Transmissible spongiform encephalopathies

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Abstract
Human prion diseases or transmissible spongiform encephalopathies (TSE) are rare transmissible diseases affecting the central nervous system. The infectious agents are composed of an abnormal isoform of a host membrane protein called "prion protein" (PrP). TSE have common features: long duration of incubation, lesions limited to the central nervous system without inflammatory or immunologic reaction but with accumulation of an abnormal form of prion protein (PrPsc) and death without any remission because of the absence of treatment. Sporadic Creutzfeldt-Jakob disease (CJD) is the most frequent form of the disease (85% of all forms of TSE) and its etiology is unknown. Its annual incidence is estimated to only 1.0–1.5 per million. Besides the typical rapidly progressive form, other forms of the disease exist and may give rise to diagnostic difficulties. Periodic electroencephalography or 14-3-3 protein detection in spinal fluid are helpful for clinical diagnosis. Currently there is no presymptomatic or early test for diagnosis. Examination of the brain after autopsy is necessary to confirm diagnosis. The etiology of other forms of TSE is known: genetic TSE (genetic CJD, Gerstmann-Straussler-Scheinker and Fatal Familial Insomnia) are caused by mutations or insertions in the PRNP gene encoding PrP, and acquired TSE (Kuru, iatrogenic CJD, variant CJD (vCDJ)) result from accidental contamination. The last reported form of TSE is vCDJ. Most vCDJ cases are observed in the United Kingdom and are highly likely to be linked to bovine spongiform encephalopathy (BSE). Low age at onset, psychiatric symptoms and/or pain preceding neurological symptoms, MRI anomalies, detection of abnormal prion protein PrPres in lymphoid system, "florid plaques" in the brain are specific of vCJD. To date, treatment of TSE is purely symptomatic.

Keywords
Transmissible spongiform encephalopathies (TSE), human prion diseases, Creutzfeldt-Jakob disease (CJD), 14-3-3 protein

Disease name and synonyms

- Transmissible spongiform encephalopathies (TSE)
- Human prion diseases

Included diseases

- Sporadic Creutzfeldt-Jakob disease (CJD)

- Genetic CJD
- Gerstmann-Straussler-Scheinker
- Fatal Familial Insomnia
- Kuru
- Iatrogenic CJD
- variant CJD

Definition

TSE are neurological diseases principally characterized by the possibility of transmission experimentally to animals or accidentally to another human. The most frequent form of human TSE is sporadic Creutzfeldt-Jakob disease (CJD) of unknown cause. This form is not a new disease and was first described in 1920 (Creutzfeldt, 1920; Jakob, 1921). Other forms are genetic (genetic CJD, Gerstmann-Sträussler-Scheinker syndrome and Fatal Familial Insomnia) and "infectious" or acquired (Kuru, iatrogenic CJD and variant CJD). TSE have common features: long duration of incubation, lesions limited to the central nervous system (CNS) without inflammatory or immunologic reaction but with accumulation of an abnormal form of prion protein (PrPsc) and death without any remission because of the absence of treatment.

Pathogenesis

TSE occur naturally in animals and humans. None evokes a host immune response and all TSE share a non-inflammatory pathologic process in the CNS with vacuolation of the grey matter ("spongiosis"). The infectious agents are unique because they are composed of an abnormal isoform of a host membrane protein called "prion protein" (PrP). The normal form of the prion protein (PrPc) is present at the surface of many cells, especially in the CNS and lymphoreticular tissue. In humans, the prion protein gene (*PRNP* gene) is located on chromosome 20. The function of PrPc remains unknown. PrPc is rich in α-helical structures, but the disease-associated isoform, PrPsc, is composed mainly of β-pleated sheet and has a tendency to aggregate. Accumulation of aggregates of PrPsc is a common feature in TSE and has probably a link with vacuolation and neuronal death.

Sporadic CJD

Sporadic CJD is the most frequent TSE form (about 85% of all forms of TSE). Its annual incidence is estimated to only 1,0–1,5 per million. It is characterized by a dementia with myoclonia and a wide spectrum of differently associated neurological symptoms. Age of patients at death is usually between 60 and 70 years old, but some cases can occur from 20 and beyond 90 years.

