Pictorial Essay of MRI Findings of Creutzfeldt-Jacob Disease (CJD)

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Learning objectives

Creutzfeldt-Jakob disease (CJD) is a rare rapidly progressive dementia, potentially fatal, due to the infection and the accumulation of prions in neurons.

In the past the role of imaging in prion disease used to be one of exclusion of other conditions.

Over the past decade the improved knowledge of magnetic resonance technique has led to a more prominent position of MRI for the diagnosis and to its inclusion in the diagnostic criteria for CJD.

Nowadays radiologists must be aware of MRI key features of CJD because sometimes only MRI findings can address to the correct diagnosis (Fig. 1 on page 2).

The purpose of this essay is:

- to introduce pathophysiology and clinical presentation of CJD.

- to review MR imaging findings in the different forms of human prion disease, describing typical and atypical MRI features.

- to illustrate possible differential diagnosis.

Images for this section:
Fig. 1: MRI of a 63 yo Patient, with subacute onset of prominent akinetic syndrome, with lack of visual symptoms or cerebellar signs. EEG demonstrated absence of a periodic electroencephalographic pattern and CSF analysis absence of 14-3-3 positivity. In this case MRI played a critical diagnostic role by showing typical findings of sCJD unless clinical features, electrophysiological pattern and CSF analysis were not suggestive for CJD. T2-wi (a, d), FLAIR (b, e) and DWI (c, f) images show bilateral and symmetrical hyperintensity of caudate (°) and of putamina (^). DWI images show the involvement of fronto-temporo-parietal cortex («ribbon sign») and of insular cortex (arrow heads).
Background

CJD is the most common form of transmissible spongiform encephalopathies in humans, caused by a prion, "a proteinaceous infectious particle" that lacks nucleic acids. The active component in prions is an abnormal protein called prion protein (PrP). Normal animal cells make a form of PrP called cellular PrP (PrPC), easily soluble, sensible to digestion by proteases and with a protective role against dementia and other degenerative problems. In animals infected with prions, abnormal PrP (PrPSc) is produced, a highly insoluble and resistant to digestion by proteases protein, that, through an autocatalytic process, promotes the conversion of the cellular PrP in neighboring neurons; this leads to further PrPSc accumulation in neurons.

1. EPIDEMIOLOGY

CJD occurs worldwide with an estimated incidence of one case per 1 million people a year and is reported in almost equal ratios between the sexes. Previous studies have reported a peak age of onset between 55 and 75 years.

2. CLINICAL PRESENTATION

Patients affected with CJD usually present a rapidly progressive dementia, visual abnormalities, and cerebellar dysfunction including muscle incoordination, gait, and speech abnormalities. Most patients develop pyramidal and extrapyramidal dysfunction during the course of the disease; some patients may also show behavioral changes. These symptoms often deteriorate very rapidly, and during the terminal stages of illness these patients develop a state of akinetic mutism. The median illness duration of CJD is 4 months (mean: 7.6 months); invariably death occurs within 12 months of illness onset in nearly 85%-90% of patients.

3. AETIOPATHOGENESIS

Four different forms of human prion disease have been described:

- **sporadic CJD**, the most common form of human prion disease. Due to the different presentation of sCJD, 5 sCJD clinical variants, based on clinical presentation, and 6 molecular subtypes have been described. In particular, considering the clinical variants, 3 clinical subtypes have been identified (the classic sCJD, the Heidenhain variant, which presents with visual disturbances, and the Oppenheimer-Brownell variant, which solely presents with ataxia, Table 1 on page 6) and 2 neuropsychiatric variants (the
cognitive and the affective variants). On the other hand, the 6 molecular subtypes (MM1, MM2, MV1, MV2, VV1, and VV2) vary with respect to age at disease onset, disease duration, early symptoms, and neuropathology. Heterogeneity in sCJD correlates with the codon 129 genotype of the prion protein gene (PRNP), in combination with the existence either of two distinct types of pathologic prion protein (PrPSc 1 or 2). The most common MM1 sCJD subtype (68% of sCJD cases) is characterized by dementia, ataxia and myoclonus. The MV2 subtype comprises 9% of sCJD cases.

