Diagnosis and Management of Creutzfeldt-Jakob Disease

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Creutzfeldt-Jakob disease (CJD) is rare, occurring in one per million people. It is difficult to eradicate from contaminated instruments, and so is important to recognise for infection control reasons. As well, there is much interest in possible changes in the epidemiology of this disease, and so familiarity is necessary among all physicians. Sporadic CJD presents in the young-old with a rapidly progressive dementia, while variant CJD presents in younger patients, initially with psychiatric symptoms. Electroencephalography, MRI and 14-3-3 protein testing are all helpful in the diagnostic process. There is no recognised therapy as yet.

Key words: Creutzfeldt-Jakob disease, variant Creutzfeldt-Jakob disease, prion, dementia.

Introduction

Although Creutzfeldt-Jakob disease (CJD) is rare, its rapid course, its infection control implications and the link between bovine spongiform encephalopathy and variant Creutzfeldt-Jakob disease (vCJD) make this disease relevant to all clinicians. The emergence of vCJD has prompted an explosion in the amount of research into the disorder, leading to new developments in both diagnosis and treatment. This paper will review the epidemiology and diagnosis of CJD, as well as possible therapies.

Prion Diseases

CJD is a member of a family of diseases, the prion diseases. The relationship with scrapie (a disease of sheep and goats) was recognised in the 1960s, but the exact nature of CJD was unknown. The agent was unusual in that it could be spread both orally and by injection, yet also could be inherited and was very resistant to inactivation. Prusiner proposed that the responsible agent was an infectious protein, and coined the term prion.[1] Prions were found to be normal components of neurons with an unclear function, although they are involved in neuronal development and function and prevention of cell death. Abnormal forms of prion protein fold into insoluble amyloid, are very resistant to degradation, and can induce conformational change in normal prion protein to the abnormal form. So a prion disease can be genetic, if a mutation in the prion gene leads to formation of abnormal prion protein, and infectious when exposure to the abnormal form leads to conformational change. Sporadic CJD is believed to represent the rare, literally one-in-a-million chance that normal prion protein will assume the abnormal conformation. Some recent work suggests that all of us have a balance in production between the two forms, and in disease there is overproduction or under-metabolism of the abnormal form, analogous to the production of abnormal amyloid in Alzheimer disease.[2]

Epidemiology

The various prion dementias can be categorised as sporadic (including most CJD), inherited (some CJD, Gerstmann-Sträussler-Scheinker syndrome and, most fatal, familial insomnia) and iatrogenic.[3] Variant CJD is infectious, caused by exposure to material containing bovine spongiform encephalopathy prions.

Iatrogenic CJD has been linked chiefly to exposure to CNS tissue, such as corneal transplants, dural grafts and human pituitary extracts.[4] Iatrogenic CJD is believed to be on the wane. For unknown reasons, most iatrogenic cases initially present more like Gerstmann-Sträussler-Scheinker syndrome, with cerebellar dysfunction rather than with the dementia and widespread cortical dysfunction of CJD.

Person-to-person transmission of CJD by transfusion has not been identified, though since animal prion diseases can be experimentally transmitted by transfusion, it is reasonable for blood agencies to be cautious in this matter.[5,6]

In Canada, the incidence of sporadic CJD is about one per million, or 30 cases each year.[7] The incidence is not increasing, despite intensive surveillance. A single case of vCJD has been identified in Canada, though it was likely acquired in the United Kingdom.[8] There are some public misgivings about the safety of the food supply in Canada, but there is no evidence that bovine spongiform encephalopathy has established itself in Canada. There is a similar disease of mostly captive but also wild deer, elk and goats, called Chronic Wasting Disease, but there is no evidence that this disease affects humans. Case reports of CJD in venison eaters have not been substantiated.[9] Chronic Wasting Disease has been identified in farmed and wild animals in Alberta and Saskatchewan.[10]

Infection Control

Prions are highly infectious, though not through casual contact between people. Universal precautions should be observed, but no isolation precautions are necessary. Any diagnostic instruments used in CJD cases (including EEG electrodes and lumbar puncture needles) should be disinfected with special procedures[11] or incinerated. If an autopsy or biopsy is requested, the pathology lab should be warned so that appropriate measures can be taken. Surgery should be avoided, as several clusters of cases have been linked to operating rooms and dental practices.[12]

Diagnosis

Clinical

Sporadic CJD should be suspected in a patient presenting with rapidly progressive dementia, particularly if a movement disorder (most often myoclonus, often in reaction to a loud noise or sud-

den movement) is present as well. Heidenhain's syndrome is a variant that presents with dementia and cortical blindness (characterised by loss of vision and reflex lid closure to a threat).[13] The median time from onset to death is 4.5 months, and clinical diagnostic criteria are presented in Table 1.[14] Men and women are equally vulnerable, and the mean age of onset is 66 years. The differential diagnosis includes stroke, delirium, various psychiatric disorders, malignancy, toxicity (including drugs), viral encephalitis, vasculitis and early-onset degenerative disorders, such as Huntington's or Wilson's disease. The iatrogenic forms and the rare Gerstmann-Sträussler-Scheinker syndrome present initially with ataxia. Fatal familial insomnia presents with sleep disorders and dementia, and in fact is not always familial.

The presentation of variant CJD is very different (Table 2).[15] The age of onset is lower (mean 26 years), the duration is longer (median 13 months) and prominent early symptoms include anxiety, withdrawal, panic attacks and headaches.[16] Painful paresthesias, such as sensation of cold or pain, are not uncommon. Over time further symptoms manifest, including dysarthria and gait disturbances, and eventually dementia. Features that may distinguish sporadic from variant CJD are listed in Table 3.