On the basis of clinical, biological, electrophysiological and neuropathological criteria, CJD cases are classified as:

- possible cases: rapidly progressive dementia with at least two of the following clinical features: myoclonia, cerebellar or visual symptoms, pyramidal or extra-pyramidal signs, akinetic mutism and duration below 2 years
- probable cases: rapidly progressive dementia with at least two of the preceding clinical symptoms and a characteristic periodic EEG or a possible case with positive 14-3-3 protein detection
- definite cases: characteristic neuropathological findings and/or PrPres in brain tissue.

Differential diagnosis

Encephalopathy with myoclonia may be due to an infectious, metabolic or toxic disorder. Elimination or treatment of the causal factor can lead to recovery. When dementia is not rapidly progressive, it can be difficult to clinically distinguish sporadic CJD from other causes of dementia as Alzheimer's disease, diffuse Lewy bodie disease or frontal dementia. When cerebellar ataxia is the prominent symptom, paraneoplastic syndrome must be excluded. With cerebral imaging, tumour or stroke can be easily eliminated.

Clinical description

Prodromal signs such as asthenia, insomnia, anxiety or depression can precede the disease, which starts with the outbreak of polymorphic neurological signs. Onset is usually insidious, ranging from weeks to months but sometimes it may be sudden. Dementia is the main symptom and is rather constant during the illness. It results in memory impairment, spatial or temporal disorientation, aphasia, apraxia or frontal symptoms. Fit of confusion or behavioural changes can be associated. Spontaneous or induced myoclonia are very frequent. Cerebellar ataxia can be observed at different stages of the disease. Cerebellar symptoms can involve upper limbs and be associated with dysarthria or nystagmus. A wide variety of visual symptoms are often observed. These may be just a feeling of distorted or blurred vision, or may be more severe with oculomotor disorders, hemianopsia or altered colour perception. Delusions can be intense and frightening. Cortical blindness may occur.

Pyramidal or extrapyramidal syndromes are less constant and can lead to rigidity. Among extrapyramidal features it is possible to observe also dystonia, tremors or various movement disorders (choreiform, athetoid, ballic, etc). Other neurological signs include paraesthesia, dysphagia, vertigo or signs of vegetative dysfunction, which are more rarely observed. Epilepsia is relatively rare (less than 20% of cases). All types of seizures can be observed and subintrant seizures are the main symptom in some cases. Motor neuron signs associated with dementia are extremely rare and associated with a longer duration of the illness. Akinetic mutism is a common state at the end of the disease: the patient becomes insensitive to any exterior stimulus but keep waking and sleeping alternately.

Clinical spectrum of phenotypes of sporadic CJD

Variations in clinical presentation of sporadic CJD are known since a long time. Different forms of the disease can be observed: the parieto-occipital or amaurotic form of Heindenhain, characterized by rapidly progressive dementia, myoclonus, visual disturbances (hallucinations, visual agnosia, cortical blindness), characteristic EEG and a short duration (Heindenhain, 1929); the Brownell and Oppenheimer form with an early and predominant cerebellar ataxia and relatively late dementia (Brownell and Oppenheimer, 1965); the thalamic form of Garcin with the association of dementia and movement disorders (Garcin *et al*., 1963); the panencephalic Japanese form characterized by a high count of cells in CSF, profound damage of the white matter and a very slow course (Mizutani *et al*., 1981; Sadatoshi *et al*., 1983).

These variations in clinical presentation suggest that different strains or different routes of infection are involved in sporadic CJD. The correlation between clinical, molecular and neuropathological data has not yet been elucidated. Six distinct groups of patients have been identified on the basis of clinical data, neuropathological features, biochemical characteristics of PrP and codon 129 polymorphism (Parchi *et al*., 1999).

