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Y. Shiga, MD, PhD; K. Miyazawa, MD; S. Sato, MD, PhD; R. Fukushima, MD; S. Shibuya, MD, PhD; Y. Sato, MD, PhD; H. Konno, MD, PhD; K. Doh-ura, MD, PhD; S. Mugikura, MD, PhD; H. Tamura, MD, PhD; S. Higano, MD, PhD; S. Takahashi, MD, PhD; and Y. Itoyama, MD, PhD

Abstract—*Objective:* To evaluate the usefulness of diffusion-weighted MRI (DWI) for the early diagnosis of Creutzfeldt–Jakob disease (CJD). *Methods:* Thirty-six consecutive patients (age 56 to 82 years) were enrolled, and 26 were examined by DWI. Nine were definite based on the World Health Organization criteria, and 27 were probable. The percentages of DWI abnormalities, periodic sharp wave complexes (PSWCs) on the EEG, detection of CSF 14-3-3 protein, and increase of CSF neuron-specific enolase (>25 ng/mL) on the first examination were compared. For DWI, 32 patients (age 31 to 84 years) who showed progressive dementia or impaired consciousness served as disease controls. *Results:* The percentage of DWI abnormalities was 92.3%, of PSWCs 50.0%, of 14-3-3 protein detection 84.0%, and of NSE increase 73.3%. Two of the 32 control subjects were falsely positive on DWI. The sensitivity of DWI was 92.3% (95% CI 74.8 to 99.5%) and specificity 93.8% (95% CI 79.2 to 99.2%). In 17 patients who did not show PSWCs on the first EEG, abnormal DWI findings were still clearly detected. Four patients who were negative for 14-3-3 protein also showed DWI abnormalities. DWI abnormalities were detected as early as at 3 weeks of symptom duration in four patients in whom PSWCs were not yet evident. *Conclusions:* DWI can detect characteristic lesions in the majority of patients with CJD regardless of the presence of PSWCs. DWI was the most sensitive test for the early clinical diagnosis of CJD; consideration should be given to its inclusion in the clinical diagnostic criteria of CJD.

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Creutzfeldt–Jakob disease (CJD) is a transmissible, progressive, fatal spongiform encephalopathy.[1] The transmission of bovine spongiform encephalopathy to humans as variant CJD[2] has focused increased attention on CJD. The cardinal manifestations of the disease are rapidly progressive dementia, generalized myoclonus, and periodic sharp wave complexes (PSWCs) on EEG. However, cases that do not consistently show such typical manifestations have been recognized, and the spectrum of disease manifestations has been extending.[3,4] An early and accurate diagnosis is important to prevent disease transmission, but diagnosis is not easy, especially in the early stage of the disease.

PSWCs on EEG have been used as one of the central diagnostic tests for CJD.[5] However, PSWCs are observed in only 60% of patients[3,4] and usually appear after the middle stage of the disease. In addition, PSWCs are not always specific for CJD.[6] PSWCs are therefore of limited use for the early diagnosis of CJD. The detection of brain-specific proteins such as 14-3-3 protein[6] and neuron-specific enolase[7] (NSE) in CSF also supports the diagnosis of CJD. Although the sensitivity and specificity of 14-3-3 protein[6] and NSE[7] are higher than those of PSWCs,[8] false-positive results are observed in several neurologic diseases such as herpes simplex encephalitis, cerebrovascular disease,[6] Hashimoto encephalopathy,[9] and paraneoplastic neurologic disorders.[10]

Recently, several reports described that diffusion-weighted MRI (DWI) could demonstrate early brain lesions in CJD patients when scans were negative on T2-weighted MRI examination (T2I).[11] In this study, we evaluated the usefulness of DWI for the early clinical diagnosis of CJD by comparing it with other MR sequences such as T2I and fluid-attenuated inversion recovery imaging (FLAIR) and with other diagnos-

See also pages 410, 436, and 450

From the Department of Neurology (Drs. Shiga, Miyazawa, and Itoyama), Tohoku University School of Medicine, Department of Neurology (Dr. S. Sato), Kohnan Hospital, Second Department of Internal Medicine (Dr. Fukushima), Hiraka General Hospital, Department of Neurology (Dr. Shibuya), Miyagi National Hospital, Department of Neurology (Dr. Y. Sato), Research Institute for Brain and Blood Vessels, Akita, Department of Neurology (Dr. Konno), Nishitaga National Hospital, Department of Neuropathology (Dr. Doh-ura), Institute of Brain Diseases, Kyushu University Faculty of Medicine, and Department of Diagnostic Radiology (Drs. Mugikura, Tamura, Higano, and Takahashi), Tohoku University School of Medicine, Japan.

