The human spongiform encephalopathies

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ABSTRACT

The human spongiform encephalopathies are a group of heterogenous, usually fatal diseases, characterized by a unique pathogenetic mechanism and distinct clinical presentation. They are classified into sporadic, familial and acquired forms. The diagnosis of spongiform encephalopathies is based on the combination of the neuropathological examination, with the clinical presentation, the laboratory findings and genetic tests. The most common sporadic form is Creutzfeldt-Jakob disease, while the main familial types are the familial types of Creutzfeldt-Jakob disease, Gerstmann-Straussler-Scheinker disease, Prion disease with cerebral amyloid angiopathy, the fatal familiar insomnia. In the present study we aim to review the main features and types of human spongiform encephalopathies, including the sporadic, familiar, and acquired forms.

Keywords: human spongiform encephalopathies, CJD, human prion diseases

INTRODUCTION

The spongiform encephalopathies are related to pathological forms of prion proteins, and usually characterized by fatal outcome and unique pathogenetic mechanism, in that they can be inherited, they can occur sporadically, or they can be infectious. Prion diseases are neuropathologically characterized by various combinations of spongiform alterations of the brain gray matter, neuronal loss, reactive gliosis, and prion protein deposition. The diagnosis of spongiform encephalopathies can be confirmed with neuropathological examination in combination with clinical presentation, laboratory findings, biochemical and genetic tests (1). The most common form of human prion diseases is Creutzfeldt-Jakob disease with a prevalence of 1-2 cases every 1 million of population, per year, while familial forms are relatively rare, consisting the 10% of total cases (2). In the present study we aim to review the main features and types of human spongiform encephalopathies, including the sporadic, familiar, and acquired forms.

EPIDEMIOLOGY

Over the period of 1990-2016 the average annual mortality rates from sporadic Creutzfeldt-Jakob disease (sCJD) in England, Wales, Scotland and Northern Ireland were, respectively, 1.13, 1.40, 1.15 and 0.83/million/year. The mortality rates from sCJD in the UK are comparable to those observed in most other European countries and elsewhere in the world, including countries that are free of Bovine Spongiform Encephalopathy (BSE). Up to 31st December 2016, 178 cases of definite or probable variant CJD (vCJD) had been identified in the UK (123 definite and 55 probable cases who did not undergo post mortem) (3).

Two populations are disproportionately affected by CJD: a population of Libyan-born Israelis and some groups in restricted areas of Slovakia where

the incidence of CJD is 60-100 times greater than expected. These clusters were postulated to be related to dietary exposure of the scrapie agent; but, this was not supported by case-controlled studies, and has been proved that these local high rates of CJD are linked to a high prevalence of codon 200 mutations in the PRNP gene. Prion-related diseases are progressive and invariably fatal with the mean duration of sporadic forms being at 8 months, and familial forms having a mean duration of 26 months, while Gerstmann-Straussler syndrome has the longest course, about 60 months (4).

Prion protein biology

The transmissible agent in prion diseases has unique features with regards to structure and the remarkable resistance to conventional forms of decontamination. Griffith and Hadlow attempting to identify the agent which was responsible for Scrapie encephalopathy, recognized that the agent was smaller than conventional viruses, did not have RNA or DNA, and could accumulate in the central nervous system (5,6). Prusiner in 1982 stated that the transmissible agent in prion diseases is a protein with a molecular weight of 27 to 30kD, and partially resistant to proteolytic cleavage (7). It was later demonstrated that this protein was a mutated isoform of a protein that normally occurs in the mammalian brain. The normal prion protein is a 253-residue peptide, translated from a single exon within the prion protein gene. The peptide undergoes a series of post-translational modifications, including a cleavage of a signal peptide, and an addition of up to two N-linked oligosaccharide chains at residues 181 and 197 (8). The normal protein contains five octapeptide repeats from codons 51 to 91 while four putative alpha helices in Prion protein are located between codons 109 and 122, 129 and 140,178 and 191, and 202 and 218. Normal prion protein is a membrane-associated protein with short half-life, and is sensitive to proteolytic digestion. Apart from the central nervous system, normal prion protein is expressed in a wide variety of tissues, and although the precise function is not completely understood, recent studies have indicated that it has a role in synaptic function and long-term potentiation (9), might be involved in circadian rhythms, and can act as a copper binding protein, with a protective role in oxidative stress related cell damage (10).

