Prions

Introduction and history:

Prions are proteinaceous infectious particles that are responsible for transmissible spongiform encephalopathies (TSEs) in humans and animals. They are very small, filterable particles which contain no genome, are resistant to heat and formaldehyde and are not inactivated by UV light. The first description of TSE came in 1936 with Cuille and Chelle’s work with scrapie, a slowly progressive neurodegenerative disease of sheep. The disease was named for the observation that infected animals had a tendency to scrape their wool off against walls. Cuille and Chelle demonstrated that scrapie was caused by a transmissible agent by injecting spinal cord material from infected sheep into uninfected animals and observing the onset of disease.

The earliest description of TSE in humans came in 1957 when Gajdusek and Zigas described a slowly progressive ultimately fatal neurologic disease in the inhabitants of the highlands of New Guinea. The disease, named kuru, occurred in people who ceremonially ate the brains of their deceased relatives. In 1959, Hadlow observed a similarity between scrapie and kuru. Today, kuru is rarely seen in New Guinea. This is both due to the research of Gajdusek and the efforts of Christian missionaries to discourage the practice of eating the brains of the deceased.

Molecular biology and properties of prions

Human prion diseases share a number of fundamental properties. Their major pathologic manifestations are confined almost exclusively to the central nervous system, they typically have long incubation periods lasting up to decades, and they are inexorably progressive and ultimately fatal. Histopathologic examination of infected tissue reveals spongiform neural tissue with a vacuolated appearance. Amyloid fibrils aggregate into tangles and astrogliosis is observed. There is usually minimal or no inflammation.

Prion protein (PrP) appears to be the major, and possibly exclusive component of prions. PrP\(^c\) (cellular) is the protein product that is thought to be the target for prion disease. In the wild type, it is a normal host glycoprotein encoded by a single exon of a single copy gene (PRNP on chromosome 20). It assumes an alpha helical structure and is located on the cell surface with a glycoinositol phospholipid anchor. Treatment with proteases results in complete digestion. In infected individuals, the PrP\(^c\) protein is deranged to become the PrP\(^sc\) (scrapie) protein. This glycoprotein assembles into beta-sheets and is located in cytoplasmic vesicles. The insoluble PrP\(^sc\) accumulates inside cells instead of being located on the cell surface. It is only incompletely digested by proteases and this insolubility is thought to contribute to storage problems and aggregation.

Clinical Manifestations of Human Disease
**Kuru** is the prototypical human prion disease. It is thought to be spread by exposure to the brain and mucous membranes of infected individuals. The disease typically begins insidiously with a prodromal phase of headaches and arthralgias. This is followed by the development of an inexorably progressive neurologic disease resulting in death within three months to two years of onset. The cardinal clinical features include cerebellar ataxia, action tremor and involuntary movement followed in the later stages of disease by progressively worsening dementia. Histologic examination of kuru brains shows neuronal loss and astrogliosis with the accumulation of PrPsc.

**Creutzfeldt- Jakob Disease (CJD)** remains a rare disease but is still the most commonly encountered human prion disease. Sporadic CJD is the most common subtype and has an onset during the 5th through 7th decades of life. It presents as lack of coordination, dementia, and motor weakness. Its incidence is 1/million and the differential diagnosis includes Alzheimer’s disease. The hereditary form of CJD is much rarer. It is typically inherited in autosomal dominant fashion although the penetrance may be variable. Iatrogenic CJD due to exposure of patients to prions in growth hormone extracted from pituitaries, corneas, and contaminated surgical instruments occurs very rarely but underlines that prion diseases are “infectious”. New variant CJD is thought to result from the ingestion of BSE (Bovine Spongiform Encephalopathy)-infected meat or bone marrow and has characteristic behavioral and cognitive disturbances. None of the reported cases are thought to have originated in the U.S. The PrPsc protein isolated from the brains of vCJD patients has the same glycosylation pattern as that of BSE PrPsc which in turn is distinct from that of sporadic CJD. BSE was first described in the U.K. in 1985. It has an incubation period of 20 mos. to 15yrs. The disease course is characterized by 3 phases. The first occurs during the first six months of infection and is of little risk to humans. This is the rationale for harvesting cattle early in life (before 2 years). During the 2nd phase the prion is concentrated in the CNS and the animal is asymptomatic and infectious. The final phase is symptomatic and infectious.

**Fatal familial insomnia** is a newly recognized familial human prion disease. Onset of disease is in middle or late life with an average disease duration of 13 months. It is characterized by autonomic dysfunction and sleep disturbances. Neuropathologic changes including neuronal loss and gliosis are found consistently in the anterior ventral and mediodorsal nuclei of the thalamus and occasionally in the olivary nucleus and cerebellar and cerebral cortex.

**Gerstmann-Straussler-Scheinker** disease is an exceedingly rare human prion disease. The majority of cases are familial with an autosomal dominant pattern of inheritance and virtually complete penetrance. The basic clinical features are those of midlife progressive spinocerebellar degeneration with associated dementia. The average duration of disease is 5 years with onset in the 40’s and 50’s. Neuropathologic changes are typical of other prion diseases except for a large accumulation of kuru-like amyloid plaques in the cerebellum.

**Diagnosis** of prion diseases is made on the basis of clinical syndrome and history. Brain biopsy/autopsy is used, as is tonsillar biopsy. The gold standard of diagnosis is western blot analysis of protease treated material. At present, there are no reasonable treatments and prevention is key.