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Address correspondence and reprint requests to Dr. Y. Shiga, Department of Neurology, Tohoku University School of Medicine, 1-1 Seiryo-machi, Aoba-ku, Sendai 980-8574, Japan; e-mail: yshiga@em.neurol.med.tohoku.ac.jp

Table 1 *Profiles of CJD patients and examination results*

Patient no.	Type	Age/sex	Duration, wk	DL	*PRNP*	PSWC	DWI	14-3-3	NSE, ng/mL
1	Sp	71/M	3	P	MM	−/+	+		
2	Sp	63/M	4	P	MM	+	+		26
3	Sp	78/M	6	P	MM	+	+	+	79
4	Sp	76/F	6	P	MM	+	+	−	22
5	Sp	61/M	7	P	MM	+	+	+	37.3
6	Sp	66/M	8	P	MM	−/+	+	+	29
7	Sp	76/F	8	P	MM	+	+	+	177
8	Sp	69/M	8	P	MM	+			
9	Sp	54/M	8	P	MM	−/+	+	+	18.4
10	Sp	69/M	8	D	VV2	−	+	+	110
11	Sp	68/M	9	P	MM	−/+	+	+	24
12	Sp	63/F	9	P	MM	+		+	56
13	Sp	74/M	10	D	MM	+			31
14	Sp	71/M	12	P	MM	+		+	25.2
15	Sp	63/F	12	P	MM	−/+	+	+	
16	Sp	79/M	13	D	MM	+		+	36
17	Sp	75/F	21	D	VV2	−	+	+	48
18	Sp	74/F	23	P	MM	+	+	+	51.4
19	Sp	59/M	24	D	MM2-T	−	−	−	15.4
20	Sp	73/F	25	P	MV	−	+	+	56.2
21	Sp	73/F	3	P		−/+	+		
22	Sp	69/M	3	P		−/+	+		50
23	Sp	67/F	6	P		+		+	95
24	Sp	70/M	8	P		+	−/+		
25	Sp	72/F	8	P		+			120
26	Sp	59/M	9	P		+	+		62
27	Sp	74/F	17	D		+		+	72
28	Sp	66/F	25	P		+		+	300
29	Fa	76/M	4	P	V1801	−	+	+	19.5
30	Fa	56/F	8	P	M232R	−/+	+	+	110
31	Fa	58/M	9	P	E200K	−/+	+		
32	Fa	72/M	12	D	V1801	−	+		60.4
33	Fa	82/F	13	P	V1801	−	+	+	32.1
34	Fa	79/M	24	D	V1801	−	+	−	13
35	Ia (Dura)	57/M	3	D	MM	−/+	+	−	18
36	Ia (Dura)	70/F	8	P		+		+	15.8

CJD = Creutzfeldt–Jakob disease; Duration, wk = duration from the onset to diagnostic examinations; DL = diagnostic level based on World Health Organization criteria; PSWC = periodic sharp wave complex; DWI = diffusion-weighted imaging; NSE = neuron-specific enolase; Sp = sporadic CJD; P = probable; MM = homozygosity for methionine at codon 129; D = definite; VV = homozygosity for valine at codon 129; MV = methionine/valine heterozygosity at codon 129; Fa = familial CJD; V180I = a point mutation of Val to Ile at codon 180; M232R = a point mutation of Met to Arg at codon 232; E200K = a point mutation of Glu to Lys at codon 200; Ia = iatrogenic CJD; Dura = a recipient of cadaveric dura mater; (−/+) = negative on the first examination but positive on the sequential examinations.

tic tests including PSWC, CSF 14-3-3 protein, and CSF NSE, which are used as the World Health Organization (WHO) CJD diagnostic criteria.[12]

Patients and methods. *Study group.* Thirty-six consecutive patients with CJD seen from January 1, 1994, to June 30, 2003, at the Department of Neurology, Tohoku University Hospital, and its related hospitals (age 56 to 82 years with a mean age of 68.9 years; 21 men) were enrolled in this study. These patients included the patients in our previous reports.[13-15] According to the WHO criteria,[12] 9 were definite and 27 were probable. A genetic study of human prion protein gene (*PRNP*) was performed in 27 patients, and 20 were sporadic CJD (17 had methionine homozygosity at codon 129 of *PRNP,* and, among those, 3 were definite; 14 were probable at the diagnostic level, and 2 who were definite had valine homozygosity and 1 who was probable had methionine/valine heterozygosity). Six had familial CJD (two definite, four probable, in which two had V180I[15] and one had E200K[16]; one had M232R).[17] Of two patients who were recipients of cadaveric dura mater (iatrogenic CJD), one was definite and one was probable (one had methionine homozygosity at codon 129 of *PRNP*). Our patients composed various clinical phenotypes of CJD including uncommon variants with rather longer clinical courses. The profiles of these patients are listed in table 1.

Disease control group. We reviewed retrospectively the clinical records of our patients who were admitted to the Department of Neurology, Tohoku University Hospital, from January 1, 1998, to June 30, 2003. Excluding patients who had an abrupt onset or symptoms suggesting meningoencephalitis, such as high fever, stiff neck, etc., 81 patients demonstrated subacute dementia or impaired consciousness progressing for 1 to several months.

Table 2 *Final diagnosis of control patients*

Final diagnosis	Total no.
Metabolic encephalopathy, including one alcoholic encephalopathy	4
Dementia with Lewy bodies	3
Corticobasal ganglionic degeneration	3
Cerebrovascular dementia	2
Viral encephalitis, including one herpes simplex encephalitis	3
Interval form of CO poisoning	3
Cryptococcal meningoencephalitis	2
Mitochondrial cytopathy	2
Progressive dementia, not otherwise specified	4
Alzheimer disease	1
CNS lymphoma	1
Multiple sclerosis	1
Temporal lobe epilepsy	1
Leukoencephalopathy, not otherwise specified	1
Ganser syndrome	1
Total	32

Thirty-two (age 31 to 84 years with a mean age of 61.9 years; 15 men) of 81 patients had undergone DWI examination. They served as disease controls for DWI because obtaining a large group of individuals with suspected CJD but with an alternative diagnosis was difficult. Of these patients, four had seriously suspected CJD, for whom the final diagnosis in two was metabolic encephalopathy that was improved by IV vitamin administration, one was mitochondrial encephalopathy as confirmed by an enzyme assay, and one was corticobasal ganglionic degeneration verified by autopsy. These controls included dementia with Lewy bodies, Alzheimer disease (AD), cerebrovascular disease, CNS infection, metabolic or mitochondrial encephalopathy, CNS malignancy, corticobasal ganglionic degeneration, interval form of CO intoxication, etc. Dementia with Lewy bodies, AD, and cerebrovascular disease are major differential diagnoses of CJD,[18] and CNS infection, encephalopathy, and CNS malignancy sometimes demonstrate positive 14-3-3 protein test in CSF,[19] which is an important diagnostic marker for CJD.[6] The disease controls are listed in table 2.

