CHAPTER 6

CREUTZFELDT-JAKOB DISEASE

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Abstract: Creutzfeldt-Jakob disease (CJD), a neurodegenerative disorder that is the commonest form of human prion disease or transmissible spongiform encephalopathies (TSEs). Four types of CJD are known: Sporadic (sCJD), familial or genetic (gCJD); iatrogenic (iCJD) and variant CJD (vCJD). The latter results from transmission of bovine spongiform encephalopathy (BSE) from cattle to humans. The combination of PrP^{Sc} peptide (either 21 kDa or 19 kDa) and the status of the codon 129 of the gene (*PRNP*) encoding for PrP (either Methionine or Valine) is used to classify sCJD into 6 types: MM1 and MV1, the most common; VV2; MV2 (Brownell/Oppenheimer syndrome); MM2; VV1 and sporadic fatal insomnia, in that order of prevalence. Genetic CJD is caused by diverse mutations in the *PRNP* gene. The neuropathology of CJD consists of spongiform change, astro- and microgliosis and poorly defined neuronal loss. In a proportion of cases, amyloid plaques, like those of kuru, are seen. PrP immunohistochemistry reveals different types of PrP^{Sc} deposits—the most common is the synaptic-type, but perivacuolar, perineuronal and plaque-like deposits may be also detected.

INTRODUCTION

Creutzfeldt-Jakob disease (CJD) was first described by two German researchers in twenties of the last century.[1-3] Modern evaluation of historic Jakob's sections revealed that only 3 of 5 cases met recent criteria of CJD.[4] The Creutzfeldt's case did not belong to the category of CJD as currently understood. CJD was transmitted to chimpanzee by Gibbs, Gajdusek and others in 1968.[5]

CJD is the most common prion disease. It occurs as sporadic, familial, iatrogenic (infectious) and genetic forms. It is thus unique as a disease, both infectious and genetic.

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CLINICAL FEATURES

Different prion diseases have somewhat different clinical profiles, but the overall typical picture is that of a uniformly progressive, fatal, encephalopathic illness with dementia, cerebellar ataxia and myoclonus being common. With no simple, absolute clinical diagnostic test for prion disease, definitive diagnosis requires neuropathology i.e., autopsy or brain biopsy. However, on the basis of internationally agreed clinical diagnostic criteria[6,7] relatively reliable clinical diagnoses can often be made.

There are no systemic abnormalities due to prion disease: No pyrexia and other index of infection and routine hematology, biochemistry and immunological tests are normal. Also there is no cerebrospinal fluid pleocytosis (although the total protein may be mildly to moderately raised). The overall diagnostic process is essentially the suspicion of prion disease based on clinical pattern, the exclusion of other diagnoses and supportive investigation findings (EEG, CSF and MRI findings which are not prion-disease specific and tonsil biopsy in the case of variant CJD).[7-11] These tests are essentially supportive tests when prion disease is already reasonably suspected; positive results must be obtained in the light of the overall clinical situation.

SPORADIC CJD (sCJD)

This is commonest form of CJD existing worldwide. Typically, it affects the middle-aged and elderly (median age at death around 65 years) and consists of a rapidly progressive dementia with cerebellar ataxia, visual disturbances and myoclonus terminating in an akinetic mute state. The median survival is only around 4 months in most countries with survival of more than two years being rare.[12] There are less common or atypical forms with different presentations and overall clinical pictures. The commonest variations in presentation are the so-called Brownell-Oppenheimer CJD (a pure cerebellar syndrome) and Heidenhain's syndrome (pure visual impairment leading to cortical blindness); they progress to a similar preterminal state as typical sCJD.[13,14] Other specific presentations exist but are exceptionally rare. Young age disease onsets (even in the second decade of life) occur but are rare and late age disease are more common. The duration of illness depends on age at onset, gender, *PRNP*-129 genotype and prion protein-type.[15] In some cases, typical features, such as myoclonus, never develop. These clinical variations are associated with pathological variations and the different clinico-pathological profiles correlate to some degree with *PRNP* codon 129 polymorphism and the prion protein-type (with the most typical forms associated with MMI and MVI characteristics).[16] Recent reports concerning the co-occurrence of more than one abnormal prion protein within a single brain have prompted to revise the clinco-pathological-molecular classification of sCJD.[17,18]

The recently described 'Protease Sensitive' prion disease is of uncertain nosological status but is a form of sporadic prion disease with distinctive neuropathological and prion protein characteristics.[19,20] Its clinical profile is not yet well delineated but it appears to have a relatively longer duration than typical sCJD.

