



Multicentre, multiobserver study of diffusion-weighted and fluid-attenuated inversion recovery MRI for the diagnosis of sporadic Creutzfeldt–Jakob disease: a reliability and agreement study



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Research article

Multicentre, multiobserver study of diffusion-weighted and fluid-attenuated inversion recovery MRI for the diagnosis of sporadic Creutzfeldt–Jakob disease: a reliability and agreement study

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ABSTRACT

Objectives: To assess the utility of the display standardization of diffusion-weighted imaging (DWI) and compare the effectiveness of DWI and fluid-attenuated inversion recovery (FLAIR) for the diagnosis of sporadic Creutzfeldt–Jakob disease (sCJD).

Design: Data of 1.5-Tesla DWI and FLAIR were obtained from 29 patients with sCJD and 13 controls. Standardization of DWI display was performed utilizing b0 imaging. Thirteen observers comprising 8 neurologists and 5 radiologists participated in standardized DWI, variable DWI (the display adjustment was observer dependent), and FLAIR sessions. The observers independently assessed each MRI for CJD-related lesions, i.e. hyperintensity in the cerebral cortex or striatum, using a continuous rating scale. Performance was evaluated by the area under the receiver operating characteristics curve (AUC).

Results: The mean AUC values were 0.84 (95% confidence intervals [CI], 0.81–0.87) for standardized DWI, 0.85 (95% CI, 0.82–0.88) for variable DWI, and 0.68 (95% CI, 0.63–0.72) for FLAIR, demonstrating the superiority of DWI ($P < 0.05$). The intraclass correlation of standardized DWI (0.74; 95% CI, 0.66–0.83) was higher than that of variable DWI (0.72; 95% CI, 0.62–0.81), whereas the intraclass correlation of FLAIR (0.63; 95% CI, 0.53–0.74) was poor, although the differences were not statistically significant.

Conclusions: Standardized DWI is as reliable as variable DWI, and the two DWI displays are superior to FLAIR for the diagnosis of sCJD. We propose that hyperintensity in the cerebral cortex or striatum on 1.5-Tesla DWI but not FLAIR can be a reliable diagnostic marker for sCJD.

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ARTICLE SUMMARY

Article focus

- Evaluation of the reliability of diffusion-weighted imaging (DWI) display standardization for the diagnosis of sporadic Creutzfeldt–Jakob disease (sCJD).
- Comparison between DWI and fluid-attenuated inversion recovery (FLAIR) for the diagnosis of sCJD.

Key messages

- Standardized DWI display is as reliable as observer-dependent DWI display.
- DWI is superior to FLAIR for the diagnosis of sCJD.
- Hyperintensity in the cerebral cortex or striatum on 1.5-Tesla DWI but not FLAIR can be a reliable diagnostic marker for sCJD.

Strengths and limitations of this study

- Strength of this study is the large number of physicians who participated in the observer performance study.
- This study was limited by the retrospective nature.

INTRODUCTION

Reliable detection of Creutzfeldt–Jakob disease (CJD) is imperative for infection control and treatment. Magnetic resonance imaging (MRI) is useful for the early diagnosis of CJD,[1, 2] whereas the utility of electroencephalography (EEG) and conventional cerebrospinal fluid (CSF) tests have been limited.[3]

Diffusion-weighted imaging (DWI) and fluid-attenuated inversion recovery (FLAIR) are key techniques for the diagnosis of sporadic CJD (sCJD) with high sensitivity and specificity when assessed by expert neurologists or neuroradiologists.[1, 4, 5]

However, the utility of MRI for general neurologists or radiologists who are not familiar with diagnosing CJD remains elusive. Moreover, standardization of MRI methodologies, which would be essential for the reproducible assessment of MRI findings of CJD cases, have not been achieved in previous studies.[1, 4, 5] DWI display conditions may particularly vary among institutions or operators,[6] which can give rise to inaccurate assessment of CJD-related lesions, specifically subtle abnormalities in the cerebral cortex. Meanwhile, although DWI seems superior to FLAIR for the detection of CJD lesions,[5] direct comparison of the two sequences is yet to be performed.