We compared the sensitivities of the positive results of MR sequences such as DWI, T2I, and FLAIR. We also assessed interobserver agreement. We compared the sensitivities of the positive results of DWI, PSWC, and brain-specific proteins such as 14-3-3 protein and NSE in CSF for making a diagnosis of CJD. PSWC and positive assay of 14-3-3 protein are included in the WHO diagnostic criteria.[12] These examinations were carried out 3 to 25 weeks after the onset with a mean duration of 10.7 weeks after the onset (see table 1).

Methods. DWI technique. Scans were performed on a number of units. A 1.5 or 1.0 T MR unit (Signa Horizon LX, GE Medical Systems, Milwaukee, WI; or Magnetom Vision, Siemens, Erlangen, Germany) was used. DWI was performed in 26 CJD cases with single-shot spin-echo echo-planar imaging. Imaging parameters were as follows: 4,700 to 5,000/93 to 120/1 or 2 (repetition time/effective echo time/no. excitations), 10 to 15 axial sections of 5- or 6-mm section thickness with a 1.5- to 3.0-mm intersection gap, 128 × 128 matrix, 220- or 230-mm field of view, and a diffusion-encoding strength (*b* factor) of 1,000 s/mm^2. In 23 of 26 CJD cases, T2I was performed, and in 17 of 26 CJD cases, FLAIR was performed. DWI, T2I, and FLAIR were performed on the same day using the same MR unit.

MRI investigation. MRI scans were assessed retrospectively as hard copies by two well-experienced neuroradiologists blind to clinical information, who examined each type of sequence separately, without referring to the other MR sequences, independently and individually. We accepted three types of high-intensity lesions as CJD-related lesions on DWI: lesions in the striatum (caudate or putaminal or both), lesions in the thalamus including the pulvinar, and lesions along the cortical ribbon (cerebral or cerebellar). We also accepted the lesions of several types in combination. We accepted not only the symmetric lesions but also asymmetric or unilateral lesions. DWI scans of the disease control group were also assessed retrospectively as hard copies combined with five DWI scans of CJD patients by the same two neuroradiologists, completely blind to clinical information to minimize observer bias.

PSWCs. EEG was recorded using the International 10–20 System. PSWCs were defined as diffuse biphasic or triphasic sharp wave complexes with a duration between 100 and 600 milliseconds and an intercomplex interval between 500 and 2,000 milliseconds.[5]

Brain-specific proteins in CSF. 14-3-3 protein immunoassay in CSF by means of western blotting was performed using a polyclonal antibody to the β isoform of 14-3-3 protein, SC 629 (Santa Cruz Biotechnology, Santa Cruz, CA). The presence of the band against the antibody, SC 629, was investigated. NSE in CSF was measured commercially using an ELISA (SRL Laboratory, Tokyo, Japan), and a value of >25 ng/mL[20] was judged as positive.

Statistical analyses of the diagnostic sensitivities of DWI, PSWCs, and NSE and 14-3-3 protein in CSF, positive rate of DWI, T2I, and FLAIR, and interobserver agreement rate were done using the Fisher exact probability test.

Results. *MRI.* DWI was examined in 26 CJD patients 3 to 25 weeks after the onset with a mean duration of 10.7 weeks. Twenty-four CJD patients showed high-intensity brain lesions by DWI examination. For both observers, the sensitivity of DWI for the CJD diagnosis was 92.3%. The interobserver agreement rate was 100%. Three patients (12.5%) showed lesions only in the caudate heads and putamen, 10 (41.7%) patients showed linear lesions only in the cerebral cortex, and 11 (45.8%) patients showed lesions in both the basal ganglia and the cerebral cortex (figure 1). Among them, only three patients (12.5%) showed lesions in the thalamus. No patients showed high-intensity lesions in the cerebellum. High-intensity lesions on DWI appeared before brain atrophy. The lesions involving the striatum were not always symmetric at the beginning but later became symmetric (figure 2), although symmetric striatal lesions are well known in CJD.[11] In some cases, the high-intensity lesions with sequential DWI did not always progress with the advance of the disease, and the signal intensity sometimes decreased with the disease progression in some lesions. In some cases, the cortical high signal varied in intensity and anatomic distribution (figure 3). In the terminal stage with profound brain atrophy, the high-intensity lesions became unclear. T2I was examined in 23 of 26 DWI-examined patients, but one T2I scan was excluded because of the low quality due to motion artifacts. One observer judged that 11 of 22 patients were positive (50.0%), and another observer judged that 8 were positive (36.4%). The interobserver agreement rate was 68.2%, and it was lower than that of DWI ($p < 0.005$). In both observers, DWI was more sensitive than T2I ($p < 0.005$ for one observer and $p < 0.0005$ for another observer). FLAIR was examined in 17 of 26 patients. One observer judged that 10 of 17 patients were positive (58.8%), and another observer judged that 7 were positive (41.2%). The interobserver agreement rate was 82.4%, and this also was lower than that of DWI ($p < 0.05$). DWI was more sensitive than FLAIR ($p < 0.01$ for one observer and $p < 0.0005$ for another observer). We show in figure 4 an example in which only DWI could detect abnormal high-intensity lesions.

