Abnormal Diffusion-Weighted Magnetic Resonance Images in Creutzfeldt-Jakob Disease

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Background: Traditional imaging methods, including computed tomography, routine magnetic resonance imaging (MRI), and magnetic resonance spectroscopy, have not been particularly useful in the diagnosis of Creutzfeldt-Jakob disease (CJD). Although abnormalities can be seen using these methods, the findings are evident only late in the disease or lack specificity or sensitivity.

Objective: To describe abnormalities on diffusion-weighted MRIs in 4 patients with proven CJD.

Methods: Diffusion-weighted MRIs were obtained on 4 patients with CJD as part of a routine MRI brain examination.

Results: In all 4 patients, diffusion-weighted MRIs of the brain demonstrated bilateral hyperintensity in the basal ganglia. In 1 patient, the most conspicuous abnormality seen in diffusion-weighted images was in the thalamus. Two patients also demonstrated hyperintensity in the cerebral cortex on diffusion-weighted images. Only 2 of 4 patients demonstrated clear abnormalities on routine (non–diffusion-weighted) MRIs. Diffusion abnormalities were visible in 1 patient within 1 month of symptom onset. The findings were most conspicuous and extensive in the patient with the longest duration of symptoms (7 months).

Conclusions: Diffusion-weighted MRI might provide a noninvasive method of identifying patients with CJD. However, further investigations must be performed to determine the specificity of these findings for CJD.

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RESULTS

In all 4 patients, the diffusion-weighted MRIs demonstrated homogeneous increased signal intensity bilaterally in deep gray matter structures (Figure 1 through Figure 4, left). Subjectively, in patient 1, the abnormalities seen in diffusion-weighted images were prominent and most pronounced in the caudate nuclei, with progressively less abnormality in the putamina (anterior more abnormal than posterior), globi pallidi, cingulate gyri, and thalami. In patients 2 and 3, the diffusion abnormalities were less pronounced overall than in patient 1. The greatest abnormalities in patient 2 were in the thalami, followed by the caudate heads and globi pallidi. In patient 3, definite diffusion abnormalities were identified only in the caudate head and body bilaterally.

In patient 4, the most prominent abnormality seen in diffusion-weighted im-
PATIENTS, MATERIALS, AND METHODS

PATIENT HISTORIES

Patient 1

Seven months before admission, a 61-year-old woman developed unsteady gait that became progressively worse. Four months before admission, she developed increasing problems with memory and intellectual function. Two weeks before admission, she demonstrated marked worsening of mental status, marked difficulty with memory, and slurring of speech. Also, 2 weeks before admission, she developed spontaneous myoclonic jerks and startle myoclonus. An electroencephalogram showed mild bilateral slowing. The neuron-specific enolase level in the CSF was 115 ng/mL. Results of a brain biopsy demonstrated spongiform encephalopathy consistent with CJD.

Patient 2

A 62-year-old man was first seen with memory loss that was progressive for 2 months. This was accompanied by sleepiness and jerking movements of his arms and legs. The symptoms significantly worsened during the 2 to 3 weeks before admission. The neuron-specific enolase level in the CSF was 60.8 ng/mL. No brain biopsy was performed.

Patient 3

A 53-year-old woman was first seen with a 1-month history of progressive dizziness, unsteady gait, headache, confusion, nausea, and vomiting. She became progressively confused and eventually combative, even with family members. An electroencephalogram demonstrated widespread burst suppression. Results of a brain biopsy demonstrated spongiform encephalopathy consistent with CJD. Immunohistochemical analysis for the protease-resistant form of the prion protein (PrP-res) was performed on formalin-fixed sections.

Patient 4

Two months before admission, a 64-year-old woman developed blurred vision for a few days. She also had difficulty using utensils and was bumping into things. Six weeks before admission, family members noted increasing forgetfulness. Unsteady gait progressed and myoclonus developed. Three weeks before admission she required assistance with walking. An electroencephalogram demonstrated widespread burst suppression. An immunoblot detected the 14-3-3 protein (PrP-res) was performed on formalin-fixed sections. Immunohistochemical analysis for PrP-res was performed on formalin-fixed sections from the frontal cortex and the cerebellum according to a method published previously. Analysis of the prion protein gene (PRNP) was performed using genomic DNA samples isolated from the frozen brain according to standard procedures. Potential point mutations were searched using a mutation mismatch detection kit (Ambion, Austin, Tex) as specified by the manufacturer. In addition, the genotype at codon 129 of PRNP was determined by digestion with the restriction endonuclease Nsp1.

