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Prion diseases: New considerations

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ABSTRACT

The transmissible spongiform encephalopathies, which include Creutzfeldt-Jakob disease, are fatal neurodegenerative disorders caused by the pathological accumulation of abnormal prion protein. The diagnosis of Creutzfeldt-Jakob disease is complex. The electroencephalogram, magnetic resonance imaging, lumbar puncture and genetic testing findings can help in the differential diagnosis of rapidly progressive dementia. There has recently been considerable debate as to whether proteins involved in the development of neurodegenerative diseases should be regarded as prions or only share prion-like mechanisms. Two recent reports described the detection of abnormal prion protein in the nasal mucosa and urine of patients with Creutzfeldt-Jakob disease. These findings raise major health concerns regarding the transmissibility of human prion diseases. We set out to address this neurological hot topic and to draw conclusions on the basis of what is known in the literature thus far.

Contents

Abbreviations: α-syn, α-synuclein; Aβ, β-amyloid; AD, Alzheimer's disease; ADAMs, a disintegrin and metalloproteinases; ALS, amyotrophic lateral sclerosis; BSE, bovine spongiform encephalopathy; CJD, Creutzfeldt-Jakob disease; CNS, central nervous system; CSF, cerebrospinal fluid; EEG, electroencephalogram; gCJD, genetic Creutzfeldt-Jakob disease; GPI anchor, glycophosphoinositol anchor; HD, Huntington's disease; iCJD, iatrogenic CJD; KYNA, kynurenic acid; MRI, magnetic resonance imaging; NDs, neurodegenerative diseases; PD, Parkinson's disease; PMCA, protein misfolding cyclic amplification; PRNP, prion protein gene; PrP^{c}, physiological prion protein; PrP^{sc}, pathological prion protein; RT-QuIC, real-time quaking-induced conversion; sCJD, sporadic Creutzfeldt-Jakob disease; SOD-1, superoxide-dismutase-1; ThT, thioflavin T; vCJD, variant Creutzfeldt-Jakob disease; WB, Western blotting.

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1. Introduction

Human prion diseases, also known as transmissible spongiform encephalopathies, are a group of rare, invariably fatal progressive neurodegenerative disorders that affect mammalian species [1]. With the present review, we intended to address several aspects of the human prion diseases.

One of the aims was to survey the possibilities of the diagnosis of Creutzfeldt-Jakob disease (CJD), and to present a concise description of recent studies that detected pathological prion protein in the nasal mucosa and urine of CJD patients. These findings raise new health care concerns. We additionally set out to address a hot topic in neurology, i.e. whether or not neurodegenerative diseases (NDs) should be regarded as prionopathies.

2. Aetiology

Human prion diseases can be divided into three aetiological groups: sporadic, genetic and acquired. Sporadic CJD (sCJD), the most frequent form of prion diseases, has an annual mortality rate of 1–1.5 per million [2]. The genetic prion diseases, which are related to mutation of the prion protein gene (PRNP) on human chromosome 20, account for approximately 5–15% of all prion diseases worldwide [3]. On the basis of their clinicopathological features they can be divided into genetic CJD (gCJD), Gerstmann-Straussler-Scheinker disease and fatal familial insomnia [4]. The acquired forms of prion diseases include iatrogenic CJD (iCJD), due to medical interventions, variant CJD (vCJD), related to bovine spongiform encephalopathy (BSE), and kuru [5]. They are responsible for 2–5% of all prion diseases.

3. The prion protein

The word prion is short for proteinaceous infectious particle, implying that prions contain only amino acids [6]. Under physiological conditions, prion protein is found on the surface of cells (this form is abbreviated as PrP^{c}), attached to the outer part of the bilipid layer of the cell membranes through a glycophosphoinositol (GPI) anchor [7]. The precise physiological function of PrP^{c} remains to be elucidated. Studies have suggested that, through signal transductional pathways, it might have a prominent role in embryogenesis, the activation and differentiation of lymphocytes, the reproduction of haematopoetic stem cells, neuritogenesis and neuronal differentiation [8–15]. In structure, PrP^{c} is comprised mainly of alpha-helices [16]. On the other hand, the pathological form of the protein (PrP^{sc}, where sc stands for scrapie) consists mostly of beta-sheets [17]. The misfolding of PrP^{c} to PrP^{sc} has a devastating effect on the central nervous system (CNS). The initial misfolding of the physiological protein can occur spontaneously (in sCJD) or it can be inherited (in gCJD). PrP^{sc} can also enter the CNS through protein ingestion (via the consumption of the meat of cattle with BSE) or by iatrogenic means (i.e. dura mater or corneal grafts). Once developed, PrP^{sc} serves as a template and can change the conformation of the physiological PrP^{c} in such a way that it will be misfolded into PrP^{sc}. This process is known as autocatalytic conversion [18]. Abnormal prions can aggregate and form soluble oligomers [19]. Increasing quantities of PrP^{sc} attach to one another and form insoluble polymers, which then make up amyloid fibres. The polymers may also break, thereby providing more nuclei for PrP^{c} to misfold into PrP^{sc}. Fig. 1 schematically illustrates the misfolding of PrP^{c} into PrP^{sc}.