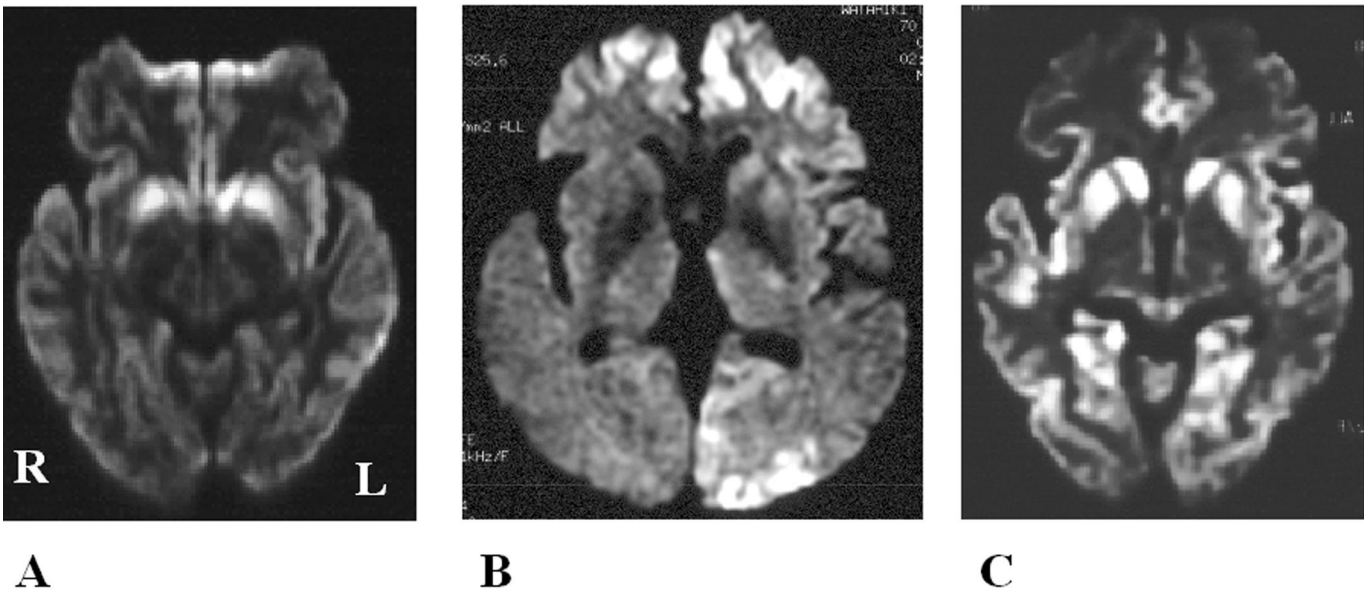

Figure 1. MRI changes seen in Creutzfeldt–Jakob disease. Three patterns of high-intensity lesions were seen: striatal lesion (A), cerebral cortical lesion (B), and a combination of both lesions (C).

DWI failed to detect any lesions in two patients at the first examination. The second DWI showed high-intensity lesions at the striatum in one of those patients. Repeated DWI scans of the other patient did not show any high-intensity lesions throughout his disease course. On the postmortem examination, protease-resistant type 2 prion protein was detected in this patient by western blot analysis using monoclonal antibody 3F4 (Signet Laboratories, Dedham, MA), and there were no spongiform changes. This case was classified as MM2-thalamic according to Parchi's classification (table 1).[3]

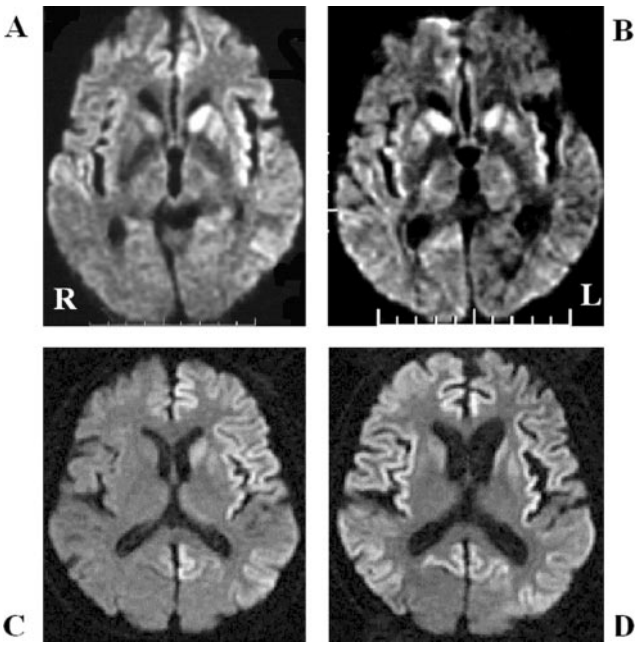

Figure 2. Chronologic change of the striatal and cortical lesions. A case of sporadic Creutzfeldt–Jakob disease (CJD) showing the progression of the basal ganglia signal changes from asymmetric (A) to symmetric (B). The interval between (A) and (B) was 2 months. A case of familial CJD with V180I mutation showing the progression of the cerebral cortex and caudate head signal changes from asymmetric (C) to symmetric (D). The interval between (C) and (D) was 4 months.