Biological findings

Usual blood investigations are normal in sporadic CJD: there is no inflammatory syndrome, no disorder of immunity, no abnormal secretion of antibodies. There is also no change of cerebrospinal fluid (CSF) components: normal count of cells, normal glucose or chlorine levels, normal or slightly increased protein level. Detection of 14-3-3 protein is very helpful for the diagnosis of sporadic CJD with high sensitivity (90 %) and specificity (95%) (Hsich *et al*., 1996; Zerr *et al*., 1998; Beaudry *et al*., 1999). False positive detection of 14-3-3 protein can be observed in encephalitis, recent stroke or subarachnoid haemorrhage, haemorrhagic lumbar puncture, paraneoplastic syndrome or seizure. 14-3-3 protein is exceptionally detectable in other dementia such as Alzheimer's disease. The presence of 14-3-3 protein in CSF is probably due to a massive neuronal death and the release of brain proteins into CSF.

Imaging

Computed tomography (CT) is normal or shows non-specific anomalies such as mild brain atrophy. Cranial magnetic resonance imaging (MRI) can show brain atrophy and in more than 50% of cases high signals on T2, flair or diffusion- weighted sequences in basal ganglia (caudate or putamen) or in cerebral or cerebellar cortex (Schroter *et al*., 2000). The precise diagnosis value of MRI anomalies has to be evaluated.

Electophysiological features

Electroencephalography (EEG) is always altered in sporadic CJD. Slow wave activity is constant and worsens as the illness progresses. Pseudo-periodic sharp waves can occur but the EEG is characteristic when periodic sharp waves of 1 Hertz appear (Court *et al*., 1995). Periodic EEG complexes can be transient: repeated recordings are necessary.

Genetic analysis

Sequencing of the prion protein (*PRNP*) gene is important to rule out a pathological mutation or insertion and to study polymorphism at codon 129: a patient can be homozygous, methionine-methionine (MM) or valine-valine (VV), or heterozygous, methionine-valine (MV). In a normal population frequencies of MV heterozygotes, MM and VV homozygotes are respectively 50%, 39% and 11% (Alperovitch *et al*., 1999). In patients with sporadic CJD the frequency of heterozygotes is lower than that of homozygotes: 17% MV, 64% MM and 19% VV (French surveillance network for the period 1992-2002). MM polymorphism at codon 129 is a risk factor for sporadic CJD.

Neuropathological diagnosis

The gold standard for the diagnosis of sporadic CJD and for all forms of TSE is the neuropathological examination of brain after autopsy. Characteristic findings are spongiosis, neuronal loss, gliosis and PrPres detection

with immunocytochemical technics. PrPres deposits can be synaptic, focal or in the shape of plaques which are rarely observed in case of sporadic CJD (10 to 15%). Western-blot analysis for detection of PrPres is also important for diagnosis.

Genetic forms of TSE

In 5 to 15% of TSE cases, mutation or insertion of nucleotides in *PRNP* gene are found. A familial history of TSE or dementia is recorded in less than 50% of cases (The EuroCJD group, 2001). This underlines the importance of genetic analysis. Transmission of all genetic forms is autosomal dominant. Clinical features depend on the type of the mutation but can show significant intrafamilial variability. Three groups of genetic TSE can be distinguished: genetic CJD, Gerstmann-Straussler-Scheinker and Fatal Familial Insomnia.

Genetic CJD

In most cases, clinical features of genetic CJD are not very different from those of sporadic CJD. In France, codon 200 mutation is the most common (Laplanche *et al*., 1994). Age at onset is a bit lower than in sporadic CJD. Mutation 178 results in a CJD phenotype when codon 129 of the allele carrying the 178 mutation codes a valine. Age at onset is younger and development is slower than in sporadic CJD. Codon 210 mutation is also frequently observed in France and in other European countries. Other mutations are rare and often detected by chance in patients suspected of sporadic CJD. Nucleotides insertions between codons 51 and 91 of the N-terminal portion of *PRNP* gene can be associated with a phenotype of CJD with an early onset and a slow progression of the disease. Clinical and neuropathological findings vary according to the number of nucleotides inserted (Laplanche *et al*., 1995).