The abnormal isoform of the prion protein accumulates in the central nervous system, has an identical amino acid sequence and the same molecular weight as the normal one, but has a much longer half-life, and is partially resistant to proteolytic digestion (11). Abnormal prion protein has a predominant beta-pleated sheet structure, with loss of the alpha helix regions, and these structural differences confer resistance to proteolytic degradation, and in the same time allow accumulation and aggregation within the central nervous system (12). The mechanisms of neurotoxicity of the abnormal prion protein are not completely understood, however a range of theories exist, from a direct toxic effect on neurons to indirect toxicity mediated by microglia and astrocytes.

HUMAN SPONGIFORM ENCEPHALOPATHIES

Sporadic Creutzfeldt-Jakob disease

Sporadic Creutzfeldt-Jakob disease (sCJD) is the most commonly diagnosed human spongiform encephalopathy, consisting about 85% of total cases, and having a prevalence of 1-2 cases, per million per annum. Both genders are equally affected, and although a wide range of ages at onset has been reported, most cases of sCJD occur in the seventh decade of life (4). sCJD usually presents with rapidly progressive dementia, ataxia, myoclonus, visual impairment, cerebellar syndrome, as well as pyramidal and extrapyramidal signs and symptoms (13). The mean duration of the disease is six months, and the diagnosis can be set, by the combination of clinical presentation, and laboratory tests. The electroencephalogram usually reveals periodic triphasic complexes in 65% of patients, cerebrospinal fluid analysis shows elevated levels of the chaperone protein 14-3-3, and the brain MRI shows restricted diffusion and hyperintensity on FLAIR sequences (14).

Although the etiology of sCJD is unknown, it has been suggested that this occurs as a consequence of a series of random stochastic events, resulting in the generation or spontaneous conversion of abnormal prion protein within the brain (15). Cohort and case control studies have failed to demonstrate any consistent predisposing factor, however genetic studies have shown that most patient with sCJD are methionine homozygotes at co-

don 129, in contrast to normal population, but the significance of this remains uncertain (16). Clinical and neuropathological heterogeneity has given rise to a wide range of syndromes, with the most common and important ones, being the Heidenhain variant with a short clinical history of cortical blindness as a prominent feature, the Brownell – Oppenheimer variant with prominent cerebellar ataxia, the Kuru- plaque variant neuropathologically characterized by amyloid plaques in the cerebellum, the Sporadic fatal familial insomnia, the cortical variant with cortical vacuoles, and the variant CJD with florid and cluster plaques in histopathological examination (17).

Variably protease-sensitive prionopathy

In 2008, 11 cases of a novel form of prion disease were reported under the term of the variably protease-sensitive prionopathy (VPSPr) in the United States. VPSPr is characterized by behavioral problems and mood changes, language deficits and aphasia, cognitive impairment, and motor signs including parkinsonism. The duration of the disease is usually longer than sCJD, and reaches the 45 months. Neuropathological examination reveals spongiform changes, particularly in the neocortical and subcortical regions of the cerebrum, and spongiform changes and microplaques in the cerebellar cortex. Since the first description of those 11 cases, 19 additional cases have been reported (18-20). The prevalence of VPSPr is low, however there seems to be a relationship between this type of spongiform encephalopathy and 129 VV genotype, although some patients of the PRNP codon 129MM and 129MV genotypes have been reported. Subsequent studies showed differences between 3 codon 129 genotypes and protease sensitivity of the abnormal prion protein (21,22).

FAMILIAL FORMS OF SPONGIFORM ENCEPHALOPATHIES

Familial spongiform encephalopathies are inherited with the autosomal dominant character and high penetrance, and include familial Creutzfeldt-Jakob disease (fCJD), Gerstmann-Straussler-Scheinker disease (GSS), variable phenotypes, and fatal familial insomnia (FFI). The first mutation to be identified in familial spongiform encephalopathies was the PRNP P102L in 1989, and since then numerous further mutations have been described, all affecting the octapeptide repeat region, and each one of them strongly related to the clinical and pathological features of the disease (17).

Familial CJD

Familial CJD's clinical and neuropathological features resemble the sporadic form, however PRNP gene mutations are found with the most common being the E200K-129M and D178-129V. Familial CJD is characterized by the isotype 1B of abnormal prion protein with cortical or diffuse spongiform degeneration, and isotype 2B with diffuse cortical spongiform degeneration and focal cerebellar plaques (23).