METHODS

In all patients, MRI was performed on a 1.5-T MRI scanner (Vision; Siemens, Iselin, NJ) with echo-planar capability. Turbo fluid attenuated inversion recovery (tFLAIR), turbo spin echo (TSE) T2-weighted, and diffusion-weighted images were obtained in the axial plane. The imaging variables (echo time in milliseconds/time to repeat in milliseconds/inversion time [TI] in milliseconds/diffusion gradient strength [b] in seconds per square millimeter) were 119/9999/2309/0 for tFLAIR, 112/6956/0/0 for TSE T2-weighted, and 123/800/0/1000 for diffusion-weighted images. In 3 patients, diffusion-weighted images in the axial plane were obtained with diffusion gradients oriented in the slice select, read, and phase directions so that a diffusion trace image could be created. The trace image is the arithmetic mean of the diffusion images, obtained by various orientations of the diffusion gradient. An apparent diffusion coefficient (ADC) map was then calculated using the 2-point method with a b value of 1000 s/mm². Note that abnormally hyperintense regions on diffusion-weighted MRIs correspond to regions of low ADC values on ADC maps. In patient 3, diffusion-weighted MRI was performed in the axial plane using a diffusion gradient (b = 1200 s/mm²) in the slice select direction only. Fat saturation was used in all echo-planar images to reduce the artifacts associated with off-resonance effects.

In 3 patients with ADC maps, quantitative ADC measurements were obtained from regions of interest in the caudate head, putamen, thalamus, globus pallidus, and cingulate gyrus. In addition, ADC was also measured in the parietal, occipital, temporal, and frontal cortices in patient 4.

Control ADC values were measured in the same regions as cited above from 7 patients who underwent imaging for indications other than dementia (4 men and 3 women; mean ± SD age, 64.9 ± 14.2 years). Mean ADC values from the individual regions of interest did not significantly differ, so all regions from all control patients were combined for an overall value (mean ± SD ADC, 74 ± 12 × 10⁻⁵ mm²/s). Using a 95% confidence level based on testing single values, ADC values of 50 × 10⁻⁵ mm²/s or lower differed significantly from those of controls.
could not be produced in patient 3. The ADC values support the subjective impression described above of the locations of diffusion abnormalities. Patients 1 and 4 had 2 regions where the ADC values differed significantly ($P = .05$) from those of the control: the caudate head and putamen in patient 1 and the globus pallidus and parietal cortex in patient 4. Other regions in each patient demonstrated low ADC values that did not reach the 95% significance level. Patient 2 had several regions with low ADC values, but none of these reached the 95% significance level. The ADC maps were quantitatively correct for coincidental $T_2$ signal abnormalities that might be present on the diffusion-weighted image. The differences in relative abnormality in various regions between the ADC values and the diffusion-weighted image most likely reflect the varying degrees of $T_2$ prolongation in the regions.

In patient 1, the $T_2$-weighted tFLAIR and TSE images demonstrated abnormal hyperintensity in the caudate nuclei and possibly the putamina (Figure 1, right). The $T_2$ signal abnormalities were more conspicuous on
the T2-weighted tFLAIR images than on the TSE T2-weighted images. However, the T2 signal abnormalities were less conspicuous than the diffusion abnormalities. In patients 2 and 3, abnormal T2 signal hyperintensity was present in the caudate nuclei, otherwise no T2 signal abnormalities were visible in the globi pallidi, putamina, thalami, or cortex on either the TSE T2-weighted or the T2-weighted tFLAIR images (Figures 2 and 3, right). Only subtle T2 signal abnormality was visible in the cerebral cortex of patient 4 on the T2-weighted tFLAIR images, in a distribution similar to the abnormality seen in diffusion-weighted images. No T2 signal hyperintensity was identified in the cerebral cortex or deep gray matter structures of patient 4 on the TSE T2-weighted images (Figure 4, right).

