Diffusion-weighted MR Imaging of Early-Stage Creutzfeldt-Jakob Disease: Typical and Atypical Manifestations

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Creutzfeldt-Jakob disease causes progressive dementia and, eventually, death. The infectious agent is thought to be proteinaceous scrapie particles. Prompt diagnosis is essential to prevent human-to-human transmission. Progressive brain atrophy and areas of high signal intensity in the cerebral cortex and basal ganglia are well-known features of Creutzfeldt-Jakob disease depicted on T2-weighted magnetic resonance (MR) images. However, in the early stage of disease, the appearance of the brain on T2-weighted MR images often is normal, and it may be impossible on that basis to reach a diagnosis. Diffusion-weighted imaging therefore has gained attention as a useful modality for the early diagnosis of Creutzfeldt-Jakob disease. Even before the appearance of the characteristic periodic synchronous discharges on the electroencephalogram, diffusion-weighted images in most cases of Creutzfeldt-Jakob disease depict areas of abnormal signal hyperintensity in the cortex and in the basal ganglia or thalamus. These imaging abnormalities are accompanied by decreased apparent diffusion coefficient values suggestive of restricted diffusion within the tissue. However, if diffusion-weighted imaging findings of abnormal high signal intensity are restricted to the cerebral cortex, it may be necessary to differentiate between Creutzfeldt-Jakob disease and other conditions that may produce progressive dementia (eg, venous hypertensive encephalopathy; chronic herpes encephalitis; and the syndrome of mitochondrial myopathy, encephalopathy, lactic acidosis, and strokelike episodes).

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Abbreviations: ADC = apparent diffusion coefficient, ECD = ethyl cysteinate dimer, EEG = electroencephalogram, FLAIR = fluid-attenuated inversion recovery, MELAS = mitochondrial myopathy, encephalopathy, lactic acidosis, and strokelike episodes, WHO = World Health Organization

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Introduction
Creutzfeldt-Jakob disease and other transmissible spongiform encephalopathies (also known as prion diseases) are characterized by progressive dementia, other neurologic abnormalities, and, eventually, death. Creutzfeldt-Jakob disease leads to spongiform degeneration of the brain, which is thought to be caused by the conversion of normal prion protein to proteinaceous infectious scrapie particles that accumulate in and around neurons and lead to cell death (1). Until recently, it was difficult to establish a diagnosis of early-stage Creutzfeldt-Jakob disease on the basis of neuroradiologic examinations alone (2,3). Recently, however, several reports have suggested that diffusion-weighted imaging can depict brain lesions in the early stage of the disease. Some investigators have asserted that the diffusion-weighted imaging features in early-stage Creutzfeldt-Jakob disease are characteristic and that diffusion-weighted imaging therefore is useful for the diagnosis of Creutzfeldt-Jakob disease before the onset of brain atrophy or observation of abnormal signal intensity on T2-weighted MR images (4–15). In this article, we demonstrate the clinical usefulness and pitfalls of diffusion-weighted imaging of early-stage Creutzfeldt-Jakob disease. Emphasis is placed on the possibility of achieving differential diagnosis by observing the distribution pattern of areas of abnormal high signal intensity on diffusion-weighted images.

Clinical Features
Human prion diseases include sporadic Creutzfeldt-Jakob disease, sporadic fatal insomnia, familial Creutzfeldt-Jakob disease, Gerstmann-Straussler-Sheinker disease, fatal insomnia, iatrogenic Creutzfeldt-Jakob disease, new-variant Creutzfeldt-Jakob disease, and kuru. The worldwide prevalence of Creutzfeldt-Jakob disease is approximately one person in 1 million, and its annual incidence is one person in 2 million. The disease affects a slightly greater number of women than of men. Approximately 90% of cases of human prion disease are classified as sporadic Creutzfeldt-Jakob disease with an unknown origin or source of infection. Hereditary disease accounts for another 10% of cases of human prion disease, and most of the remaining cases are represented by Gerstmann-Straussler-Sheinker disease (16). The possible causes of iatrogenic Creutzfeldt-Jakob disease include corneal transplantation (17); ingestion of prion–contaminated human growth hormone (18); and transplantation of cadaveric dura mater, which was common in Japan during the 1980s. The latter caused iatrogenic Creutzfeldt-Jakob disease in 97 patients before 2003 (19). The emergence of a new variant of Creutzfeldt-Jakob disease, mainly in western Europe, was reported recently. The new variant has many similarities to bovine spongiform encephalopathy and is thought to be transmitted from cattle to humans (20–22). Kuru, a prion disease first discovered after World War II among the aboriginal Fore people of New Guinea, is transmitted as a result of ritualistic oral ingestion of all body parts, including the brain. The incidence of kuru declined markedly with the end of cannibalism (23).