High-intensity DWI lesions that were in agreement with our criteria were observed in the disease control patients. One observer judged that a 69-year-old woman with cryptococcal meningoencephalitis and a 60-year-old woman with interval form of CO poisoning were falsely positive. Another observer judged that a 48-year-old woman with herpes simplex encephalitis and a 47-year-old with alcoholic encephalopathy were falsely positive. For both observers, the false-positive rate was 6.3% and the interobserver agreement rate was 87.5%. No highly CJD-suspected patients demonstrated high-intensity lesions. The sensitivity of DWI was 92.3% (95% CI 74.8 to 99.5%) and specificity 93.8% (95% CI 79.2 to 99.2%).

DWI detected the brain lesions before the appearance of PSWCs on EEG in 10 patients. DWI abnormalities were detected as early as at 3 weeks of symptom duration in four patients in whom PSWCs were not yet evident. In seven of eight patients who did not show PSWCs throughout their disease course, the first DWI clearly demonstrated the brain lesions (see table 1).

PSWCs on EEG. EEG was recorded from all 36 patients. Eighteen of 36 (50.0%) patients showed PSWCs that fit the criteria on the first EEG. In 10 of 18 PSWC-negative patients, sequential EEG showed PSWCs. However, eight patients (22.2%) did not show PSWCs in further sequential EEG recordings. The genetic analysis of *PRNP* demonstrated that four had a point mutation of V180I and one had MV at codon 129, and the postmortem examination revealed that two had VV2 and one had MM2-thalamic (see table 1). Generally, these types of CJD patients do not show PSWCs.[3]

Brain-specific proteins in CSF. The 14-3-3 protein was examined in 25 patients and NSE in 30. Twenty-one of those 25 patients (84.0%) were positive for 14-3-3 protein

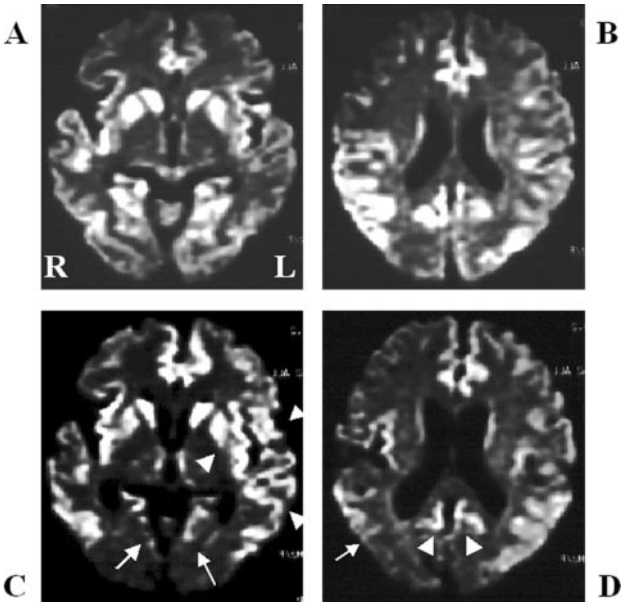

Figure 3. Chronologic change of the cortical lesions in sporadic Creutzfeldt–Jakob disease (sCJD). The cortical high intensity seen in a case of sCJD changed with time, with both increases and decreases in signal intensity in different areas. The high intensity in the bilateral occipital cortices (A) decreased (C, arrows), whereas the signal intensity in the left insular and temporal cortices (A) apparently increased (C, arrowheads). The interval between (A) and (C) was 1 month. The high intensity in the right temporal cortex and bilateral occipital cortices (B) decreased (D, arrow for the left temporal cortex and arrowheads for the bilateral medial occipital cortices). The interval between (B) and (D) was 1 month. Note that the high-intensity lesions depicted in diffusion-weighted imaging did not simply expand with the advance of the disease.

and 22 of those 30 patients (73.3%) were positive for NSE. In 24 patients examined for both brain-specific proteins, 16 were positive for both, 4 were negative for both, and 4 NSE-negative patients were positive for 14-3-3 protein (see table 1).

Comparison of sensitivity of DWI, PSWCs on EEG, and brain-specific CSF protein assay in diagnosing CJD. The sensitivity of DWI examined for the differential diagnosis was 92.3%, of PSWCs 50.0%, of 14-3-3 protein 84.0%, and of NSE 73.3%. DWI was more sensitive than PSWCs ($p < 0.0005$). 14-3-3 protein was more sensitive than PSWCs ($p < 0.01$). DWI tended to be more sensitive than 14-3-3 protein and NSE, but the differences were not significant ($p = 0.36$ and $p = 0.06$) (figure 5). In all 10 patients who had PSWCs in the sequential EEG recording, the lesions had already been detected earlier by DWI. DWI was positive in three of four 14-3-3 protein-negative patients and in six of seven NSE-negative patients. In only one patient who was classified as a rare variant of MM2-thalamic,[3] DWI, PSWC, 14-3-3 protein, and NSE were all negative.