In around two-thirds of sCJD cases, the electroencaphelogram (EEG) shows characteristic periodic bi- or tri-phasic complexes at some stage of the illness.[8] The cerebrospinal fluid (CSF) 14-3-3 protein test is positive in the majority of cases. Cerebral magnetic resonance imaging (MRI) frequently shows basal ganglia

(putamen and caudate) and cortical hyperperintesity, especially on FLAIR and DWI sequences.[7,9] These investigation results vary with respect to *PRNP*-129 genotype and prion protein-type.[21]

Neuropathology of Sporadic Creutzfeldt-Jakob Disease

sCJD comprises broad spectra of clinico-pathological variants. In nongenetic cases of prion diseases, neuropathological examination is the only way to establish the diagnosis of definite disease. The brain biopsy in all transmissible spongiform encephalopathies (TSEs), sCJD included, is extremely rarely undertaken so definite cases in most instances are recognized during autopsy.

The gross pathology of the brain in sCJD is not characteristic, most often a various degree of focal or diffuse brain atrophy is observed. On the contrary, the microscopic changes are very distinctive. The classic triad of histopathological findings for CJD consists of marked neuronal loss, spongiform change and astrogliosis. Additionally, various forms of deposits of PrP^{Sc} are observed.

Spongiform change (Fig. 1) is the most specific microscopic alteration in CJD and is characterized by a fine vacuolation of the neuropil of the gray matter with round or oval vacuoles varying from 20-200 microns in diameter. Ultrastructurally, the vacuoles are localized in cell processes, mainly dendrites and contain curled membrane fragments and amorphous material.[22] Infrequently, vacuolation may also be seen within the cytoplasm of larger neurons within the cortex. The vacuoles may appear in any layer of the cerebral

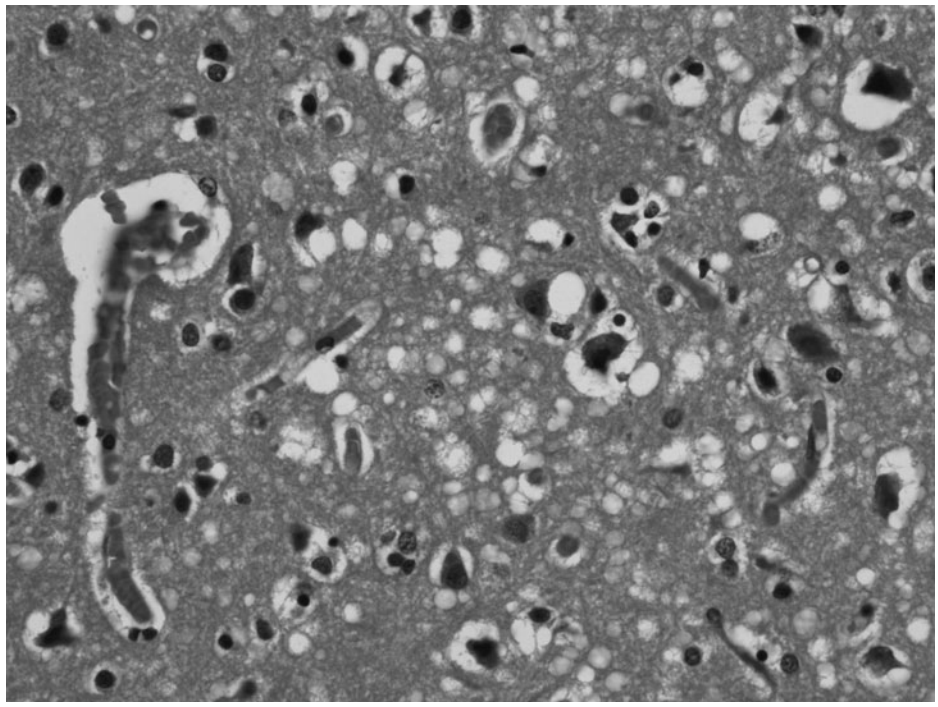

Figure 1. Typical spongiform change. Haematoxylin and eosin stain.

cortex. Distribution of spongiform change varies from case to case and between subtypes of sCJD but usually it is also observed in the basal ganglia, thalamus and the cerebellar cortex. In some cases, spongiform change may become confluent, resulting in large vacuoles which substantially distort the cortical architecture (status spongiosus).[23] Spongiform change must be distinguished from nonspecific "spongiosis" which may be observed in Alzheimer's disease, dementia with Lewy bodies and also in hypoxic damage or brain oedema.

The neuronal loss seems to be selective in prion diseases. GABAergic neurons are considered the main target of neuronal loss in experimental prion diseases and in CJD.[23,24] Interestingly, the hippocampus and dentate gyrus, which are most vulnerable areas in many neurodegenerative diseases, are relatively well preserved in most cases of CJD.[25]

Immunohistochemical reaction for the prion protein (PrP) is the gold standard for diagnosis of human prion diseases. Since most of anti-PrP antibodies do not discriminate between normal (PrP^{c}) and pathological (PrP^{Sc}) isoforms of prion protein, special pretreatments are required to eliminate reaction with PrP^{C}.[25] There are several patterns of PrP-immunoreactivity in human brains, these include: Synaptic pattern (fine dot-like deposits) (Fig. 2); pericellular/perineuronal pattern (dot-like deposits around neuronal perikarya) (Fig. 3); coarse deposits (granular or patchy/perivacuolar deposits) (Fig. 4); plaque-like deposits (not visible without PrP-immunohistochemistry and not showing congophilia or other tinctorial characteristics of amyloid) (Fig. 5); Kuru-plaques (visible in routine staining, congophilic and exhibiting tinctorial features of amyloid).

