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Latest on Prion diseases: Creutzfeldt-Jacob disease

Prion diseases or Transmissible subacute spongiform encephalopathies (TSSE) represent a heterogeneous group of neurodegenerative diseases in humans and animals. According to SB. Prusiner's theory (1982), prion diseases are protein diseases; viral hypotheses or theories involving a nucleic acid have now practically been abandoned. The common factor in these diseases is the accumulation of an abnormal protein (pathological prion protein) derived from physiological prion protein (PrP), normally found in healthy subjects, in the brain.

Prion protein (PrP) is an infecting protein

The arguments in favour of this "dogma" are that only the accumulation of PrP is detectable; PrP is proportional to the infectiosity; denaturation decreases infectious risk; "prion protein-free" (PrP 0/0) mice are not infectable; and PrP gene mutations are sufficient to cause the disease. Finally, a more recent argument (2005) is that the disease could have been transmitted by producing a mutated synthetic PrP and inoculating it by the intracerebral route in the mouse.

PrP is a protein fixed to the cellular membrane via a phosphatidyl inositol group; it has two carbohydrate residues and is organised into alpha helixes and beta sheets. Pathological PrP is differentiated from normal cellular PrP by its conformation as a protein richer in beta sheets. In this way, it acquires its infectiosity and specific heat- and protease-resistance characteristics. Pathological PrP appears to be characterised in that it binds with newly synthesised cellular PrP and converts it to an abnormal protein by applying its conformation. In this way, PrP would appear to be capable of reproducing itself and transmitting the infection. Due to its high resistance, particularly to cellular enzymes, it would appear to accumulate in the neurones and induce their death.

Creutzfeldt-Jacob disease (CJD)

Several forms exist. Sporadic CJD is the most frequent (85 % of cases): the disease occurs spontaneously, apparently at random. In 10 to 15 % of cases, it is of genetic origin, due to a mutation on the gene coding PrP. Finally, in some (rare) cases, the source of the disease is iatrogenic, essentially due, in France, to growth hormone (GH) treatments administered between 1983 and 1985. In 1996, a new form of CJD, referred to as variant CJD (vCJD) was described by researchers in the UK. The clinical profile differs from the three known forms, but the neurological tissue study indicated contamination by a single agent. The source of the contamination is found in food, via the agent for bovine spongiform encephalopathy (BSE, or "mad cow disease").

The peak number of cases of vCJD was observed in 1999-2000, particularly in the UK and, to a lesser extent, in France (approximately 180 patients in all).

According to a model developed in 2001, the prediction of the number of cases of vCJD in France in the future is modest: 33 cases (0-100), given that one million subjects have been in contract with BSE.

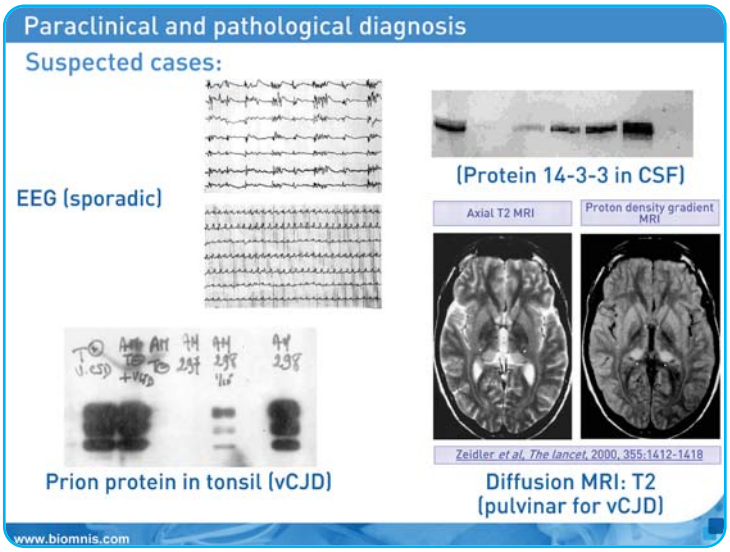
Sporadic CJD and variant CJD: clinical symptoms

Sporadic CJD occurs in subjects of an average of 65 years of age. It is suggested in the case of cognitive disorders and behaviour disorders (personality, memory, character disorders followed by intellectual degeneration, apathy, confusion, delusion) which progress very rapidly (in 3 to 18 months) to dementia, akinetic mutism, myoclonia and death. This progression is the most frequent (70% of cases). In approximately one third of cases, the onset is a cerebellar syndrome with transient episodes of loss of balance, dizziness, nystagmus which progress to cerebellar syndrome (cortical blindness, pyramidal, extra-pyramidal syndrome) followed by myoclonia, akinetic mutism, and death. Finally, very rare cases of patients directly entering the coma phase have been described.