The clinical manifestations of Creutzfeldt-Jakob disease differ according to the stage of disease. At onset, most patients experience nonspecific symptoms that may include generalized fatigue, character disorganization, visual disturbances, depression, and insomnia. Rapidly progressive mental deterioration with dementia, the most characteristic clinical finding, begins within a few weeks after onset. As the disease progresses, pyramidal and extrapyramidal symptoms develop, with the appearance of periodic synchronous discharges on the electroencephalogram (EEG) and of myoclonus, both of which are characteristic features of Creutzfeldt-Jakob disease. A few months later, the akinetic mutism stage begins. Patients typically die of a respiratory tract infection within 1 year of the disease onset (24).

Diagnostic Dilemma and the Importance of Early Diagnosis
In Creutzfeldt-Jakob disease, periodic synchronous discharges on the EEG are a characteristic clinical finding. However, periodic synchronous discharges usually are observed only in the later stages of the disease and sometimes are not manifested at all during the entire course of the disease. The immunoassay for cerebrospinal fluid protein 14-3-3, an important biochemical marker of Creutzfeldt-Jakob disease, also is a useful diagnostic test. However, this protein may be present in other central nervous system disorders, and its presence is not pathognomonic of Creutzfeldt-Jakob disease (25). Histopathologic confirmation is required for a definitive diagnosis. Brain biopsy, a highly accurate method of diagnosis, therefore may be necessary; however, false-negative results sometimes are obtained because the samples were collected from an unaffected area. In addition, brain biopsy is invasive and costly. It also poses a risk of secondary infection to medical personnel and, subsequently, patients. Under these circumstances, Creutzfeldt-Jakob disease is extremely difficult to diagnose, especially at an early stage, and it is frequently confused with other causes of dementia. The World Health Organization...
WHO criteria for the diagnosis of Creutzfeldt-Jakob disease are listed in Table 1. Because Creutzfeldt-Jakob disease is an infectious disease of the central nervous system, the brain, spinal cord, and optic tissues are believed to be the most likely sources of infective material, and the tissue specimens and body fluids must be handled with special care (26–29). Human-to-human transmission has been reported (30). Improving the accuracy of noninvasive early diagnostic methods would help to limit transmission of the disease (14). No cure yet exists for Creutzfeldt-Jakob disease, and early detection does not alter the outcome. Although trials of treatment with quinacrine and chlorpromazine are in progress, the effectiveness of treatment is unknown. Nevertheless, early detection of the disease will be even more important when effective therapeutic measures are available (31).

Neuropathologic Features

The neuropathologic features of Creutzfeldt-Jakob disease cover a wide spectrum in their intensity and distribution. The characteristic histopathologic features of Creutzfeldt-Jakob disease are spongiform degeneration of the neurons and their processes, neuronal loss, intense reactive astrocytic gliosis, and amyloid plaque formation. Spongiform degeneration is observed in the cerebral cortex, putamen, caudate nucleus, thalamus, and hippocampus. At electron microscopy, the spongiform degeneration is mostly observed in the form of vacuoles located in the neuropil between the nerve cell bodies. The vacuoles are round or oval in shape and vary in diameter from 5 to 25 μm. In the late stage of the disease (status spongiosus), the vacuoles become very large, up to 100 μm in diameter, and are surrounded by a dense meshwork of reactive astrocytosis (32).

