Correlation of Diffusion-Weighted Magnetic Resonance Imaging With Neuropathology in Creutzfeldt-Jakob Disease

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Background: Although the diagnosis of Creutzfeldt-Jakob disease (CJD) is straightforward in fully developed cases, a definitive diagnosis can be difficult early in the course of the illness. T2-weighted magnetic resonance imaging (MRI) signal abnormalities, and recently, diffusion-weighted MRI abnormalities, have been described in patients with CJD, suggesting the utility of MRI in the early recognition of CJD.

Objective: To correlate diffusion-weighted MRI signal abnormalities with neuropathologic changes in CJD.

Materials and Methods: Diffusion-weighted MRI and neuropathologic changes of 2 patients with autopsy-proven CJD were examined in a blinded fashion by a neuroradiologist and a neuropathologist.

Results: Areas of bright signal on diffusion-weighted MRI correlated with a higher degree of spongiform changes.

Conclusion: Diffusion-weighted MRI in CJD demonstrates specific-signal abnormalities that correlate well with areas of the most severe and characteristic neuropathologic changes.

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CREUTZFELDT-JAKOB disease (CJD) is a fatal prion-mediated neurodegenerative illness characterized by rapidly progressive dementia, a cerebellar-extrapyramidal syndrome, diffuse myoclonus, and periodic discharges on electroencephalography. Progress in our understanding of this group of disorders continues at a prodigious rate although the definitive confirmation of symptomatic prion disease still requires pathologic examination, most reliably performed post mortem. Immunoassay for cerebrospinal fluid protein 14-3-3 is a useful biochemical marker for CJD. Its positive predictive value varies in different clinical settings, and it may be detectable in other neurodestructive processes. Computed tomographic examination in patients with CJD may demonstrate atrophy, as does the gross appearance of the brain in advanced cases.

Increased T2-weighted and diffusion-weighted (DW) magnetic resonance imaging (MRI) signal has been described in the basal ganglia of subjects with sporadic CJD. Abnormal fluid-attenuated inversion recovery images on MRI have also been reported in the thalamus (pulvinar sign) of patients with variant CJD. Variant CJD is a disease characterized by onset in a younger age group, early neuropsychiatric features, and the occurrence of prominent sensory symptoms with neurologic signs such as ataxia and involuntary movements later in the course of the disease.

We describe 2 patients with autopsy-proven CJD who had abnormal DW MRIs early in the course of their illness. The areas of specific signal abnormalities in both patients correlated with the neuropathologic findings of spongiform encephalopathy.

REPORT OF CASES

PATIENT 1

Over the course of 5 weeks, this 65-year-old, right-handed man developed progressive forgetfulness, social withdrawal, gait disturbance, and decreased speech. His father died of CJD 23 years earlier. Findings from the physical examination disclosed dysphasia, bilateral extrapyramidal signs, and widespread resting, action, and startle myoclonus.
Magnetic resonance imaging data were acquired on a 1.5-T scanner (General Electric Medical Systems, Milwaukee, Wis), including T1-weighted and fast spin-echo T2-weighted images. The DW imaging was performed with contiguous slices 3.3 mm thick and a b-factor of 1000 s/mm² along 1 of 3 orthogonal axes (x, y, or z). A set of T2-weighted images was acquired in an identical manner except that the b-factor was 5 s/mm². From the 3 DW images an average DW image was derived automatically as the geometric mean of the individual signal intensities (SIs) in each pixel: $\text{SI} (\text{DW}) = \sqrt[3]{\text{SI}_x \times \text{SI}_y \times \text{SI}_z}$. The apparent diffusion coefficient (ADC) was calculated for each pixel in these images from the formula $\text{ADC} = \frac{\ln(\text{SI}(\text{T2})/\text{SI}(\text{DW}))}{(1000 - 5)}$. The apparent diffusion coefficient values are multiplied by $10^6$ for presentation, so the final ADC values have units of $10^{-6}$ mm²/s.