T2-weighted images obtained before and after gadodiamide (0.1 mmol/kg intravenously; Omniscan, Nycomed, Princeton, NJ) administration in all 4 patients were unremarkable except for mild diffuse atrophy commensurate with the patients’ ages.

Histological or biochemical analysis of brain tissue samples from patients 3 and 4 revealed changes consis-
Creutzfeldt-Jakob disease is a rare neurodegenerative disorder characterized, in most patients, by rapidly progressive dementia, myoclonus, and ataxia. It is usually fatal within 1 year of the onset of symptoms. Creutzfeldt-Jakob disease is one of several transmissible or hereditary spongiform encephalopathies, which include kuru, Gerstmann-Sträussler syndrome and familial fatal insomnia in humans. It is pathogenetically linked to the intracerebral accumulation of an abnormal PrP-res. Worldwide prevalence of the disease is about 0.25 to 2.00 per million per year. The average age of symptom onset is about 65 years.

Recently, a new variant form of CJD was reported in Great Britain. New variant CJD differs from typical sporadic CJD, particularly in its younger age of onset (some patients have been in their teens), the frequency of certain clinical findings such as psychiatric or sensory symptoms at onset, and the presence of PrP-positive amyloid plaques with unique morphologic findings on histopathologic examination.

Clinical diagnosis of CJD is often difficult. Results of routine CSF analysis are often normal or demonstrate mildly elevated total protein levels. An abnormally high concentration of CSF neuron-specific enolase is reported to be useful in differentiating CJD from other demending illnesses. Also, the immunoassay detection of 14-3-3 protein in CSF is reported to be highly sensitive and specific for CJD, although not yet diagnostic without histopathologic confirmation. Electroencephalograms characteristically demonstrate pseudoperiodic sharp-wave complexes in CJD, but this finding is absent in about 20% to 40% of patients with sporadic or familial CJD and in all patients with the new variant CJD.

Confirmatory diagnosis of CJD or other prion diseases still relies on results of brain biopsy or autopsy with histological or biochemical examination. Histologically, the primary feature of CJD is spongiform degeneration of the gray matter, characterized by individual and clustered vacuoles in the neuropil or within neuronal and glial elements. The demonstration of PrP-res in brain tissue by immunohistochemical analysis or with the more sensitive Western blot immunodetection represents the most specific (100%) and sensitive test for the diagnosis of CJD that is available to date.

There have been numerous reports of abnormal findings in patients with CJD on routine (non–diffusion-weighted) MRIs. Examination by MRI sometimes demonstrates an abnormally high signal on T2-weighted images in the basal ganglia, including the caudate nuclei, putamina, and globi pallidi. Although these findings are nonspecific, together with the clinical history they can help establish a diagnosis of probable CJD. Many patients with CJD do not demonstrate abnormalities on T2-weighted images. It was observed in a single patient with CJD that cortical signal abnormalities were more visible on tFLAIR images than on TSE T2-weighted images. In a hamster model of spongiform encephalitis, it was demonstrated that the hyperintensity seen in T2-weighted images corresponds to areas of glio-
The findings seen in T2-weighted and diffusion-weighted images were most pronounced in patient 1. This patient underwent imaging 7 months after the onset of symptoms compared with 2, 1, and 2 months after onset for patients 2, 3, and 4, respectively. Therefore, imaging findings may be visible 1 month after onset of symptoms, and these findings might become more extensive and conspicuous with time.

In patient 4, the T2 signal abnormalities were much more subtle than the diffusion abnormalities. However, in this patient, only TSE T2-weighted images were obtained. T2-weighted tFLAIR images might have been more sensitive than TSE T2-weighted images for demonstrating the subtle gray matter T2 signal abnormalities in these patients.

