrP in man[447] and animals,[12] and that blood can transmit scrapie in animals.[499,500] Nevertheless, there are a number of puzzling features,[501] and about half of all studies of infectivity in blood have been negative,[502] including assays in primates inoculated with human blood.[73] There has therefore been much speculation about whether or not blood products might transmit the disease.[281] This would, of course, have major implications for patients receiving all types of blood product, especially groups such as those with haemophilia.[503] However, five epidemiological studies have shown no excess of prior blood transfusion in patients with CJD over controls,[280,504–508] making transmission by blood transfusion, if it happens at all, a rare event.[509]

Patients who develop CJD have occasionally been demonstrated to have donated blood before developing the illness.[501–515] This has caused concern, and in a few cases it has been suggested that CJD has, in fact, developed in some of the recipients,[511,513,515] though a causal link has never been substantiated.[516] In one case, 35 units of blood donated by a patient who subsequently developed CJD were traced to their recipients, and none of the recipients has so far developed CJD.[512] Nevertheless, it is clearly important that patients with known CJD,[517] or those at risk of developing the disease,[518] do not donate blood, and extreme vigilance is required in general.[501,519] In the UK, blood for transfusion is now routinely leucodepleted.

Other routes of transmission

Dietary transmission has long been suspected, with particular reference to eating sheep's eyeballs,[520] raw meat,[508] or the brains of various animals.[508,521–527] However, most epidemiological studies have failed to show a significant effect of eating organs, including brain,[507,528] in sporadic CJD. The association of vCJD with BSE has been discussed above, but, though often suggested,[529] it is still not clear that the method of transmission is dietary.

Several other possibilites have been suggested for transmission, in particular procedures which involve lymphoid tissue such as tonsillectomy or appendicectomy,[165] and, of course, blood products (see above) since it appears that the lymphoreticular system plays an important role in the propagation of infection following parenteral inoculation.[530,531] Other medical procedures have been looked at retrospectively, including EMG, lumbar puncture and vaccination, and no increased risk of CJD has been found.[508]

As mentioned above, occupational exposure to animals or animal products has been suggested,[133–136] but recent epidemiological work has shown no increased

risk, except in the case of exposure to leather or fertiliser containing hoof and horn,[508] findings of uncertain significance.

Dentistry has also been suggested as a potential risk,[458] though this claim has not been supported by later studies.[280] The possibility of vertical transmission (mother to child) has been considered, but has not occurred in three documented cases,[455,469,498] nor has it been described in kuru.[532] Curiously, one substantiated example of conjugal CJD (occurring in husband and wife) has been reported,[533] and a recent report describes a cat and its owner both developing a TSE within months of each other.[534] The significance of these cases is uncertain, and they may be purely coincidental.

Transmission routes of ophthalmological relevance

It has been shown experimentally that it is possible to transmit TSEs by inoculation of infected material into the eye.[3,535,536] That the cornea is infectious has been demonstrated in various animals,[537–539] including man.[538,540] There are, in theory, two possible routes of entry into the brain following inoculation into the eye. The first is direct, via the visual pathways.[541,542] The second involves peripheral spread via the blood following leakage of the inoculum from the infected eye.[543] Both might be relevant to man.

Corneal transplantation

There have been three case reports in the literature describing human-to-human transmission of CJD via corneal transplantation. Of these, the first was in 1974,[4] and this represents the only definite case of transmission by this route. The other two represent probable[263] and possible[544] cases of transmission.[289] Occasionally, other ophthalmic procedures have been reported in patients who subsequently developed CJD, such as photocoagulation,[56] cataract removal[56] or prior surgery for congenital glaucoma,[107] but these are probably incidental findings and will not be discussed further. The cases involving corneal transplantation will be dealt with in more detail.

- Duffy *et al.*[4,545] described the case of a cadaveric corneal graft, the donor being a 55-year-old man with a 2 month history of ataxia, memory deficit, myoclonus and involuntary movements who was later found to have pathologically confirmed CJD. The recipient was a 55-year-old woman with Fuchs' corneal dystrophy who developed symptoms of lethargy, nausea and ataxia some 18 months after surgery, and died after a further 9 months. Not only was she confirmed to have died from CJD at post-mortem,[73] but a homogenate of her brain subsequently produced CJD when injected into a chimpanzee.[73] Though the transplanted cornea itself was not retained for study, this is generally accepted to be a definite case of transmission.[73,289]
- Uchiyama *et al.*[544] described the case of a 63-year-old woman who developed autopsy-proven CJD 15 months following a corneal transplant. Unfortunately, details of the donor were not given, so this must be regarded as a possible case of transmission.[289]
- Heckmann *et al.*[263] described the clinical features of CJD 30 years following corneal transplantion from a donor who had a 3 month history of incoordination, memory loss, involuntary movements and myoclonic jerks whose autopsy later confirmed CJD. Unfortunately, while the recipient developed a rapidly progressive cerebellar syndrome with dementia and myoclonic jerks, and the EEG was typical, no histological proof of the diagnosis of CJD was ever obtained, so this must remain a probable case of transmission.[289]