Table 1
WHO Criteria for Diagnoses of Sporadic and Iatrogenic Creutzfeldt-Jakob Disease

<table>
<thead>
<tr>
<th>Sporadic Creutzfeldt-Jakob Disease</th>
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<tbody>
<tr>
<td>Definite: Positive findings at standard neuropathologic examination, immunocytochemical analysis, or Western blot analysis (confirmed protease-resistant PrP) or presence of scrapie-associated fibrils at histopathologic analysis.</td>
</tr>
<tr>
<td>Probable: Progressive dementia, at least two of four clinical features (myoclonus, visual or cerebellar signs, pyramidal or extrapyramidal signs, akinetic mutism), and an atypical EEG during any illness of any duration or a positive result at 14-3-3 cerebrospinal fluid assay and survival of less than 2 years, plus the absence of other routine findings suggestive of an alternative diagnosis.</td>
</tr>
<tr>
<td>Possible: Progressive dementia, at least two of four clinical features (myoclonus, visual or cerebellar signs, pyramidal or extrapyramidal signs, akinetic mutism), and no EEG or an atypical EEG and survival of less than 2 years.</td>
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</tbody>
</table>

<table>
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<tr>
<th>Iatrogenic Creutzfeldt-Jakob Disease</th>
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</thead>
<tbody>
<tr>
<td>Progressive cerebellar syndrome in a recipient of human cadaveric pituitary hormone, or sporadic Creutzfeldt-Jakob disease with a recognized exposure risk (eg, antecedent neurosurgery with duramatal implantation).</td>
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</tbody>
</table>

The Role of MR Imaging

The MR imaging findings of Creutzfeldt-Jakob disease that were reported previously are abnormal high-signal-intensity areas in the cerebral cortex and basal ganglia and rapidly progressive brain atrophy on T2-weighted images; however, the early diagnosis of Creutzfeldt-Jakob disease with conventional MR imaging sequences is extremely difficult. Therefore, MR imaging has been used mostly to monitor the progression of the disease and determine the prognosis. On the other hand, findings of periodic synchronous discharges on the EEG and elevated levels of 14-3-3 protein in the cerebrospinal fluid previously were considered highly reliable diagnostic markers of Creutzfeldt-Jakob disease. Fluid-attenuated inversion recovery (FLAIR) images tend to reveal cortical abnormalities and may help to detect lesions that T2-weighted images fail to depict (10). At MR spectroscopy, N-acetylaspartate may be decreased in the early stage of disease (33). Single photon emission computed tomography (SPECT) performed with technetium 99m (⁹⁹mTc)–ethyl cysteinate dimer (ECD) has been reported to show decreased regional cerebral blood flow in the brain regions that correspond to areas with abnormal high signal intensities on diffusion-weighted images (34). However, the brain MR spectroscopic and SPECT findings are nonspecific for the diagnosis of Creutzfeldt-Jakob disease.

Diffusion weighting is a unique MR imaging technique that provides image contrast dependent on the molecular motion of water, which may be substantially altered in diseases that cause changes in the viscosity of fluid in and around cells or changes in the membranous constituents.
Abnormalities on diffusion-weighted images have been observed in many disease conditions. The technique is now used in various settings and for various purposes, including the early detection of acute brain infarction (35). There are many reports of the use of diffusion-weighted imaging to depict brain lesions in patients with Creutzfeldt-Jakob disease (4–15).

However, to the best of our knowledge, in only one study were the diffusion-weighted imaging features of Creutzfeldt-Jakob disease investigated before the appearance of periodic synchronous discharges on the EEG. As the disease progresses, brain atrophy becomes apparent and areas of abnormal high signal intensity are observed in the basal ganglia. FLAIR images in most patients show abnormal cortical areas of high signal intensity that T2-weighted images fail to depict. In this disease stage, diffusion-weighted images often show changes in the distribution and signal intensity of abnormalities. In the terminal stage of disease, the abnormalities in the cortex and basal ganglia in some cases disappear (Fig 1). Such changes may be attributable to changes in brain tissue from mild spongiform degeneration to status spongiosus (14). Other chronologic changes in the pattern of lesions on diffusion-weighted images in Creutzfeldt-Jakob disease have been reported. With disease progression, the abnormal high-signal-intensity areas, which are initially limited to the caudate nucleus on diffusion-weighted images, may spread to the anterior portion of the putamen, and lesions involving only the anterior portion of the putamen may progress to involve the entire region (13,14). These results prompted us to hypothesize that proteinaceous infectious scrapie particles accumulate in the caudate nucleus in the early stage of Creutzfeldt-Jakob disease and subsequently spread to the putamen through the caudatolenticular gray bridges.