- **inherited CJD** are a group of autosomal dominantly inherited conditions, together with Gerstmann-Straussler-Scheinker Syndrome (GSS) and familial fatal insomnia. Comprise approximately 15% of human prion disease and are caused by point mutations (such as P102L, P105L, E200K) or insertions (such as the 144 base pair octapeptide repeat insertion) in the gene that controls formation of the normal prion protein on chromosome 20; the clinicopathological spectrum is also affected by polymorphisms at codon 129 of the prion protein gene. The presentation is heterogeneous and depends on the mutation. The most common pathogenic mutation is E200K mutation.

- **new variant CJD (vCJD)**, also known as "mad cow disease", or bovine spongiform encephalopathy (BSE), is a massive common source epidemic, caused by infected meat and bone meal fed primarily to dairy cows with the intention to get high-quality beef. The characteristic clinical features differ from those of other prion diseases. vCJD predominantly affects a young age group (median age 26 years, occurring in males and females equally). There are early psychiatric and behavioural symptoms and in half concurrent sensory symptoms such as limb pain and dysesthesia occur. As the disease progresses, neurological features become more prominent, particularly ataxia and cognitive impairment. The disease has a median duration of 13 (range 6-39) months.

- **infectious CJD** include Kuru and iatrogenic CJD. Kuru, first recognized in 1957 in New Guinea and linked to ritualistic cannibalism, now is disappearing because of the cessation of these rituals. Iatrogenic Creutzfeldt-Jakob disease (iCJD) is mainly associated with dura mater (DM) grafts and administration of human growth hormones (hGH).

### 4. DIAGNOSIS

Definitive diagnosis consists of brain biopsy.

In the past imaging features were no part of the diagnostic criteria for sCJD, which relied more on clinical, neurohistopathological, EEG (triphasic periodic complexes) and CSF features (positivity for 14-3-3 protein). Role of imaging in prion disease used to be one of exclusion of other conditions.
Nowadays MRI of the brain is the most sensitive technique and is required in all patients with a clinical suspicion of CJD. As a matter of fact it has been included in the diagnostic work up for sCJD (UCSF 2011 MRI criteria, Table 2 on page 6).

Images for this section:

<table>
<thead>
<tr>
<th>sCJD</th>
<th>Characteristics</th>
</tr>
</thead>
</table>
| Classic          | • Onset of cognitive symptoms (cognitive decline, amnesia, language impairment, executive dysfunction, and/or disorientation) and ataxia at illness onset, without visual disturbances.  
• Clinical presentation within 1 mo of illness onset.  
• Short interval between symptom onset and diagnostic testing (CSF 14-3-3 protein, EEG, and brain MRI).  
• Survival time 3 mo  
• Predominance of PrPSc type 1 |
| Heidenhain       | • Onset of diplopia, blurred vision, cortical blindness, and/or visual hallucinations at illness onset. |
| Oppenheimer- Brownell | • Ataxia in the absence of other presenting symptoms at illness onset. |

Table 1: Modified from Brian et al. (2009) Characteristics of Established and Proposed Sporadic Creutzfeldt Jacob Disease Variants Arch Neurol 66(2):208-215. 5 sCJD variants have been studied, based on clinical presentation. In particular have been studied 3 clinical subtypes: classic sCJD, Heidenhain variant (visual disturbances), and Oppenheimer-Brownell variant (which solely presents with ataxia)and 2 neuropsychiatric variants: cognitive and affective sCJD variants. sCJD subtypes have different EEG, molecular and MRI characteristics.
<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>UCSF 2011 criteria</th>
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<tbody>
<tr>
<td>MRI definitely CJD</td>
<td>DWI &gt; FLAIR hyperintensity in:</td>
</tr>
<tr>
<td></td>
<td>1. Cortex (&gt;1 gyrus) and striatum</td>
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<tr>
<td></td>
<td>Classic pathognomonic criteria:</td>
</tr>
<tr>
<td></td>
<td>• Cingulate, striatum, and &gt;1 neocortical gyrus</td>
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<tr>
<td></td>
<td>Supportive for subcortical involvement:</td>
</tr>
<tr>
<td></td>
<td>• Striatum with anterior-posterior gradient</td>
</tr>
<tr>
<td></td>
<td>• Subcortical ADC hypointensity</td>
</tr>
<tr>
<td></td>
<td>Supportive for cortical involvement:</td>
</tr>
<tr>
<td></td>
<td>• Asymmetric involvement of midline neocortex or cingulate</td>
</tr>
<tr>
<td></td>
<td>2. Cortex only (&gt;3gyri)</td>
</tr>
<tr>
<td>MRI probably CJD</td>
<td>1. Unilaterale striatum or cortex ≤ 3 gyri</td>
</tr>
<tr>
<td></td>
<td>2. Bilateral striatum or posteromesial thalamus</td>
</tr>
<tr>
<td></td>
<td>3. FLAIR &gt; DWI hyperintensities</td>
</tr>
<tr>
<td>MRI probably not CJD</td>
<td>1. Only FLAIR/DWI abnormalities in limbic area, normal ADC maps</td>
</tr>
<tr>
<td></td>
<td>2. DWI hyperintensities due to artifact</td>
</tr>
<tr>
<td></td>
<td>3. FLAIR &gt; DWI hyperintensities</td>
</tr>
</tbody>
</table>