Gerstmann-Straussler-Scheinker syndrome (GSS)

GSS is a rare familial and always genetic form of TSE. The main characteristics are a slow development of disease (several years in many cases) and the presence of multicentric PrP plaques on histopathological examination. Codon 102 mutation is the most common. The illness starts at the age of 40 with cerebellar ataxia as the main symptom; oculomotor or pyramidal signs and dementia occur in a second time. Codon 117 is more rarely observed (Malluci *et al*., 1999). In a large French family, symptoms vary from a generation to another: dementia alone manifests in the first three generations, dementia with pseudobulbar and pyramidal signs appear in the following generations (Tranchant *et al*., 1991). Myoclonia, cerebellar signs, epilepsy or lower motor neuron signs are inconstant. Other mutations (105, 198, 217) have been observed in one family and led to cerebellar or pyramidal symptoms.

Fatal Familial Insomnia (FFI)

This is an uncommon form of TSE with few families in France and around the world. Codon 178 mutation is associated with a methionine at codon 129. Clinical features are particular associating a sever insomnia with significant delusions, vegetative symptoms (loss of circadian rhythms, dyspnoea, loss of thermoregulation…), motor impairment, myoclonia and dementia. Anomalies on arousal and sleep EEG are observed, but arousal EEG is not periodic. On neuropathological examination, gliosis is predominant in anterior and dorsomedian thalamic nuclei, cortical lesions and spongiosis are rare (Hauw *et al*., 1996).

Acquired forms of TSE

Acquired forms of TSE are due to accidental inoculation of the agent to human through cannibalistic rituals (Kuru), therapeutic procedures (iatrogenic CJD), transmission of the agent of bovine spongiform encephalopathy (BSE) or mad cow disease (vCJD).

Kuru

Kuru was observed in the Fore population of New-Guinea between 1950 and 2000 (Gajdusek and Zigas, 1957). This form was secondary to cannibalistic rituals: women and children were orally contaminated with the absorption of brain and viscera, whereas men consumed less infectious tissues (muscles) and were at lower risk of Kuru. Kuru was the first TSE experimentally transmitted to animals (Gajdusek *et al*., 1966). In contrast to sporadic CJD, clinical symptoms in Kuru were stereotyped. The disease started with cerebellar ataxia, tremor, oculomotor anomalies, dysarthria. Patients became bedridden in a state of akinetic mutism and died after one year. Cannibalism ban in 1960 has led to the progressive disappearance of Kuru.

Iatrogenic CJD

In 1974, the first case of iatrogenic CJD was recognized in the recipient of a corneal graft from a donor who died of CJD (Duffy *et al*., 1974). Two other possible cases of corneal graft-related CJD have occurred in the last decade (Uchiyama *et al*., 1994; Heckmann, 1997). Seven cases resulting from

contaminated stereotactic intracerebral EEG needles or neurosurgical instruments were identified in the 1970's (Bernoulli *et al*., 1977; Foncin *et al*., 1980; Will *et al*., 1982). The two most important causes of iatrogenic CJD remain dura mater grafts and contaminated cadaveric human growth hormone (hGH) (Brown *et al*., 2000).
Between the 1980's and 2000 the total number of CJD after dura mater grafts was 114 (8 cases in France and the highest number of cases in Japan) (Brown *et al*., 2000). The route of entry of the infectious agent into the CNS is intracranial and juxta cerebral. Clinical presentation resembles that of sporadic CJD with a preponderance of cerebellar onsets but with a rapid progression of the disease (6 months in average) and a high proportion of periodic sharp waves on EEG and 14-3-3 detection in CSF.
Iatrogenic CJD after treatment with hGH is more frequent in France with a total of 74 patients who died between 1991 and 2000 (Brown *et al*., 2000). This form of CJD occurs also in the United-Kingdom (35 cases) and the USA (22 cases). Manufacturing 's methods of the hormone probably explains the observation of this form of CJD in these three countries. Clinical symptoms in iatrogenic CJD are closer to those of Kuru than those of sporadic CJD: symptoms are stereotyped with cerebellar ataxia, oculomotor disorders, pyramidal syndrome and tremor at onset. Dementia and myoclonia are relatively late onset symptoms. Total duration of illness is 18 months in average with a state of akinetic mutism at the end (Billette de Villemeur *et al*., 1996). EEG is exceptionally periodic and 14-3-3 protein is detected in CSF 6 months or more from the onset (Brandel *et al*., 2001). MM polymorphism at codon 129 is a risk factor for this form of CJD in France but not in the United-Kingdom (Brandel *et al*., 2003). In France total duration of illness is longer in heterozygotes (MV) compared to homozygotes (VV or MM).