What imaging methods should be used to evaluate a patient for Creutzfeldt-Jakob disease? In our recent practice, we have chosen MR imaging for the initial examination of patients with progressive dementia. We usually apply T2-weighted fast spin-echo sequences, single-shot spin-echo echo-planar sequences for diffusion-weighted imaging, and FLAIR sequences. All images, except those obtained with FLAIR sequences, are acquired in the axial plane. We usually perform FLAIR imaging in the coronal plane to evaluate frontal parietal regions as well as medial temporal regions of the cortex. Optimal repetition times and echo times are selected for the individual imaging systems. The diffusion-weighted imaging parameters are as follows: repetition time msec/echo time msec, 4500–5700/90–123; number of signals acquired, one; 12–15 axial sections, each with a thickness of 5 or 6 mm, and a 1.5–3.0-mm intersection gap; 128 × 128 matrix; 220-mm field of view; and diffusion-encoding gradient strengths (b values) of 0 and 1000 sec/mm². To evaluate the severity and the pattern of diffusion restriction without an interface from T2 shine-through, apparent diffusion coefficient (ADC) mapping also is essential. The T2-weighted imaging parameters are 3458–4900/90–123; 20 axial sections, each with a 5-mm section thickness, and a 1.5–3.0-mm intersection gap; a 256 × 256 matrix; and a 210–230-mm field of view. The FLAIR imaging parameters are 5700–9000/100–120; inversion time msec, 1700–2200; 4–5-mm section thickness; 1.5–3.0-mm intersection gap; 192 × 192 or 256 × 256 matrix; and 210–230-mm field of view (14).

During the examination, if there is a possibility that another dementia-type disorder is present, we may use additional MR imaging techniques, such as gadolinium-enhanced T1-weighted imaging, MR angiography, or MR venography.

### Abnormalities on Diffusion-weighted Images

The diffusion-weighted imaging abnormalities reported for Creutzfeldt-Jakob disease include regions of abnormal high signal intensity in the cortex, caudate nucleus, putamen, and thalamus with a distribution pattern that does not correspond to that of the arterial circulation. In early-stage Creutzfeldt-Jakob disease, high-signal-intensity abnormalities are most frequently observed in the cortex (13,14). The cortical abnormalities may be unilateral or bilateral, diffuse or focal, and symmetric or asymmetric. Abnormalities of the basal ganglia also may be unilateral or bilateral, and the caudate nucleus is most often involved. Some authors have suggested that these diffusion-weighted imaging findings may be characteristic of Creutzfeldt-Jakob disease and may provide a diagnostic clue before the onset of brain atrophy or the observation of abnormal signal intensity on T2-weighted MR images (4–15).

