Creutzfeldt-Jakob Disease: A Rare Cause of Dementia in Elderly Persons

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Creutzfeldt-Jakob disease (CJD) exists in inherited, acquired (variant and iatrogenic), and spontaneous (sporadic) forms. Although iatrogenic and variant forms of CJD usually affect relatively young persons, all forms may affect elderly persons, especially sporadic CJD. Sporadic CJD is a rare cause of dementia among middle-aged and elderly persons, and typical cases are clinically fairly distinct from more common forms of neurodegenerative dementias. However, clinical diagnosis can be a challenge for those who are not experienced with the disease. Fortunately, certain investigations can be very helpful. Although many cases of CJD (especially sporadic CJD) are not thought to be acquired illnesses, there is still a potential for onward transmission, and certain precautions are necessary to protect public health.

Creutzfeldt-Jakob disease (CJD) is now divided into 4 forms on the basis of cause and clinico-pathological profile (table 1). Unfortunately, the media (and, indeed, others) sometimes fail to carefully distinguish them.

The neuropathological features of prion disease are essentially neurodegenerative: neuronal loss, astrocytic proliferation, spongiform change, and deposition of an abnormal disease-related form of PrP in tissues [4, 5]. All prion disease are brain illnesses typically involving dementia; they are universally progressive, fatal, and presently incurable.

What is PrP? PrP is a normal cellular protein, of uncertain function, that, in humans, is encoded by the PrP gene (PRNP), which is located on chromosome 20. In prion diseases, there are post-translational conformational changes, from the normal predominantly \( \alpha \)-helical structure (PrP\(^{C} \)) to a more \( \beta \)-sheeted form (PrP\(^{Sc} \)). The precise mechanism of this change is unclear, and its cause is believed to vary with different prion diseases. Once the process begins, PrP\(^{Sc} \) continues to cause PrP\(^{C} \) to convert in an auto-catalytic amplification. PrP\(^{Sc} \) and PrP\(^{C} \) have different physico-chemical properties. In particular, PrP\(^{Sc} \) is relatively insoluble, is relatively resistant to protease degradation, tends to accumulate in tissues, and forms amyloid deposits. PrP\(^{Sc} \) is related to disease pathogenesis and infectivity, but the precise relationships are unclear [3, 6]. Following protease treatment of PrP\(^{Sc} \), a significant core protein remains (designated PrP\(^{Res} \)) that is found in 2 different sizes (type I and type II). In addition, there are different glycosylation patterns of the disease-related protein (A and B). Thus, the underlying PrP...
Table 1. Prion diseases.

<table>
<thead>
<tr>
<th>Disease</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Animal</td>
<td></td>
</tr>
<tr>
<td>Scrapie</td>
<td>Naturally occurring disease of sheep and goats</td>
</tr>
<tr>
<td>TME</td>
<td>Disease of farmed mink</td>
</tr>
<tr>
<td>BSE</td>
<td>Disease of cattle, first reported in 1987</td>
</tr>
<tr>
<td>BSE-related diseases</td>
<td>Transmission of BSE to cats (FSE) and other animals</td>
</tr>
<tr>
<td>Human</td>
<td></td>
</tr>
<tr>
<td>Kuru</td>
<td>Confined to Papua New Guinea</td>
</tr>
<tr>
<td>CJD</td>
<td>The most common human prion disease, existing in the 4 following forms: sporadic, genetic, iatrogenic, and variant (described in 1996)</td>
</tr>
<tr>
<td>Genetic prion diseases</td>
<td>Rare autosomal dominant inherited diseases, including GSS and FFI</td>
</tr>
</tbody>
</table>

NOTE. BSE, bovine spongiform encephalopathy; CJD, Creutzfeldt-Jakob disease; FFI, fatal familial insomnia; GSS, Gerstmann, Sträussler, Scheinker syndrome; TME, transmissible mink encephalopathy.

found in disease can be classified (e.g., as IIB) [7–9]. These resultant protein types vary between different forms of prion disease; thus, they help to distinguish them.

What is the role of PRNP? PRNP, the relevant gene, is important in the disease process. In genetic forms, the role is believed to be directly causal, but PRNP has effects in all forms of CJD. In particular, there is a common polymorphism at codon 129 of the open reading frame, whereby either methionine (M) or valine (V) may be encoded. This genotype affects susceptibility to prion diseases, may influence the incubation period in acquired cases, and can even affect the clinico-pathological phenotype of the resulting disease (figure 1) [8, 10].