The brain was obtained post mortem and fixed in 10% neutral-buffered formalin. Tissue blocks from the first case were obtained from the left occipital parasagittal cortex and bilateral temporal poles, thalamus, striatum, and parasagittal frontal and parietal cortex. Tissue blocks from the cerebellum and right occipital parasagittal cortex were unavailable. In the second case, the entire right cerebral hemisphere was frozen for biochemical studies; tissue blocks were sampled from the left thalamus; basal ganglia; frontal, temporal, and occipital cortex; and cerebellum.

Tissue was embedded in paraffin, sectioned at 6 µm, stained with hematoxylin-eosin, and examined by light microscopy. A neuropathologist (P.F.) who was blinded to the MRI results examined all of the slides. A score for each region of interest was derived based on an overall score from the multiple fields examined.

Observations were made independently for each of the following 4 measures: the cytoarchitectural integrity of that region, degree of neuronal loss, degree of spongiform change, and reactive astrocytosis. A score of 0 to 3 was assigned to each measure. For each variable grade 0 represented the absence of any significant pathologic changes. Grade 1 represented mild spongiform change with early vacuolar degeneration in the neuropil and neurons; cytoarchitecture mildly disrupted; and astrogial nuclei increased in number and size. Grade 2 represented extensive spongiform change with focal confluence of vacuoles; cortical cytoarchitecture disrupted with loss of polarity of neurons and some depletion of nerve cells; and clear proliferation of fibrillary astrocytes. Grade 3 represented severe spongiform change with extensive confluence of vacuoles; severe disruption of cortical architecture with prominent neuronal loss; and extensive glial proliferation. A possible minimum of 0 and a maximum score of 12 thus generated was used to define and compare the varying degrees of pathologic changes in the different regions of interest.

Corresponding neuropathologic and MRI data were available for 17 regions of interest. All variables were compared statistically (Statview 5.0.1 for Macintosh; SAS Institute, Cary, NC). The (ordinal) neuropathologic variables were correlated with corresponding ADC values using the Spearman rank correlation and to the dichotomous qualitative variable (presence or absence of DW MRI changes) using the Mann-Whitney test.

The results of the biochemical and hematologic profiles were normal. Noncontrast computed tomographic and routine MRI scans of the head showed no abnormalities. Electroencephalography showed diffuse slowing with triphasic waves. Cerebrospinal fluid was negative for protein 14-3-3. Genetic studies demonstrated GAG (glutamine) to AAG (lysine) substitution at codon 200 and M/M (methionine/methionine) homozygosity at codon 129 of the PRNP gene. The DW MRIs disclosed specific signal abnormalities. The patient died 4 weeks later.

**PATIENT 2**

Over the course of 4 weeks this 56-year-old, left-handed woman developed memory difficulty, blurred vision, and progressive gait unsteadiness. Limb and truncal ataxia was noted on neurologic examination. Generalized and startle myoclonus became apparent during the course of her hospitalization. Results of the biochemical and hematologic profiles were normal.

Her initial noncontrast cranial computed tomographic and MRI scans showed no abnormalities. Electroencephalography demonstrated diffuse slowing with triphasic waves. Cerebrospinal fluid was negative for protein 14-3-3. The DW MRIs showed specific signal abnormalities. The patient died about 5 weeks after being discharged from the hospital.

**RESULTS**

**RADIOLOGICAL EXAMINATION**

**Case 1**

T1-weighted MRIs showed mild sulcal prominence. The T2-weighted fast spin-echo sequences (Figure 1) revealed abnormal increased signal bilaterally in the corpus striatum (Figure 1C). The DW signal abnormality in the bilateral corpus striatum appeared much more prominent than the T2-weighted abnormality (Figure 1D). The DW MRIs showed increased signal in the deep cortical layers of the left temporal lobe extending to the perisylvian region and in the bilateral parasagittal frontal, parietal, and occipital cortex as well as the left frontal cortex (Figure 1B). These regions did not appear hyperintense on T2-weighted images (Figure 1A). Bright DW MRI signals corresponded with restricted diffusion (low ADC values), most notably in both basal ganglia (right basal ganglia $\text{ADC} = 4.17 \times 10^{-6}$ mm²/s, left basal...
ganglia ADC = 457 × 10^−6 mm²/s) and the left temporal lobe (635 × 10^−6 mm²/s).