Discussion. MRI had not been thought to be a sensitive noninvasive diagnostic test of CJD[21]; it was previously thought that EEG was the most reliable diagnostic test.[5] Increased signal intensity in the basal ganglia on T2I was first described in 1988,[22] and it was demonstrated that MRI was useful in depicting the lesions of CJD.[23] Although the usefulness of DWI for the early diagnosis of CJD has been suggested,[11,13] no one has compared the ability to depict the lesions among MR sequences such as T2I, FLAIR, and DWI or the accuracy of DWI in diagnosing CJD, especially for the early clinical diagnosis of CJD, with other noninvasive tests including EEG. In this study, we found that the sensitivity of DWI was 92.3% and that DWI was significantly more sensitive than conventional T2I and FLAIR in detecting the CJD-related lesions. T2I and FLAIR, whose sensitivities were 40 to 50%, are inadequate as a test for the first-line differential diagnosis. Further, the CJD-related lesions that we demonstrated on DWI were not detected in a small number of controls with AD, dementia with Lewy bodies, and cerebrovascular dementia, which are the major differential diagnoses of CJD.[18] We have demonstrated the superiority of DWI over the other noninvasive diagnostic tests by comparing its sensitivity with that of PSWCs on EEG, 14-3-3 protein, and NSE examined for the differential diagnosis. Unexpectedly, the interobserver agreement rate of DWI was 100%, and it was significantly higher than that of T2I and FLAIR. This indicates that DWI, which can depict the CJD-related lesions clearly and reliably, may represent a very important diagnostic test for the differential diagnosis. As we demonstrated previously,[13] DWI is more tolerant of motion artifacts than T2I and FLAIR. This advantage is especially important in CJD patients with the involuntary movement of myoclonic jerk. This tolerance may be one of the reasons for the higher sensitivity and the higher interobserver agreement rate of DWI compared with T2I and FLAIR.

The positive rates of T2I by our two observers were 36.4 and 50.0%, and these were significantly lower than a previously reported positive rate for T2I of 79.3%.[23] We think that this discrepancy can be accounted for by the difference in the time when the MRI was examined; the mean duration for our patients from the onset to MRI examination was 10.7 weeks (2.6 months), whereas that of the previous report was 8.1 months.[23] A positive rate for T2I of 67.3% was also reported; however, the positive rate of the first T2I in that report was 43.2%.[24] This is almost the same as in our results.

Currently, PSWCs play a central role in the diagnosis of CJD.[12] However, in the case of PSWC-negative patients, the diagnosis of CJD is sometimes difficult, and such cases are classified as "possible CJD."[12] We have demonstrated in this study not only that DWI was positive earlier than the presence of PSWCs but also that DWI was positive in CJD subjects without PSWCs throughout their disease. In the suspected CJD patients who are diagnosed as "possible CJD," the accuracy of the diagnosis is different between DWI-positive patients and DWI-negative patients. The likelihood of CJD is higher in

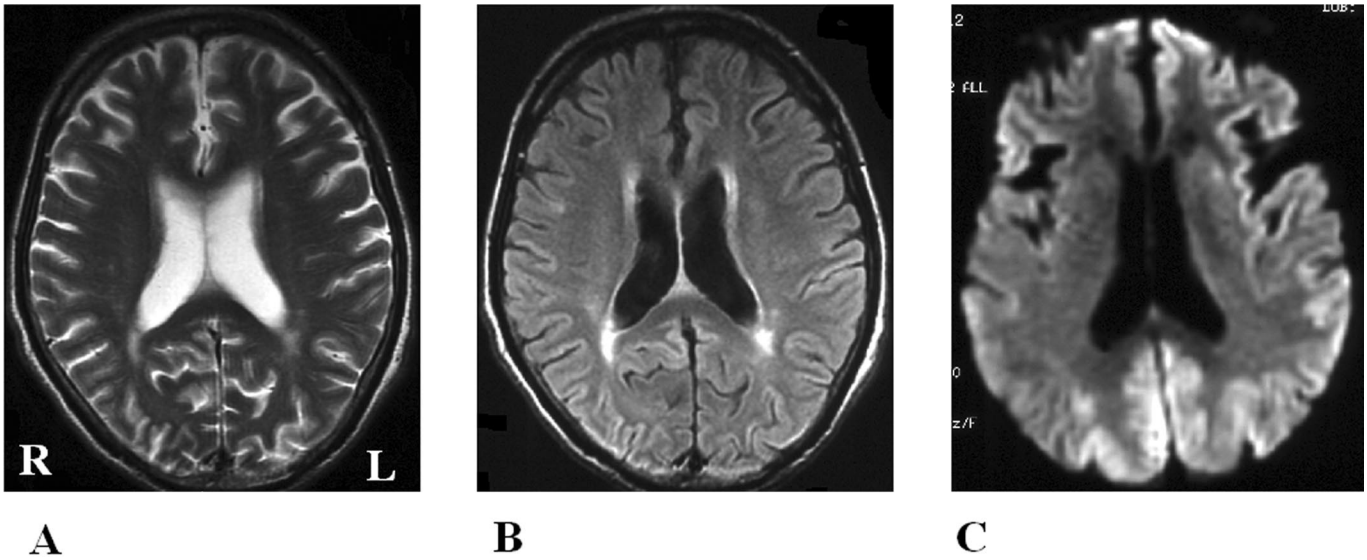

Figure 4. Comparison of conspicuity of Creutzfeldt–Jakob disease–related changes of the same patient on different MRI sequences. T2-weighted imaging (A) and fluid-attenuated inversion recovery imaging (B) show normal findings, and diffusion-weighted MRI (C) demonstrates high-intensity lesions in the cerebral cortex.

DWI-positive patients and lower in DWI-negative patients.