Variant CJD affects younger subjects, 29 years of age on average, but not exclusively (cases from 18 to 74 years of age). Psychiatric symptoms are predominant with apathy, anxiety,

emotional lability, aggression, insomnia, depression, illusions, hallucinations. Persistent pain (stinging, unpleasant sensations, diffuse pain), walking and balance disorders (cerebellar syndrome, pyramidal syndrome), memory disorders, involuntary movements and, finally, dementia, myoclonia and akinetic mutism then occur. Death occurs on average 14 months after the onset of symptoms.

Paraclinical and pathological diagnosis



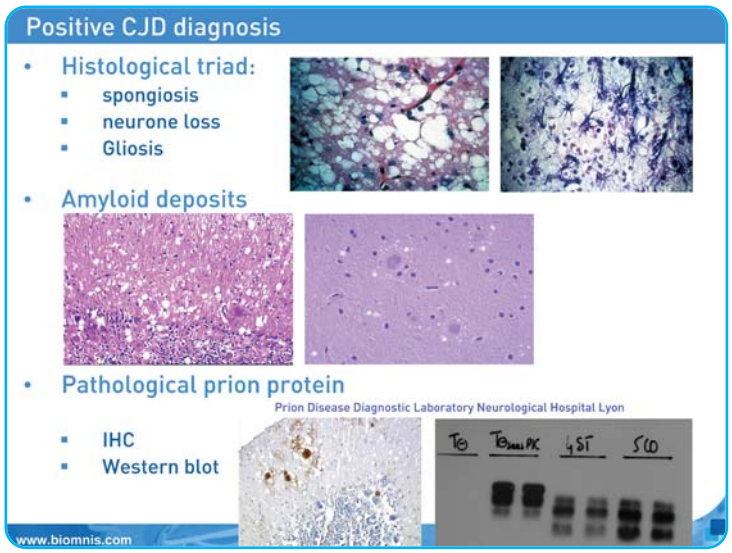
In a suspected case of sporadic or variant CJD, the evaluation includes an electroencephalogram (EEG) (characteristic three-phase pseudoperiodic slow waves), an MRI (significant diagnostic value in sporadic forms), Western blot protein 14-3-3 screening in CSF, and PrP screening in the tonsil (significant in variant forms; constantly negative in sporadic forms).

Protein 14-3-3 is a neuronal lysis marker. In genetic forms, its sensitivity and specificity are 90 %. In the "variant" form, its sensitivity is only 60 %; but increases drastically at the end of the progression of the disease (in pre-mortem, but it is no longer very useful for diagnosis). It is beneficial to screen CSF, in a rapid cognitive degeneration context, but screening should not be performed systematically due to the high number of false positives (herpetic encephalitis, non-Hodgkin's lymphoma in brain region, etc.) and approximately 10 % false negatives are observed in sporadic forms (positive results may be obtained at a later stage). For this reason, it is not considered as an exclusion criterion for the disease.

Other markers have been studied: aldolase assayed in CSF would appear to have a good sensitivity (98 %) but a mediocre specificity, around 70 % (its negative predictive value would appear to be significant, however); neurospecific enolase (NSE) has now been abandoned.

Protein 14.3.3 screening in CSF is the only pathological test recommended by WHO, for CJD diagnosis.

Positive diagnosis of CJD



At the present time, positive diagnosis is obtained post-mortem, based on the histological triad: spongiosis, neurone loss and gliosis. In approximately 15% of cases, amyloid deposits are found. In the "variant" form, these deposits are accompanied by spongiosis vacuoles referred to as "florid plaque". Pathological PrP is detected by means of immunohistochemistry (it is diffuse or in plaques) or Western blot, given that the antibodies used detect not only pathological PrP but also cellular PrP other than in the case of a prior proteinase K treatment, which destroys cellular PrP.

Towards pre-symptomatic detection?

No validated CJD diagnostic blood test is available to date. However, four teams can claim encouraging results. Castilla and Soto (Nat Med 2005) succeeded in detecting PrP in the plasma of animal models (hamster), by increasing the detection sensitivity by a factor of 1 to 10 million by placing in contact with pathological CJD brain and patient sera. A. Lane (Clin Chem 2003) succeeded in obtaining a measurable concentration of pathological PrP by means of ELISA. A. Grosset (Peptides 2005) detected pathological PrP after developing peptides resembling a central part of the protein. Finally, H. Perron developed for Biomérieux (Neuroprion Dusseldorf Oct 2005) a blood test using streptomycin, capable of capturing and concentrating pathological PrP. A blood test to detect CJD may be available within the next 1 to 2 years.

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