CJD and Prion Diseases

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Prions

Stanley Prusiner proposed the "prion hypothesis" in 1982. He defined "prion" as a proteinaceous infectious particle that lacks nucleic acid, composed exclusively of a single kind of protein molecule, PrP^{sc}. He proposed that these particles could act as infectious agents. In 1995 Prusiner was awarded the Nobel Prize for his prion work.

The prion agent is a protein, denoted by the notation PrP^{sc} . PrP^{sc} is a conformationally altered form of a normal, host-encoded cell membrane glycoprotein called PrP^{c}. The essence of the prion hypothesis was that PrP^{sc} impresses its abnormal conformation on normal PrP^{c}, thus generating additional PrP^{sc}. This was an entirely novel pathogenic mechanism, based on a self-propagating change in protein conformation. This hypothesis and its subsequent scientific proof could have remained an obscure area of investigation until it was recognized that prions were responsible for an important group of human diseases, especially Creutzfeld-Jacob disease. This led to widespread public interest.

Creutzfeldt-Jakob disease (CJD) is one of the spongiform encephalopathies, a group of diseases that share a number of features including a progressive neurological course, characteristic histopathology, and causal agents that have an unusual resistance to sterilization. Several forms of CJD are recognized. The most recently characterized type is variant CJD (vCJD). vCJD has attracted considerable public and media attention because of the increasing evidence of a causal link with bovine spongiform encephalopathy (BSE) in cattle.

The agent that causes CJD was difficult to identify. It has unusual physical properties, with a peculiar resistance to conventional sterilization processes (formalin, ultrafiltration, standard autoclaving, ionizing and UV radiation, and a number of enzymes).

CJD is associated with PrP^{SC}, which is found in high concentrations in affected central nervous system (CNS) tissues. This protein has an identical primary structure to a normal cell membrane protein known as PrP^{C}. However, the native PrP^{C} form has an -helical 3-dimensional configuration, while the disease-associated PrP^{SC} form is that of a -pleated sheet. The abnormal configuration leads to a propensity for protein aggregation, particularly in the CNS. It is believed that PrP^{SC} protein is the causal agent of CJD.

HistopathologyofCJD

The characteristic histological feature of CJD is the presence of spongiform changesin the gray matter of the brain, particularly the occipital, frontal and cerebellar cortex and basal ganglia. There is a notable absence of an inflammatory response. The definitive histological diagnosis is made by the immunocytochemical demonstration of the disease-related form of the PrP protein in the brain. The histological changes in vCJD differ from those seen in other forms of CJD. In particular, a large number of PrP amyloid plaques surrounded by a halo of spongiform change ('florid plaques') are seen, particularly in the cerebral and cerebellar cortical gray matter.

CJDSubtypes

The clinical diagnosis of all forms of CJD can be difficult *in vivo*, and a definite diagnosis of CJD depends on post-mortem examination or brain biopsy. Clinical diagnostic criteria have been developed which allow a reasonably confident diagnosis in the majority of cases. No pre-mortem investigation has been shown to be entirely accurate, but the role of neuroimaging is becoming increasingly important, both in the positive diagnosis of CJD, and in the exclusion of other possible diagnoses. MRI has become particularly important as other *in vivo* tests such as tonsillar or brain biopsy, are associated with a small but real risk of morbidity.

Four main sub-types of CJD are recognized, with distinct epidemiological and clinical characteristics. sCJD and vCJD have been more extensively studied from a radiological perspective. Familial CJD is an inherited form of the disease which arises from mutations in the prion protein gene (PrP). Iatrogenic CJD has been linked to previous neurosurgery (particularly dural grafts), and the use of cadaveric pituitary extracts as a source of growth hormone and human gonadotrophins.

SporadicCJD(sCJD)

Sporadic CJD (sCJD) is the best known and commonest form of CJD. It has an incidence of 1 1.5 per million population per annum. It occurs in the 60-75 year age group. It is characterized by a very rapidly progressive dementia, myoclonus, cerebellar ataxia and cortical blindness, which progresses akinetic mutism and death. 50% of patients are dead within 5 months of symptom onset. Two non-radiological tests have been shown to be useful in the diagnosis of sCJD: EEG changes with generalized periodic triphasic sharp wave complexes appear in 65% of patients late in the disease, and CSF electrophoresis for the 14-3-3 protein.

ImagingofsCJD

CT performed early in the natural history of the disease is usually normal. Cerebral and cerebellar atrophy occur later. Abnormalities on MRI in sCJD were reported as early as 1988. These were described as hyperintense signal changes in the putamen and caudate head. The putamen and caudate changes are usually symmetrical on long TR imaging. These MRI changes may occur early, before EEG changes are evident. High signal and swelling in the cerebral and cerebellar cortex can also be occasionally detected with long TR sequences, though are more conspicuous on FLAIR and especially DWI sequences.

Cortical involvement can occur early. Cortical atrophy is a late feature, and the degree of atrophy correlates with the duration of disease. White matter hyperintensity is also sometimes seen in the centrum semiovale in both sCJD and vCJD.

