



Lab Lines

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PRION DISEASE

Introduction and Background

Prion is the abbreviation for "proteinaceous infectious particle." Prions were discovered by Stanley Pruisner, M.D., who received the 1997 Nobel Prize for Medicine for this discovery. Prion diseases represent a novel class of transmissible, invariably fatal brain diseases affecting both man and animals:

- Man: Creutzfeldt-Jacob disease [CJD]
- Sheep and Goats: scrapie
- Cows: bovine spongiform encephalopathy [BSE]

The infectious protein (PrP^{sc} or CJD) lacks RNA and DNA and represents a post-translational conformational change which increases beta pleating of a normal cell protein (PrP^c) which is highly expressed in neurons. PrP^{sc}/CJD is insoluble, proteinase K resistant and appears to be produced by a chain reaction once the abnormal protein is introduced. After up to 10 years of incubation, the accumulation of PrP^{sc}/CJD in the brain causes the following:

- Neuronal loss
- Reactive gliosis
- Characteristic spongiform changes in the neuropil
- Amyloid plaques (in 10% of cases)

Affected brains do not mount an immunologic/inflammatory response to the prion protein due to the fact that it is a normal, though modified, cell protein.

CJD was first described by Creutzfeldt, then by Jacob in the 1920's. CJD occurs sporadically with an incidence of 1/1,000,000 inhabitants/year worldwide. Familial cases are less common (about 10%) and iatrogenic cases account for up to 5%. All acquired cases are due to direct inoculation via infected corneal or dural grafts, stereotactic electrodes and human gonadotropin and growth hormones. Infection by the oral route has not been conclusively shown to cause CJD in man.

In animals transmission via food products is possible and was responsible for the 1986 outbreak of mad cow disease (BSE) in England. A much higher infectious dose (>40,000 times the parenteral dose in mice) is required for peroral transmission. The mad cow epidemic apparently developed due to the feeding of cattle with scrapie-infected offal. A change in offal processing in the early 1980's was responsible for the PrP^{sc} infectivity of this protein supplement. Previously, the same agricultural practice had not caused a spread of scrapie to other species, even though scrapie had occurred for at least 200 years.

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A few cases of a new variant CJD characterized by prominent amyloid plaques and a younger age of onset has been observed in England and France. Though inconclusive, this variant may have been transmitted from food products containing PrP^{sc} - note that hamburgers and sausages contained cow brain products including from possibly "mad cows" until 1989 - leaving the chilling (but now decreasing) possibility for a major CJD outbreak. The danger of BSE-transmitted CJD appears to be declining because of an offal ban that went into effect in 1989 (aimed at preventing PrP^{sc} spread) and there has been no report of any change in the overall CJD incidence in areas with BSE.

Prion diseases may share a common pathophysiologic mechanism with other neurodegenerative diseases in the accumulation of insoluble proteins. Other examples include:

- Accumulation of amyloid proteins in patients with Alzheimer's disease
- Expansion of translated CAG trinucleotide repeats in genetic diseases such as Huntington's chorea and cerebellar ataxias

The accumulation of such abnormal proteins causes toxic effects and progressive neuronal dysfunction.

Clinical Presentation

After nonspecific prodromal symptoms, a rapidly progressive dementia and myoclonus with periodic sharp waves on EEG develops. Death occurs with a median disease duration of 6 months.

Diagnosis

The definite diagnosis rests on one of the following:

- 1) The detection of the abnormal CSF protein, 14-3-3, which is not related to the PrP^{CJD}. The test for this protein has a sensitivity of 96% and a specificity of 99%.
- 2) Histoblot technique based on the proteinase K resistance of the abnormal PrP^{CJD/SC} protein. This requires a brain biopsy or autopsy.

Precautions

Though no transmission of CJD has ever been documented from a patient to a health care worker, parenteral transmission of brain and CSF and even blood

must be prevented by the use of personal/universal precautions and decontamination by autoclaving or chemicals (sodium hypochlorite, chlorine bleach). Because formalin fixation of the brain does not prevent infectivity, the addition of 5% sodium hypochlorite to the fixative is recommended. Alternatively, tissue blocks may be soaked in 95% formic acid for 1 hour prior to histologic processing. Precautions are especially important as there is no treatment available for CJD.

Summary

Prion diseases represent a novel transmissible disease class the causative agent of which is lacking RNA and DNA (i.e. are not related to any known pathogen). Prion infection invariably leads to a fatal brain disease via infection with what is a normal cell protein that has undergone an abnormal conformation change. Because of the conformational change the protein is insoluble and accumulates in the brain. Transmission is possible between species and occurs mainly parenterally but can occur through oral exposure with highly infectious doses.

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