Diffusion-Weighted Magnetic Resonance Imaging in Probable Creutzfeldt-Jakob Disease

A Clinical-Anatomic Correlation

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Background: Creutzfeldt-Jakob disease (CJD) is a rare transmissible disease that typically causes a rapidly progressive dementia and leads to death in less than 1 year. Although a few anecdotal reports suggest that diffusion-weighted magnetic resonance imaging may help substantiate premortem diagnosis of CJD, detailed correlation between radiographic data and clinical, electrophysiologic, and metabolic parameters is not available.

Methods: Signal abnormalities on diffusion-weighted images in 3 consecutive patients with probable CJD were correlated with psychometric features, electroencephalographic findings, and functional images with either positron emission tomography or single photon emission computed tomography.

Results: Focality of abnormalities on diffusion-weighted image, not apparent on routine magnetic resonance images, correlated closely with clinical manifestations of CJD. The topographic distribution of signal abnormality on diffusion-weighted image corresponded with abnormal metabolism or perfusion on positron emission and single photon emission computed tomographic scans. In 2 cases, the laterality of diffusion abnormalities correlated with periodic sharp wave activity on electroencephalograms.

Conclusion: These findings extend previous observations that suggested a diagnostic and localizing utility of diffusion-weighted imaging in CJD.

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REPORT OF CASES

CASE 1

A 68-year-old, previously healthy woman with 6 years of formal education was evaluated for visual disturbance that progressed for 1 month. She initially reported that objects a few meters away appeared as if they were just in front of her eyes. On one occasion, she even mentioned that the sign on a building several blocks away looked close enough to touch. During the following weeks, her visual dysfunction progressed rapidly to the point that she had difficulty finding the bathroom in her house; she walked as if she were blind, using tactile cues to guide ambulation. The patient also showed difficulty reaching for objects under visual

CREUTZFELDT-JAKOB disease (CJD) is a rare transmissible disease that causes rapidly progressive dementia associated with cerebellar ataxia, myoclonic movements, and both pyramidal and extrapyramidal findings. Abnormalities detected on brain magnetic resonance images (MRIs) in patients with CJD include increased signal in the striatum or thalamus on T2-weighted images, diffuse cortical atrophy, and periventricular white matter lesions.1-7 Despite clinical and pathologic evidence of cortical involvement in CJD,8 conventional MRIs rarely demonstrate cortical abnormalities other than diffuse atrophy. We recently observed 3 patients with clinical findings consistent with probable CJD. Their diffusion-weighted MRIs showed asymmetric high signals in cortical areas or caudate nucleus. A few prior case reports on diffusion-weighted imaging in CJD provided minimal clinical-anatomic correlation.9,10 The present report correlates abnormalities on diffusion-weighted image with clinical features, abnormalities on 18F-fluorodeoxyglucose–positron emission tomography (PET) or single photon emission computed tomography (SPECT), and periodic sharp wave activity on electroencephalography (EEG).
PATIENTS AND METHODS

PATIENTS

The cases described herein met criteria for probable CJD, including rapidly progressive dementia of less than 1 year, ataxia, and myoclonus, with periodic sharp wave complexes on EEG. A semistructured neuropsychological test was attempted in all patients but was individualized depending on the patient’s performance. The testing was designed to screen attention, language and related functions, visuoconstructive ability, memory, and frontal executive function. The presenting symptoms and neurologic and neuropsychological findings are summarized in the Table.

IMAGING TECHNIQUES

Fast fluid attenuated inversion recovery (FLAIR) images, T1- and T2-weighted images, and diffusion-weighted images were obtained using a 1.5-T MRI scanner (Signa; GE Medical Systems, Milwaukee, Wis). The diffusion-weighted images were acquired using a multislice, single-shot, spin echo, echo planar sequence with a repetition time of 6500 milliseconds and an echo time of 96.8 milliseconds. Diffusion-weighted imaging was performed with a 128 × 128 matrix, a 28 × 28-cm field of view, a section thickness of 5 mm, an intersection space of 2 mm, and a diffusion gradient strength of 2 b values (0 and 900 s/mm²). Isotropic diffusion images were obtained in the axial plane, with diffusion gradients applied along 3 orthogonal directions (x-, y-, and z-axes). In all patients, apparent diffusion coefficient (ADC) values were calculated at 3 different cortical regions of diffusion abnormality according to the Stejskal and Tanner formula.