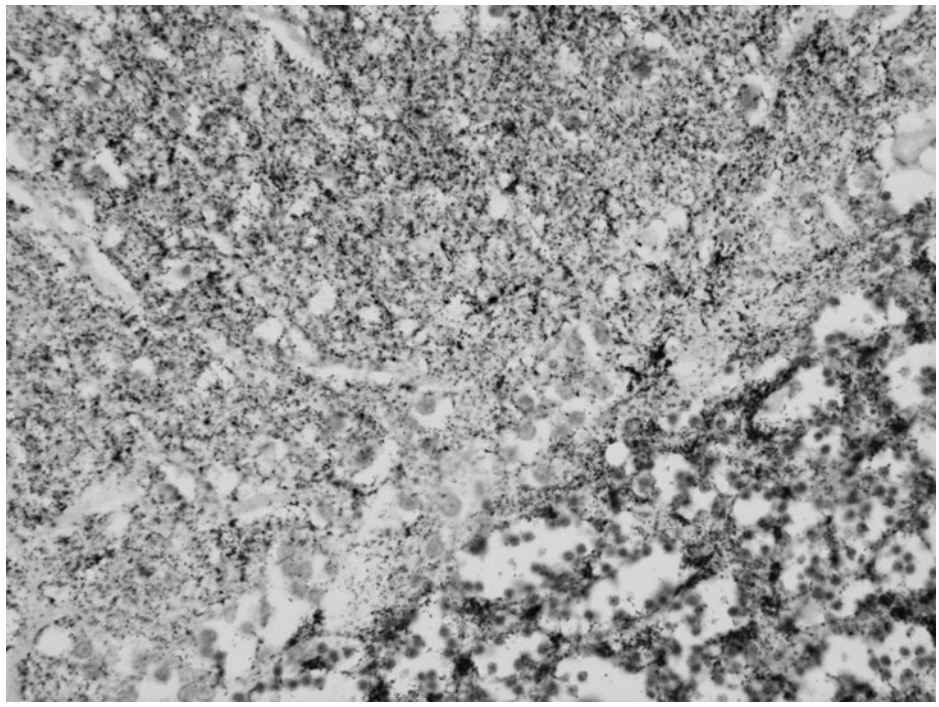

Figure 2. Synaptic pattern (fine dot-like deposits). PrP-immunohistochemistry.

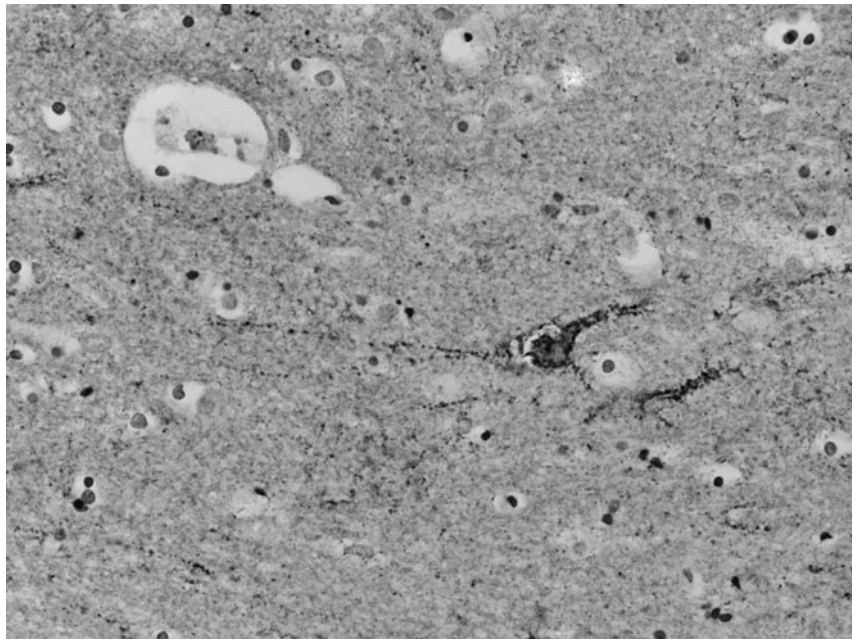

Figure 3. Pericellular/perineuronal pattern (dot-like deposits around neuronal perikarya). PrP-immunohistochemistry.