Gerstmann-Straussler-Scheinker disease

Gerstmann-Straussler-Scheinker disease is characterized by a cerebellar syndrome accompanied by pyramidal signs and progressive cognitive impairment usually leading to dementia. The neuropathological spectrum of the disease consists of multicentric PrP-amyloid plaques in the cerebral and cerebellar cortex, with or without spongiform changes. A number of point mutations resulting in a similar clinicopathological phenotype has been described, however mutations F198S and Q217R are associated with neocortical neurofibrillary tangles in addition to widespread multicentric and unicentric prion protein – amyloid plaques (24).

Prion disease with cerebral amyloid angiopathy (PRP-CAA)

PRP-CAA is characterized by selective vascular wall accumulation of PrP-amyloid deposits, and is related to rare stop mutations in PRNP gene. The clinical course is usually a relatively prolonged progressive cognitive decline leading to dementia, while the common histological features are vascular and perivascular amyloid deposits, minimal spongiform change, and tangle accumulation in neurons near the affected vessels (25).

Prion disease associated with octapeptide repeat region insertional mutations (variable phenotypes)

The clinical manifestations of this group of prion diseases are highly variable both in terms of dis-

ease duration, and in phenotype. Patients with up to four additional copies of the octapeptide repeats, have a clinical phenotype similar to sporadic CJD with rapidly progressive dementia and similar electroencephalographic findings. Patients with larger numbers of extra repeats, present with a more variable clinical phenotype, often with ataxia and other movement disorders. Neuropathological examination shows unusual linear prion protein deposits in the molecular layer of the cerebellum, and somewhat variable histological features (26).

Fatal familiar insomnia

Fatal familiar insomnia is characterized by sleep disturbance, dysautonomia, motor signs and mild progressive cognitive abnormalities. The onset of the disease varies between 18 and 60 years and the mean disease duration from 8 months to 3 years. It is noteworthy that in Basconia a number of cases of fatal familial insomnia with catatonic features have been described (27). From the neuropathological point of view the disease is characterized by severe neuronal loss and gliosis in the anterior thalamic nuclei and in the hypothalamus, in the inferior olivary nuclei, and to a lesser extent in the cerebral and cerebellar cortex, and the absence of spongiform change or abnormal prion protein deposition. In some cases, tissue blots obtained from sections of paraffin-embedded tissue may show abnormal prion protein deposition in the entorhinal cortex. Fatal familiar insomnia is caused by a mutation in codon 178 at the PRNP gene (17).

ACQUIRED PRION DISEASES

Kuru encephalopathy

Kuru encephalopathy was described among the Fore tribe of Papua New Guinea in the 1950s and is characterized by progressive ataxia and tremor with marked emotional instability Rapidly progressive dementia was not a common feature. The Fore people ritualistically cooked and consumed body parts of their family members following their death to symbolize respect and mourning. Because the brain is the organ enriched in the infectious agent prion, women and children, who consumed brain and viscera, had much higher likelihood of being infected than men, who preferentially consumed muscles (28). The disease was associated with ritu-

alistic cannibalism, and now extinct, with some of last symptomatic patients sustained incubation periods of around 40 years (29). Neuropathological examination revealed amyloid plaques, so-called Kuru plaques in the cerebellum and particularly in the granular layer, and spongiform changes in the cerebellum, the basal ganglia, and the thalamus, with a variable distribution in the cerebral cortex (30).

Iatrogenic CJD

The first case of iatrogenic CJD was reported in 1974 in a patient who had a corneal transplant, and since then more than 400 cases have been identified, the majority of which have been recipients of autopsy-derived human pituitary hormones or human dura mater grafts. The clinical features are variable, ranging from a similar to sporadic CJD presentation, to a progressive cerebellar ataxia, focal neurological symptoms and dementia. The clinical presentation and incubation times are related to the route of infection. The central route is characterized by a shortest incubation period, and the peripheral route has a longer incubation period (31). The neuropathological examination reveals findings similar to the sporadic CJD (17).

