Abnormal Diffusion-Weighted Magnetic Resonance Imaging in Creutzfeldt-Jakob Disease Following Corneal Transplantations

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Background: The value of magnetic resonance imaging of the brain in the diagnosis of iatrogenic cases of Creutzfeldt-Jakob disease has been questioned.

Objective: To illustrate the value of magnetic resonance imaging of the brain in the diagnosis of iatrogenic Creutzfeldt-Jakob disease.

Methods: Case report.

Results: A patient with a history of 3 corneal transplantations exhibited the alien hand sign on initial examination. Diffusion-weighted magnetic resonance imaging of the brain revealed prominent cortical diffusion abnormalities. During the following months, the patient developed rapidly progressive dementia. The diagnosis of Creutzfeldt-Jakob disease was proven by brain biopsy.

Conclusion: Brain magnetic resonance imaging, particularly diffusion-weighted magnetic resonance imaging, can be very helpful in the diagnosis of Creutzfeldt-Jakob disease, even in suspected iatrogenic cases.

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Creutzfeldt-Jakob disease (CJD) is a rare spongiform encephalopathy clinically characterized by rapidly progressive dementia, myoclonus, ataxia, visual disturbances, pyramidal and extrapyramidal features, and an inexorable fatal outcome. Although most frequently sporadic, iatrogenic transmission of the disease has occurred in recipients of contaminated corneal grafts, cadaveric human growth hormone, and dura mater grafts. Abnormalities on diffusion-weighted magnetic resonance imaging (DWI) have been previously observed in patients with CJD, and DWI has been suggested to be useful for the early diagnosis of the disease. However, these changes have not been observed in iatrogenic cases, raising questions about potential differences between sporadic and iatrogenic CJD. We report a case of iatrogenic CJD with alien-hand syndrome at initial examination and striking signal changes on DWI after corneal transplantations.

A 56-year-old right-handed man noticed progressive loss of dexterity of his right hand. Subtle initially, this symptom worsened rapidly, rendering the hand useless for complex movements. At 2 months, his right hand started to exhibit involuntary movements that were unrecognized by the patient. On one occasion, his right hand punched his left eye to the patient's amazement, and on several occasions he was unable to find objects he was holding with his right hand. One month later, his left hand also became apraxic, and jerky movements appeared in the right arm. Around that time, the family began to observe changes in the patient's behavior and cognition. He became less talkative and withdrawn. Six months after the onset of his symptoms, the patient was admitted to another hospital. On admission, he was described to show akinetic mutism and myoclonic movements in the upper extremities. These movements were successfully controlled with valproic acid. Restricted diffusion in bilateral parieto-occipital cortices was disclosed on DWI. Cerebral vasculitis was suspected and the patient was treated with steroids and cyclophosphamide. However, continuous clinical deterioration occurred during his 5-week hospital stay, with development of sphincter incontinence and swallowing difficulties. The patient was transferred to our institution 7 months after the initial symptoms.

The patient's medical history included 3 cadaveric corneal transplantations (6, 4, and 2 years previously) in the left eye and an unclear rheumatologic condition characterized by Raynaud phenomenon and recurrent hand swelling. He also had a history of alcohol abuse but had remained abstinent for more than 25 years.
At our initial examination, he was stuporous most of the time; when he was awake he was mute and profoundly abulic. He had bilateral rigidity and hyperreflexia. His motor inactivity was occasionally interrupted by involuntary, although seemingly purposeful, movements of the right hand. Extensive blood work results were unremarkable except for positive antinuclear (titer 1:160), anti-SS-A (anti-Ro), and antiribonucleoprotein antibodies. Cerebrospinal fluid (CSF) was acellular, with a normal glucose concentration and a protein level of 120 mg/dL. Cultures were negative and there were no oligoclonal bands on electrophoresis. No paraneoplastic markers (anti-Hu, anti-Yo, anti-Ri) were present in either serum or CSF. Testing for 14-3-3 protein was not performed. Results of an electroencephalogram (EEG) performed 3 days postadmission showed continuous generalized slowing of the background rhythms.

A new brain magnetic resonance image (MRI) revealed fairly symmetric bilateral cortical hyperintensity primarily involving the parieto-occipital regions. An abnormal signal was also seen in the putamina bilaterally and in the right caudate head. These findings were best visualized on a fluid-attenuated inversion recovery (FLAIR) sequence (Figure 1A). There was no mass effect or abnormal enhancement. The DWI showed extensive areas of restricted diffusion involving most prominence the parieto-occipital regions but also both frontotemporal lobes (Figure 1B), which correlated with dark signals on the apparent diffusion coefficient map (Figure 1C). Perfusion MRI did not reveal any focal defect and the widespread diffusion abnormalities did not correspond to any vascular distribution. Proton MR spectroscopy showed a decreased peak of N-acetyl aspartate in both frontal lobes.