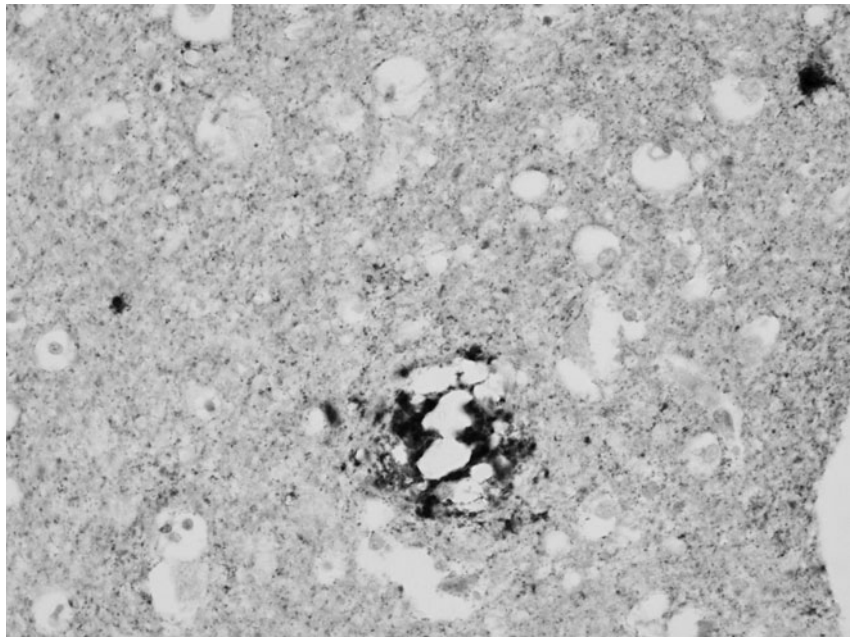

Figure 4. Coarse deposits (granular or patchy/perivacuolar deposits). PrP-immunohistochemistry.

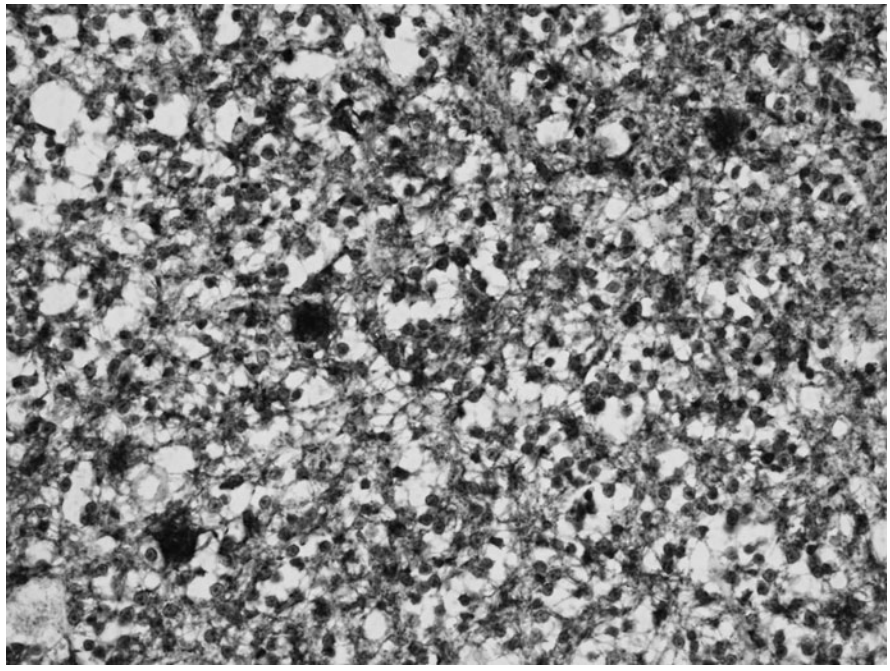

Figure 5. Plaque-like deposits (not visible without PrP-immunohistochemistry and not showing congophilia or other tinctorial characteristics of amyloid). PrP-immunohistochemistry.

It should be noted that both spongiform change and PrP-immunoreactivity may be focal and in some cases staining of several blocks is required.[25] In addition to the abovementioned patterns, PrP-immunoreactivity may be observed in neuronal perikarya as diffuse immunoreactivity, dot-like immunoreactivity or intracytoplasmic inclusions. Discrete PrP deposits were detected in the posterior root nerve fibres,[26] skeletal muscle[27] and in vessel walls.[28]

Six subtypes of sporadic Creutzfeldt-Jakob disease with distinctive clinico-pathological features have been identified largely based on two types of PrP^{Sc} and the status of polymorphic codon 129 of the prion protein gene (*PRNP*) that encodes either for methionine (M) or for valine (V).[16] Two major human PrP^{Sc} types were identified by Parchi et al;[16] Type 1 with a relative molecular mass of 21 kDa and the primary cleavage site at residue 82 and Type 2 with relative molecular mass of 19 kDa and the primary cleavage site at residue 97. The two PrP^{Sc} types, in conjunction with the codon 129 of *PRNP* genotype provided a molecular basis for the disease classification.[16,29] More recently, cases presenting more than one PrP^{Sc} type and mixed histopathological features were described leading to new classifications.[30,31] Currently, in addition to predominant pure subtypes of sCJD, mixed subtypes are also recognized.[18] In our opinion, for a routine neuropathological examination the classic Parchi and Gambetti classification[16] is the most useful. The six subtypes differ in distribution of pathological changes, clinical features and molecular characteristics.