The differential diagnosis for basal ganglia changes mimicking sCJD include hypoxia, CO poisoning, hypoglycemia, haemolytic-uraemic syndrome, encephalitis, mitochondrial disorders (e.g. Leigh's disease), Wilson's disease and Huntington's disease. High signal in the pulvinar may suggest the diagnosis of vCJD but the pulvinar signal intensity remains lower than the putamenal signal change, and the patient's age and the clinical course help distinguish the two CJD subtypes.

VariantCJD(vCJD)

In 1996 a new clinically distinct form of CJD was described, variant CJD (vCJD). There is now overwhelming epidemiological, pathological and molecular biological evidence in support of the theory that the link is via BSE contaminated food. Over 120 cases have been identified worldwide, most of them in the UK. Because of the long latency of the disease, the total number of cases that may occur in the future remains unknown, and careful surveillance of incident cases continues.

vCJD has a median younger age of onset (median age 26 years) than sCJD (median age 65 years), and a more slowly progressive duration of disease (mean 14 months for vCJD versus 5 months for sCJD). The clinical picture of vCJD is also relatively distinct from other forms of CJD. The presenting symptoms are usually non-specific. The initial symptoms are commonly sensory (sensation of cold, paraesthesia or pain), and / or psychiatric (withdrawal, depression, fleeting delusions). Other features include abnormal eye movements and involuntary movements. The disease is histopathologically distinct from sCJD, with deposition of PRP^{SC} protein particularly marked in the thalamus, with a characteristic feature of histologically distinct 'florid plaques'.

The non-imaging diagnostic tests used in sCJD are often negative in vCJD. EEG does not show the characteristic periodic activity seen in sCJD. In CSFthe 14-3-3 marker has a much lower sensitivity and specificity in vCJD. The detection of the PrP^{SC} protein in tonsillar biopsy may be diagnostically useful

ImagingofvCJD

CT is not helpful. MRI was initially reported to be unremarkable in most patientswith vCJD, but subsequently symmetrical hyperintensity of the pulvinar nucleus of the thalamus on T2-weighted and proton density-weighted axial images in the majority of patients has been shown to be a highly sensitive sign of disease, being found in about 80% of histologically confirmed cases. In the appropriate group of patients, with clinical features consistent with vCJD the specificity of the pulvinar sign may be as high as 95%.

There are characteristic hyperintensity changes in other areas in vCJD, including the dorsomedial nuclei of the thalamus. This gives a characteristic 'hockey-stick' appearance. Other regions may be involved, including the tectal plate and periaqueductal gray matter, and occasionally the cortex and deep

white matter. Cerebralatrophy is seen in only a minority of patients with vCJD, even with advanced disease. The pulvinar sign is currently the best non-invasive *in vivo* diagnostic test of vCJD.

One of the most important clinical differential diagnoses of vCJD is sCJD. MRI differentiates between the two forms of the disease in most cases. The thalamic hyperintensity occurs in sCJD and familial CJD but no case has been reported showing the pulvinar to be brighter than the putamen. Other conditions that cause thalamic hyperintensity include CO poisoning, Japanese Nipositu encephalitis, Wernicke's encephalopathy, bithalamic glioma, and thalamic infarction (basilar artery or deep cerebral venous thrombosis, benign intracranial hypertension (BIH), and post-infectious encephalitis.

MRI Imaging Techniques:

T1-weighted imaging is the least useful sequence in imaging CJD. It is invariably normal except in the rare occurrence of very heavy deposition of PrP^{SC} protein in the basal ganglia, resulting in putamenal high signal. Enhancement with gadolinium is not a feature of CJD.

Where both PDWI and T2WI scans are available, the subjective conspicuity of basal ganglia hyperintensity on PDWI is consistently superior. It may result from partial volume artefact from adjacent CSF obscuring the pulvinar changes on T2WI.

With FLAIR the basal ganglia changes and the cortical changes are considerably more conspicuous than on either T2WI or PDWI. This sequence is very useful in the MRI diagnosis of CJD, particularly with respect to the detection of cortical changes.

In sCJD abnormalities on DWI have been reported earlier in the course of the disease than on any other imaging sequences, and may allow monitoring of disease progression. Cortical gray matter and thalamic changes are better depicted than on conventional long TR sequences. In sCJD, it has been postulated that a restriction in diffusion results from intraneuronal microvacuolation, the precursor to the advanced spongiform vacuolation visible at post mortem. Despite the low spatial resolution, the abnormalities in CJD are sometimes striking. DWI is a relatively fast sequence to acquire, and is increasingly important in the diagnosis of CJD.

Conclusions

All forms of CJD are untreatable and fatal at present. However, accurate and early diagnosis is a pre-requisite to the development of effective treatment, allows better understanding of transmission, and helps provide information on the natural history of CJD, which is particularly important for patients with the disease and their relatives. Characteristic MRI changes are seen in many patients, and the distribution of these changes frequently allows an accurate radiological diagnosis and distinction between subtypes. Though histological changes are present throughout the brain, the changes on MRI are most conspicuous as hyperintensity in the deep gray matter nuclei, in particular the putamen and caudate in sporadic CJD, and the pulvinar of the thalamus in variant CJD.

References

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