To address these issues, we investigated the utility of a newly proposed

standardization method of DWI display[6, 7] and compared the effectiveness of DWI and FLAIR for the diagnosis of sCJD, particularly for differentiating between abnormal and normal signals by neurologists and radiologists who are not necessarily CJD experts. We conducted a multicentre, multiobserver case-control study and evaluated observer performance with receiver operating characteristics (ROC) analysis.

METHODS

Subjects

Patients diagnosed with sCJD by the CJD Surveillance Committee of Japan[8] from October 2005 to September 2010 were eligible to participate in this study. The accuracy of the diagnosis was defined as follows: definite, i.e. pathologically verified cases; probable, i.e. cases with neuropsychiatric manifestations compatible with sCJD and periodic sharp wave complexes (PSWCs) on EEG without pathological examinations; and possible, i.e. cases with the same findings as probable sCJD, but no PSWCs on EEG.[8, 9] The World Health Organization (WHO) criteria[10] were not applied because the assay of CSF 14-3-3 protein, which is required by the WHO criteria, was standardized only since April 2009 in Japan.[11] The prion protein gene (*PRNP*) was analyzed in the open reading frame after extracting DNA from patients'

blood.[12, 13] For neuropathological examinations, brain sections were stained with routine techniques, and immunohistochemistry was performed using the mouse monoclonal antibody 3F4 (Senetek, MD Heights, MO).[12] For PrP^{Sc} typing, frozen brain tissues were homogenized and analyzed by western blot for proteinase K-resistant PrP using the 3F4 antibody.[14] Assays for CSF γ -isoform of 14-3-3 protein,[11] total tau protein (cut-off value, 1300 pg/ml),[15] and real-time quaking-induced conversion (RT-QUIC)[16] were performed in patients whose CSF samples were available. The following patients were eligible as disease controls: patients who were suspected to have prion disease by primary physicians but were denied to have prion disease by the Committee or those who were diagnosed with other neurological disorders at Tokushima University Hospital from October 2005 to September 2010. We requested physicians who had referred patients to the Committee to provide initial MRI data of eligible patients.

This study was approved by the Medical Ethics Committee of Kanazawa University and the Ethics Committees of the Tokushima University Hospital and Tokyo Medical and Dental University. Written informed consent was obtained from all patients or their families.

Magnetic resonance imaging

DWI, b0, and FLAIR images were converted to the Digital Imaging and Communication in Medicine (DICOM) format. When the DICOM data contained patient information, it was excluded by one of the investigators (M.H.) before the observer performance study. All MRI studies were performed on 1.5-Tesla scanners at each hospital. Quadrature detection head coils or multichannel head coils were used. DWI was performed using the single-shot spin-echo echo planar imaging technique with the following parameters: repetition time, 4000–8000 ms; echo time, 70–100 ms; b value, 1000 s/mm²; slice thickness, 5 mm; matrix size, 128 × 80–128 × 128; field of view, 220–230 mm; 16–20 contiguous axial sections parallel to a line through the anterior and posterior commissures were obtained from each patient. The scanning parameters of FLAIR were as follows: repetition time, 8000–10000 ms; inversion time, 2000–2500 ms; effective echo time, 105–120 ms; matrix size, 256 × 192–320 × 224; field of view, 210–220 mm; slice thickness, 5–6 mm with 1–1.5 mm interslice gaps; and 19–20 slices per patient.

Display methods

Two display methods were used for DWI: standardized and variable. In the standardized display, the window width and level settings were constant for all

evaluations and could not be changed. Details of the standardized display have been reported elsewhere.[6] In brief, the window width and level were as follows: window width = SI_{b0} and window level = $SI_{b0}/2$, where SI_{b0} represents the signal intensity in the normal-appearing subcortical region on b0 imaging.[6] One radiologist (M.H.) manually measured SI_{b0} within a circular region of interest. The calculated window width and level were applied to all images. In the variable display mode, regarded as the most reliable for assessment of DWI, each observer was able to change the window width and level settings on the monitor according to preference. FLAIR was assessed with the variable display method, because no standardized methods are currently available for FLAIR display.