Any patient having received a corneal transplant presenting with cerebellar signs, gait disorder, mental deterioration, dysarthria, visual/oculomotor signs, myoclonus and/or pyramidal signs should be suspected of having CJD.[264]

Recently, ocular tissue from a donor later found to have sporadic CJD was transplanted into three separate patients,[546] an event considered sufficiently newsworthy to be reported in the *London Times*[547] and the medical press[548] at the time, and to be the subject of a report commissioned by the Royal College of Ophthalmologists.[549] In fact, the donor was known to be terminally ill from a known carcinoma of the lung, and it was not until some 8 months later that examination of her brain revealed CJD.[550] In retrospect, she had had a few weeks' history of odd gait and memory disturbance prior to her death, but this was presumed to have been due to cerebral secondaries. The recipients have subsequently had their grafts removed, but their future remains uncertain some two and a half years after surgery. This case highlights how important it is that guidelines as to which patients should not have their corneas harvested for transplantation are widely available and adhered to[551] (see below).

The possibility of transmission of CJD by corneal transplantation has been previously reviewed.[552,553] It has been suggested that in the USA, based on statistics from the Eye Bank Association of America, at most 4.2 cases of CJD would be available to donate their corneas each year. This represents less than 0.01% of all donors, and the authors conclude that the relative risk of transmitting CJD is therefore minute compared with the benefit conferred to transplant recipients' sight.[289] The low level of risk has been compared with that of other hazards, such as death from general anaesthetic.[546] Strictly speaking, the above calculations do not include patients who might possibly be incubating vCJD. The number of such persons is unknown, but the possibility of transmission of vCJD via blood has resulted in the policy of leucodepletion (see above). There may be a similar difference between CJD and vCJD with respect to corneal transmissibility.

Applanation tonometry

In view of the known infectivity of the eye, the possibility that applanation tonometry might transmit the disease has been suggested,[554–556] and one group has consistently found that patients with CJD were significantly more likely to have had tonometry in the past.[554,555,557] This has not always been found,[59,66] and it has been suggested that the large odds ratio may be related to the fact that many patients have tonometry for visual symptoms during the prodrome of their illness.[558] Recent case–control studies have shown no increased risk of previous eye surgery,[507,508] and one found no increased risk of previous ophthalmological examination, presumably including tonometry.[508]

Transmission to medical/paramedical personnel

Epidemiological studies have sometimes reported an excess of cases of CJD among health care workers, including nurses, physicians and dentists,[56,64,66] though the difference is not always significant.[66] This is nevertheless potentially worrying, and there have been specific case reports of CJD occurring in a neurosurgeon,[559] a neuropathologist,[416] two histopathology technicians,[560,561] a physician who trained as pathologist,[562] a general surgeon who worked in a pathology department[563] and an orthopaedic surgeon who handled dura mater.[564] However, the largest epidemiological study to date,[508] and a meta-analysis of previous case–control studies,[507] have shown no excess risk to health workers at all. To our knowledge, there have been no reported cases of CJD occurring in ophthalmologists.

Management

Guidelines for various procedures were issued as early as 1974 (cerebral biopsies),[565] 1975 (autopsies)[566] and 1977 (patient handling).[567] More up-to-date consensus statements have recently been issued.[310,568,569] Specific aspects dealing with ophthalmic practice are dealt with below, but further guidelines can be found in a publication by the Advisory Committee on Dangerous Pathogens.[569]

Management of patients

Ward management

Epidemiological evidence suggests that, from the general point of view, patients with, or suspected of having, TSEs can be nursed on an open ward. There is no evidence of infectivity in saliva, body secretions or excreta, and these should therefore be treated as potentially infectious in line with standard infection control procedures.[569] When nursing such patients, disposable items should be used wherever possible and incinerated afterwards. For sampling and processing of biological specimens, personnel should use gowns, gloves, masks and eye protection. Catheters and needles should be destroyed. Pins used for routine testing of pain sensation must be discarded after use in any patient. Potentially contaminated biological products, including secretions, blood, CSF and other body fluids, should be incinerated.[570]

