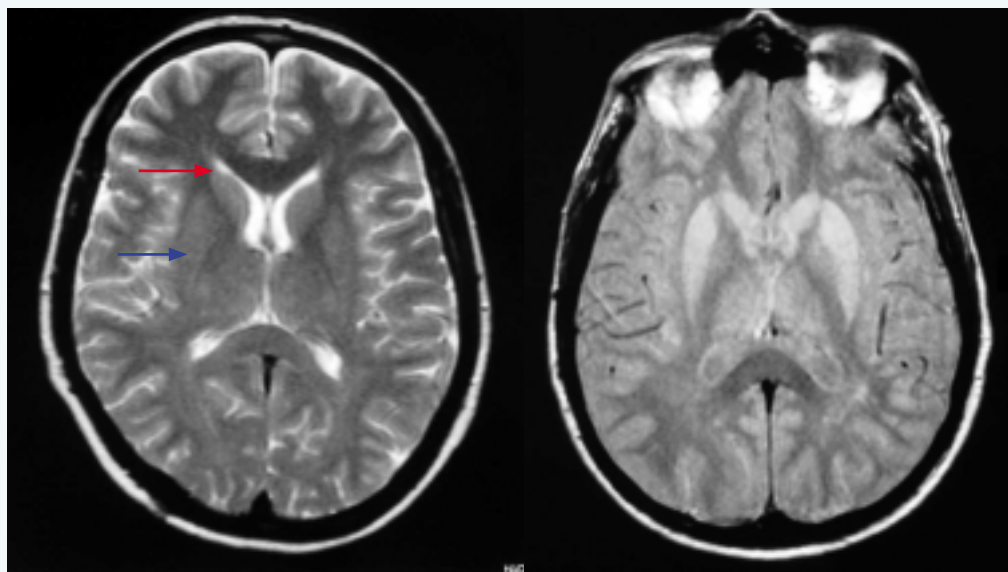


NEUROIMAGING

Figure 1 MRI of sporadic CJD.
 (a) Normal patient: the putamen (red arrow) and caudate head (blue arrow) are isointense or hypointense to cortical grey matter on T2-weighted images.
 (b) Sporadic CJD, proton density image: symmetrical marked hyperintensity is present in the putamen and caudate head. Similar changes can be seen on T2-weighted and FLAIR images.



Creutzfeldt-Jakob

Introduction

Creutzfeldt-Jakob Disease (CJD) is a rare fatal neurological disease, with four distinct forms. Sporadic CJD (sCJD) is the most common and is characterized by a rapidly progressive dementing illness, associated with EEG abnormalities and CSF protein changes (14-3-3 protein). In addition, there are characteristic magnetic resonance imaging (MRI) changes, consisting of basal ganglia (putamen and caudate head) hyperintensity. Although these abnormal appearances overlap with other diseases, their presence is diagnostically useful. In variant CJD (vCJD), the form of CJD associated with bovine spongiform encephalopathy (BSE), the pulvinar sign – a characteristic appearance of bilateral hyperintensity in the posterior nuclei of the thalamus – is highly specific for the diagnosis of variant CJD in the appropriate clinical context. This article reviews these and other MRI appearances of CJD.

Background

The transmissible spongiform encephalopathies (TSE) are a group of diseases affecting man and other animals, characterized by a fatal progressive neurological illness, characteristic neuropathological changes, and a causal agent that does not require a nucleic acid template. Creutzfeldt-Jakob disease (CJD) is the most common form in man, although other forms are recognized, including Kuru, Gerstmann-Sträussler-Scheinker disease and Fatal Familial Insomnia (all very rare). A number of forms of CJD are found in man, including sporadic CJD (sCJD, the most common form), familial CJD (very rare), iatrogenic CJD (from cadaveric hormone-related transmission or neurosurgical procedures, increasingly rare), and the recently-described variant CJD (vCJD, increasingly common) (Lowman et al. 2001). In many European and other countries, CJD is established as, or is soon to become, a notifiable disease, with most

countries having dedicated national CJD surveillance units.

An unusual feature is that the transmissible agent in CJD and other TSEs is resistant to many routine sterilization procedures, including standard autoclaving. The agent is thought to be a prion protein which catalyses the conversion of normal isomeric native prion protein (PrP^C) into the PrP^{Sc} form. Characteristic neuropathological changes are described throughout the brain, including intraneuronal vacuolation and spongiform change, neuronal loss and astrocytic proliferation, associated with deposition of PrP^{Sc} protein.