Each observer judged as false positive 2 of 32 disease controls. However, two observers did not agree on the result: one observer judged DWI of cryptococcal meningoencephalitis and interval form of CO poisoning as false positive, and another observer judged DWI of herpes simplex encephalitis and alcoholic encephalopathy as false positive. However, a careful history taking and the presence of pleocytosis in the CSF study significantly reduced the possibility of CJD. DWI was very useful to distinguish CJD from AD, vascular dementia, and dementia with Lewy bodies, which are the major differential diagnoses of CJD[18] and account for the vast majority of dementia in elderly patients.[25] DWI of mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes (MELAS), Wilson disease, and Wernicke encephalopathy can demonstrate similar abnormalities. However, the clinical course and laboratory findings easily distinguish them from CJD. DWI in hypoglycemia,[26] anoxia,[27] and reversible posterior leukoencephalopathy syndrome[28] has also been reported to demonstrate high-intensity lesions similar to those of CJD. However, these have peculiar episodes, and the onset is apparently different from that of CJD. We must mention a 15-year-old boy with a final diagnosis of CNS lupus who was referred to the Japanese CJD Surveillance Committee. His consciousness disturbance developed subacutely, and his DWI showed scattered high-intensity lesions in the cerebral cortex and basal ganglia. His neurologic symptoms improved after the administration of prednisolone. CNS vasculitic disease also needs to be excluded in the differential diagnosis.

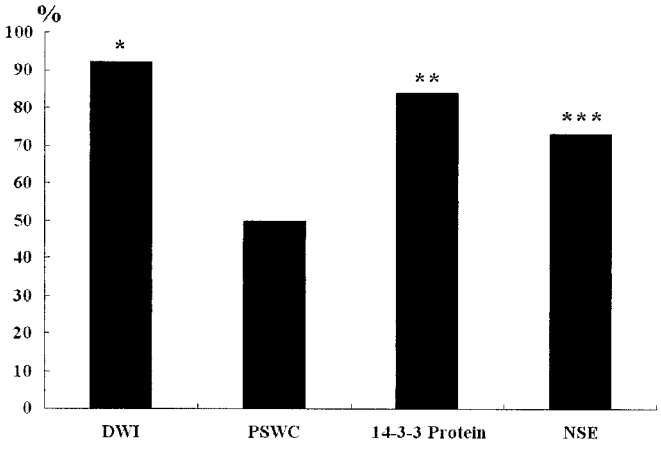

*Figure 5. Percentage of Creutzfeldt–Jakob disease cases with positive test. The positive rates of diffusion-weighted MRI (DWI), periodic sharp wave complexes (PSWCs), 14-3-3 protein, and neuron-specific enolase (NSE) examined for the differential diagnosis were 92.3, 50.0, 84.0, and 73.3%. *DWI was more sensitive than PSWCs ($p < 0.0005$). **14-3-3 protein was more sensitive than PSWCs ($p < 0.01$). *DWI tended to be more sensitive than 14-3-3 protein ($p = 0.36$) and NSE ($p = 0.06$). ***NSE tended to be more sensitive than PSWCs ($p = 0.053$). However, these were not significant.*

The kinds of pathologic findings that correlate with the CJD-related high-intensity lesions demonstrated in DWI are still controversial. Spongiform changes[29] and prion protein deposits[30] are candidates. The time lag from DWI examination to postmortem pathologic examination impedes an accurate understanding. The postmortem examination in one case of familial CJD with V180I whose DWI showed prominent high intensity in the cerebral cortex revealed severe spongiform changes and rather weak prion protein staining there immunohistochemically. The postmortem examination in a patient with spo-

radic CJD with MM2-thalamic whose DWI demonstrated negative findings throughout the disease course revealed no spongiform changes and rather weak prion protein staining. Based on our limited experience, we speculate that the high-intensity lesions depicted by DWI are related to spongiform changes rather than to prion protein deposition; however, more animal and postmortem studies are required to confirm this. It remains unclear why some high-intensity lesions become less prominent with the advance of the disease. We need to accumulate radiopathologic studies for several types of CJD.

The weaknesses of this study are that the number of ideal controls, CJD suspects with a final alternative diagnosis, was too small, because it was difficult to obtain a large number of such patients, and also the lack of pathologic diagnosis in the majority of CJD patients, with the result that only 9 of 36 patients were definite because of the difficulty in obtaining a postmortem examination in many cases. To overcome these weak points, a multicenter analysis of pathologically verified CJD patients and ideal controls is needed.

Last, in interpreting the results of the diagnostic tests, we must understand that such laboratory tests as DWI, brain-specific protein, and EEG reflect different aspects of the disease. Brain-specific proteins reflect the ongoing rapid and massive destruction of the neurons, and EEG reflects the current state of the injured brain.

