Prion Diseases

Human prion diseases are rare transmissible, fatal, neurodegenerative illnesses linked to the aberrant misfolding of the normal cellular prion protein (PrP^C). These diseases can be categorised by aetiology and phenotype, and currently a definite diagnosis can only be confirmed upon examination of the brain, with neuropathological assessment and/or immunochemical detection of misfolded forms of the prion protein (PrP^{Sc}). The different aetiologies of prion diseases (described in more detail below) can influence clinical symptoms, including age at disease onset and duration of illness, as well as histological features and results of diagnostic investigations.

Sporadic CJD: Sporadic Creutzfeldt-Jakob disease (CJD) accounts for approximately 85-90% of all human prion diseases, and occurs at a rate of approximately 1.4 cases per million head of population, worldwide, per annum [1]. Sporadic CJD encompasses cases where there is no known exposure event to the transmissible agent, or no mutation found within the prion protein gene (*PRNP*). Sporadic CJD is a rapidly progressive neurological disease, with symptoms typically including dementia, myoclonus, cerebellar ataxia, pyramidal or extra-pyramidal signs, which usually progress to akinetic mutism and ultimately death. Typically, onset of disease is late within the sixth decade of life, and duration of illness is 4-6 months [2]. Other than age, an increased association with methionine homozygosity (MM) at the polymorphic codon 129 of the *PRNP* [3-5], a past medical history of surgery [6-8], there appears to be no specific risk factors for development of sporadic CJD. Sporadic CJD can also be sub-typed into different prion strains, which can be differentiated both clinically and by the signature of misfolded proteins seen on biochemical examination [3-5]. Pre-mortem diagnostic investigations usually involve electroencephalography (EEG), as periodic sharp-wave complexes are often observed, magnetic resonance imaging (MRI) as high signal on T2 flair or diffusion weighted sequences can be seen, and CSF 14-3-3 protein testing, which in the right clinical setting is approximately 90% sensitive and specific for CJD [9].

Inherited prion diseases: Inherited prion diseases account for approximately 10-15% of human prion diseases, and include familial CJD, Gerstmann-Straussler-Scheinker syndrome (GSS) and fatal familial insomnia (FFI). These diseases are causally linked to a coding mutation within *PRNP* on chromosome 20, and over 30 of these mutations have now been described. Familial prion diseases are autosomal dominant, however are not always 100% penetrant, with carriers sometimes remaining disease-free until death at old age. This fact contrasts with symptomatic genetic prion disease sufferers typically being younger than what is observed for sporadic CJD, and having a longer illness duration, although this is also dependent on the specific mutation [10]. Intra-pedigree variation in phenotype also occurs, where within one kindred there can be very different disease presentations with respect to onset age or illness duration. Further, there are some cases of a mutation being identified in a patient without a family history of neurodegenerative or any other neurological disorder [10].

Acquired CJD: Prion diseases arising due to a known exposure to the infectious agent are classified as acquired, and are rare. They may be acquired through a medical procedure (also called iatrogenic CJD, iCJD), or ingestion of infectivity, as is the case of kuru and variant CJD. Kuru is a transmissible prion disease exclusively affecting members of a particular linguistic group located in the Eastern Highlands of Papua New Guinea, and is now largely eradicated due to the cessation of ritual cannibalistic funeral practices [11]. Transmission of prions has also occurred through direct surgical contact of the infectious prions with the brains of the recipient [12, 13]. Numerous cases of 'Lyodura' associated iCJD are recognised whereby cadaveric dura mater was inadvertently harvested from persons who died from a prion disease, and were then grafted to neurosurgical patient recipients to repair dural breaches [14], efficiently transmitting disease. A similar scenario

occurred in cases of corneal transplant associated iCJD. Direct transmission has also occurred through the use of contaminated neurosurgical instruments, which despite standard hospital sterilisation techniques, were able to transfer infectious prions into the recipient patient. Non-surgical transmission of iCJD has also occurred, and is characterised by a protracted incubation period. The inadvertent harvesting of cadaveric human pituitary hormones from deceased CJD patients, which were then used to treat patients with fertility problems (as in the cases of gonadotrophins) or short stature (as in the case of growth hormones), resulted in transmission of disease. However this type of transmission is becoming rarer, since the introduction of synthetic hormones [12, 15]. Variant CJD (vCJD) is perhaps the most famous acquired prion disease, and has not been detected in Australia. It is now accepted that vCJD is caused by the same prion strain as bovine spongiform encephalopathy (BSE) in cattle [16, 17], and is transmitted via exposure to BSE contaminated tissue, most likely through consumption of prion infected meat. Cases of secondary transmission of vCJD through contaminated blood of a pre-symptomatic vCJD carrier have also been reported [18]. Variant CJD also has a distinct clinical and neuropathological phenotype, most notably the average age of sufferers being much younger, the predominance of psychiatric symptoms and sensory disturbance, and disease duration being much longer when compared to sporadic CJD [19, 20].

Accurate ante-mortem diagnosis of human prion disease is often difficult, due to the diverse clinical manifestations of the disease and different prion strains, with obvious public health implications due to the infectious nature of this prion agent.

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