What is the nature of the transmissibility? CJD has characteristics that are not unique. Other neurodegenerative illnesses (such as Alzheimer disease) involve the deposition of an abnormally folded protein; however, CJD is transmissible. The precise nature of the infective agent is uncertain. PrP<sup>Sc</sup> is generally associated with infectivity and the “prion theory” holds that PrP<sup>Sc</sup> is either itself the agent or a major component of it and that no specific DNA and/or RNA is involved [2, 4].

HOW COMMON IS CJD, AND HOW DOES IT PRESENT?

Genetic CJD. Genetic CJD is associated with a number of mutations of the PRNP gene that are currently believed to be directly pathogenic. The inheritance is autosomal dominant with generally complete or high penetrance (varying somewhat from mutation to mutation). The clinico-pathological disease phenotype is rather variable, depending at least in part on the particular underlying mutation [11]. Genetic CJD is very rare, causing around 5 deaths per year in the United Kingdom. There are 2 important facts for the nonspecialist. First, genetic CJD can clinically mimic other forms of CJD, and a family history of the illness may be absent. Second, despite its inherited nature, disease onset can be late in life and is, therefore, a very rare cause of dementia in elderly persons [11].

Sporadic CJD. Sporadic CJD has a worldwide distribution, with an annual mortality rate of approximately 1–2 deaths per million cases. Principally, it affects middle-aged and elderly persons (in the United Kingdom, the median age at death is 67 years [range, 20–95 years]) [12, 13]. There is a sharply increasing incidence associated with increasing age, but with a decrease in incidence among persons >70 years old, it is uncertain whether this represents a true decrease in incidence or a reflection of underascertainment of cases among very elderly persons (figure 2). The cause is unknown; the current theory favors either a spontaneous change in PrP structure or a somatic PRNP mutation that leads to an abnormal form of protein. However, it remains possible that sporadic CJD is an acquired illness, and 2 case-control studies have reported prior surgery as a risk factor [14, 15]. Spontaneous occurrence would be expected to produce a continuing increase in the number of
cases with increasing age, and it is certainly possible that cases among elderly persons are overlooked, being misdiagnosed as other conditions without autopsy being performed. In 1997, De Silva et al. [16] argued that cases in elderly persons in the United Kingdom were not being overlooked, noting that cases of sporadic CJD in elderly persons were not different from cases in younger persons and that the typical clinical picture was relatively striking and unusual. A more recent publication cited evidence to the contrary, reporting that the greatest relative increase in the number of cases of sporadic CJD in the United Kingdom from 1970 to 1999 had been among persons ≥70 years old [17]. This trend has continued, with an increase in the number of CJD-related deaths per year in the ≥70-years-old age group in England and Wales from ~1 to ~25 in recent years (figure 2) [13]. Many cases of sporadic CJD follow a relatively uniform course; patients present with a rapidly progressive dementia that is accompanied by other features, including cerebellar ataxia, visual loss, and myoclonus. There is, however, a significant degree of clinical (and corresponding pathological) heterogeneity that is especially found in the features at onset. For example, some individuals present with an isolated cerebellar ataxia or an isolated progressive visual loss (leading to cortical blindness) prior to the development of progressive cognitive impairment [12, 18]. The typical clinical progression of sporadic CJD is strikingly rapid; the median duration in the United Kingdom is 4 months, with approximately two-thirds of patients dying within 6 months. Some cases even progress from the first symptom to death in 4 weeks, and the patient’s condition may worsen on an almost daily basis. The ability to walk and speak are often lost early. In a typical case, the progression culminates in a terminal akinetic mute state with myoclonus. In some cases, the illness progresses more slowly, with durations of ≥1 year in slightly less than 15% of patients and of ≥2 years in only 5% of patients [12, 18]. Even when accounting for possible underascertainment of cases, sporadic CJD is a rare cause of dementia among elderly persons, compared with typical causes, such as Alzheimer disease, but the usual clinical picture is striking and rather distinct from the usual presentations of more common neurodegenerative illnesses. There are highly atypical cases of sporadic CJD that include slowly progressive dementia syndromes that can be difficult to differentiate from more common illnesses, such as Alzheimer disease, but these are exceptionally rare. The basis for this heterogeneity is not entirely understood, and a detailed discussion is outwith the remit of this review. However, this heterogeneity does, in part, reflect different codon 129 genotypes, and there is some correlation with the disease-related PrP type. A molecular- and clinico-pathological classification of sporadic CJD has been proposed, with cases being designated as MM1, MV2, and so on [8]. Although certain clinico-pathological features tend to be associated with certain PRNP-129–PrP-type combinations, such classification is not altogether clear cut. In addition, there are recent reports of >1 PrP type being found in a single brain [7, 9, 19].