We evaluated 10 patients with Creutzfeldt-Jakob disease (three men, seven women; age range at symptom onset, 57–73 years; mean age at symptom onset, 67.3 years) between February 1997 and December 2004 at our hospital and its affiliates. Nine cases were sporadic and one was iatrogenic. All patients had progressive dementia and died within 2 years of the onset of symptoms (range, 3–22 months; mean, 8.8 months). The MR imaging examination and the immunoassay for 14-3-3 protein in the cerebrospinal fluid were
Figure 1. Sporadic Creutzfeldt-Jakob disease in a 72-year-old woman with left hemiparesis. (a–c) MR images obtained 7 weeks after the onset of dementia and 2 weeks before the appearance of periodic synchronous discharges on the EEG and a negative result at testing for the 14-3-3 protein level in cerebrospinal fluid. Axial T1-weighted (a) and axial T2-weighted (b) images show no abnormalities. The diffusion-weighted image (c) reveals symmetric bilateral areas of abnormal high signal intensity in the frontotemporal region of the cerebral cortex, caudate nuclei, and putamen. (d–f) MR images obtained after disease progression to akinetic mutism, 27 weeks after the onset of symptoms. The T1-weighted image (d) shows marked cerebral atrophy. The T2-weighted image (e) shows periventricular white-matter signal hyperintensity and caudate nucleus atrophy. Asymmetric bilateral areas of high signal intensity are visible in the basal ganglia in e. The diffusion-weighted image (f) shows that the bilateral areas of high signal intensity in the basal ganglia have disappeared. High signal intensity is noticeable only in the insula and the thalamus in f. (g) Photomicrograph (original magnification, ×20; hematoxylin and eosin stain) shows severe spongiform vacuolar degeneration and neuronal loss of the gray matter neuropil (ie, status spongiosus) in a specimen from the cerebral cortex.
performed before the onset of periodic synchronous discharges on the EEG in all cases. The interval from symptom onset to the MR imaging examination ranged from 3 to 24 weeks (mean, 5.6 weeks). After the initial MR imaging examination, periodic synchronous discharges became apparent on the EEG in all cases. The interval from the initial MR imaging examination to the onset of periodic synchronous discharges on the EEG ranged from 1 to 11 weeks (mean, 4.3 weeks). Two cases were diagnosed at autopsy as definite Creutzfeldt-Jakob disease, and the other eight were diagnosed in the clinical setting as probable Creutzfeldt-Jakob disease according to WHO diagnostic criteria. Diffusion-weighted images showed high-signal-intensity abnormalities unrelated to arterial blood circulation in all patients. Abnormal cortical signal intensities were seen in all patients, bilaterally in seven patients and unilaterally in three. Abnormal signal intensities were seen in the caudate nucleus in five patients (bilaterally in four and unilaterally in one), in the putamen in four patients (bilaterally in two and unilaterally in two), and in the thalamus in one patient (unilaterally). In all cases in which high-signal-intensity abnormalities were observed in the putamen, areas of abnormal high signal intensity also were observed in the cerebral cortex and in the caudate nucleus. In no case were the high-signal-intensity abnormalities on diffusion-weighted images limited to the posterior portion of the putamen. In four patients, abnormalities were observed in the same areas on FLAIR images as on diffusion-weighted images. No abnormal signal intensity was seen on T2-weighted images, except in one case, in which high-signal-intensity abnormalities were observed in the cortex. Low ADC values were observed in the areas with abnormal high signal intensity on diffusion-weighted images.

MR spectroscopic imaging revealed a decrease in N-acetylaspartate in two cases, a finding that corresponded to high-signal-intensity abnormalities on diffusion-weighted images. Brain perfusion imaging with $^{99m}$Tc-ECD SPECT revealed decreased regional cerebral blood flow corresponding to high-signal-intensity abnormalities on diffusion-weighted images in all cases. The 14–3–3 protein test result was positive in eight cases (Table 2). Thus, in our experience, diffusion-weighted imaging had higher sensitivity for

### Table 2: Clinical and Imaging Characteristics of Creutzfeldt-Jakob Disease in 10 Patients

<table>
<thead>
<tr>
<th>Patient No./Age (y)/Sex</th>
<th>High-Signal-Intensity Abnormality at MR Imaging†</th>
<th>Decreased N-acetylaspartate at MR Spectroscopy</th>
<th>Decreased Regional Blood Flow at SPECT</th>
<th>Increased 14–3–3 Protein in CSF</th>
</tr>
</thead>
<tbody>
<tr>
<td>1*/72/F</td>
<td>NA</td>
<td>B(C,CN,P)</td>
<td>NA</td>
<td>B(C,P)</td>
</tr>
<tr>
<td>2/65/M</td>
<td>NA</td>
<td>R(C,CN,P,T)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>3*/57/F</td>
<td>NA</td>
<td>B(CN), L(C,P)</td>
<td>NA</td>
<td>L(C,P)</td>
</tr>
<tr>
<td>4/62/M</td>
<td>No</td>
<td>B(C,CN), R(P)</td>
<td>Yes</td>
<td>R(C)</td>
</tr>
<tr>
<td>5/73/F</td>
<td>B(C)</td>
<td>B(C)</td>
<td>NA</td>
<td>B(C)</td>
</tr>
<tr>
<td>6/62/F</td>
<td>B(C,CN,P)</td>
<td>B(C,CN,P)</td>
<td>NA</td>
<td>B(C,P)</td>
</tr>
<tr>
<td>7/67/F</td>
<td>B(C)</td>
<td>B(C)</td>
<td>Yes</td>
<td>B(C)</td>
</tr>
<tr>
<td>8/71/F</td>
<td>B(C)</td>
<td>B(C)</td>
<td>No</td>
<td>B(C)</td>
</tr>
<tr>
<td>9/69/F</td>
<td>No</td>
<td>B(C,CN)</td>
<td>NA</td>
<td>B(C)</td>
</tr>
<tr>
<td>10/75/M</td>
<td>No</td>
<td>B(C)</td>
<td>NA</td>
<td>B(C)</td>
</tr>
</tbody>
</table>