Observer performance study

Eight neurologists (6–27 years of experience; mean, 12 years; board-certified, 6) and five radiologists (5–25 years of experience; mean, 12.8 years; board-certified, 4; neuroradiologist, 1) participated in the observer performance study at The University of Tokushima Graduate School (persons, 6; neurologists, 3) and Tokyo Medical and Dental University (persons, 7; neurologists, 5 including N.S. and Y.S.). Before the test, the observers were informed that the purpose of the study was to evaluate their performance in detecting MRI lesions compatible with CJD, i.e. hyperintensity in the

cerebral cortex or striatum, regardless of signal changes in other regions including the thalamus. Three sessions were conducted: standardized DWI, variable DWI, and FLAIR. To reduce the effect of learning, the interval between reading sessions was 1 week or longer. The order of the three sessions was randomized among the observers. Using computer randomization, images of patients with and without sCJD were intermixed. All cases were presented in the same randomized order to the observers in each session. Each observer independently viewed all slices of each MRI study on the same type of monitors (Let'snote, Panasonic, Osaka) using INTAGE Realia Professional (Cubernet, Tokyo) run on Windows XP (Microsoft). The observers were allowed to adjust the window width and level only in variable DWI and FLAIR sessions but not in the standardized DWI session. Observers were blinded to any clinical information including age, sex, and diagnosis.

Each observer used a continuous rating scale of a line-marking method to rate his or her confidence level on the paper format independently. At the left end of the line, a confidence level that lesions compatible with CJD were definitely absent was indicated, whereas at the right end, a confidence level that lesions were definitely present was indicated. Intermediate levels of confidence were indicated by the different positions on the line between the two ends. The distance between the left

end and the marked point was converted to a confidence level that could range from 0 to 100, as described elsewhere.[17]

Statistical Analyses

Observer performance was evaluated using ROC analysis with SPSS version 19 (IBM, Armonk, NY). The ROC curves for each observer indicated the ratio of the true-positive fraction to the false-positive fraction at each confidence level. The area under the ROC curve (AUC) was used to compare observer performance for accurately detecting CJD lesions. Intraclass correlations were calculated in the neurologist group, the radiologist group, and for all observers by two-way random consistency measures using the SPSS software. In all the analyses, P values of less than 0.05 were considered statistically significant.

RESULTS

Patients and controls

MRI data from 85 patients were provided. Of these, 42 subjects from 15 hospitals (including authors' institutions) were eligible for this study after excluding cases that were diagnosed with non-sporadic CJD or lacked the required MRI sequences. This study cohort included 29 patients with sCJD (men, 11; mean age, 71 years; duration

before MRI, 4.4 ± 6.1 months), 3 patients who were suspected of CJD but eventually diagnosed as negative by the Committee, and 10 patients diagnosed with other neurological disorders. Of the 29 sCJD patients, 4 had definite, 24 had probable, and 1 had possible CJD. Twenty-six cases underwent *PRNP* analysis; 24 were homozygous for methionine at codon 129, and 2 were heterozygous with methionine and valine at codon 129. Of the 4 definite cases, PrP^{Sc} was type 1 in two cases, type 1+2 in one case, and type 2 in one case. Eleven of 15 CSF samples from probable sCJD cases were positive for PrP^{Sc} by RT-QUIC (table 1).

Diagnoses for 3 prion-denied patients were immune-mediated encephalopathy, juvenile Alzheimer's disease, and frontotemporal dementia. Other neurological controls were diagnosed with Alzheimer's disease, Parkinson's disease, spinocerebellar degeneration, vascular dementia, old cerebral infarction, benign paroxysmal positional vertigo, dizziness, temporal arteritis, cervical spondylosis, and diabetic neuropathy.