Variant CJD

In 1996, a novel form of prion disease with unusual clinical, biological, and pathological features was identified by the National CJD Surveillance Unit in the United Kingdom, and Up to 31st December 2016, 178 cases of definite or probable vCJD had been identified in the UK (32). 58% of cases were males and 42% females. The median age at onset was 26½ years and the median age at death 28 years. The youngest case was aged 12 years at onset while the oldest case was aged 74 years. The median duration of illness from the onset of first symptoms to death was 14 months, ranging from 6 to 114 months. A causative relationship between vCJD and the epidemic of bovine spongiform encephalopathy in cattle seemed likely. The clinical presentation includes psychiatric and/or sensory manifestations at onset, followed by severe progressive ataxia, extrapyramidal and pyramidal signs, and a progressive dementia, which in some cases was severe (33). The EEG is abnormal, however it does not show the characteristic abnormalities seen in sporadic CJD, and brain MRI shows

symmetrical areas of hyperintensity on FLAIR sequences in the posterior thalamus, the so-called pulvinar sign, which is highly characteristic and has been incorporated into the diagnostic criteria (34). CSF analysis may exhibit elevated phosphorylated tau, and the neuropathological examination shows large numbers of florid plaques with a widespread distribution in the cerebral cortex and in the cerebellum. The lesions comprise of a central eosinophilic amyloid core with radiating bundles of amyloid fibrils, surrounded by spongiform chang-

es. Other neuropathological features include extensive abnormal prion protein accumulation both in small cluster plaques and diffuse deposits, with spongiform changes most marked in the caudate nucleus and putamen, and extensive neuronal loss and gliosis in the posterior thalamic nuclei. Western blot analysis has shown a characteristic abnormal prion protein isotype with a glycosylation pattern similar to that seen on Western blot analysis for abnormal prion protein in cattle with Bovine Spongiform Encephalopathy (17).

TABLE 1. *Sporadic CJD diagnostic criteria (Adapted from: a) Global Surveillance, diagnosis, and Therapy of Human Transmissible spongiform Encephalopathies: Report of WHO consultation, February 9-11, 1998, Geneva, Switzerland; and b) Zerr, I, Kallenberg K, Summers DM, et al. Brain 2009, 132; 2659-2668.)*

Progressive dementia; **and** at least two out of the following four clinical features: 1. Myoclonus 2. Visual or cerebellar signs 3. Pyramidal/extrapyramidal signs 4. Akinetic mutism **AND** the absence of a positive result for any of the three laboratory tests that would classify a case as "probable" (see tests a-c above) **AND** duration of illness less than two years **AND** without routine investigations indicating an alternative diagnosis.
Probable: Rapidly progressive dementia; **and** at least two out of the following four clinical features: 1. Myoclonus 2. Visual or cerebellar signs 3. Pyramidal/extrapyramidal signs 4. Akinetic mutism **AND** a positive result on at least one of the following laboratory tests: • a typical EEG (periodic sharp wave complexes) during an illness of any duration; and/or • a positive 14-3-3 cerebrospinal fluid (CSF) assay in patients with a disease duration of less than 2 years • Magnetic resonance imaging (MRI) high signal abnormalities in caudate nucleus and/or putamen on diffusion-weighted imaging (DWI) or fluid attenuated inversion recovery (FLAIR) **AND** without routine investigations indicating an alternative diagnosis.
Possible: Progressive dementia; **and** at least two out of the following four clinical features: 1. Myoclonus 2. Visual or cerebellar signs 3. Pyramidal/extrapyramidal signs 4. Akinetic mutism **AND** the absence of a positive result for any of the three laboratory tests that would classify a case as "probable" (see tests a-c above) **AND** duration of illness less than two years **AND** without routine investigations indicating an alternative diagnosis.

TABLE 2. *Iatrogenic CJD diagnostic criteria (Adapted from: a) Global Surveillance, diagnosis, and Therapy of Human Transmissible spongiform Encephalopathies: Report of WHO consultation, February 9-11, 1998, Geneva, Switzerland; and b) Zerr, I, Kallenberg K, Summers DM, et al. Brain 2009, 132; 2659-2668.)*

Progressive cerebellar syndrome in a recipient of human cadaveric-derived pituitary hormone; **Or** sporadic CJD with a recognized exposure risk, e.g., antecedent neurosurgery with dura mater implantation.

TABLE 3. *Familial CJD diagnostic criteria (Adapted from: a) Global Surveillance, diagnosis, and Therapy of Human Transmissible spongiform Encephalopathies: Report of WHO consultation, February 9-11, 1998, Geneva, Switzerland; and b) Zerr, I, Kallenberg K, Summers DM, et al. Brain 2009, 132; 2659-2668.)*

Definite or probable CJD
plus
definite or probable CJD in a first degree relative;
and/or Neuropsychiatric disorder
plus
disease-specific PrP gene mutation.

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