A brain biopsy was performed on the fourth day of the admission. A pathologic examination of the tissue sample obtained from the right frontal lobe revealed spongiform degeneration of the cortex typical of CJD.

Repeated EEG obtained nearly 2 weeks later showed bilateral independent spikes and sharp waves superimposed on a slow and disorganized background; the epileptiform activity was more prominent in the right hemisphere and was seen in association with episodic twitching of the left upper and lower extremities. No typical periodic sharp-wave complexes were seen. The patient died a few days later in a hospice, 7 months after the onset of the first symptom.

**COMMENT**

The clinical diagnosis of CJD is often difficult, especially early in the course of the disease. Symptoms and signs may vary and corroborative findings, such as the presence of periodic sharp-wave complexes on EEG or detection of the 14-3-3 protein in the CSF, but neither are fully sensitive nor always specific, as is well illustrated by our case.

Isolated myoclonic alien hand has been reported before as the sole initial clinical feature on initial examination in 2 patients with CJD. The alien hand sign is described as a feeling of estrangement between the patient and one of his or her hands. It results in involuntary, seemingly purposeful movements of the hand with the patient's denial of its ownership. Commonly associated with callosal lesions, this sign has also been documented with dominant mesial cortical injury. In fact, 2 different types of alien hand have been described, one "frontal" in the dominant hand and the other “callosal” in the nondominant hand. However, this anatomic classification and the localizing value of the sign have been questioned because alien hand has occurred in cases of corticobasal ganglionic degeneration and Alzheimer disease. Nevertheless, the damage of the mesial frontal cortex clearly seen on DWI

*Figure 1. Comparison of fluid-attenuated inversion recovery (FLAIR), diffusion-weighted magnetic resonance imaging, and apparent diffusion coefficient (ADC) map. A, Axial FLAIR image at the level of the lateral ventricles reveals cortical hyperintensity in the parieto-occipital regions bilaterally (arrows). There is some frontal involvement, but it is far less apparent. Fluid-attenuated inversion recovery parameters used were repeat time/echo time/inversion time 6000/128/2000 milliseconds. B, Diffusion-weighted images at the same level showing posterior abnormalities, which are much more striking in appearance (arrows). Bilateral involvement is better appreciated as well. C, Corresponding ADC map demonstrates cortical hypointensity in regions of diffusion abnormality (arrows), indicating restricted diffusion rather than “T2 shine-through.”*
Bilateral symmetric high signal intensities affecting the caudate nuclei and the putamina on long repetition-time MRIs have yielded a 67% sensitivity and 93% specificity for the diagnosis of CJD. However, routine MRI may be less sensitive to some cortical abnormalities visible on DWI as demonstrated by our case. The sensitivity of DWI in the diagnosis of CJD remains to be established but promises to be markedly superior to that of T2-weighted images, especially in early stages of the illness. In addition, DWI seems to be useful to monitor the progression of the disease and has been shown to correlate well with clinical findings, as it did in our case. Good correlation was also found with disturbed metabolism by nuclear medicine scans and EEGs.

The pathogenesis of restricted diffusion in brains with CJD is not yet elucidated, but it could be related to the initial accumulation of abnormal cytoplasmatic vacuoles preceding the development of spongiform degeneration and gliosis. These latter changes are thought to be responsible for the high intensity signals seen on T2-weighted and proton density–weighted MRI. Our patient had a normal result on perfusion scan despite his prominent diffusion abnormalities. This uncommon combination of findings should direct attention away from ischemia and toward other conditions, including CJD. Magnetic resonance proton spectroscopy showed a decreased peak of the neuronal marker N-acetyl aspartate in our case as it has in advanced cases of CJD in the past.

Confirmation of horizontal transmission of CJD is not possible in this case since we were unable to identify the corneal donors. However, the history of 3 different corneal transplantsations clearly increases the likelihood of iatrogenic transmission. This is particularly important because, to our knowledge, this is the first report of MR signal changes in iatrogenic CJD. Previously reported iatrogenic CJD cases had no abnormal signal on MRI. Thus, potential underlying differences between sporadic and iatrogenic CJD were suspected. The imaging abnormalities in our case are indistinguishable from those seen in sporadic CJD. Our findings are in concert with the similarities in pathologic examination observed between sporadic and iatrogenic CJD. We believe that technical issues (low-field systems, protocols not including FLAIR and DWI) may have accounted for the lack of sensitivity of MR in previous iatrogenic cases.

In summary, this case illustrates the usefulness of MR techniques, particularly FLAIR and DWI, in the diagnosis of cases of CJD with atypical clinical manifestations, even when iatrogenic transmission is suspected.

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