In cases 1 and 3, PET images were obtained 30 minutes after intravenous injection of 370 MBq (10 mCi) of 18F-fluorodeoxyglucose using a PET scanner (Advance PET scanner, GE Medical Systems). The scanner’s in-plane resolution was 4.9 mm, and the axial resolution was 3.9 mm full width at half maximum. Patients fasted for at least 4 hours before acquisition of PET images. The PET images were reconstructed parallel to the canthomeatal plane using a Hanning filter (cutoff frequency, 4.5 mm) and displayed in a 128 × 128 matrix (pixel size, 1.95 × 1.95 mm with a slice thickness of 4.25 mm). Attenuation correction was performed with a standard calculated method using a series of ellipses. In case 2, SPECT images were acquired using a triple-headed rotating scintillation camera (Prism 3000XP; Picker International, Cleveland, Ohio) equipped with fan-beam collimators. The patient received 1110 MBq (30 mCi) of technetium Tc 99m ethylcysteinate dimer intravenously as a bolus. Data acquisition began 60 minutes after tracer administration and lasted 20 minutes. Axial sections of 3.5-mm thickness were reconstructed parallel to the canthomeatal plane by filtered back projection in a 128 × 128 matrix using a Metz filter (filter parameter X = 3.15). Attenuation correction (the Chang method) was then performed using a uniform attenuation coefficient of 0.11 cm⁻¹. Both PET and SPECT scans were acquired at rest in low ambient light and noise. The time interval between MRI and PET or SPECT imaging was 3 days in case 1, 4 days in case 2, and 1 day in case 3.

The results of blood studies, including chemistry, syphilis serology, serum ammonia, human immunodeficiency virus serology, and thyroid function test, were unrevealing. Peripheral tumor markers were negative, as were chest radiographs and abdominal ultrasonography. Examination of cerebrospinal fluid (CSF) revealed no abnormalities. An EEG performed during admission showed generalized slowing, more marked in the right hemisphere, and periodic sharp wave complexes maximal in frontal areas bilaterally. At discharge 8 weeks after onset, she could not walk unassisted and was nearly mute. Myoclonus had spread to the neck muscles. She developed high fever and died of pneumonia 2 weeks after discharge.

CASE 2

A 51-year-old, previously healthy man, a university graduate, was referred to our hospital because of a rapidly progressive dementia. Other than a 15 pack-year smoking history, his medical history was unremarkable. About 6 weeks before evaluation, he complained of dizziness, nausea, and vague neck discomfort. Within 2 weeks, he developed visual illusions in which the city streets appeared vertically oriented and flat surfaces such as roads looked uneven. During the next week, the patient mentioned that streets appeared unusually narrow, and he began to show difficulty finding his way around familiar places. One week before admission, he developed
memory disturbance, poor impulse control, and unsteady gait. The patient became unable to recognize faces of family members and suffered visual hallucinations, insomnia, and agitation.

His score on the Korean version of the Mini-Mental State Examination indicated severe dementia (8/30). He was oriented poorly to time and place, could not perform serial subtraction, and failed to recall any words after a brief delay. His responses to interview were delayed, and he showed frequent word-finding pauses in conversation. Severe dementia and poor cooperation precluded more detailed neuropsychological examination.

Cranial nerve examination findings were unrevealing. The results of motor examination were remarkable only for dystonia in the left hand superimposed on continuous myoclonic movements. Reflexes were hyporeactive with flexor plantar responses. His gait was broad based and ataxic.

The patient was screened with the same blood tests performed in case 1, and all findings were within normal limits. The EEG performed on admission showed periodic sharp wave complexes that were maximal in the right frontal area (Figure 1, top). His condition continued to deteriorate, resulting in a bedridden, mute state with generalized myoclonus by 8 weeks after onset. A follow-up EEG 2 weeks later demonstrated generalized triphasic sharp wave complexes with a period of about 1 second.

CASE 3

A 71-year-old farmer with 6 years of education had been in good health until 1 month before admission when he developed memory dysfunction. Word-finding difficulty appeared 2 weeks later. The results of the initial neurologic examination were unrevealing except for grasp response present on the right hand.

Language assessment using the Western Aphasia Battery revealed dysfluent speech with perseveration (fluency 5/10, information content 3/10), impaired comprehension (1.75/10), and relatively preserved repetition (7.9/10). He correctly identified 16 of 60 items on the Korean version of the Boston Naming Test (less than the first percentile). Further testing disclosed Gerstmann syndrome (agraphia, acalculia, and right-left disorientation without finger agnosia), ideomotor apraxia, constructional apraxia (Rey-Osterrieth Complex Figure copy 6/36, less than the first percentile), and perseveration on Luria loop and graphomotor sequences. Performance on the Hopkins Verbal Learning Test was also very poor (less than the first percentile), although performance may have been hindered by aphasia. However, the patient retained social graces and insight despite his neurologic deficits. At discharge 2 weeks later, he demonstrated markedly decreased verbal output, dystonia, and myoclonus confined to the right hand and unsteady gait.