The accumulation of aberrant prion proteins inside neurons will eventually lead to programmed cell death (apoptosis). Misfolded proteins are normally degraded in cells via proteosomes or autolysomes [19]. However, PrP^{sc} can evade these clearance

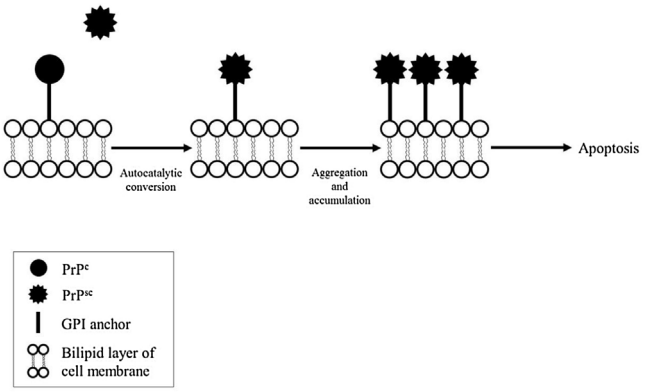

Fig. 1. Schematic illustration of PrP^{c} misfolding into PrP^{sc}. Through autocatalytic conversion, the already developed PrP^{sc} helps to promote the change in the conformation of PrP^{c}, and causes further PrP^{c} to misfold into PrP^{sc}. These abnormal proteins then aggregate, accumulate and lead to apoptosis.
Abbreviations;: PrP^{c}: physiological prion protein (cellular): PrP^{sc}: pathological prion protein (scrapie): GPI anchor: glycophosphoinositol anchor

Table 1
The characteristics of prion protein.

1.	They are misfolded proteins
2.	They evade cellular clearance mechanisms
3.	They are capable of autocatalytic conversion and aggregation
4.	They show cell-to-cell propagation
5.	They can be transmitted, and are therefore infectious

pathways and accumulate in cells. It remains unclear exactly how PrP^{sc} aggregates exert neurotoxic effects. A small number of mechanisms have been proposed which, individually or acting in parallel, can lead to programmed cell death [20]. PrP^{c} has been demonstrated to have a neuroprotective effect [21]. The conformational change of the protein may therefore lead to increased levels of oxidative and endoplasmic reticulum stress. Moreover, overloading and the consequent dysfunction of the ubiquitin-proteosome and endosome-lysosomal systems by accumulated PrP^{sc} could induce apoptosis. Another theory postulates that the loss of function of PrP^{c} might play a significant role in the synaptic alterations and dendritic atrophy observed in transmissible spongiform encephalopathies. The exact signal transductional pathways and proteins involved in the above-mentioned apoptosis-inducing mechanisms have not yet been elaborated.

PrP^{sc} has the further characteristic attribute that it can propagate from cell to cell. Autopsies on patients who died from transmissible spongiform encephalopathy have demonstrated that PrP^{sc} is found throughout the brain. The pathological form of the protein can be transmitted between individuals, and also between species. The consumption of the meat of cattle infected with BSE caused a major epidemic in Great Britain not too long ago [22].

The main characteristics of prion proteins are summarized in Table 1.

4. The prion hypothesis of neurodegenerative diseases

Parkinson's disease (PD), degenerative parkinsonisms, Alzheimer's disease (AD), Huntington's disease (HD) and amyotrophic lateral sclerosis (ALS) are all NDs, and they share some common pathomechanisms. These include glutamate-induced excitotoxicity, impaired Ca^{2+} homeostasis, the production of reactive oxygen species, a mitochondrial dysfunction, neuroinflammation and an altered tryptophan metabolism [23–26]. Our research group has investigated the roles of neuroactive kynurenines in various NDs. The key components of the tryptophan degradation pathway include kynurenic acid (KYNA),