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Disease

Sporadic CJD

Sporadic CJD (sCJD) is the most common form of CJD, although it is still rare, with an incidence of 1.2 per million per annum. Most patients developing the disease are 60–75 years old, although cases in younger people (< 50 years) have been described. Clinically the disease is characterized by a rapidly progressive dementing illness, culminating in akinetic mutism. Neurological features seen during the illness reflect widespread neuronal damage, and include myoclonus, cerebellar ataxia, pyramidal and extrapyramidal signs and cortical blindness. Death ensues rapidly, usually within about 5 months of symptom onset. There is no known effective treatment.

Although histopathological confirmation was initially required to confirm the diagnosis, this is no longer necessary because disease-defining criteria have been established (World Health Organization 1998). The role of investigations in the diagnosis of CJD has been comprehensively reviewed elsewhere (Collins *et al.* 2000). The clinical diagnosis of CJD depends on identification of appropriate clinical features, supported by characteristic EEG changes (periodic triphasic sharp wave complexes, seen in two-thirds of patients) and CSF protein electrophoresis findings (raised 14-3-3 protein, sensitivity and specificity 85%–95%).

Imaging of sporadic CJD

Brain computerized tomography (CT), position emission tomography (PET) and single proton emission computerized tomography (SPECT) are either normal or nonspecific in appearance. Advanced cerebral atrophy (focal or diffuse) is a common feature on all forms of cerebral imaging.

On MRI, characteristic marked hyperintensity (relative to cortical grey matter signal intensity) of the caudate head and putamen is seen in 70–80% of cases (Fig. 1) (Finkenstaedt *et al.* 1996; Schroter *et al.* 2000). The specificity of this sign is around 90%, although this varies with the control population assessed (Schroter *et al.* 2000). The changes are usually symmetrical, but asymmetrical hyperintensity is seen in 10–20% (Fig. 2). False positive scans can occur, because

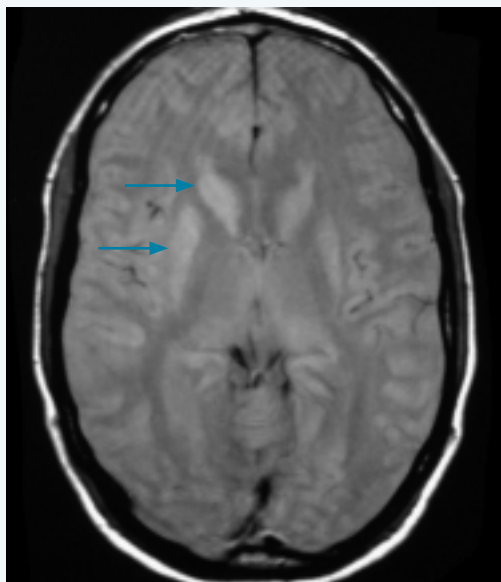


Figure 2 MRI of sporadic CJD, proton density image: asymmetrical changes are seen in 10–20% of cases, here with hyperintensity most obvious in the right putamen (long arrow) and caudate head (short arrow) compared with the left.

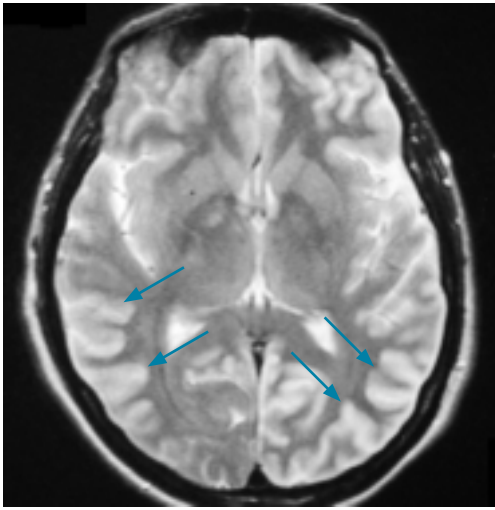


Figure 3 MRI of sporadic CJD, T2-weighted image showing cortical high signal and swelling (arrows), thought to be of an early feature.

the normal putamen is sometimes slightly higher signal than the cortical grey matter on some MRI scans, and therefore putamenal hyperintensity must be interpreted with caution for some sequences, such as proton density-weighted images.

Patchy high signal is also occasionally seen in other areas of grey matter, such as the cerebral cortex (Fig. 3), when it may mimic acute encephalitis. Other grey matter nuclei that are occasionally affected include the globus pallidus, amygdalo-hippocampal complex, peri-aqueductal grey matter, and thalamus (though in sCJD the signal intensity in the thalamus remains lower than the signal in the putamen, vide infra). Rarely, high signal in the white matter has also been described.