Should a needle-stick injury occur, or an abrasion be contaminated with blood or body fluids, current guidelines are that the wound should be gently encouraged to bleed, gently washed with warm soapy water (avoiding scrubbing), rinsed, dried and covered with a waterproof dressing. Splashes into the eye or mouth should be dealt with by thorough irrigation.[569] Various suggestions have been put forward for more active treatment following inoculation with a TSE agent, including excision and treatment with oral steroids: prednisolone 60 mg a day for 7 days followed by 45 mg a day for 7 days,[571] or dextran sulphate (molecular weight 500 kDa) 400 mg/kg intramuscularly or oral doses of pentosan polysulphate 1200 mg daily for 3 months.[572]

Management of known or suspected cases during ophthalmic surgery

While there have only been three reported instances of ophthalmologically transmitted CJD,[4,263,544] it remains theoretically possible that CJD might be transmitted via ophthalmic operating instruments. The UK CJD Surveillance Unit is aware of five patients with CJD who had intraocular surgery during their prodromal phase during the years 1990–1995 (R.G. Will, personal communication). By analogy with neurosurgical instruments, there is a theoretical risk that CJD might be transmitted by ophthalmic instruments used on such patients.

The possibility of transfer of CJD by operating equipment was noted as early as 1977,[567] and guidelines as to the use of instruments were suggested then and subsequently.[567,569,570,573–578] A synthesis of the guidelines would suggest that during operations on the eye on known, suspect or at risk patients:

- the least possible number of persons should take part in the operation, and those present should wear waterproof gowns, gloves, and face masks with transparent plastic visors to protect the eyes;
- the operation should take place at the end of the list;
- a one-way flow of instruments should be maintained;
- where possible, disposable equipment should be used;
- in suspected cases, instruments which have been in contact with the patient should either be destroyed or quarantined until the diagnosis is confirmed or refuted (and destroyed if the diagnosis is confirmed). Ophthalmic and neuro-ophthalmic features are discussed in the accompanying paper.[2]

It has been suggested that the costs involved in destroying instruments are likely to be small, as extremely few patients will be involved,[577] and one possible method of coping with the problem is to have a dedicated set of instruments, as has been advocated in neurosurgical practice.[291]

From the anaesthetic viewpoint, guidance differs. The UK Advisory Committee on Dangerous Pathogens (ACDP) states that all instruments should be destroyed when used on suspect or known cases.[569] Elsewhere, it has been recommended that all disposable equipment be destroyed and that the laryngoscope be sterilised by immersion in a 5% sodium hypochlorite solution for 1 hour.[570] For 'at risk' groups, the ACDP allows for reuse of instruments used outside the central nervous system (CNS) if they are properly decontaminated.[569]

Selection of donors for corneal transplantation

The potential for contamination through grafting any tissue depends on five things:[579]

- the nature of the donor organ;
- the stage of the infection of the donor at the time of the graft;
- the screening of the donor;
- the nature of the surgery associated with the graft process;
- the physical or chemical treatment which might be applicable to the graft.

With respect to corneal transplantation, the potential for the cornea to transmit CJD is well established,[4,263,544] as is the relatively high infectivity of the eye itself.[538,540] Treatments which would render a cornea non-infective would almost certainly damage its optical properties, and are therefore not applicable. The only way to reduce the likelihood of transmission, therefore, is to screen potential donors, and to reject any who are, or might be, symptomatic from CJD or at risk of developing the disease. However, this will still not exclude the possibility of iatrogenic transmission completely: patients may be asymptomatic for a period before developing overt clinical features, and during this stage there is no effective screening test. Such patients are still potentially infective.

One potential solution would be to cease corneal transplantation altogether, but this seems totally inappropriate[553] granted that the potential number of donors who might harbour CJD is extremely small,[576] one study calculating it to be between 0.005% and 0.009%.[289] Accordingly, guidelines have been issued regarding the rejection of potential donors.[580] The European Eye Bank Association has provided guidelines for several years, and these are available in the UK through the Royal College of Ophthalmologists (www.rcophth.ac.uk). If these are followed, the risk of transmitting CJD has been considered to be acceptable compared with the potential benefits to sight in corneal recipients.[553]

In summary, the following should not be considered as potential donors:

- Any patient with known CJD, GSS or FFI, or any form of degenerative dementia or subacute encephalopathy.[546,579]
- Any patient dying of unknown cause,[553] or suffering from CNS disease of unknown aetiology.[289]
- Any recipient of human cadaveric pituitary-derived hormones.[488,553,576,579]
- Any recipient of a human dura mater graft.[576] Note that detecting such patients may be difficult because most recipients are not aware that they have received a dural graft. Extending this group to all those who have undergone a neurosurgical procedure would eliminate the vast majority of dural graft recipients but could be too restrictive.
- Any patient belonging to a family with CJD, GSS or FFI.[546,576,579,581,582] The degree of blood relativity is a matter of debate, but should probably include at least sibling, parent, grandparent, child or grandchild.