Case 2

T2-weighted images showed slight symmetric hyperintense signal bilaterally in the putamen and caudate nucleus

Figure 1. Case 1. Axial magnetic resonance images. T2-weighted image through the temporal lobes (A) demonstrates no signal abnormality while the diffusion-weighted image (B) demonstrates increased signal in the left temporal cortex. T2-weighted image (C) demonstrates mildly increased signal in the basal ganglia while diffusion-weighted imaging (D) demonstrates bright signal in the basal ganglia bilaterally.

Figure 2. The DW MRIs showed focal areas of increased signal in the left putamen but not in the right putamen. The left parietal and superior occipital lobes showed cortical gyriform hyperintensity, and bilateral frontal parasagittal areas showed similar features (Figure 2B). The DW MRIs also showed hyperintensity of the left cerebellar cortex with
sparing of the deeper nuclear structures (Figure 2D). Areas of abnormal signal on the DW MRI indicated restricted diffusion.

NEUROPATHOLOGIC EXAMINATION FINDINGS

Case 1

The region of the left temporal lobe corresponding to the abnormal area on DW MRI showed complete loss of cortical cytoarchitecture and severe spongiform change with areas of confluent vacuolation, an advanced degree of neuronal loss, and some reactive astrocytosis (Figure 3A) (Table). In the right temporal lobe, which did not show changes on MRI, spongiform changes were mild with minimal neuronal loss, no astrocytic reaction, or preservation of the cortical cytoarchitecture (Figure 3B). Basal
ganglia showed marked spongiform degeneration and an advanced degree of reactive astrocytosis. Varying degrees of spongiform change were seen throughout the entire brain.

**Case 2**

The region of the left occipital lobe corresponding to the abnormal signal on DW MRI showed severe spongiform changes with an advanced degree of neuronal loss, disrupted cytoarchitecture, and reactive astrocytosis (Figure 4B). Examination of the left cerebellar hemisphere showed a moderate degree of spongiform changes with neuronal loss and some reactive astrocytosis (Figure 4A). The frontal cortex and basal ganglia on the left side showed a moderate degree of spongiform change with some loss of cytoarchitecture while the neuronal loss and reactive astrocytosis were minimal. The left thalamus showed areas of minimal change intermingled with areas of normal-appearing tissue. Findings from the examination of the left temporal cortex were remarkable for minimal spongiform changes. No amyloid plaques were present.

**CORRELATIONS**

The 4 different measures of neuropathologic damage all correlated strongly with each other (Spearman rank correlation; \( P < 0.005 \) for all comparisons). The DW MRI scores correlated strongly (Mann-Whitney test) with cytoarchitectural loss (\( P = 0.03 \)), neuronal loss (\( P = 0.007 \)), and spongiform changes (\( P = 0.02 \)), but not astrocytosis (\( P = 0.07 \)). The ADC correlated with cytoarchitectural loss (\( r^2 = 0.56; \)

<table>
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<th>Region of Interest</th>
<th>Cytoarchitecture</th>
<th>Neuronal Loss</th>
<th>Spongiform Changes</th>
<th>Astrocytosis</th>
<th>Overall Score</th>
<th>ADC Values, ( 10^{-6} ) mm/s</th>
<th>DW MRI</th>
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*ADC indicates apparent diffusion coefficient; DW MRI, diffusion-weighted magnetic resonance imaging.*
P<.001), neuronal loss (r²=0.75, P<.001), spongiform changes (r²=0.44, P=.01), and astrocytosis (r²=0.57, P=.003).

Although the number of data points is small, several general statements can be made regarding thresholds of the different variables. In general, an ADC score of 700 or less was associated with a positive DW MRI signal. Moreover, a positive DW MRI signal was almost always associated with a spongiosis score of 2 or more or, somewhat less consistently, with a total pathologic score of 5 or more. Similar correlations with the other pathologic variables appeared to be less consistent.