These basal ganglia changes have been seen with several MRI sequences, including T2-weighted images, proton density-weighted images, Fluid Attenuated Inversion Recovery (FLAIR) images and Diffusion Weighted Imaging (DWI). Several of the described abnormalities, particularly the earlier features of cortical hyperintensity, are best seen on FLAIR and DWI. The hyperintensity appears to correspond histologically with marked astrocytosis. T1-weighted imaging is invariably normal in sCJD, and contrast enhancement is not a feature of the disease.

A number of other conditions may cause bilateral high signal changes in the basal ganglia, although the clinical features and/or other imaging appearances are usually clearly distinguishable from sCJD (Table 1). Clinically, the most common differential diagnoses are Alzheimer's disease, Huntington's disease, and variant CJD.

Variant CJD

In 1996 a new clinically and neuropathologically distinct form of CJD was recognized in the UK (Will *et al.* 1996). This form is characterized by a younger age of onset (median 29 years, although a confirmed case has been identified recently in a 74-year-old-male), longer duration of disease (median 14 months), and a rather different clinical picture to CJD. At the time of writing, 120 cases of vCJD have been diagnosed, with 114 occurring in the UK.

The presenting symptoms are usually nonspecific, commonly with sensory (sensation of cold or paraesthesia) and psychiatric (withdrawal, depression, fleeting delusions) symptoms. The diagnosis is often made late because of the nonspecific nature of these initial symptoms. Other neurological features include cerebellar signs, abnormal eye movements, and involuntary movements (myoclonus, chorea, dystonia).

The histopathology of vCJD is also distinct from sCJD, with astrocytosis and neuronal loss being particularly prominent in the pulvinar of the thalamus, and with characteristic 'florrid plaques' seen in the cerebral cortex. In vCJD, the EEG and CSF 13-4-4 have a much lower sensitivity than for sCJD. Tonsillar biopsy may be useful, but is invasive and has yet to be fully validated in a large group of patients. Criteria for the *in vivo* diagnosis of probable vCJD have been defined, and include MRI features (Will *et al.* 2000).

MRI of vCJD

The thalamus is a major relay for sensory information ascending from the spinal cord and brainstem to the primary and other cortical sensory regions. The pulvinar is one of the posterior nuclei of the thalamus, and has multiple reciprocal connections with sensory cortex, particularly the visual cortex. Normally the pulvinar is significantly hypointense relative to basal ganglia and cortical grey matter (Fig. 4a).

A characteristic distribution of hyperintensity in the pulvinar of the thalamus is found in vCJD. The degree of hyperintensity is greater than that seen in the putamen or cortical grey matter, and is known as the 'pulvinar sign' of vCJD (Fig. 4b). In the largest series published to date (28 cases), this sign, which was initially described on T2-weighted and proton density-weighted images, is 80% sensitive and 100% specific in the appropriate patient group (Zeidler *et al.* 2000), and the sensitivity has increased to 90% with improvements in MRI technology. However, it is worth noting that, in the original series, the pulvinar sign was overlooked in two-thirds of cases at the original referring hospital, emphasizing the importance of vigilance for this sign in suspected cases. The pulvinar hyperintensity can be seen in most imaging planes (Fig. 5), though is best appreciated on axial scans, where the thalamus, basal ganglia and cortex can all be compared on a single slice. Attempts to quantify

Table 1 Differential diagnosis of bilateral basal ganglia high signal on MRI

Sporadic CJD
Wilson's disease
Hypoxia
Carbon monoxide poisoning
Mitochondrial disorders
Hypoglycaemia
Haemolytic uraemic syndrome
Encephalitis
Huntington's disease
Bilateral capsulostriate infarction