The UK Transplant Support Service routinely asks whether a post-mortem is pending on a potential donor; if it is, no tissue is issued until the results of that post-mortem are known.[551] A negative histological examination of a small piece of frontotemporal cortex from any cadaver used as a source of tissue grafts would add reassurance and has been recommended for dural graft donors in the United States. However, whether this would be practical for all corneal donors is a matter for debate.[582]

Table 4. *Decontamination procedures*[310,474,569,573,574,579,584,585]

Fully effective (recommended) procedures

- Steam autoclaving for 1 h at 132°C [But NB: Not formol-fixed tissue[586] unless a formic acid step is included in fixation[587]]
- Immersion in 1 N NaOH for 1 h at room temperature

Partially effective procedures:

- Steam autoclaving at either 121°C or 132°C for 15–30 min
- Immersion in 1 N NaOH for 15 min, or lower concentrations (less than 0.5 N) for 1 h
- Immersion in bleach (undiluted, or up to 1:10 dilution) for 1 h
- 4 M guanidine thiocyanate seems very promising[588]

Ineffective procedures

- Acetone, alcohols, β-propiolactone, boiling, chlorine, detergents, dry heat, ethanol, ethylene oxide sterilisations, formaldehyde solution, glutaraldehyde, hydrochloric acid, hydrogen peroxide, iodine and iodophors, Lysol, peracetic acid, phenolics, potassium permanganate, quaternary ammonium compounds, sodium dichloroisocyanurate, sodium hypochlorite (if too dilute), ionising, ultraviolet or microwave irradiation

Management of instruments

Prions are resistant to almost all the procedures generally used to inactivate conventional viruses. Effective and ineffective methods of decontamination are given in Table 4.

In the case of corneal transplantation, it is possible to use only disposable instruments in harvesting corneas from donors, and in the subsequent processing during eye banking. Similarly, disposable corneal trephines and blocks can be used. These procedures would seem sensible to minimise any potential risk of transmitting CJD via instruments.

Rizzo and colleagues[558] raised concern about the transmission of CJD by applanation tonometry following three of their patients undergoing this procedure for visual symptoms during the prodrome of CJD, and suggested that disposable heads should be used. Even though a significant association of CJD with intraocular pressure monitoring has occasionally been noted (see above), the American Neurological Association Committee on Health Care Issues report on handling of affected materials[574] did not mention tonometer heads.[556] Nevertheless, routine decontamination would seem sensible[554,555,557] and, for definite, suspected- or at-risk cases, it would be appropriate to use disposable tonometer heads, or an electronic tonometer with a disposable rubber diaphragm (e.g. a Tonopen). The UK Government's Spongiform Encephalopathy Advisory Committee has recently recommended that opticians dispose of trial contact lenses after each use because of the risk of transmitting vCJD.[583] This may also have implications for the use of disposable tonometer heads in routine applanation tonometry in the UK.

Summary

This article attempts to summarise our current understanding of TSEs as they affect man. Specific aspects relevant to ophthalmological practice, in particular the management of patients in day-to-day clinical practice and with respect to corneal transplantation, have been discussed. In the companion article[2] we discuss the specific ophthalmic and neuro-ophthalmic features of these diseases.

Appendix. List of abbreviations used

ACDP	Advisory Committee on Dangerous Pathogens
BSE	Bovine spongiform encephalopathy
CJD	Creutzfeldt–Jakob disease
CSF	Cerebrospinal fluid
CT	Computed tomography
EEG	Electroencephalogram/electroencephalography
ERG	Electroretinogram/electroretinography
FFI	Fatal familial insomnia
GSS	Gerstmann–Sträussler–Scheinker disease
hGH	Human growth hormone
hPG	Human pituitary gonadotrophin
met	Methionine
MBM	Meat and bone meal
MRI	Magnetic resonance imaging
PET	Positron emission tomography
PrP	Prion protein
PSWC	Periodic sharp wave complexes
SFI	Sporadic fatal insomnia
SPECT	Single photon emission computed tomography
TSE	Transmissible spongiform encephalopathy
CJD	(new) Variant Creutzfeldt–Jakob disease
val	Valine
VER	Visual evoked response
WHO	World Health Organization

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