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Prion Disorders and Sleep

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Prion disorders are characterized by an accumulation in the brain of aggregates of pathologic isoforms of the prion protein (PrP) that become resistant to the action of proteinases and are called PrP^{Res} (Res for resistant) or PrP^{Sc} (Sc for scrapie). Several types of aggregated conformational isomers of PrP are known (prion strains), all host encoded. According to the "protein only" hypothesis, they derive from the transformation of the normal cellular prion protein (PrP^{C}), with the abnormally conformed protein PrP^{Sc} acting as a template to promote the conversion of PrP^{C} to PrP^{Sc}. This conversion forms the basis of the transmissibility of the prion diseases, if not their pathogenicity [1,2]. Several prion diseases are found among animals, including scrapie in sheep and goats, transmissible mink encephalopathy, chronic wasting disease of deer and elks, and bovine spongiform encephalopathy (BSE). Human prion diseases (ie, Creutzfeldt-Jakob disease [CJD], transmissible spongiform encephalopathy, or infectious amyloidosis) represent inexorably fatal diseases with no known effective treatment. Although mercifully rare, these diseases are nonetheless the object of fascinating enquiries into the molecular mechanisms of protein inheritance. Prion diseases display protean clinical features, among them several sleep disturbances. These sleep disorders are reviewed herein after a brief account of the history, classification, and main characteristics [3,4].

History, classification, and clinical features of the prion diseases

Prion diseases were identified in 1921 by Jakob who referred to a previous case described by Creutzfeldt in 1920. This newly described category of disorders has since been identified as CJD. In 1954 Jones and Nevin described the prototypical features of electroencephalographic (EEG) and spongiform changes, and, later, Gajdusek and Hadlow studied kuru and pointed out its similarities with scrapie. In 1966 kuru was transmitted to experimental animals, and in 1968 Gibbs and collaborators transmitted human CJD. In 1989 Hsiao and coworkers

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reported the first prion protein gene (*PRNP*) mutations. Further advances saw the description of fatal familial insomnia (FFI) in 1986, the discovery of BSE by Wells and colleagues in 1987, and the description of a variant of CJD (vCJD) by Will and collaborators in 1996. Remarkably, prion diseases may occur as infectious (in about 6% of cases), sporadic apparently spontaneous (in about 84%), and inherited diseases (in about 10%).

Infectious prion diseases

Most infectious prion diseases (or infectious CJD, [iCJD]) are iatrogenic, transmitted by parenteral inoculation or intramuscular injection of material infected with PrP^{Sc}. Affected patients have included recipients of corneal transplants or human dura mater grafts derived from persons who died of CJD and patients who have undergone stereotactic depth electrode implantation with electrodes that had been used in persons with CJD. In the cases of neurosurgical transmission, the clinical features have been identical to those of sporadic CJD (sCJD), but, in a few cases, a cerebellar syndrome developed after dura mater grafting. Administration of human growth hormone in children and of human gonadotropins in women for infertility has caused iCJD with features of a progressive cerebellar syndrome, similar to kuru. Kuru, indeed, represents the prototypical iCJD and is found in the Okapa region of Papua New Guinea, prevalently affecting women and children and attributed to endocannibalism, whereby the eating of brain, viscera, and powdered bones of dead people affected with the disease causes a pure cerebellar syndrome without dementia after a median incubation of 12 years. The duration of this fatal disease, which has now practically disappeared, is less than 24 months. The latest iCJD is vCJD, in which prevalently young people (mean age of 29 years at onset) develop a long-duration illness with early psychiatric symptoms and a terminal stage similar to sCJD after exposure to BSE and transmission by the oral route (BSE spinal cord tissue included in the animal and human food chain).

Sporadic prion diseases (sporadic Creutzfeldt-Jakob Disease)

These diseases cause a progressive multifocal neurologic dysfunction, with prominent features of myoclonic involuntary movements, severe cognitive impairment, and death within a few months. Prodromal symptoms are behavior and personality changes and insomnia and depression, whereas, in later stages, cognitive impairment and ataxia predominate. Sporadic prion diseases affect mainly adult and elderly persons (40–80 years of age), and their clinical course has been divided into three sequential stages. Stage 1 (mean duration of 9 weeks) is characterized by dizziness, headache, depression, and anxiety, with nervousness, fatigue, sleep loss, and loss of appetite. Stage 2 (mean duration of 10 weeks) involves cortical function impairment and visual disturbances, and imbalance and disequilibrium predominate. In stage 3 (mean duration of 14 weeks), patients present with myoclonus and dementia preceding death. In sporadic prion diseases, several clinical variants are known: the Heidenhain variant with initial blurred vision, visual field restriction, cortical blindness, metamorphopsia, and visual hallucinations; the Brownell-Oppenheimer variant with an initial pure cerebellar syndrome; the panencephalic variant with primary extensive involvement and spongiosis of the white matter; and the amyotrophic variant with features of lower motor neuron disease. Other variants (myoclonic, thalamic, dyskinetic) have also been reported [3].

Sporadic prion diseases may have odd presentations (sudden strokelike onset) and unusual clinical features, such as generalized convulsive or focal nonconvulsive status epilepticus, epilepsia partialis continua, ballistic movements of one limb, generalized chorea and focal dystonia with myoclonic jerking, and Wernicke-Korsakoff syndrome. Unfortunately, the most useful diagnostic criterion for sporadic prion disease remains its duration, which encompasses, from first symptom to death, only about 5 months with a rapid decline to a state of akinetic mutism.

Inherited prion diseases

The prion protein is encoded by the gene *PRNP* located on the short arm of chromosome 20. Overall, 55 pathogenic mutations (24 missense, 27 insertions of 24 base pairs, 2 deletions, and 2 nonsense mutations) have been reported [4]. Moreover, 16 polymorphisms (normal variants) in the gene have been described, the most relevant being the 129 codon *PRNP* polymorphism that specifies for either methionine (129M) or valine (129V). This common polymorphism is a modifying factor in the phenotype of many prion diseases, including iatrogenic and sCJD. Inherited prion diseases are transmitted in an autosomal dominant fashion and fall under three main phenotypes: familial CJD (fCJD), FFI, and Gerstmann-Sträussler-Scheinker disease (GSS). Mixed phenotypes and phenotypes lacking distinctive features are also known.

fCJD displays the same clinical features as sCJD. fCJD is associated with many missense *PRNP* mutations, the most frequent one being the E200K 129M (especially found among Libyan Jews). Its clinical course and features resemble sCJD but sometimes