Electroencephalogram

The typical EEG pattern often seen in CJD has periodic sharp waves. Their presence may become more frequent as the disease progresses, and is more common in end-stage disease, although one-third to one-half of subjects may never have this finding.[17-19] The sensitivity and specificity of the detection of periodic sharp wave complexes in the EEG in a large sample were 66% and 74%, respectively.[18] Provocative measures, such as noise, may help to bring them out during an EEG recording. Some authors have found a close relationship between sharp waves and myoclonus, making the EEG relatively unhelpful.[20] Even if this is true, the finding of this abnormality on EEG can help the clinician confirm the suspected diagnosis. The EEG pattern is rarely seen in vCJD.[21]

Magnetic Resonance Imaging

There is a characteristic MRI finding in vCJD of bilateral bright signals in the pulvinar.[22] In the original report, this was found in 78% of cases and in none of the controls. High-signal also may be found in the caudate and putamen.[21] Similar bilateral basal ganglia findings have been reported in sporadic CJD,[23] though the pulvinar is usually less bright than other regions in sporadic CJD.[15] These findings are best seen on T2, FLAIR or proton-density images.

Table 1

World Health Organization Criteria for the Clinical Diagnosis of Sporadic Creutzfeldt-Jakob Disease

Probable Creutzfeldt-Jakob Disease ***(must meet each criteria, A through D)***
A: Progressive dementia
B: At least two of: – myoclonus – visual or cerebellar disturbance – pyramidal/extrapyramidal dysfunction – akinetic mutism
C: One or both of: – a typical EEG during an illness of any duration – a positive 14-3-3 CSF assay and a clinical duration to death < 2 years
D: Routine investigations should not suggest an alternative diagnosis
Possible Creutzfeldt-Jakob disease ***(must meet each criteria, A through D)***
A and B as for probable Creutzfeldt-Jakob disease, plus:
C: No EEG or atypical EEG
D: Duration < 2 years

Adapted from World Health Organization, 1998.

Table 2

World Health Organization Diagnostic Criteria for Variant Creutzfeldt-Jakob Disease

I.	A: Progressive neuropsychiatric disorder B: Duration of illness > 6 months C: Routine investigations do not suggest an alternative diagnosis D: No history of potential iatrogenic exposure E: No evidence of a familial form of prion disease
II.	A: Early psychiatric symptoms B: Persistent painful sensory symptoms C: Ataxia D: Myoclonus or dystonia or chorea E: Dementia
III.	A: EEG does not show typical appearance of sporadic CJD (or EEG not done) B: MRI scan shows bilateral symmetrical pulvinar high signal
IV.	Positive tonsil biopsy
Definite vCJD:	I.A and positive neuropathology
Probable vCJD:	All of I *and* four of II *and* all of III *or* all of I *and* IV
Possible vCJD:	All of I *and* four of II *and* III.A

Adapted from World Health Organization, 2001.

Cerebrospinal Fluid 14-3-3 Protein

Measurement of the 14-3-3 protein in cerebrospinal fluid is a possible diagnostic test for CJD that has been added to the clinical criteria,[24] although it is not yet widely available. It is seen in various brain disorders, including stroke and viral encephalitis, and so should only be used as a confirmatory test when CJD is clinically suspected. The reported sensitivity and specificity ranges from 90–97% and from 84–100%, respectively.[18,24-26] It is less sensitive (50%) in vCJD.[27] Although other proteins also have been proposed as useful, none have been as closely or successfully studied as 14-3-3.

Tonsil Biopsy

In a very small case series, tonsil biopsies were positive for abnormal prion protein in patients with vCJD, though not in sporadic CJD.[28] More recent research has found the abnormal prion protein in the olfactory mucosa of patients with sporadic CJD.[29] If these results are replicated, this may become a definitive diagnostic test for living patients.

Treatment

The older literature is full of reports of various agents having positive effects in CJD and other prion diseases. However, none of these agents, such as dapsone, amphotericin B or various antivirals, have demonstrated consistent clinical efficacy.[30-33]

Prusiner (who received the Nobel Prize for his prion work) found that chlorpromazine and quinacrine both inhibit the misfolding of normal prion protein.[34] An Italian research group has found that tetracycline binds to the abnormal protein, and may also inhibit its progression.[35] Although not published, it is my understanding that the clinical experience with these agents has not been promising. Animal studies have also been negative.[36] It is my belief, however, that if a definitive diagnosis is made at a time when a patient still has some quality of life, then a trial of chlorpromazine, quinacrine (not marketed in North America) or tetracycline is appropriate.

Researchers have synthesized agents that disrupt the prion protein or stimulate its degradation.[37,38] In a highly-publicised case, a British youth with vCJD was treated with a formulation of one of these agents infused into his cerebral ventricles.[39]

Table 3

Features Which May Help Distinguish Between Sporadic and Variant Creutzfeldt-Jakob Disease

	Variant CJD	Sporadic CJD
Early clinical features		
Psychiatric symptoms	Yes	No
Sensory symptoms	Yes	No
Rapid clinical progression	No	Yes
Age	Younger than 40 years	Older than 40 years
Duration	Greater than 12 months	Less than six months

Adapted from World Health Organization, 2001.

Conclusion

Although CJD is rare, its infection control implications make it important to recognise. It is unlikely that any of us in Canada will encounter a case of vCJD, but we should be vigilant, particularly the family physicians and psychiatrists to whom these patients will initially present. The disease is clinically recognisable, and an EEG and MRI can help in the diagnosis, as well as testing for the 14-3-3 protein, if possible. There is no recognised treatment, but this may well change over the next few years.

There is a Canadian surveillance program for CJD. Any suspected or confirmed cases should be reported. Information is available at: http://www.hc-sc.gc.ca/pphb-dgspsp/hcai-iamss/cjd-mcj/index.html. ◆

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