Subtype 1: (sCJDMM1 and sCJDMV1)

This subtype is observed in patients who are MM homozygous or MV heterozygous at codon 129 of the PrP gene (*PRNP*) and carry PrP^{Sc} Type 1. Clinical duration is short, 3-4 months.[32] The most common presentation in sCJDMM1 patients is cognitive impairment leading to frank dementia, gait or limb ataxia, myoclonic jerks and visual signs leading to cortical blindness (Heidenhain's syndrome).

Neuropathologically, subtype 1 sCJD is characterized by the presence of fine spongiform change, astrogliosis and neuronal loss. Spongiform change affects all layers of the cerebral cortex except for the first; in the cerebellum, it affects the molecular layer. The cerebral neocortex, is more severely affected than basal ganglia, thalamus and the cerebellum while the brain stem is virtually spared. The hippocampal cortex is spared. PrP-immunoexoression shows synaptic pattern of staining. Most intensive immunolabelling is observed in the areas of most severe histopathological changes. The immunostaining is often not uniform and some large regions may remain unstained.[16,32]

Subtype 2: (sCJDVV2)

This is the second most common subtype of sCJD. It accounts for about 16% of all cases[32] and corresponds to the previously described cerebellar/ataxic variant. The mean age at onset is about 60 years and the clinical duration is approximately 6 months with a 3-18 month range. Ataxia is often among the presenting signs. Cognitive impairment, myoclonus and pyramidal signs affected the majority of the patients with progression of the disease.

The spongiform change often shows a laminar distribution and it is more severe in the frontal than in the occipital cortex which is relatively spared. In this subtype, the limbic structures including the hippocampal gyrus shows spongiform degeneration, although the lesions in the entorhinal cortex are more severe. The topography of the lesions shows that the caudal brain regions are more severely affected than the rostral regions. The PrP-immunohistochemical hallmark of this subtype is the presence of focal PrP^{Sc} aggregates that look-like plaques (plaque-like) but do not contain PrP amyloid. These plaque-like deposits are Congo red and thioflavine S negative and are not visible in a routine H and E staining. Other distinctive features are strong perineuronal pattern of immunoreactivity, with intense labeling along neuronal processes, especially prominent in the basal ganglia and thalamus. A diagnostic feature of this subtype is the immunostaining pattern of the cerebellum that shows intense immunostaining in the Purkinje and upper granule cell layers with the presence of numerous plaque-like formations.[16,32]

Subtype 3: (sCJDMV2)

This subtype accounts for 9-10% cases of sCJD and also corresponds to the ataxic variant (Betty Brownell/Oppenheimer syndrome). The duration of disease differs significantly from that of previous subtypes, with the average of 17 months. Ataxia also is the most common presenting sign, but cognitive and mental signs and symptoms are more common than in the sCJDVV2 patients.[32] Neuropathologically, this subtype is similar to sCJDVV2. The main difference is the presence of the kuru plaques in the Purkinje cell layer and superficial granule cell region of the cerebellum; and the lack of

significant cerebellar cortical atrophy. Kuru plaques are typical amyloid, congophilic plaques similar to those of kuru. Furthermore, coarse spongiform change, which may be either focal or widespread, is occasionally present and brain stem lesions are less severe.[16,32]

Subtype 4: (sCJDMM2)

The fourth subtype is found in 2-8% of cases. The mean age at onset is 65 years and the average disease duration is 16 months. Cognitive impairment and aphasia are most often observed. Myoclonic jerks and pyramidal signs are also common in later stages of the disease. The characteristic feature of this type is spongiform change with large vacuoles (coarse spongiosis). The vacuoles are several times larger than the typical vacuoles of Type 1 sCJD and are widespread in the cerebral cortex, basal ganglia and thalamus. PrP-immunohistochemistry shows intense staining at the rim of the large vacuoles additionally, synaptic pattern may also be observed and some plaque-like deposits are not uncommon.[16,32]

Subtype 5: (sCJDVV1)

The most uncommon subtype affecting about 1% of all cases of sCJD. Average age at onset is 39 years (range, 24-49 years) and the disease duration is approximately 15 months. This subtype is frequently referred to as "early onset sCJD".