Table 1 Clinical profiles of patients with sporadic Creutzfeldt–Jakob disease

No	Age/ sex	Diagnosis	Codon129/ PrP ^{Sc}	14-3-3/ total tau	RT-QUIC	Pre-MRI duration (months)
1	69/M	Definite	MM/1	++	+	-2*
2	77/F	Definite	MM/1	++	+	19
3	75/F	Definite	ND/1+2	++	+	3
4	65/M	Definite	MM/2	-/-	-	12
5	69/M	Probable	MM	ND	-	0.5
6	72/F	Probable	MM	ND	ND	0.5
7	77/F	Probable	MM	-/-	+	0.5
8	72/M	Probable	MM	ND	ND	1
9	63/M	Probable	MM	++	+	1.5
10	88/F	Probable	MM	ND	ND	1.5
11	75/M	Probable	MV	ND	ND	1.5
12	56/M	Probable	MM	++	+	2
13	67/M	Probable	MM	++	-	2
14	70/M	Probable	MM	++	+	2
15	70/F	Probable	MM	++	+	2
16	74/F	Probable	MM	++	-	2
17	84/F	Probable	MM	+/-	+	2
18	85/F	Probable	MM	-/+	+	2
19	49/F	Probable	ND	++	+	2
20	74/F	Probable	MV	++	+	2.5
21	54/F	Probable	ND	ND	ND	2.5
22	61/M	Probable	MM	ND	ND	3
23	72/F	Probable	MM	+/-	-	3
24	81/F	Probable	MM	-/-	+	3
25	70/M	Probable	MM	++	+	6
26	83/F	Probable	MM	++	ND	9
27	67/F	Probable	MM	++	-	15
28	84/F	Probable	MM	++	-	26
29	57/F	Possible	MM	ND	ND	4

*MRI was obtained two months before the symptom onset.[2]
CJD, Creutzfeldt–Jakob disease; MM, homozygous for methionine; MV, heterozygous with methionine and valine; ND, not done; RT-QUIC, real-time quaking-induced conversion.

Diagnostic performance

We investigated the diagnostic performance of standardized DWI, variable DWI, and FLAIR images assessed by 8 neurologists and 5 radiologists using ROC analysis. Mean AUC values obtained from the 3 sessions were compared within the neurologist group, the radiologist group, and all observers (figure 1, table 2). The AUC values for standardized and variable DWI were not different within each professional group or for the total observer group. On the other hand, AUC values for FLAIR were significantly lower than DWI displayed by either method ($P < 0.05$).

Table 2 Areas under the receiver operating characteristic curves (AUCs)

	Neurologists	Radiologists	All observers
sDWI	0.86 (0.82–0.90)	0.82 (0.77–0.88)	0.84 (0.81–0.87)
vDWI	0.86 (0.82–0.90)	0.83 (0.77–0.89)	0.85 (0.82–0.88)
FLAIR	0.69 (0.63–0.75)	0.66 (0.58–0.73)	0.68 (0.63–0.72)

Means (95% confidence intervals) are indicated.

DWI, diffusion-weighted imaging; FLAIR, fluid-attenuated inversion recovery; sDWI, standardized DWI; vDWI, variable DWI.

Rating agreement

To measure the extent to which the observers agreed when rating the MRI findings, intraclass correlations were calculated. The intraclass correlation of the standardized DWI was the highest among the three display conditions in the neurologist group, the radiologist group, and all observers although the difference was not significant. In contrast, the intraclass correlation of FLAIR was poor (figure 2).

DISCUSSION

We demonstrated that standardized DWI was as useful as variable DWI, and that both DWI displays are superior to FLAIR for the diagnosis of sCJD when assessed by multiobservers with various specialty backgrounds.

Our standardization method of DWI display was originally proposed as an easy-to-use way to decide the window width and level for DWI even in emergency settings.[6] Indeed, this method was demonstrated as useful for detecting acute ischemic lesions on DWI.[7] Results of the present study shows the standardization method is also reliable for diagnosis of sCJD, in which DWI is one of the key sequences. We suggest some advantages of standardized DWI over variable DWI although there was no statistical difference between the two methods. First,

standardized DWI can be helpful for physicians who can refer only to hardcopies, but not softcopies. Second, even for doctors who can readily refer to softcopies and thus variable DWI, the standardization method can simplify assessment procedure without any disadvantages. Third, the standardization can facilitate direct comparison of DWI findings from different CJD patients.