Iatrogenic CJD. Iatrogenic CJD is simply CJD (most likely sporadic CJD) that is transmitted from one person to another by medical or surgical treatment (table 2) [20]. It is important to note that all forms of prion disease are potentially transmissible, even, remarkably, autosomal dominantly inherited genetic diseases. In addition, there are increasing concerns that variant CJD will lead to significant secondary transmission, with 2 reported cases of probable blood transmission [21, 22].

Patients with cases related to human growth hormone typically present as with progressive cerebellar ataxia with only late cognitive impairment, and are usually relatively young, reflecting the use of human growth hormone treatment during child-

Figure 2. Mortality rates (per 1 million persons) associated with sporadic Creutzfeldt-Jakob disease in the United Kingdom across different age groups showing increases over 3 time periods, particularly among elderly persons.
Table 2. Iatrogenic Creutzfeldt-Jakob disease (CJD): recognized causes and worldwide occurrence.

<table>
<thead>
<tr>
<th>Cause</th>
<th>Comment</th>
<th>Approximate total no. of cases worldwide</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human growth hormone</td>
<td>Related to use of cadaveric-derived human growth hormone from pituitary glands</td>
<td>165</td>
</tr>
<tr>
<td>Human dura mater</td>
<td>Related to use of cadaveric-derived human dura mater in surgery</td>
<td>136</td>
</tr>
<tr>
<td>Neurosurgical and depth electroencephalogram electrodes</td>
<td>Transmission via contaminated instruments and/or depth electrodes</td>
<td>6</td>
</tr>
<tr>
<td>Human gonadotrophin</td>
<td>Transmission via human-cadaveric derived hormone</td>
<td>5</td>
</tr>
<tr>
<td>Ophthalmological</td>
<td>Transmission via corneal transplants</td>
<td>3</td>
</tr>
<tr>
<td>Blood</td>
<td>Probable instances of infection via blood donated by donors with variant CJD</td>
<td>2</td>
</tr>
</tbody>
</table>

Table 3. Cases of variant Creutzfeldt-Jakob disease worldwide, as of January 2006.

<table>
<thead>
<tr>
<th>Country</th>
<th>No. of patients judged to have been infected in country</th>
<th>No. of patients judged to have been infected while in the United Kingdom</th>
</tr>
</thead>
<tbody>
<tr>
<td>United Kingdom</td>
<td>159</td>
<td>159</td>
</tr>
<tr>
<td>France</td>
<td>15</td>
<td>0</td>
</tr>
<tr>
<td>Republic of Ireland</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Italy</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Spain</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Portugal</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>The Netherlands</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Saudi Arabia</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>United States</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Canada</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Japan</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

**NOTE.** Cases are attributed to a country according to the normal country of residence at the time of onset of illness. However, this country is not necessarily the same as the country in which persons have been infected.

The clinical features of other forms of iatrogenic CJD are generally similar to those of sporadic CJD.

**Variant CJD.** Variant CJD was first identified in 1996, and the earliest that onset of symptoms has been identified is 1994 [23]. It is considered to be a result of bovine spongiform encephalopathy in cattle entering human food, with the risk period in the United Kingdom being generally accepted as being approximately 1980–1996 [24].

Most cases to date have occurred in the United Kingdom (the country with the highest incidence of bovine spongiform encephalopathy), but cases have been identified in other countries, especially France (table 3).

The current UK data suggest an epidemic that is decreasing, with deaths in the United Kingdom having peaked in the year 2000 (with only 9 deaths in 2004 and 5 in 2005 that have been identified to date) [25]. However, caution must be expressed regarding the interpretation of these figures, not least because all patients who have been tested to date (139 of 159 patients in the United Kingdom) have had PRNP-129 MM (figure 1), and there are good theoretical reasons for believing that other 129 genotypes will be affected and that they will have a longer incubation period. There is evidence that, in variant CJD, lymphoreticular tissues (such as tonsil and appendix tissues) are affected prior to brain involvement [26, 27]. A survey of routine surgical appendix specimens showed that 3 of >12,000 were positive for variant CJD–related PrPSc. By simple extrapolation, this could mean that there are ~237 people per 1 million of the UK population with bovine spongiform encephalopathy infection [27]. Following dietary exposure to bovine spongiform encephalopathy, an incubation period of at least a few years would be expected, and it is possible that subclinical infection might occur (with reticulo-endothelial colonization but with no clinical disease).