**Table 2:** Modified from P.Vitali et al. (2011) Diffusion-weighted MRI hyperintensity patterns differentiate CJD from other rapid dementias Neurology;76:1711-1719. UCSF 2011 criteria for MRI diagnosis of CJD
Imaging findings OR Procedure details

MRI is the modality of choice to image CJD. CT in the majority of cases (80%) is negative. It may show rapidly progressive atrophy and ventricular dilatation (20%).

MRI protocol can’t leave out Diffusion weighted images (DWI), Fluid attenuated inversion recovery (FLAIR) and FSE/TSE T2-wi on axial planes. A complete study could include T2 FSE/GRE on coronal plane, spectroscopy and FSE/TSE T1-wi after Gadolinium (Fig. 2 on page 9).

The best diagnostic clue is progressive T2 hyperintensity in basal ganglia, thalamus and cerebral cortex. Predominantly gray matter is involved; white matter is usually involved only in the late stages.

Specific signal alterations in the different subtypes of CJD have been identified.

- **In sporadic CJD** (Fig. 3 on page 10, Fig. 4 on page 10, Fig. 5 on page 11) bilateral high signal in the caudate and in the putamen is usually found, with an higher sensitivity of DWI rather than T2-wi or FLAIR. With respect to the clinical classification, in the Heidenhain variant, which causes visual disturbances, cortical parieto-occipital lesions are usually demonstrated. With respect to the six molecular subtypes, different MRI signal alterations may be present and, although differential diagnosis between the most common types of molecular sCJD subtypes (MM1 and MV2) is clinical, the high frequency of thalamic hyperintensity in the MV2 subtype may correctly address the Radiologist.

- **Inherited CJD** has imaging findings and neuropathology that are usually similar to the most common forms of sCJD (cortical atrophy and hyperintensities on FLAIR and DWI in the basal ganglia, in the thalamus and in the cortex).

- **Variant CJD** is characterized by "pulvinar sign", currently part of the WHO diagnostic criterie for vCJD, and the "hockey stick sign"(Fig. 6 on page 13). The former is defined as bilateral symmetrical pulvinar high signal, relative to the signal intensity of other deep grey matter nuclei and cortical grey matter, using T2WI, PDw, FLAIR and axial DWI sequences. The latter as high signal in both pulvinar and dorsomedial thalamic nuclei.

- **Infectious CJD** has MRI findings largely resembling those seen in sCJD, as the cortex and basal ganglia are mainly affected.

**DIFFERENTIAL DIAGNOSIS**
In front of MRI findings of cortical ribbon alterations and DWI hyperintensities, radiologists should take into account also other conditions such as herpes encephalitis, MELAS, epileptic status, arterial infarct and in certain cases venous infarct (Table 3 on page 13).

All these conditions differ from CJD because of their acute onset and of the swelling of the structures involved.

Moreover each of them has some typical findings that can address the differential diagnosis. In particular herpes encephalitis (Fig. 8 on page 15 a,b,c) usually involves limbic system, MELAS (Fig. 7 on page 14 a,b,c) and epileptic status (Fig. 7 on page 14 d,e,f,g) appear as focal cortical hyperintensity instead of diffuse cortical hyperintensity, generally involving pulvinar, instead of caudate or putamina. Arterial (Fig. 8 on page 15 d,e,f) and venous infarct differ from CJD because of the unilateral involvement, generally following the vascular distribution, with edema in both and hemorrhage in venous infarct.