The neuropathological hallmark of this subtype is the dissociation between the severity of fine spongiform change, gliosis and occasionally neuronal loss and the PrP-immunostaining that is faint and of a synaptic pattern. Interestingly, the hippocampal cortex is more affected and the thalamus and the cerebellum are less affected brain regions.[16,32]

Subtype 6: Sporadic Fatal Insomnia (sFI)

Another rare subtype accounts for about 2% of all cases of sporadic prion disease. Only a few proven cases of this subtype have been reported. Its phenotype is indistinguishable from that of fatal familial insomnia (FFI), hence the name "sporadic fatal insomnia" (sFI) has been coined.[33,34] The major pathology is observed in the thalamus, especially the medial dorsal and anterior ventral nuclei, that show a profound neuronal loss and astrogliosis but generally without spongiform change. Other brain regions are less affected and PrP-immunoreactivity is minimal or even absent. Astrogliosis and neuronal loss are also minimal in basal ganglia and cerebellum.[16,32]

GENETICS OF PRION DISEASE (gPD)

This has a very varied clinico-pathological phenotype, partly depending on the underlying *PRNP* mutation but other factors are obviously relevant, including the *PRNP* 129 genotype.[35] Historically, it comprises three main clinico-pathological phenotypes: Genetic CJD (gCJD), Gerstmann-Sträussler-Scheinker disease (GSS) and fatal familial insomnia (FFI). Classical GSS presents as a progressive cerebellar ataxia with relatively late cognitive features and FFI begins with prominent sleep and autonomic disturbances.

In gCJD, the mean age at onset is slightly younger and illness duration is longer than in sCJD. The inheritance of gPD is autosomal dominant with variable (generally high) penetrance. However, a family history may be absent in around 40% of cases.[36] The commonest mutation disease is E200K-CJD which typically clinically resembles sCJD, although a polyneuropathy may be present. Given the variable clinical phenotypes of gPD, the potential similarity to sCJD and the frequently absent family history, *PRNP* mutation testing (which can be undertaken on a blood sample) is necessary to definitively distinguish gPD and sCJD; such testing should be considered in a wide variety of neuropsychiatric illnesses.

IATROGENIC CJD (iCJD)

This appears to have most commonly arisen from cadaveric-derived human growth hormone (hGH-CJD) (mostly in France, UK and USA) and dura mater grafts (mostly in Japan). The incubation period is potentially long but varies with cause (mean of 11 years in dura mater-related cases and 15 yrs in hGH-CJD). In general, it resembles sCJD with the age at onset reflecting the age of exposure and the incubation period. However, hGH-CJD tends to have a relatively young age at onset, reflecting the age at which hormone treatment is given and presents differently—as a progressive cerebellar syndrome, with relatively minor and late cognitive features.[37,38]

VARIANT CREUTZFELDT-JAKOB DISEASE (vCJD)

It affects significantly younger age group and progresses more slowly (in the UK: Mean age at onset, 28 years; mean duration of illness, 14 months) compared with sCJD. Notably, the initial symptoms are prominently psychiatric and behavioural with the absence of clear, specifically neurological features.[39] Painful sensory symptoms may be present.[40] As the illness progresses, cerebellar ataxia is usually prominent with cognitive impairment and involuntary movements, including chorea, dystonia and myoclonus.[41] All cases of definite and probable vCJD (as defined by the current internationally accepted diagnostic criteria) have been *PRNP*-129 MM individuals. There is a report of one possible case in an MV individual.[42] The incubation period of vCJD is expected to vary with *PRNP*-129 genotype (any effect on clinico-pathological expression is unknown; the reported MV case was clinically indistinguishable from the MM cases). Variant CJD has occurred as a secondary, iatrogenic illness, resulting from blood transfusion; these cases have been clinically identical to primary dietary cases.[43] The EEG usually does not show the periodic activity seen in sCJD; being reported in two cases but only in the very late disease stages.[44] The CSF 14-3-3 is positive in less than half the cases.[45] The cerebral MRI shows hyper intensity in the posterior thalamus (the 'Pulvinar Sign') in over 90% of cases, especially on FLAIR and DWI sequences.[10] In vCJD, in contradistinction to other prion diseases, a tonsil biopsy may show the disease-specific abnormality of PrP^{Sc}.[11]

vCJD was reported as a novel form of human prion disease in a series of 10 patients in the United Kingdom (UK) by Will et al in 1996.[46] Since then, additional cases have been identified both in the UK (currently 173 cases) and 47 cases in 10 other countries, with France having the second largest total (25 cases at time of writing). The incidence

of vCJD has declined in the UK in recent years, although small numbers of new cases are still being identified.

Surveillance of CJD was re-instated in the UK in 1990 following the identification of an epidemic of a novel prion disease in cattle, bovine spongiform encephalopathy (BSE). The evidence for a link between BSE and vCJD was first suggested on the basis of epidemiology; however, subsequent laboratory and biological studies have indicated that the infectious agent responsible for vCJD is identical to the BSE agent.[47] vCJD is therefore unique amongst human prion diseases since it represents an acquired infection across a species barrier, namely from bovines to humans. The most likely route of primary infection in vCJD is by the oral route, via meat products contaminated with the BSE agent.[48]