The age distribution of variant CJD is striking; patients are notably young (figure 3). The median age at onset is 26 years, contrasting with the age profile of sporadic CJD [12, 18]. However, older individuals have been affected, 1 of whom is 74 years old (figure 3). Interestingly, the age profile has not changed over the period of the UK epidemic; it is not clear whether this reflects age-related dietary exposure, an age-dependent incubation period, or age-dependent susceptibility. However, variant CJD is, at least presently, a very rare cause of dementia in elderly persons. The relatively uniform clinical and pathological features have not varied by age and are different from those of sporadic CJD. The typical presenting symptoms are psychiatric or behavioral in nature, often involving depression, social withdrawal, and anxiety; initial diagnoses have often been for a psychiatric illness [28]. Other features may be present, notably, persistent, painful sensory symptoms. After a mean of 6 months, ataxia develops, often with choreiform, dystonic, or myoclonic involuntary movements. Progressive cognitive impairment ensues, and other signs may oc-
cur, including rigidity and hyperreflexia. The later stages are similar to those of sporadic CJD, with terminal akinetic mutism occurring in many cases. The mean survival time is 14 months, but some patients have survived >3 years after onset of the first symptom (figure 3) [12, 18, 29].

**HOW DO I DIAGNOSE CJD?**

**General points.** There is no simple, noninvasive test for CJD in living patients; definitive diagnosis requires neuropathological examination of brain tissue (by brain biopsy or during autopsy). Biopsy is an invasive procedure, and it is arguably reasonable only in cases for which there is a possibility of an otherwise undiagnosed and potentially treatable illness. Fortunately, in the majority of cases, a highly probable diagnosis can be made using typical clinical features and other investigations, but the involvement of a clinical neurologist is usually required. Various common and characteristic clinical features have been incorporated into diagnostic criteria accepted by the World Health Organization [29, 30].

The exclusion of other possible diagnoses depends on the clinical context. Investigations have 2 broad roles: to confirm and/or exclude other possibilities and to detect abnormalities supportive of a diagnosis of CJD. Advice regarding diagnosis can be obtained from a variety of expert organizations (see Appendix).

**Genetic and iatrogenic CJD.** Genetic CJD is confirmed by detection of a relevant PRNP mutation (on a blood test) in an appropriate context (i.e., in the clinical picture of prion disease and/or neuropathological confirmation). The diagnosis of iatrogenic CJD depends on the identification of a relevant preceding procedure.

**Sporadic CJD.** The diagnosis of sporadic CJD may be supported by 3 investigations: electroencephalogram, CSF analysis, and cerebral MRI [18, 31].

In a majority of cases (but not all), the electroencephalogram shows generalized, synchronous, periodic discharges at some stage. Although not totally unique to sporadic CJD, these findings in an electroencephalogram are very suggestive in the appropriate clinical context. If sporadic CJD is not found initially, the electroencephalogram can be repeated, perhaps on a weekly basis [18, 31].

Estimation of the CSF 14-3-3 level is very helpful (the National Creutzfeldt-Jakob Disease Surveillance Unit [NCJDSU] provides a national CSF 14-3-3 service; see Appendix). A lumbar puncture will usually be performed for suspected cases as an important part of excluding other possible illnesses. Since 14-3-3 is a normal neuronal protein that is found in elevated levels in most cases of sporadic CJD, it must be stressed that a CSF 14-3-3 test result may be positive in a variety of neurological conditions; the test’s specificity for sporadic CJD is highly context dependent. Also, a negative test result cannot absolutely exclude sporadic CJD [31].

Cerebral imaging, preferably MRI, is indicated in all suspected cases to exclude other possible illnesses. However, in sporadic CJD, certain characteristic MRI changes may be observed, particularly high signal changes in the anterior basal ganglia [32, 33].

