How Mad is Mad?
Creutzfeld-Jacob Disease

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The term "prion" has been defined as a small proteinaceous infectious pathogen containing protein that lacks nucleic acid. Prions have been associated with a variety of neurodegenerative diseases. There is a great deal of interest that surrounds these unusual agents capable of causing human and animal disease, particularly when some varieties have been linked to the food chain. Creutzfeld-Jacob and variant Creutzfeld-Jacob disease are, therefore, the Bug of the Month for October 2005.

What is Creutzfeld-Jacob disease?

Creutzfeld-Jacob disease (CJD) belongs to a group of neurodegenerative disorders caused by prions, including CJD, variant CJD (vCJD), kuru, Gerstmann-Straussler-Scheinker syndrome and fatal familial insomnia. These diseases share certain pathologic features, such as neuronal loss, proliferation of glial cells, absence of an inflammatory response and small neutrophilic vacuoles that lend the spongiform appearance.

Presently, there are four forms of CJD, including sporadic (sCJD), variant, familial and iatrogenic forms. The sporadic variant is responsible for 85% to 95% of cases worldwide. Of particular interest is vCJD because of its link to Bovine spongiform encephalopathy (BSE). There have been 165 cases worldwide of vCJD as of April 2005, including one in Canada.

What are the clinical features of vCJD?

The mean age at presentation is 29 years, with the onset of illness followed by death in a mean of 14 months (Table 1). In the variant form, psychiatric and sensory abnormalities are the most prominent presenting symptoms. Sensory changes are characterized by dysesthesias and paresthesias. Of note, other neurologic features can include ataxia, cognitive impairment, involuntary movements, immobility, unresponsiveness and mutism. The most prominent psychiatric symptoms are depression, apathy, anxiety and psychosis.

Table 1

Comparison of the sporadic and variant forms of Creutzfeld-Jacob disease

Parameters	sCJD	vCJD
Mean age at onset (years)	65	29
Mode of transmission	Sporadic	Contaminated meat
Presenting symptoms	Rapid cognitive decline (memory, judgement and concentration early on)	Psychiatric and sensory dysfunction
Mean duration of illness (months)	4.5 (fatal)	14 (fatal)
EEG	Periodic sharp wave complexes	Normal/slow wave activity
MRI	Variable/putamen caudate signal sensitivity	Pulvinar/hockey stick signs
Best test	CSF 14-3-3 protein, highly sensitive and specific (appropriate clinical context)	Tonsillar tissue biopsy
Tissues affected other than CNS	Spleen and muscle	Spleen, lymph nodes, muscle, GI tract, tonsils

sCJD: Sporadic Creutzfeld-Jacob disease
vCJD: Variant Creutzfeld-Jacob disease
EEG: Electroencephalogram
MRI: Magnetic resonance imaging
CSF: Cerebrospinal fluid
CNS: Central nervous system
GI: Gastrointestinal

What are the clinical features of sCJD?

sCJD differs from the variant form in a number of key ways (Table 1). The mean age at the onset of illness is 65 years and the mean duration is 4.5 months (before death). The two cardinal features of sCJD are myoclonus and a rapid cognitive decline. Memory, judgment and concentration impairment often present early, before rapid dementia, depression and higher cortical dysfunction. Myoclonus is present in 90% of cases; however, it may present at any point throughout the illness. Other manifestations include extrapyramidal and cerebellar signs, as well as evidence of corticospinal tract compromise.

The CSF analysis is positive for the 14-3-3 protein in only 50% of cases.

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How is sCJD diagnosed?

Diagnosis of sCJD relies on demonstration of the typical clinical features, like rapidly progressive dementia associated with neurologic deficits (including cerebellar and visual dysfunction) and myoclonus. The presence of these findings and the exclusion of other processes raises the clinical suspicion.

Electroencephalogram (EEG) studies show a steady decline in normal background rhythms associated with periodic sharp wave complexes. The cerebral spinal fluid (CSF) analysis should be benign, but demonstrates a positive 14-3-3 protein, which is approximately 94% sensitive and specific for sCJD in the correct clinical context.

Finally magnetic resonance imaging (MRI) that delineates a characteristic signal change in the putamen and caudate is suggestive of sCJD.

How is vCJD diagnosed?

Diagnosis of vCJD poses a diagnostic challenge because of the early prominence of psychiatric symptoms. In vCJD, the EEG is significant for the absence of the periodic sharp wave complexes characteristic of sCJD. The MRI may demonstrate signal hyperintensity in the pulvinar and dorsomedial thalamus (the "pulvinar" and "hockey stick" signs, respectively). The CSF analysis is positive for the 14-3-3 protein in only 50% of cases. The most useful diagnostic tool seems to be tonsillar tissue biopsy. If the tissue establishes the presence of the prion protein in the appropriate clinical context, this is the most sensitive and specific method of diagnosis.

What is the link between BSE and VCJD?

The connection between BSE and its transmission to humans, causing infection, is increasingly well supported. The outbreak of vCJD in 1996 in the UK, following the dramatic rise in BSE with approximately 50,000 infected cattle entering the human food chain, lends particularly strong support. In fact, of the 165 (155 of them from the UK) documented cases, thus far, only one case of an Italian women has not been linked to any kind of exposure. It is, however, interesting to note that, despite rather large exposure, the numbers of those infected has remained significantly small.

This seems to be related to:

- low concentrations of prions in milk and meat,
- inefficient oral infection,
- species barriers and
- low incidence of genetic predisposition (like homozygosity for methionine at codon 129 of the prion gene).