PATHOPROFILE
: PRION DISEASES

doi: 10.35493/medu.43.4
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ABSTRACT
Prions refer to abnormal misfolded proteins which propagate rare, rapidly progressive, and inevitably fatal neurodegenerative infectious diseases affecting both humans and non-human mammals.[1-3] The most common human prion disease is Creudtzfeldt-Jakob disease (CJD), aetiologically categorized as either (1) sporadic (sCJD), (2) acquired via infection (aCJD), (3) hereditary (hCJD), or (4) variant (vCJD).[1,2] vCJD, in particular, is commonly known due to its contraction via consumption of beef infected with Bovine Spongiform Encephalopathy, also known as Mad Cow Disease: a similarly fatal prion disease affecting cows.[2] Regardless of the causative mechanism, all CJDs are characterized by the rapid decline in cognitive function, myoclonus (involuntary twitching and/or jerking of muscles), akinetic mutism, and ultimately, death in all cases.[1-3] As suggested by the aforementioned symptoms, CJD is considered a rapidly progressive dementia (RPD), alongside Alzheimer's, Huntington's, and Parkinson's disease.[4]

RISK FACTORS
Although sCJD accounts for 85% of CJD cases, current literature has not identified concrete risk factors due to the stochastic misfolding of prions.[2] However, age has been shown to influence sCJD, with an average age of onset of 60 years old.[5] Numerous genetic factors have also been implicated in sCJD. Specifically, a heterozygous genotype at codon 129 of the PRNP gene, the prion protein gene, has displayed protective factors against the spontaneous prion misfolding in sCJD.[6] Furthermore, a genome-wide association study conducted by Jones et al. identified two loci that may increase risk of sCJD.[7] These include risk variants located in, or nearby, STX6 and GAL3ST1.[6] As for aCtJD, risk factors are virtually absent due to advances in clinical practices which mitigate risk of infection, such as the sanitization of neurosurgical instruments previously used on patients with CJD.[2]

DIAGNOSIS
CJD is difficult to diagnose as it shares numerous symptoms with RPD. To provide a definitive diagnosis of CJD, a brain biopsy or autopsy must be performed so a pathologist can examine the brain tissue.[8,9] Typical histopathological findings suggesting CJD include neuronal loss, spongiform degeneration, and astrogliosis.[10] Due to this challenging nature of confirming diagnosis, medical professionals must rely on probable diagnostic criteria, which consists of a conjunction of laboratory testing and identification of clinical features. According to the Centers for Disease Control and Prevention, this diagnostic criteria includes a positive result on an electroencephalogram, a cerebral spinal fluid assay, or a magnetic resonance imaging brain scan. In addition to the aforementioned laboratory tests, identifying symptoms such as rapidly progressive cognitive impairment, myoclonus, and visual or cerebellar problems offer a more probable diagnosis of CJD.[11]

MECHANISM
Part 1: Prion Proteins
CJD arises from the conversion of normal cellular prion proteins (PrP^{C}) into a misfolded aggregated and pathogenic form called scrapie (PrP^{Sc}).[12] PrP^{C} are cell-surface glycoproteins, which are proposed to be involved in protection against apoptosis, transmembrane signalling, and synaptic formation.[13] To complete the previously mentioned functions, PrP^{C} are characterized by their highly α-helical structure, detergent-solubility, and susceptibility to protease digestion. On the other hand, PrP^{Sc} are conformationally altered isoforms, effectively adopting the opposite characteristics with a β-sheet structure, detergent-insolubility, and resistance to protease digestion.[10,]

Part 2: Transformation of PrP^{C} to PrP^{Sc}
Represented by the different classifications of CJD, PrP^{Sc} can be acquired in several different ways, denoted by the four characterizations of CJD. Regardless of the categorization of CJD, the transformation process of the prion proteins remains consistent in which the PrP^{Sc} acts as a template for the conversion of PrP^{C}, seeding the formation of an alternative self-replicating state with a different protein folding pattern.[12,14] Although the exact molecular mechanism of the conversion of PrP^{C} to PrP^{Sc} is unknown, a study using molecular-dynamics simulations by Chen et al. suggests large conformational changes of the C-terminal globular domain and

other structural domains in response to harsh conditions of high temperatures and low pH.[15] Ultimately, as the PrP^{Sc} conformation self-propagates, there is exponential accumulation of the misfolded isoform in the neurons of the central nervous system (CNS).[12]

Part 3: Degeneration of the CNS

The beginning stages of CJD appear to be associated with synaptic dysfunction. The human prion protein is enriched in the synapses of neuromuscular junctions and the CNS and thus, the conversion of PrP^{C} to PrP^{Sc} results in the accumulation of PrP^{Sc} in synaptic structures.[16] The toxicity of the accumulated PrP^{Sc} begins to induce the release of pro-inflammatory cytokines and reactive oxygen species by activated microglial cells, resulting in neuronal cell death by apoptosis.[17] CJD is also characterized by spongiform degeneration in which small vacuoles occupy the gray matter of the brain, which is hypothesized to be caused by autophagic cell death.[16] As the degree of neuronal cell death progresses, initial symptoms of slurred speech, dizziness, and vision problems rapidly become more severe with the complete loss of coordination and speech. Finally, patients enter a vegetative state in the final stages of CJD before their death.[18] The fatal outcome of this disease can be attributed to extensive neuronal death by autophagy and apoptosis.[16]

TREATMENT

Clinical studies investigating potential CJD treatments are hindered by its scarcity and rapid prognosis.[6] In fact, the median duration of patient survival is 4.5 months following symptom onset, with 90% of patients surviving less than 1 year.[3] Currently, there are no known treatments to impede or stop the destruction of neurons as a result of prion diseases.[6] Existing therapies thus opt to alleviate symptoms and support patients and their families in coping with CJD.[6] For example, opiates and anti-seizure medication may be prescribed to diminish pain and myoclonus, respectively.[6] Other typically treated symptoms include urinary and bowel inconsistency, dysphagia, and blindness or vision loss.[19] Eventually, once patients cannot move and/or speak, full-time care is administered to attend to their daily needs.[6] Ultimately, patients may draw up an advance directive: a treatment plan detailing preferences in care for when that the patient enters a vegetative state and cannot communicate anymore.[19] It is also worthy to acknowledge current exploration of potential CJD treatments. Notably, Mead et al. conducted the very first experimental treatment targeting human prion diseases in 2022, administering anti-PrP^{C} monoclonal antibody (mAb) therapy to 6 CJD patients.[20] Their findings suggest favorable concentrations of anti-PrP^{C} mAbs in CSF and brain tissue, encouraging future exploration in this potentially groundbreaking CJD treatment.[20]

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