**Variant CJD.** In variant CJD, an electroencephalogram does not typically show the periodic pattern of sporadic CJD. The CSF 14-3-3 test is not as sensitive or as specific as it is in sporadic CJD [34]. The cerebral MRI is extremely helpful; in >90% of cases, a characteristic high signal change is observed in the posterior thalamus (the “pulvinar sign”); this is not absolutely specific, but other possible causes should be relatively easily distinguished on clinical grounds. It is usually seen on T2-weighted images, but fluid-attenuation inversion recovery (FLAIR) sequences are significantly more sensitive [33, 35]. MRI scans have revealed the sign at only 3 months of illness; if findings of an initial scan are negative, then a repeat scan is worth consideration. The involvement of reticulo-endothelial tissue in variant CJD means that tonsil biopsy may detect variant CJD–related PrPSc; the procedure is relatively invasive, and negative findings cannot absolutely exclude the diagnosis. However, it can be diagnostically useful, particularly in clinically uncertain or MRI-negative cases [18].

**WHAT ARE THE INFECTION RISKS OF CJD?**

Secondary transmission of all cases of CJD can occur in certain circumstances, as demonstrated by the occurrence of iatrogenic CJD. In sporadic CJD, CNS tissues have the highest potential for infectivity; the risk of variant CJD may be greater because of the involvement of lymphoreticular tissues. A number of policies have been instituted to reduce the risk of onward transmission (e.g., policies regarding blood transfusion and surgery). However, routine contact and nursing care does not carry any risk. If invasive procedures are to be performed, then suitable precautions should be taken. In the United Kingdom, the De-
partment of Health has guidance available on its Web site, and the UK Health Protection Agency has a CJD Incidents Panel to provide advice on issues regarding possible transmission (see Appendix). Other countries will have their own arrangements. Some families and clinicians may wish to consider endoscopically inserted percutaneous endoscopic gastronomy (PEG) feeding tubes. In the United Kingdom, the NCJDSU is able to loan specific endoscopes for this purpose (see Appendix).

WHAT SHOULD I DO IF I HAVE A SUSPECTED CASE?

Although CJD is not a formally notifiable disease in the United Kingdom, clinicians (and pathologists) have been asked to notify the National Creutzfeldt-Jakob Disease Surveillance Unit and the National Prion Clinic of any suspected cases (see Appendix below), both for research and public health protection purposes. Within the United Kingdom, both units are able to provide advice regarding diagnosis and management, and both may wish to see the patient and the family. Currently, there is no proven effective treatment for CJD, but the NPC is responsible for the UK Medical Research Council–funded Prion-1 treatment trial (see Appendix below), and trials of potential treatments are being considered in other countries. Within the United Kingdom, NCJDSU is responsible for a Department of Health–funded National Care Package that can provide advice (and funding) for care givers. There is also a recommendation to inform the local consultant for Communicable Disease Control of any suspected case of CJD, and there are similar arrangements in other countries. There are experienced, helpful support organizations (see Appendix below).

CONCLUSIONS

CJD is a very rare illness that may be acquired by infection and secondarily transmitted. The most common form (sporadic CJD) affects only approximately 1–2 people per million per year, most of whom are middle aged or elderly, with possible underascertainment of cases among people with older age. The illness profile is usually a striking one, but most clinicians will not have had much (if any) previous experience with cases, and there is no simple, noninvasive diagnostic test for living patients. However, the clinical features and certain investigations should allow a reasonably confident clinical diagnosis in most instances, and there are national surveillance and research units in the United Kingdom and many other countries that can provide advice and help.

Acknowledgments

I am grateful to Jan McKenzie (National Creutzfeldt-Jakob Disease Surveillance Unit) for her help in the preparation of this manuscript. 

Potential conflicts of interest. R.K. has spoken at meetings organized by Baxter’s.

APPENDIX

There are a number of organizations (whose Web sites may link to other sources of information) that can provide advice and support:

- The National Creutzfeldt-Jakob Disease Surveillance Unit, Edinburgh, United Kingdom (http://www.cjd.ed.ac.uk)
- The CJD Incidents Panel at the Health Protection Agency, London, United Kingdom (http://www.hpa.org.uk)
- The National Prion Clinic, Queen Square, London, United Kingdom (http://www.uclh.nhs.uk)
- The UK MRC PRION-1 Trial (http://www.prion.ucl.ac.uk)
- The CJD Support Network (http://www.cjdsupport.net)
- The Human Bovine Spongiform Encephalopathy Foundation (http://www.hbsef.org)
- The CJD Foundation, Akron, Ohio (http://www.cjdfoundation.org)
- The UK Department of Health (http://www.dh.gov.uk/PolicyAndGuidance/HealthAndSocialCareTopics/CJD)

References


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