DWI and FLAIR have been reported as useful markers for the diagnosis of CJD. Of these, DWI has been assumed to be the most sensitive, although without direct evidence.[1, 5, 18] Hyperintensity in the cerebral cortices, the striatum or both indicate the diagnosis of CJD. The striatum hyperintensity is anterior-dominant at early stages of the disease.[19] MRI lesion profiles reportedly differ among molecular subtypes of sCJD,[20, 21] which was not reproduced in a recent study.[5] Zerr et al. proposed that high signal abnormalities in caudate nucleus and putamen or at least two cortical regions (temporal, parietal, or occipital lobes) either in DWI or FLAIR, together with typical clinical signs can be diagnostic for probable sCJD.[4] Based partly upon their report, “high signal in caudate/putamen on MRI brain scan” has been used as one of the laboratory findings in the diagnostic criteria for probable sCJD in the European CJD Surveillance System (EUROCJD) since January 2010.[22] However, their criteria did not distinguish DWI and FLAIR, thereby

maintaining ambiguity about the diagnostic values of MRI in situations where DWI is not available. Our data indicate that FLAIR without DWI is unreliable for the diagnosis of sCJD. On the other hand, high signals in the cerebral cortex have not been regarded as diagnostic in the EUROCD criteria, probably because cortical abnormalities are less reliable on conventional MRI. Our results suggest that, using standardized or variable DWI but not FLAIR, cortical signals can also be utilized as a diagnostic marker.

Meanwhile, Young et al. reported that the sensitivity and the specificity of DWI and FLAIR for the diagnosis of CJD are 91% and 95%, respectively.[23] More recently, Vitali et al. reported that hyperintensity greater on DWI than FLAIR is diagnostic for sCJD, whereas hyperintensity greater on FLAIR than DWI is characteristic for non-prion rapidly progressive dementia.[5] Furthermore, reduction of apparent diffusion coefficient in subcortical (striatum) hyperintensity regions on DWI is supportive for sCJD.[5, 24, 25] These findings can be greatly helpful for differentiating sCJD from other rapidly progressive dementia. However, assessment of FLAIR lesions tends to vary among physicians, particularly among neurologists, as shown by the present study, and standardized methods for FLAIR or apparent diffusion coefficient map have not been established until date. Therefore, clinical

criteria which require DWI but not necessarily FLAIR or apparent diffusion coefficient will be more readily applicable.

As many as 13 neurologists and radiologists from different institutions participated in the observer performance study, although the sample size of patients was relatively small. Notably, the observers had various specialty backgrounds such as stroke neurologists, neurophysiologists, experts in dementia or prion disease, and general and neuroradiologists. This variety simulates practical situations in which the diagnosis of suspected CJD cases may be made by physicians who do not necessarily specialize in prion disease.

This study has some limitations. First, we did not evaluate patterns of cortical involvement suggestive of sCJD[4, 5] because we had to address whether DWI or FLAIR is suitable for detecting cortical lesions in the first place. Second, we did not assess the difference among sCJD subtypes[21] because majority of our cases had a typical phenotype and were homozygous for methionine; thus, they were compatible with MM1 sCJD. Until date, MM2 thalamic-type sCJD remains a diagnostic challenge in MRI-based assessment; thalamic hypoperfusion or hypometabolism on SPECT or PET can be useful.[26] Third, majority of the control patients were not

those who were suspected to have CJD. However, the principle aim of the present study was to establish a display method which reliably distinguishes potentially CJD-associated signals from normal signals. Thus, our results provide a practical foundation for utilizing DWI as a general diagnostic marker of sCJD when combined with previous findings.[1, 4, 5]

Although neuropathological confirmation of the diagnosis of sCJD was obtained in few cases, we performed RT-QUIC, a newly established CSF PrP^{Sc} amplification assay which achieved greater than 80% sensitivity and 100% specificity for CJD.[16]

Overall, 15 of 29 cases (51.7%) were pathologically proven or confirmed by RT-QUIC to have CJD. It will be important to further evaluate accurate diagnostic ability (sensitivity and specificity) of DWI in a prospective cohort of suspected CJD patients, i.e. consecutive patients registered to the CJD surveillance who will also undergo CSF confirmation tests or neuropathological analyses.