Neuropathology of vCJD

The brain in vCJD is often unremarkable on macroscopic inspection, but in cases with a long disease duration (over 20 months) there may be both cerebellar and cerebral cortical atrophy.[49] The microscopic features of vCJD are distinct from other forms of human prion disease (Table 1): Large fibrillary amyloid plaques surrounded by a corona or halo of spongiform change, known as florid plaques, are the most striking feature (Fig. 6A). These are widespread throughout the cerebral cortex, particularly in the occipital cortex and are also present in the cerebellar molecular layer. Smaller fibrillary plaques without surrounding spongiform change are present in the basal ganglia, thalamus and cerebellar granular layer. Florid plaques are not specific for vCJD, as similar lesions have been identified in smaller numbers in dura mater-associated cases of iatrogenic CJD in Japan.[50]

Spongiform change in vCJD is most severe in the putamen and caudate nucleus, while neuronal loss and gliosis is most severe in the posterior thalamus, particularly the pulvinar (Fig. 6B).[49] The distribution of thalamic neuronal loss and gliosis correlates with the areas of hyper intensity seen on MRI scans (particularly in T2-weighted or FLAIR sequences) within the pulvinar in vCJD patients.[10] Immunohistochemistry for PrP shows a characteristic pattern of accumulation in the brain in vCJD. The florid plaques label intensely and this technique also demonstrates large numbers of smaller plaque-like lesions in clusters, which are not evident on routine stains. Pericellular accumulation of

Table 1. Neuropathological diagnostic criteria for vCJD

Cerebral and cerebellar cortices	Numerous florid plaques in routine stained sections
	Multiple small cluster plaques in PrP stained sections
	"Feathery" pericellular and pericapillary PrP accumulation
Caudate nucleus and putamen	Severe spongiform change
	Perineuronal and focal periaxonal PrP accumulation
Posterior thalamic nuclei	Marked neuronal loss and astrocytosis
	Scanty spongiform change and amyloid plaques
Brainstem and spinal cord	Perineuronal and granular PrP accumulation
Biochemistry	Type 2B PrP^{Sc} on Western blot analysis

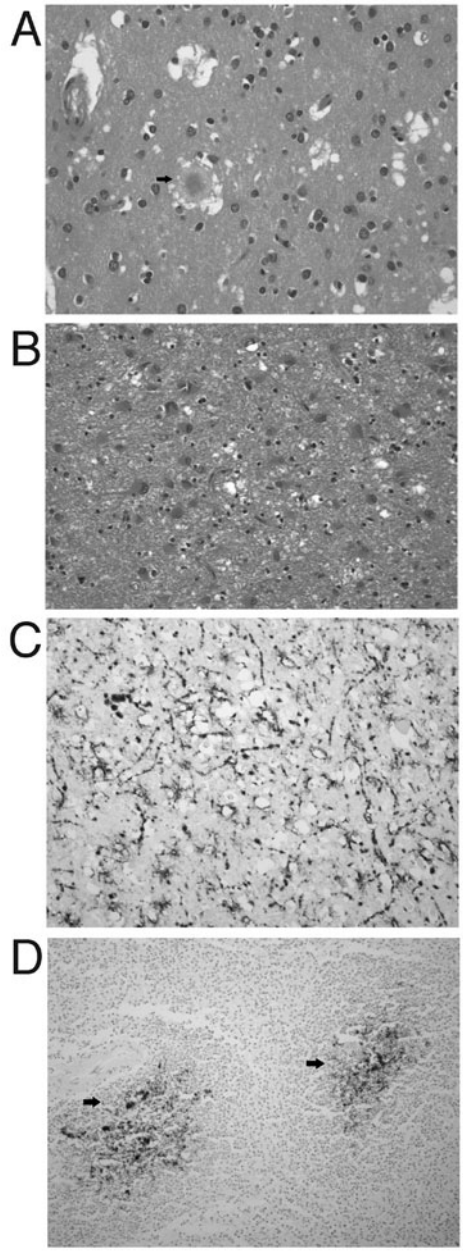

Figure 6. A) The florid plaque (arrow) in the occipital cortex in vCJD consists of a fibrillary amyloid core surrounded by a corona of spongiform change. Haematoxylin and eosin stain. B) The pulvinar nucleus in vCJD shows sever neuronal loss and astrocytosis, with little spongiform change and no amyloid plaque formation. Haematoxylin and eosin stain. C) Prion protein accumulation in the putamen in vCJD is perineuronal and periaxonal, with a beaded deposists in linear profiles. PrP-immunohistochemistry, KG9 anti-prion protein antibody. D) Prion protein accumulation in the tonsil in vCJD is concentrated within germinal centres (arrows), in follicular dendritic cells and macrophages. PrP-immunohistochemistry, KG9 anti-prion protein antibody.