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References

1. Masters CL, Harris JO, Gadujeck DC, et al. Creutzfeldt–Jakob disease: patterns of worldwide occurrence and the significance of familial and sporadic clustering. Ann Neurol 1979;5:177–188.
2. Will RG, Ironside JW, Zeidler M, et al. A new variant of Creutzfeldt–Jakob disease in the UK. Lancet 1996;347:921–925.
3. Parchi P, Giese A, Capellari S, et al. Classification of sporadic Creutzfeldt–Jakob disease based on molecular and phenotypic analysis of 300 subjects. Ann Neurol 1999;46:224–233.
4. Zerr I, Schulz-Schaeffer WJ, Giese A, et al. Current clinical diagnosis in Creutzfeldt–Jakob disease: Identification of uncommon variants. Ann Neurol 2000;48:323–329.
5. Steinhoff BJ, Räcker S, Herrendorf G, et al. Accuracy and reliability of periodic sharp wave complexes in Creutzfeldt–Jakob disease. Arch Neurol 1996;53:162–166.
6. Zerr I, Bodemer M, Gefeller O, et al. Detection of 14-3-3 protein in the cerebrospinal fluid supports the diagnosis of Creutzfeldt–Jakob disease. Ann Neurol 1998;43:32–40.
7. Zerr I, Bodemer M, Räcker S, et al. Cerebrospinal fluid concentration of neuron-specific enolase in diagnosis of Creutzfeldt–Jakob disease. Lancet 1995;345:1609–1610.
8. Zerr I, Pocchiari M, Collins S, et al. Analysis of EEG and CSF 14-3-3 proteins as aids to the diagnosis of Creutzfeldt–Jakob disease. Neurology 2000;55:811–815.
9. Echebarria H, Saiz A, Graus F, et al. Detection of 14-3-3 protein in the CSF of a patient with Hashimoto's encephalopathy. Neurology 2000;54:1539–1540.
10. Saiz A, Graus F, Dalmau J, et al. Detection of 14-3-3 protein in the cerebrospinal fluid of patients with paraneoplastic neurological disorders. Ann Neurol 1999;46:774–777.
11. Bahn MM, Parchi P. Abnormal diffusion-weighted magnetic resonance images in Creutzfeldt–Jakob disease. Arch Neurol 1999;56:577–583.
12. Zeidler M, Gibbs CJ Jr, Meslin F. WHO manual for strengthening diagnosis and surveillance of Creutzfeldt–Jakob disease. Geneva: World Health Organization, 1998:47–51.
13. Murata T, Shiga Y, Higano S, et al. Conspicuity and evolution of lesions in Creutzfeldt–Jakob disease at diffusion-weighted imaging. AJNR Am J Neuroradiol 2002;23:1164–1172.
14. Fukushima R, Shiga Y, Nakamura M, et al. MRI characteristics of sporadic CJD with valine homozygosity at codon 129 of the prion protein gene and PrPSc type 2 in Japan. J Neurol Neurosurg Psychiatry 2004;75:485–487.
15. Jin K, Shiga Y, Shibuya S, et al. Clinical features of Creutzfeldt–Jakob disease with V180I mutation. Neurology 2004;62:502–505.
16. Inoue I, Kitamoto T, Doh-ura K, et al. Japanese family with Creutzfeldt–Jakob disease with codon 200 point mutation of the prion protein gene. Neurology 1994;44:299–301.
17. Satoh A, Goto H, Satoh H, et al. A case of Creutzfeldt–Jakob disease with a point mutation at codon 232: Correlation of MRI and neurologic findings. Neurology 1997;49:1469–1470.
18. UK Creutzfeldt–Jakob Disease Surveillance Unit. Creutzfeldt–Jakob disease surveillance in the UK eleventh annual report 2002. 2003.
19. Lamstra AW, van Meegen MT, Vreyling JP, et al. 14-3-3 testing in diagnosing Creutzfeldt–Jakob disease. A prospective study in 112 patients. Neurology 2000;55:514–516.
20. Beaudry P, Cohen P, Brandel JP, et al. 14-3-3 protein, neuron-specific enolase, and S-100 protein in cerebrospinal fluid of patients with Creutzfeldt–Jakob disease. Dement Geriatr Cogn Disord 1999;10:40–46.
21. Zeidler M, Will RG, Ironside JW, et al. Magnetic resonance imaging is not a sensitive test for Creutzfeldt–Jakob disease. Br Med J 1996;312:844.
22. Gertz HJ, Henkes H, Cervos-Navvaro J. Creutzfeldt–Jakob disease: correlation of MRI and neuropathologic findings. Neurology 1988;38:1481–1482.
23. Finkenstaedt M, Szudra A, Zerr I, et al. MR imaging of Creutzfeldt–Jakob disease. Radiology 1996;199:793–798.
24. Schröter A, Zerr I, Henkel H, et al. Magnetic resonance imaging in the clinical diagnosis of Creutzfeldt–Jakob disease. Arch Neurol 2000;57:1751–1757.
25. McKeith IG, Galasko D, Kosaka K, et al. Consensus guidelines for the clinical and pathologic diagnosis of dementia with Lewy bodies (DLB): Report of the Consortium on DLB International Workshop. Neurology 1996;47:1113–1124.
26. Finelli PF. Diffusion-weighted MR in hypoglycemic coma. Neurology 2001;57:933–935.
27. Arbelaez A, Castillo M, Mukherji SK. Diffusion-weighted MR imaging of global cerebral anoxia. AJNR Am J Neuroradiol 1999;20:999–1007.
28. Mukherjee P, McKinstry RC. Reversible posterior leukoencephalopathy syndrome: evaluation with diffusion-weighted MR imaging. Radiology 2001;219:756–765.
29. Mittal S, Farmer P, Kalina P, et al. Correlation of diffusion-weighted magnetic resonance imaging with neuropathology in Creutzfeldt–Jakob disease. Arch Neurol 2002;59:128–134.
30. Haïk S, Dormont D, Fandeux BA, et al. Prion protein deposits match magnetic resonance imaging signal abnormalities in Creutzfeldt–Jakob disease. Ann Neurol 2002;51:797–799.