In conclusion, we suggest that hyperintensity in the cerebral cortex or striatum assessed on the standardized or variable DWI scanned with 1.5-Tesla machines can be a reliable first-line, on-site diagnostic marker for sCJD.

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Competing interests None.

Ethics approval This study was approved by the Medical Ethics Committee of Kanazawa University and the Ethics Committees of the Tokushima University Hospital and Tokyo Medical and Dental University.

Patient consent Obtained.

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REFERENCES

1. Shiga Y, Miyazawa K, Sato S, *et al.* Diffusion-weighted MRI abnormalities as an early diagnostic marker for Creutzfeldt–Jakob disease. *Neurology* 2004;**63**:443–449.

2. Satoh K, Nakaoka R, Nishiura Y, *et al.* Early detection of sporadic CJD by diffusion-weighted MRI before the onset of symptoms. *J Neurol Neurosurg Psychiatry* 2011;**82**:942–943.

3. Chitravas N, Jung RS, Kofskey DM, *et al.* Treatable neurological disorders misdiagnosed as Creutzfeldt–Jakob disease. *Ann Neurol* 2011;**70**:437–444.

4. Zerr I, Kallenberg K, Summers DM, *et al.* Updated clinical diagnostic criteria for sporadic Creutzfeldt–Jakob disease. *Brain* 2009;**132**:2659–2668.

5. Vitali P, Maccagnano E, Caverzasi E, *et al.* Diffusion-weighted MRI hyperintensity patterns differentiate CJD from other rapid dementias. *Neurology* 2011;**76**:1711–1719.

6. Sasaki M, Ida M, Yamada K, *et al.* Standardizing display conditions of diffusion-weighted images by using concurrent b0 images: a multivendor multi-institutional study. *Magn Reson Med Sci* 2007;**6**:133–137.

7. Hirai T, Sasaki M, Meada M, *et al.* Diffusion-weighted imaging in ischemic

- stroke: effect of display method on observers' diagnostic performance. *Acad Radiol* 2009;**16**:305–312.
8. Nozaki I, Hamaguchi T, Sanjo N, *et al*. Prospective 10-year surveillance of human prion diseases in Japan. *Brain* 2010;**133**:3043–3057.
9. Masters CL, Harris JO, Gajdusek DC, *et al*. Creutzfeldt–Jakob disease: patterns of worldwide occurrence and the significance of familial and sporadic clustering. *Ann Neurol* 1979; **5**:177–188.
10. WHO. Global surveillance, diagnosis and therapy of human transmissible spongiform encephalopathies: report of a WHO consultation. In: *World Health Organization: Emerging and Other Communicable Diseases, Surveillance and Control*. Geneva:WHO;1998
11. Satoh K, Tobiume M, Matsui Y, *et al*. Establishment of a standard 14-3-3 protein assay of cerebrospinal fluid as a diagnostic tool for Creutzfeldt–Jakob disease. *Lab Invest* 2010;**90**:1637–1644.
12. Kitamoto T, Shin RW, Doh-ura K, *et al*. Abnormal isoform of prion proteins accumulates in the synaptic structures of the central nervous system in patients with Creutzfeldt–Jakob disease. *Am J Pathol* 1992;**140**:1285–1294.
13. Kitamoto T, Ohata M, Doh-ura K, *et al*. Novel missense variants of prion protein in Creutzfeldt–Jakob disease or Gerstmann–Sträussler syndrome. *Biochem*