PrP is also detected in an amorphous or feathery distribution around small neurones and astrocytes in the cerebral and cerebellar cortex. Occasional perivascular accumulation of PrP is also present around capillaries in the cerebral and cerebellar cortex, but there is no evidence of an amyloid angiopathy. The basal ganglia shows a perineuronal and periaxonal pattern of PrP positivity, often in a linear distribution (Fig. 6C).[49]

Peripheral Pathology in vCJD

In contrast to other forms of human prion disease, immunohistochemistry for PrP shows positivity in a variety of peripheral neural tissues, including sensory and autonomic ganglia.[51] There is also intense positivity for PrP within germinal centres in lymphoid tissues that colocalises to follicular dendritic cells (Fig. 6D).[11,51] Infectivity in both lymphoid and peripheral nervous tissues in vCJD has been demonstrated experimentally.[52] The accumulation of PrP positivity in lymphoid follicles allows tonsil biopsy to be used as an aid to premortem diagnosis in some cases of vCJD.[11] Furthermore, it has been shown that PrP positivity could be detected in lymphoid follicles in the appendix prior to the onset of clinical disease.[53] This finding has been explored in a retrospective prevalence study of PrP accumulation in appendix and tonsil tissues in the UK.[54,55] These studies suggest that the number of clinical cases of vCJD to date may not reflect accurately the true number of infections with BSE in the UK population and it is interesting to note that two of the positive appendix cases were subsequently shown to be *PRNP* codon 129 valine homozygotes.[54,56]

vCJD exhibits a characteristic PrP^{res} isoform in the brain—Type 2 PrP^{Sc} with predominance of the diglycosylated form, designated Type 2B (Fig. 7).[51] This has not

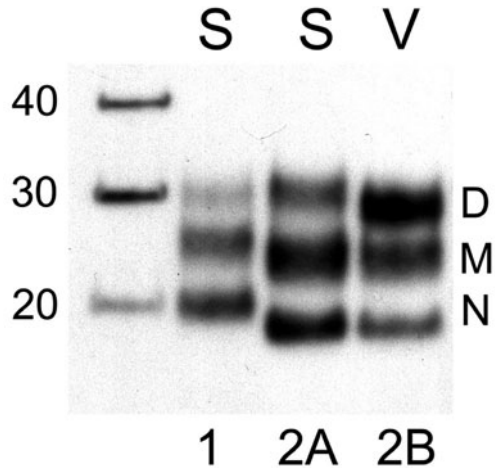

Figure 7. Western blot analysis of protease-resistant prion protein (PrP^{res}) in frontal cortex samples from two cases of sporadic CJD (S), contrasted with a case of variant CJD (V). The sizes of the molecular weight markers are given in kDa and the three PrP^{res} glycoforms are labelled as D (diglycosylated), M (monoclycosylated) and N (nonglycosylated). PrP^{res} Type 1 (nonglycosylated band ~21kDa) and Type 2 (nonglycosylated band ~19kDa) are typical of different forms of sporadic CJD. The PrP^{res} found in variant CJD has a nonglycosylated band of ~19kDa, but is characterised by a predominance of the diglycosylated form and termed Type 2B to distinguish it from the 2A isoform of sporadic CJD in which the mono- or nonglycosylated forms predominate.

Table 2. *PRNP* codon 129 genotype in prion diseases (probable and definite cases)

Codon 129 Genotype (%)	MM	MV	VV
Normal population	39	50	11
Sporadic CJD	63	19	18
Variant CJD	100	-	-

Abbreviations: M, methionine; V, valine.

been detected in sporadic CJD and is therefore useful as a biochemical marker of vCJD infection.[31] The widespread distribution of PrP^{res} and infectivity in vCJD tissues indicates that the disease might be transmitted accidentally by medical or surgical procedures.[51,52] In support of this concern, there have been four incidences of apparent transmission of vCJD infectivity by blood transfusion, three of which resulted in the clinical onset of vCJD 6.5-8 years after transfusion in recipients who were *PRNP* codon 129 methionine homozygotes.[43] The fourth recipient died around 5 years after transfusion of an unrelated cause, but without clinical features of vCJD or any other neurological disease.[57] However, PrP^{Sc} accumulation was detected biochemically and by immunohistochemistry in the spleen and a lymph node (but not in the brain or spinal cord), indicating asymptomatic vCJD infection in the recipient, who was a *PRNP* codon 129 heterozygote.[57] A similar case in an elderly adult haemophiliac patient in the UK has recently been described, where PrP^{res} was detected biochemically in the spleen of a PRNP codon 129 heterozygote patient with no clinical or neuropathological evidence of vCJD.[58] The most likely source of vCJD infection in this case appears to be vCJD—contaminated plasma products.[58]

All patients with the histologically proven vCJD have been methionine homozygotes at codon 129 in the *PRNP* (Table 2), but one recent case of possible vCJD in a *PRNP* codon 129 heterozygous patient has been reported.[42] It remains to be established whether BSE infection in other human *PRNP* genotypes will result in a further increase in vCJD cases in the UK; continuing surveillance is required to address this important tissue.

CONCLUSION

CJD has been the first prion disease of worldwide occurrence and is unique. Causative agents are various forms of prion proteins which are mostly in misfolded form to generate the disease. It occurs either as sporadic, iatrogenic and variant (all are infectious) or a familial (genetic but also transmissible) forms. The diseases is strongly influence by the genetic backround.

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