Note.—Creutzfeldt-Jakob disease was sporadic in all patients except patient 3, in whom it was iatrogenic. B = bilateral, C = cerebral cortex, CN = caudate nucleus, CSF = cerebrospinal fluid, L = left hemisphere, NA = not applicable (imaging study not performed), P = putamen, R = right hemisphere, T = thalamus.

*The diagnosis of Creutzfeldt-Jakob disease in these patients was definite (confirmed at histopathologic analysis). The diagnosis in the other eight patients was probable Creutzfeldt-Jakob disease.

†Abnormal high signal intensity was found at T2-weighted MR imaging only in the right cerebral cortex in patient 7. T2-weighted images in all other patients were normal.
detecting abnormalities before the appearance of periodic synchronous discharges on the EEG than did FLAIR imaging (14). In most patients with Creutzfeldt-Jakob disease, high-signal-intensity abnormalities were observed both in the caudate nucleus and the cerebral cortex. This pattern is characteristic even in the early stages of the disease (Figs 2–4). In patients with this pattern of MR imaging findings and with progressive dementia, Creutzfeldt-Jakob disease is more strongly indicated than is any other dementia-inducing disorder.

Figure 2. Sporadic Creutzfeldt-Jakob disease in a 65-year-old man 10 weeks after the onset of dementia, insomnia, and optical hallucinations and 4 weeks before the appearance of periodic synchronous discharges on the EEG. (a) Axial T2-weighted image shows no abnormalities. (b) Diffusion-weighted image shows bilateral areas of abnormal high signal intensity in the cerebral cortex, caudate nuclei, putamen, and thalamus.

Figure 3. Iatrogenic Creutzfeldt-Jakob disease after a cadaveric dura mater transplantation in a 57-year-old woman. Images were obtained 7 weeks after the onset of progressive dementia and right hemiplegia and 4 weeks before the appearance of periodic synchronous discharges on the EEG. (a) Axial T2-weighted image shows no areas of abnormal signal intensity and only postoperative changes in the left parieto-occipital region. (b) Diffusion-weighted image shows areas of abnormal high signal intensity in the left cerebral cortex and the bilateral caudate nuclei. (c) Photomicrograph (original magnification, ×20; hematoxylin and eosin stain) shows spongiform (vacuolar) degeneration of the gray matter neuropil in a specimen from the cerebral cortex.
The high-signal-intensity lesions depicted on diffusion-weighted images are thought to represent vacuolization of the neuropil. If the vacuoles have a diameter of less than 20 μm, gliosis or astrocytosis leads to a restriction of water diffusion in the affected tissue, compared with that in normal tissue. Therefore, lesions that are caused by proteinaceous infectious scrapie particles are depicted as high-signal-intensity abnormalities with decreased ADC values at diffusion-weighted imaging (11). For various reasons, brain biopsy is problematic and its use is strictly limited in patients with Creutzfeldt-Jakob disease. Nevertheless, the correlation of pathologic findings with diffusion-weighted imaging findings in patients with early-stage Creutzfeldt-Jakob disease may provide useful clues to the nature of the disease. Diffusion-weighted imaging is very useful for the diagnosis of Creutzfeldt-Jakob disease even at an early stage, and the technique should be included in the imaging examinations of patients with progressive dementia.

It should be kept in mind that, especially in the early stages of disease, the high-signal-intensity abnormalities may be restricted to the cerebral cortex on diffusion-weighted images (Figs 5, 6) (14). In this setting, the diffusion-weighted imaging findings alone may be misleading, and the findings at MR imaging with other sequences and at clinical examination should be carefully considered.