Variant CJD (vCJD)
vCJD is a new form first described in the United-Kingdom in 1996, ten years after the first description of BSE (Will *et al*., 1996). Some characteristics lead to differentiate vCJD from sporadic CJD. Mean age at onset of symptoms (29 years) is particularly young. Psychiatric symptoms and sensory disturbance (pain, paresthesia…) are earlier non specific features remaining the most prominent symptoms for some months. Cerebellar ataxia and pyramidal syndrome are the first neurological disturbances. Dementia, involuntary movements (myoclonia or chorea) occur secondarily (Zeidler *et al*., 1997). Before death, patients are usually in an akinetic mutism state. Progression and total duration of the disease (18 months in average) look like Kuru and iatrogenic CJD after hGH treatment. EEG is never periodic, 14-3-3 protein is positive in half of the cases and all patients have MM polymorphism at codon 129. Observation of posterior thalamic high signals ('pulvinar' or 'hockey stick' signs) on T2, Flair or diffusion weighted imaging is important for the diagnosis just as tonsil biopsy when PrPres is detected (Zeidler *et al*., 1997; Zeidler *et al*. 2000). Diagnosis is confirmed with neuropathological data. Lesions are mainly distributed in basal ganglia and thalamus. The more striking feature is the presence of Kuru plaques surrounded with spongiosis: "florid plaques". This type of plaques and their abundance were never seen before in humans.
Many arguments support the existence of a link between vCJD and BSE:
- epidemiological argument: appearance of vCJD 10 years after BSE, in the country where BSE was "epidemic";
- experimental arguments: intracerebral inoculation of BSE agent to three macaques resulted in appearance of clinical symptoms of spongiform encephalopathy with "florid" plaques on brain examination (Lasmezas *et al*., 1996), all cases secondary to BSE agent, vCJD included, have an electrophoretic profile of type 4 (or 2B) on Western-blot analysis (Collinge *et al*., 1996), clinical and neuropathological signs in mice inoculated with BSE agent are dramatically stereotyped (Bruce *et al*., 1997).

Treatment
There is no curative treatment for TSE. Many drugs were tested in cells culture or in animals: antibiotics, antiviral, antifungal, modulators of the immune response, hormones, antimitotics, polyanions, Congo red… Some of these molecules increase duration of incubation in animals but have no effect on clinical symptoms and the fatal issue of the disease. Ongoing research aims at developing molecules that interact with the structure of PrP or at testing immunisation in order to develop a vaccine. Randomised control trials are difficult in such rare diseases and would require international collaboration. In 2001, the report of a possible effect of quinacrine, an antiparasitic drug, led many countries to authorize the compassionate use of this molecule in the treatment of TSE. No significant improvement was reported, notably in France (Haïk *et al.*, in press).

Current treatment of TSE remains symptomatic and requires a careful nursing at home or at hospital.

Conclusion

TSE are transmissible diseases of uncertain origin. On a clinical level, various and diversely associated symptoms of sporadic form contrast with the stereotyped phenotype of Kuru, iatrogenic CJD after hGH and vCJD. This raises the question of different strains of prion or routes of propagation of the agent. In order to limit transmission of the disease and to develop therapeutic procedures it remains important to develop an early diagnostic test. The diagnosis of CJD must indeed be done as soon as possible because of the particular precautions, which must be respected: decontamination or incineration of certain materials, exclusion of blood donations.

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