Images for this section:

**Fig. 2:** A complete MRI protocol can’t leave out Diffusion weighted images (DWI), Fluid attenuated inversion recovery (FLAIR) and FSE/TSE T2-wi on axial planes and
could include T2 FSE/GRE on coronal plane, spectroscopy and FSE/TSE T1-wi after Gadolinium.

**Fig. 3:** 68 yo women with sCJD, with subacute onset of ataxia and dementia. FLAIR (b and e) and DWI (c and f) images show high signal in basal ganglia (° and ^) and in occipital gyri (arrows).
**Fig. 4:** 61 yo women with sCJD, with subacute onset of confusion, deterioration of consciousness with progressive progression. MRI findings typical for CJD with main cortical involvement (arrows). FLAIR (b and e) and DWI (c and f) show high signal in fronto-parietal cortex bilaterally, in right temporal cortex and in left occipital; less defined is the hyperintensity in the head of caudate bilaterally (°).
**Fig. 5:** 71 yo women with sCJD, with dementia, gait disturbance, delirium of persecution, respiratory failure. MRI findings typical for CJD with an asymmetrical involvement of basal ganglia (°and ^) where an antero-posterior gradient is evident, and of cortex (frecce). FLAIR (a,b,c) and DWI (d,e,f) images show asymmetrical hyperintensity of
fronto-temporo-parietal cortex and of basal ganglia. ADC maps (g,h,i) show low signal in basal ganglia and in the cortex.

**Fig. 6:** Modified from "R.G. Macfarlane et al.(2007) Neuroimaging findings in human prion disease. J Neurol Neurosurg Psychiatry ;78:664-670" FLAIR and DWI in a patient con vCJD demonstrate hyperintensity in the dorsomedial thalamic nuclei and pulvinar bilaterally ("hockey stick Sign")
Table 3: Radiological Differential Diagnosis of CJD.

<table>
<thead>
<tr>
<th></th>
<th>Findings in common with CJD</th>
<th>Typical findings, not in common with CJD</th>
</tr>
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<tbody>
<tr>
<td><strong>Herpes Encephalitis</strong></td>
<td></td>
<td>• Limbic System involvement</td>
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<tr>
<td><strong>Arterial infarct</strong></td>
<td>• Cortical ribbon alteration</td>
<td>• Acute onset</td>
</tr>
<tr>
<td><strong>Venous infarct</strong></td>
<td>• DWI hyperintensity</td>
<td>• Arterial vascular distribution</td>
</tr>
<tr>
<td><strong>MELAS</strong></td>
<td></td>
<td>• Unilateral</td>
</tr>
<tr>
<td><strong>Epileptic status</strong></td>
<td></td>
<td>• Hemorrhage</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Venous vascular distribution</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Unilateral</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Edema</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Focal cortical vs diffuse cortical</td>
</tr>
<tr>
<td></td>
<td></td>
<td>hyperintensity</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Pulvinar hyperintensity vs caudate and putamina</td>
</tr>
</tbody>
</table>

![MRI images](image-url)

**Table 3**: Radiological Differential Diagnosis of CJD.
Fig. 7: Radiological differential diagnosis: patient with MELAS (a,b,c) and patient with epileptic status (d,e,f,g).

Fig. 8: Radiological differential diagnosis: patient with herpes encephalitis (a,b,c) and patient with arterial infarct (d,e,f)
Conclusion

CJD is a rare pathology, heterogeneous as for clinical presentation, as for radiological findings, but could and should be suspected in front of a rapidly progressive dementia, evolving over days to weeks. Although definitive diagnosis consists of brain biopsy, currently a close collaboration among Clinicians and Radiologists, as well as the increasing experience of imaging in human prion disease, may reduce the need for the more invasive testing. Diagnostic criteria of CJD (clinical, electrophysiological and radiological) have been well defined. In particular some MRI key features have been found and have been included in the diagnostic criteria for CJD. In some sporadic types, MRI findings can address to the correct diagnosis, even in front of uncertain clinical and electrophysiological data. For this reason their knowledge must become part of the cultural baggage of any Radiologist.

References


Personal Information