Creutzfeldt-Jakob Disease: Spectrum of Magnetic Resonance Imaging findings

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Learning objectives

The purpose of our educational exhibit is to:

1- Describe the key clinical and physiopathological elements of Creutzfeldt-Jakob disease.

2- Illustrate and describe imaging findings on Magnetic Resonance Imaging that suggest the diagnosis of Creutzfeldt-Jakob Disease.

3- Determine the main differential diagnosis of this disease.
Prion diseases (also known as transmissible spongiform encephalopathies), are a family of rare progressive neurodegenerative disorders, that affect both humans and animals. They are characterized by long incubation periods, and typical changes of brain tissue, including neuronal loss, proliferation of glial cells, a failure to induce inflammatory response, and the presence of small vacuoles within the neuropil, which produces a spongiform appearance. Human prion diseases, although variable in clinicopathological phenotype, are transmissible, progressive and invariably fatal neurodegenerative conditions.

The causative agents of prion diseases are believed to be prions. These are proteins that are unique in their ability to reproduce on their own and become infectious. These pathogenic agents are transmissible and are able to induce misfolding of a host-encoded prion protein, which is found mostly in the brain. Although its physiological function is still poorly understood, the abnormal folding of the prion proteins leads to brain damage and the characteristic signs and symptoms of the disease.

Creutzfeldt-Jakob disease (CJD), kuru, Gerstmann-Sträussler-Schenker syndrome, and fatal familial insomnia are included in prion diseases group, but it is not a closed group and a new type of this disease has recently been identified.

CJD is the most common human prion disease and has a worldwide distribution. It is a very rare entity and the worldwide incidence is 0.5-1.0 cases per million per year, and is characterized by dementia, myoclonus and ataxia. Sporadic (sCJD), familial (fCJD), iatrogenic (iCJD), and a variant form of CJD (vCJD) are all recognized. About 85 to 95 percent of CJD cases are sporadic, while 5 to 15 percent are due to fCJD; iCJD generally accounts for less than 1 percent. Clinical signs such as rapidly progressive dementia, cerebellar or visual signs, pyramidal or extrapyramidal signs and akinetic mutism associated with typical changes in ancillary diagnostic tests, such as the presence of periodic sharp wave complexes on electroencephalogram, the presence of protein 14-3 - 3 in the cerebrospinal fluid, and typical changes on MRI support the diagnosis of sCJD, and a combination of these different elements allows to classify the disease as possible or probable, according to World Health Organization (WHO) criteria. It occurs equally in both sexes with a peak age of onset between 55 and 75 years.

vCJD, first described in 1996, is a rare but important cause of dementia and death in young patients. It is most probably caused by the transmission of the bovine spongiform encephalopathy agent to humans.
A diagnosis of definite CJD can be made only by neuropathologic examination, either by in vivo biopsy of brain tissue or at postmortem examination.
Findings and procedure details

Radiology plays now a significant role in the diagnosis of Creutzfeldt-Jakob disease (CJD). Magnetic Resonance Image (MRI) has played an increasingly important role since basal ganglia abnormalities on T2-weighted images have been described. MRI criteria have been established, giving a sensitivity and specificity >90% for probable CJD.

This section is intended to identify imaging features that suggest, in the appropriate clinical context, the diagnosis of CJD.

CJD primarily involves the gray matter structures of the brain. White matter changes are much less found, and if present, are usually a late finding.

Computed Tomography (CT) are frequently normal, especially in the early stages of the disease (Fig.1). With its progression, a pattern of rapidly progressive cerebral atrophy is described in follow-up studies, with ventricular dilatation and sulcal enlargement (Fig.2), also seen in MRI.

MRI is the imaging procedure of choice. It is a useful tool in the diagnosis of CJD but the characteristic changes are often not identified at initial scan in the early stages of disease. Its findings may be bilateral or unilateral, and symmetric or asymmetric.

T1 weighted image (T1WI) scans are often normal (Fig.3) and remain on T1WI post gadolinium administration (CJD does not enhance) (Fig.4).