The results of routine blood tests, tumor markers, abdominal sonography, and CSF studies were normal. His EEG showed asymmetric periodic sharp wave complexes with left hemisphere predominance and occasional spikes with left frontal or bifrontal maxima (Figure 1, bottom). Abnormalities involved the right hemisphere on repeated EEG 2 weeks later. For 4 weeks after discharge, his condition progressed swiftly to a veg-
etative state, including myoclonus in both arms and trunk. He died at home 10 weeks after onset.

**RESULTS**

The FLAIR and T₁- and T₂-weighted MRIs performed on admission revealed no abnormalities in case 1. In contrast, the diffusion-weighted image disclosed increased signal in both temporoparietal areas, more marked on the right, and the right frontal lobe and caudate nucleus (Figure 2, top). The results of repeated diffusion-weighted imaging 4 weeks later remained unchanged. The PET scan showed hypometabolism in areas corresponding to abnormalities detected on diffusion-weighted image (Figure 2, bottom).

In case 2, the diffusion-weighted image after 6 weeks revealed increased signal in the right frontal and temporoparietal areas (Figure 3, top). Although no abnormalities were detected in FLAIR images initially, retrospective examination disclosed subtle hyperintense signal in the same areas. The T₁- and T₂-weighted images failed to reveal changes observed in the diffusion-weighted images and FLAIR sequences. The cerebral SPECT scan showed areas of decreased perfusion that corresponded with high signal regions observed on diffusion-weighted images (Figure 3, bottom).

At 4 weeks after onset of symptoms, the diffusion-weighted image for case 3 showed increased signal mainly in the dorsolateral frontal region, temporoparietal area, insular cortex, cingulate gyrus, and caudate nucleus of the left hemisphere. Less prominent increased signal also involved the right insular cortex and frontal operculum (Figure 4, top). The patient’s PET scan demonstrated hypometabolic areas of similar topography, with an additional lesion located in the right parietal lobe (Figure 4, bottom).

In all patients, the ADC values of cortical regions with diffusion abnormality ranged from 0.34 to 0.40 \( \times 10^{-3} \text{mm}^2/\text{s} \). These values fall well under the mean ADC of normal gray matter reported in previous studies.¹⁹,²⁰

**COMMENT**

Although brain tissue from our patients was not available for pathologic examination, all our patients manifested a rapidly progressive dementia associated with myoclonic movements and ataxia. The presence of periodic sharp waves on EEG further bolsters the clinical diagnosis of probable CJD.²¹ The differential diagnosis of this particular clinical and electrophysiologic constellation includes herpes simplex encephalitis, limbic encephalitis, hepatic encephalopathy, and progressive multifocal leukoencephalopathy. However, the absence of fever or inflammatory cells in the CSF makes herpes encephalitis less plausible. Paraneoplastic limbic encephalitis also seems insupportable, since it frequently produces CSF pleocytosis and infrequently causes prominent ataxia or myoclonus. Furthermore, we found no evidence of malignant neoplasms in our patients. Lastly, there was no indication of either hepatic dysfunction or immunodeficiency, and MRI findings were not suggestive of either hepatic encephalopathy or progressive multifocal leukoencephalopathy.
Figure 3. Case 2. Diffusion-weighted magnetic resonance (top) and corresponding single photon emission computed tomographic (bottom) axial images performed 6 weeks after onset showing abnormalities in right frontal and temporoparietal areas.

Figure 4. Case 3. Diffusion-weighted magnetic resonance (top) and corresponding positron emission computed tomographic (bottom) axial images performed 4 weeks after onset showing abnormalities in the left frontal, temporoparietal lobe, insular cortex, cingulate gyrus, caudate nucleus, and possibly right insular cortex and frontal operculum.
Despite abundant clinical and pathologic evidence of cortical damage in CJD, routine MRI protocols often fail to identify corresponding abnormalities. Most often, MRI can find only generalized atrophy. Fluid attenuation sequences may increase the yield of MRI in detecting cortical abnormalities. 1-10,22-24 Adjacent CSF signal may obscure abnormalities on conventional MRIs that are suppressed with FLAIR.