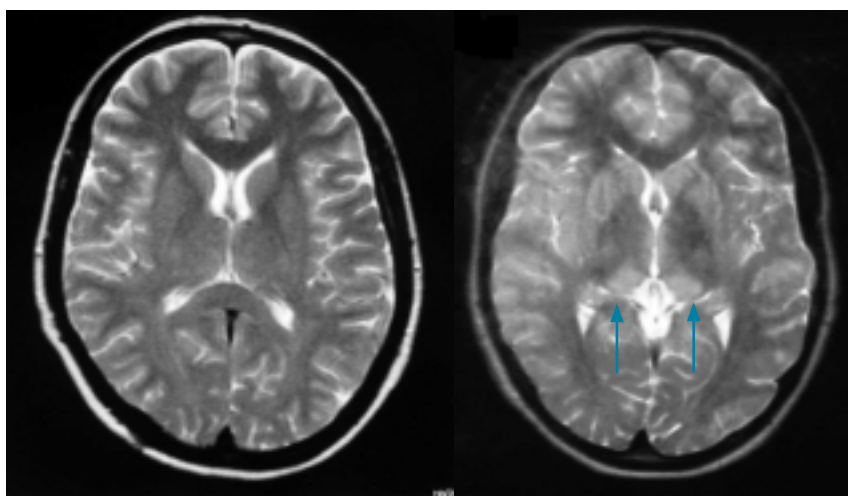


Figure 4 MRI of variant CJD: (a) Normal patient, T2 weighted image: the normal thalamus (arrows) is homogeneously hypointense relative to the putamen, caudate head and cortical grey matter. (b) 'The pulvinar sign' T2-weighted image: the signal intensity of the pulvinar (posterior thalamus) is hyperintense to the signal of other grey matter (arrows). This is a highly specific sign of vCJD and can be seen on T2-, proton density, FLAIR and DWI images.

the intensity changes are presently under assessment.

As in sCJD, FLAIR images appear to be more sensitive than T2- and proton density-weighted images, although cases with negative FLAIR imaging and positive proton density imaging have been seen. It is likely that both proton density and FLAIR imaging are required to exclude the presence of the sign (Collie *et al.* 2001).

In addition to pulvinar signal changes, hyperintensity is also seen in the dorsomedial nuclei of the thalamus in 75% of cases, giving a 'hockey stick' appearance (Fig. 6). Periaqueductal grey matter and centrum semiovale white matter

Figure 5 MRI of variant CJD, FLAIR sagittal image: on sagittal images, the anterior margin of the thalamic involvement can be seen particularly well (arrows).

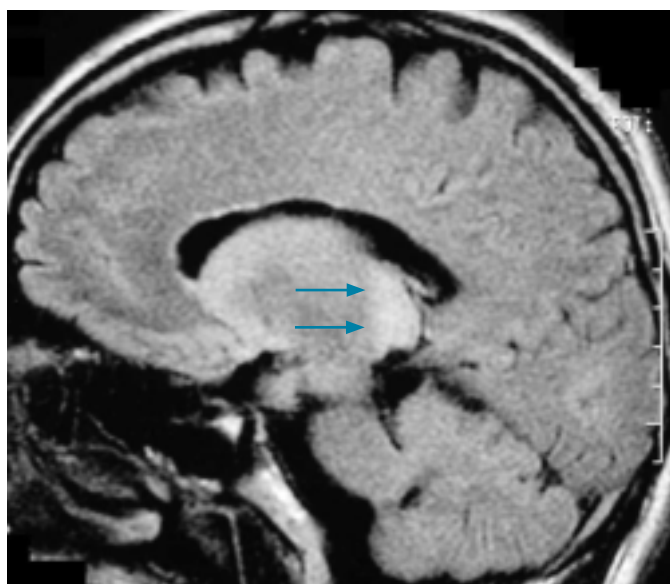


Figure 6 MRI of variant CJD, FLAIR image: the 'hockey stick' sign: hyperintensity in the dorsomedial nuclei is also a common finding, giving a characteristic configuration to the changes (arrows). These changes are often most conspicuous on FLAIR images.

Table 2 Differential diagnosis of thalamic high signal on MRI: all differ from variant CJD clinically and or affect different thalamic nuclei to vCJD

Variante CJD
Sporadic CJD
Central cerebral vein thrombosis
'Tip of the basilar' syndrome
Basilar artery dissection
Benign intracranial hypertension
Thalamic infarction
Post-infectious encephalopathy
Bithalamic glioma
Japanese encephalitis
Wernicke's encephalopathy
Transient dysaesthesia of unknown origin
Alper's syndrome
Carbon monoxide poisoning

hyperintensity has also been described. Cerebral atrophy is a relatively rare feature in vCJD, T1-weighted imaging is normal, and contrast enhancement has not been described.

Although there is a long differential diagnosis of hyperintensity in the thalamus (Table 2), the presence of high signal limited to the pulvinar of the thalamus in conditions other than vCJD is very rare, and these conditions are clinically clearly distinct.

Conclusions

Although CJD remains a rare group of diseases, it has attracted much interest, particularly because of the discovery of iatrogenic cases, and transmission through the food chain from BSE in cattle. From an imaging perspective, it is also unusual, because of the recent discovery of characteristic deep grey matter nuclei changes, which are surprisingly sensitive and specific for the disease. Further work is required to assess the sensitivity and specificity of these signs in larger groups of patients, and to assess whether the changes can be quantified in a clinically useful manner.

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