**COMMENT**

A definitive diagnosis of CJD rests on the demonstration of the neuropathologic triad of neuronal loss, spongiform change, and reactive astrocytosis in the absence of an inflammatory reaction. When present, amyloid plaques that stain with α-PrP antibodies are diagnostic of CJD.13 However, these pathologic changes vary considerably from case to case. Spongiform degeneration of the cortex occurs in virtually all cases regardless of the clinical presentation and consists of round to oval vacuoles 5 to 25 µm in diameter located in the neuropil between nerve cell bodies. At times their presence may be the only neuropathologic clue to the diagnosis of spongiform encephalopathy. Late-stage disease, recognized as “status-spongiosis” by Masters and Richardson,3 is characterized by larger 100-µm vacuoles surrounded by a dense meshwork of reactive astrocytic processes. Though earlier attempts failed to demonstrate parenchymal changes on MRI,10 in 1988 Gertz et al3 described an increased T2-weighted MRI signal in the basal ganglia of a 55-year-old woman with proven CJD. Numerous publications since then have consistently demonstrated bilaterally symmetric, diffuse hyperintense abnormalities in the basal ganglia on the T2-weighted MRI of patients with CJD.12,13 Recently,14 an increased T2-weighted signal was described in the thalamus (pulvinar sign) in 28 of 36 patients with variant CJD. Definite MRI signal changes were also demonstrated in a hamster model of scrapie.16

Diffusion-weighted MRI is a newer technique that noninvasively images molecular water proton diffusion processes occurring on a micrometer scale. The observed proton diffusion rate and direction reflect the molecular and macromolecular barriers, or hindrances, that the proton experiences during its translation process.15 This technique, when used in the demonstration of an acute ischemic infarct, reflects a shift of relatively faster-translating extracellular water protons into a more hindered intracellular environment correlating with cytotoxic edema in the acute phase of an ischemic infarct.

Diffusion-weighted MRIs signal changes encountered in CJD probably are a result of microvacuolation of neuritic processes heralding spongiform degeneration. Vacuoles with a diameter of 5 to 20 µm would provide a population of mobile water molecules with a long T2 yet with a restricted diffusion range. Diffusion can be visualized by a “diffusion sphere” (or ellipsoid, for asymmetric diffusion) whose radius R=(2Dt)½ is the mean-squared displacement of a particle with diffusion coefficient D from the center of the sphere in time t.7 For D=625×10⁻⁶ mm²/s (typical for tissues, see Table) and t=80 ms (a typical diffusion time for a DW sequence), R=10 µm; therefore, a vacuole diameter of less than about 20 µm would provide restricted diffusion compared with normal tissue.

Bahn et al16 were able to demonstrate increased DW MRI signal in the caudate nuclei, putamina, thalami, cingulate gyri, and right inferior frontal cortex of a patient with proven CJD in whom the T2-weighted MRIs showed a slightly increased signal in the caudate nucleus and putamen. Other workers17,18 noted similar observations. Recently Samman et al19 have demonstrated a positive correlation between MRI signal changes and spongiform degeneration in a 68-year-old patient with CJD.

In our patients, characteristic DW MRI signal abnormalities in the basal ganglia and deeper cortical layers suggested the diagnosis of CJD early in the course of their illness, even before the diagnostic abnormalities were noted on electroencephalography or in protein 14-3-3 values. Though T2-weighted signal abnormalities were also

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**Figure 4.** Case 2. A, Neuropathologic changes in the neuropathologic features of the cerebellar cortex consist of typical spongiform change in the molecular layer (hematoxylin-eosin, original magnification ×200). B, Neuropathologic changes of the occipital cortex clearly demonstrate the advanced degree of spongiform change, neuronal loss, and reactive astrocytosis (hematoxylin-eosin, original magnification ×400).
Diffusion-weighted magnetic resonance imaging provide a highly sensitive method of identifying areas of involvement in CJD. This observation may facilitate the earlier diagnosis of this disease.

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