Also in patient 4, type 1 PrP-Res and methionine homozygosity at codon 129 were confirmed, demonstrating that this patient had the myoclonic variant of CJD. The distribution of diffusion abnormalities in patient 4 largely paralleled the expected distribution of histological abnormalities in the myoclonic variant of CJD: with the greatest involvement in the neocortex, most prominent in the occipital lobes, with the basal ganglia involved to a lesser extent.

Histological and immunohistological findings in patient 3 were also consistent with the myoclonic variant of CJD. An ADC map could not be produced in this patient. However, the diffusion signal abnormality appeared most severe in the caudate nuclei. This patient had the shortest duration of symptoms before scanning (1 month). It is possible that the early signal abnormalities of CJD are best seen in the caudate nuclei. Alternatively, an ADC map might have demonstrated cortical abnormalities similar to those seen in patient 4.

If a unique imaging feature is identified for each of the different CJD variants, imaging could be used to determine the specific CJD variant of patients. This information is clinically relevant because of the different natural histories of the disease in patients with distinct variants of CJD.

Diffusion-weighted images are a routine part of our brain MRI examination. Diffusion images have been produced for at least several hundred patients, including all pathologic patients seen in a busy tertiary referral center. Diffusion abnormalities in the basal ganglia and thalami, with the appearance such as those reported here, have not been identified in any patients except these 4 patients with CJD. Although anecdotal, this suggests that these findings are specific for CJD. A masked prospective investigation of the specificity of diffusion imaging in patients who present with possible CJD would be interesting and useful.

No patients with known CJD have been examined by us using diffusion-weighted imaging who have not been found to have abnormal hyperintensity in the basal ganglia. However, sensitivity of diffusion-weighted MRI for CJD cannot be accurately assessed with such a small number of patients.

The ADC maps demonstrate decreased diffusion in the same distribution as the abnormal hyperintensity seen on the diffusion trace images, but in addition, the ADC maps also supply a quantitative measure of the degree of diffusion abnormality in these regions (Tables 1 and 2). The ADC measurements in patients 1 and 4 demonstrated significantly decreased ADC values in 2 regions (Tables 1 and 2). Patient 2 had low values of ADC in many regions, but none of these reached the 95% significance level.

The abnormalities seen on the diffusion-weighted images are more striking than might be suggested by the ADC values because of the synergistic effect of abnormalities of T2 and ADC on the diffusion-weighted images. The signal seen in the diffusion-weighted images is proportional to the product of the original T2 signal and the fraction of the signal remaining after the diffusion gradient has been applied. The ADC is inversely related to this fractional residual signal (a low value of ADC would be associated with a high fractional residual signal). Therefore, when there is coincidental T2 prolongation (bright on T2-weighted images) and restricted diffusion (low ADC) there is a “positive reinforcement” of the observed intensity on a diffusion-weighted image. This results in a brighter signal (relative to the rest of the image) than would be seen on a T2-weighted image. In other words, the contrast between the lesion and healthy tissue is increased. The term “T2 shine-through” would not describe this effect because it more accurately refers to a situation in which the ADC value is normal or increased but, because of a coincidental long T2, the region nonetheless appears bright on diffusion-weighted images. Because of the synergistic effect of prolonged T2 and decreased ADC, the findings of CJD are expected to be more conspicuous on a diffusion-weighted image than on either a T2-weighted image or an ADC map. The findings in these 4 patients support the use of diffusion-weighted images in the diagnosis of CJD.

The pathophysiological basis of restricted diffusion seen in these patients with CJD is unknown. However, because the area of diffusion abnormality is larger than that of the T2 signal abnormality, the observed restricted diffusion might be related to an accumulation of abnormal vacuoles in the cytoplasm. A coalescence of these vacuoles leads to spongiform degeneration and precedes the development of gliosis.

The clinical use of diffusion imaging for the diagnosis of CJD must be confirmed with additional pa-
tients. If confirmed, studies of a temporal relationship between the onset of dementia and the appearance of a diffusion abnormality would be appropriate.

Abnormalities on diffusion-weighted MRIs are herein reported in 4 patients with proven CJD. If these findings are confirmed by additional studies, diffusion-weighted MRI may be useful in the evaluation of patients with suspected CJD. In addition, further investigations must be performed to determine the specificity of these findings for CJD.

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