Figure 4. Sporadic Creutzfeldt-Jakob disease in a 62-year-old woman 3 weeks after the onset of progressive dementia and 6 weeks before the appearance of periodic synchronous discharges on the EEG. (a, b) Axial diffusion-weighted images at two different levels show areas of abnormal high signal intensity in the cerebral cortex on both sides. Subtle high-signal-intensity areas in the caudate nucleus and the anterior portion of the putamen also are visible. (c) Axial ADC map from diffusion-weighted imaging shows the cortical lesions as areas of decreased signal intensity, with the most striking decreases visible in the caudate nucleus and putamen.

Figure 5. Sporadic Creutzfeldt-Jakob disease in a 67-year-old woman 9 weeks after the onset of progressive dementia and visual hallucinations and 9 weeks before the appearance of periodic synchronous discharges on the EEG and a negative result for 14-3-3 protein testing in the cerebrospinal fluid. (a) Axial T2-weighted MR image shows an area of subtle abnormal signal hyperintensity in the right temporo-occipital cortex. (b–d) Axial diffusion-weighted images show bilateral areas of abnormal high signal intensity at three different levels in the cerebral cortex. (e) Axial ADC map from diffusion-weighted imaging shows the lesions as areas of decreased signal intensity. (f) Coronal FLAIR image shows areas of abnormal high signal intensity in the cerebral cortex that correspond to but are less obvious than those observed on the diffusion-weighted images. (g) MR spectroscopic image reveals a decrease of N-acetylaspartate in the head of the right caudate nucleus. (h) Statistical parametric maps of brain perfusion, obtained with 99mTc-ECD SPECT 2 days before MR imaging, reveal areas of perfusion deficit that correspond to the areas of abnormal high signal intensity on diffusion-weighted images. However, these findings are nonspecific for Creutzfeldt-Jakob disease.
Differential Diagnosis with Diffusion-weighted Imaging

Early-stage Creutzfeldt-Jakob disease should be clinically differentiated from other disorders associated with dementia (Table 3). Alzheimer disease is not characterized by abnormalities on diffusion-weighted images. Vascular dementia is associated with evidence of multiple infarcts, but diffusion-weighted imaging abnormalities are observed only in the area of a recent infarction, and there is no diffuse cortical involvement; thus, it should be easy to distinguish this entity from Creutzfeldt-Jakob disease. Most brain neoplasms likewise can be easily differentiated from Creutzfeldt-Jakob disease on diffusion-weighted images (35). If the diffusion-weighted imaging abnormalities are restricted to the cerebral cortex, the major differential diagnoses are MELAS, venous hypertensive encephalopathy, and chronic herpes simplex encephalitis (36–47).

MELAS

MELAS is a genetic metabolic disorder that induces subacute dementia. Although MELAS may mimic Creutzfeldt-Jakob disease, it typically is manifested in a younger age group than is Creutzfeldt-Jakob disease. The clinical history includes a period of normal early development followed by symptoms of dementia, lactic acidosis, and exercise intolerance. On diffusion-weighted images, abnormal cortical signal hyperintensities are depicted in the early stages of MELAS. On T2-weighted MR images and FLAIR images, the lesions appear as gyriform areas of severe swelling that spares the underlying white matter, a feature that is never observed in early-stage Creutzfeldt-Jakob disease (Fig 7). The ADC values in MELAS vary, and some authors have suggested that diffusion-weighted imaging abnormalities associated with decreased ADC values may reflect early-stage cytotoxic edema caused by an increasing energy demand and a resultant imbalance between the energy requirement and the availability of adenosine triphosphate (36–38).

Table 3
Differential Diagnosis of Early-Stage Creutzfeldt-Jakob Disease

<table>
<thead>
<tr>
<th>Disorder</th>
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<tbody>
<tr>
<td>Alzheimer disease</td>
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<tr>
<td>Vascular dementia</td>
</tr>
<tr>
<td>Mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes (MELAS)</td>
</tr>
<tr>
<td>Cortical venous thrombus</td>
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<tr>
<td>Central nervous system lymphoma and other brain neoplasms</td>
</tr>
<tr>
<td>Viral encephalitis (eg, chronic herpes simplex encephalitis)</td>
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</table>