In contrast, diffusion-weighted imaging performed shortly after onset of probable CJD revealed multifocal regions of increased cortical signal intensity. Increased signal on diffusion-weighted image results from restricted diffusion of water molecules and occurs in areas of acute ischemic injury. 25-28 Stroke seems an improbable cause for the radiographic findings described herein, however, since the patients were without stroke risk factors or embolic sources. Moreover, symptoms evolved over several weeks, and the distribution of signal abnormality did not coincide with specific vascular territories.

Bahn et al 9 presented the first experience with diffusion-weighted imaging in a patient with CJD. Their patient's diffusion-weighted image demonstrated bilateral symmetric high signal in the basal ganglia, thalami, cingulate gyri, and right inferior frontal cortex. More recently, Demaerel et al 10,11 measured ADC values in 2 patients with biopsy-confirmed CJD in whom diffusion-weighted images suggested diffuse abnormality of cortex and basal ganglia. Our patients with probable CJD likewise showed diffusion abnormalities that were asymmetric and located mainly in the cortex with relatively minimal involvement of subcortical gray matter.

The present report extends the earlier findings through correlation of diffusion-weighted image data with clinical features, EEG findings, and the results of metabolic imaging. Early in the illness, the localization implicated by the elemental neurologic examination and mental status testing roughly matched the distribution of increased signal in diffusion-weighted images. Similarly, areas of abnormal signal on diffusion-weighted image corresponded closely with regions of decreased glucose utilization on PET scans or reduced perfusion on SPECT scans. The laterality of periodic sharp wave discharges on EEG also coincided with the topography of diffusion abnormalities in 2 of 3 patients.

The paucity of detailed clinical-anatomic correlation in patients with CJD may result from rapid progression to profound impairment by the time diagnosis is clearly established. Our patients were assessed relatively early in their disease, and, as reported in other studies, 27-30 they all presented with asymmetric clinical features. In patient 1, the initial examination was consistent with biparietal injury, resulting in Balint syndrome, Gerstmann syndrome, constructional apraxia, and ideomotor apraxia. The patient’s left hemispatial neglect, left pronator drift, and left arm rigidity and myoclonus indicated more widespread damage within the right hemisphere. The diffusion-weighted image in patient 1 showed abnormal signal in the temporoparietal regions bilaterally and in the right frontal lobe and caudate nucleus. The severe dementia and poor cooperation in patient 2 precluded detailed behavioral testing. However, the laterality of dystonia and myoclonus in the left hand matched the predominant abnormality in the right hemisphere on diffusion-weighted images. Patient 3 experienced aphasia out of proportion to other cognitive deficits, in addition to a grasp response and involuntary movements of the right hand, all of which indicate left hemisphere dysfunction. The diffusion-weighted image confirmed diffusion abnormalities located predominantly in the left hemisphere.

A distinctive, early symptom in patients 1 and 2 was metamorphopsia, including both macropsia and micropsia. Previous reports assert that persistent metamorphopsia most often follows temporoparietal injuries, with right posterior lesions more often associated than left. 31,32 The present observations accord with these reports, since both patients 1 and 2 demonstrated bilateral temporoparietal right hemisphere predominance on both diffusion-weighted images and PET scans.

The ADC values in patients with CJD and diffusion abnormalities are variable. Bahn et al 9 reported a reduction of ADC values more than 50% of normal in basal ganglia. Demaerel et al 10 measured ADC values in 2 patients that were normal or above the mean ADC value of normal gray matter; 1 of the patients had high signal abnormalities on T2-weighted image, a result suggesting possible T2 shine-through effect. In agreement with the report by Bahn and associates, 9 our findings indicate the presence of restricted diffusion rather than T2 shine-through, not only because ADC values in our patients were much lower than those of normal gray matter but also because there were no corresponding signal abnormalities on T2-weighted images.

The physicochemical basis for diffusion abnormalities in CJD remains unclear. Microscopic examination of brain regions with high signal on T2-weighted or diffusion-weighted image disclosed vacuolization of the neuronal characteristic of spongiform encephalopathy 22,23 or astrogliosis. 11 Thus, abnormalities on diffusion-weighted image may reflect reduced diffusion of water molecules due to compartmentalization within vacuoles. Alternatively, deposition of b-pleated sheet conformation of the prion protein may somehow restrict the free diffusion of water.

In conclusion, abnormalities on diffusion-weighted image correlated with clinical findings and disturbed metabolism by PET and SPECT scans and neurophysiologic findings by EEG. The findings of diffusion-weighted image may enhance premortem diagnostic accuracy in CJD. Furthermore, abnormal signal may help improve yield of stereotaxic biopsy by guiding the surgeon to foci of maximum pathologic significance. Lastly, diffusion-weighted imaging might provide an index of response to novel treatments for prion disease as they are developed.

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