On T2 weighted image (T2WI) / Fluid Attenuated Inversion Recovery (FLAIR), hyperintensity in the basal ganglia (mostly anterior caudate and putamen), thalami, and cerebral cortex are the most frequently reported imaging findings in classic sCJD (Fig.5,6). The involvement of the cerebral cortex, described in serial studies as the most common early manifestation, is mostly described in the frontal, temporal and parietal lobes, and is often asymmetric. These signal changes show restricted diffusion on Diffusion Weighted Image (DWI), which shows, therefore, hyperintensity in the striatum and thalami. Very common on DWI is the gyriform restricted diffusion in the cerebral cortex (cortical ribboning) (Fig.7).

DWI has been described by several authors as being the most sensitive MR imaging technique in the diagnosis of CJD. Studies reported a sensitivity of up to 100%. However, the underlying pathomechanism explaining the decrease in isotropic water diffusibility indicated by DWI is not yet fully understood. DWI is a fast technique, hence, is much less vulnerable to interference by motion artifacts. This sequence should therefore be
part of all imaging studies in patients who were clinically either definite or probable for the diagnosis of CJD based on the WHO criteria.

DWI is very useful in distinguishing CJD from the differential diagnoses of CJD, including Alzheimer´s disease, vascular dementia, and dementia with Lewy bodies.

Infectious meningoencephalitis, mitochondrial encephalopathy, lactic acidosis, Wilson´s disease, and Wernicke´s encephalopathy can also cause signal changes similar to those found in CJD. However, these can usually be distinguished from CJD based on clinical and CSF findings.

DWI shows a decrease of the apparent diffusion coefficient (ADC) in the affected areas, most probably because of the characteristic neuropathologic spongiform neuropil changes (Fig.8).

Recent studies described new signals in the variant form (vCJD): the "pulvinar" sign, due to a bilateral symmetrical T2 hyperintensity of pulvinar nuclei of thalami (Fig.9); and the "hockey stick" sign: bilateral symmetrical T2 hyper intensity involving pulvinar and medial dorsal thalamic nuclei (posteromedial thalamus) (Fig.10). These alterations are seen in 90% of vCJD cases, but can also occur in sCJD. In the appropriate clinical context, demonstration of the pulvinar sign on MR images is a highly accurate diagnostic sign for vCJD.
Images for this section:

**Fig. 1:** CT examination without identifiable anomalous densities at the level of the basal ganglia (left image) or cerebral cortex (right image).

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Fig. 2: CT examination showing pattern of brain atrophy, here with ventricular dilatation and sulcal enlargement.

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**Fig. 3:** T1WI scans are often normal.

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**Fig. 4:** T1WI post gadolinium administration, with no areas of abnormal uptake.

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**Fig. 5:** T2WI showing hyperintensities in the striatum (left image) and the cerebral cortex, here bilateral parietal predominance (right image).

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Fig. 6: MRI FLAIR images showing hyperintensities in the striatum (left image) and the cerebral cortex, bilateral parietal predominance here (right image).

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**Fig. 7:** DWI images showing hyperintensities (restricted diffusion) in the striatum (right image), and the cortex, bilaterally, giving a gyriform pattern (cortical ribboning)(left image).

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Fig. 8: ADC map showing decrease of the apparent diffusion coefficient in the striatum.

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**Fig. 9:** T2WI (left image) and FLAIR (right image), illustrating the "pulvinar" sign.

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**Fig. 10:** FLAIR image (left) and DWI image (right), showing hyper intensity involving the posteromedial thalamus ("hockey stick" sign).

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Conclusion

It is now recognized the important role that MRI have played in the diagnosis of CJD. Although, the characteristic changes are often not identified in the early stages of disease, therefore, a close correlation with clinical and other laboratory data is essential for a correct diagnosis.

DWI is considered the most sensitive MR imaging technique in the diagnosis of CJD; its findings allow the radiologist to suspect the diagnosis at an earlier stage of disease, thereby allowing appropriate treatments to be instituted.

Because it is a rare disease, many radiologists are not familiar with the imaging findings. Therefore, when the disease is suspected, even if the first examination was described as normal, it should be reviewed by an experienced neuroradiologist.
References