Figure 6. Sporadic Creutzfeldt-Jakob disease in a 71-year-old woman 3 weeks after the onset of progressive insomnia and left hemiparesis and 8 weeks before the appearance of periodic synchronous discharges on the EEG. (a) Axial T2-weighted MR image shows no abnormalities. (b) Diffusion-weighted image shows areas of abnormal high signal intensity in the right cerebral cortex. (c) Axial ADC map from diffusion-weighted imaging shows the lesions as areas of decreased signal intensity.
Figure 7. MELAS in a 41-year-old woman with subacute progressive personality changes, depression, and confusion. (a–c) Axial diffusion-weighted images at three different levels show regions of abnormal high signal intensity restricted to the cerebral cortex, similar to our findings in patients with Creutzfeldt-Jakob disease. (d, e) Axial T2-weighted image (d) and coronal FLAIR image (e) show lesions with severe gyriform swelling that does not extend to the underlying white matter. These features are never seen in early-stage Creutzfeldt-Jakob disease.
Venous Hypertensive Encephalopathy
Several disease processes may cause venous hypertensive encephalopathy. Dural arteriovenous fistula (an arteriovenous shunt located within the dura mater) has received attention as a potential cause of reversible dementia, but its clinical signs and symptoms are often nonspecific. The same symptoms of dementia may be caused by venous hypertension with resultant gliosis and petechial hemorrhages (39–41). Although progress in MR imaging has made the diagnosis of venous hypertensive encephalopathy easier, precise diagnosis of this entity remains problematic. On diffusion-weighted images, venous infarction sometimes is depicted as a high-signal-intensity abnormality in the cortex that resembles a lesion in Creutzfeldt-Jakob disease. Three-dimensional gadolinium-enhanced MR angiography may help achieve the correct diagnosis (Fig 8) (42).

Chronic Herpes Encephalitis
Herpes simplex encephalitis is the most common viral infection of the central nervous system. Patients present with alterations in mental status, seizures, dementia, and often headaches. Most cases of herpes simplex encephalitis are acute, and the neurologic symptoms worsen rapidly; however, chronic cases of herpes simplex encephalitis also have been reported. On T2-weighted MR images, high-signal-intensity abnormalities typically are seen in the medial temporal regions and in some cases involve the frontal lobe. Diffusion-weighted imaging is more sensitive than T2-weighted imaging for the detection of abnormalities in herpes simplex encephalitis; however, if the lesion is unilateral, the diffusion-weighted imaging findings may be confused with those of Creutzfeldt-Jakob disease. The affected regions in herpes simplex encephalitis show necrotic or hemorrhagic parenchymal swelling in the early stage (Fig 9), a feature that is never observed in Creutzfeldt-Jakob disease (43–47).

Summary
Creutzfeldt-Jakob disease should be suspected in any case in which areas of abnormal signal hyperintensity are depicted on diffusion-weighted images in the cerebral cortex and deep gray matter, especially in the caudate nucleus, even when other characteristic clinical findings, such as periodic synchronous discharges on the EEG and elevated 14–3–3 protein levels in the cerebrospinal fluid, are absent.

Noninvasive early diagnosis helps to prevent the transmission of Creutzfeldt-Jakob disease. Moreover, early detection of the disease can be expected to become more important as effective therapeutic measures become available.
On the other hand, in the early stages of Creutzfeldt-Jakob disease, the areas of abnormal high signal intensity on diffusion-weighted images may be restricted to the cerebral cortex. In this circumstance, differentiation from other, curable disorders of the nervous system, which also may be manifested by progressive dementia and by areas of abnormal cortical signal intensity on diffusion-weighted images, is essential.

References


In most patients with Creutzfeldt-Jakob disease, high-signal-intensity abnormalities were observed both in the caudate nucleus and the cerebral cortex. This pattern is characteristic even in the early stages of the disease.

The high-signal-intensity lesions depicted on diffusion-weighted images are thought to represent vacuolization of the neuropil.

It should be kept in mind that, especially in the early stages of disease, the high-signal-intensity abnormalities may be restricted to the cerebral cortex on diffusion-weighted images.

If the diffusion-weighted imaging abnormalities are restricted to the cerebral cortex, the major differential diagnoses are MELAS, venous hypertensive encephalopathy, and chronic herpes simplex encephalitis.

Noninvasive early diagnosis helps to prevent the transmission of Creutzfeldt-Jakob disease. Moreover, early detection of the disease can be expected to become more important as effective therapeutic measures become available.