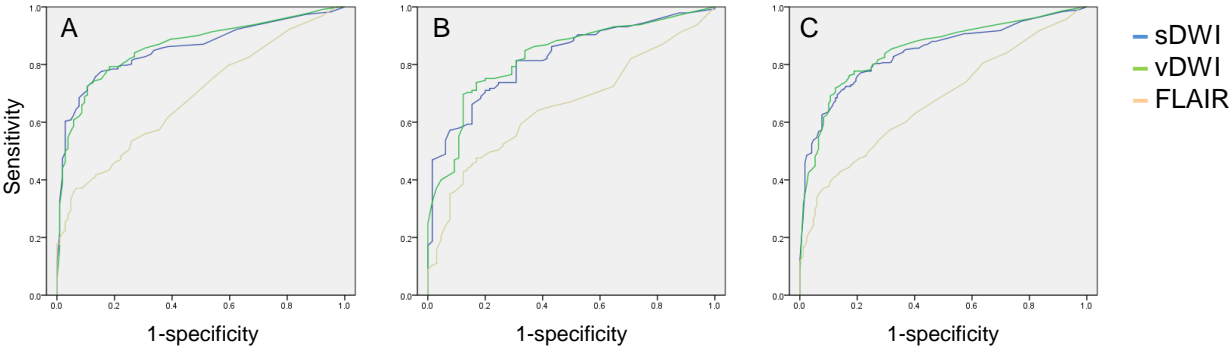
- Biophys Res Commun* 1993;**191**:709–714.
14. Shimizu S, Hoshi K, Muramoto T, *et al.* Creutzfeldt–Jakob disease with florid-type plaques after cadaveric dura mater grafting. *Arch Neurol* 1999;**56**:357–362.
15. Satoh K, Shirabe S, Eguchi H, *et al.* 14-3-3 protein, total tau and phosphorylated tau in cerebrospinal fluid of patients with Creutzfeldt–Jakob disease and neurodegenerative disease in Japan. *Cell Mol Neurobiol* 2006;**26**:45–52.
16. Atarashi R, Satoh K, Sano K, *et al.* Ultrasensitive human prion detection in cerebrospinal fluid by real-time quaking-induced conversion. *Nat Med* 2011;**17**:175–178.
17. Hirai T, Korogi Y, Arimura H, *et al.* Intracranial aneurysms at MR angiography: effect of computer-aided diagnosis on radiologists’ detection performance. *Radiology* 2005;**237**:605–610.
18. Kallenberg K, Schulz-Schaeffer WJ, Jastrow U, *et al.* Creutzfeldt–Jakob disease: comparative analysis of MR imaging sequences. *Am J Neuroradiol* 2006;**27**:1459–1462.
19. Murata T, Shiga Y, Higano S, *et al.* Conspicuity and evolution of lesions in Creutzfeldt–Jakob disease at diffusion-weighted imaging. *Am J Neuroradiol* 2002;**23**:1164–1172.

20. 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.
21. Meissner B, Kallenberg K, Sanchez-Juan P, *et al.* MRI lesion profiles in sporadic Creutzfeldt–Jakob disease. *Neurology* 2009;**72**:1994–2001.
22. Diagnostic criteria for sporadic CJD from 1 January 2010. In: National Creutzfeldt–Jakob Disease Surveillance Diagnostic Criteria [online]. Available at: www.cjd.ed.ac.uk/criteria.htm. Accessed October 3, 2011.
23. Young GS, Geschwind MD, Fischbein NJ, *et al.* Diffusion-weighted and fluid-attenuated inversion recovery imaging in Creutzfeldt–Jakob disease: high sensitivity and specificity for diagnosis. *Am J Neuroradiol* 2005;**26**:1551–1562.
24. Lin YR, Young GS, Chen NK, *et al.* Creutzfeldt–Jakob disease involvement of rolandic cortex: a quantitative apparent diffusion coefficient evaluation. *Am J Neuroradiol* 2006;**27**:1755–1759.
25. Fujita K, Nakane S, Harada M, *et al.* Diffusion tensor imaging in patients with Creutzfeldt–Jakob disease. *J Neurol Neurosurg Psychiatry* 2008;**79**:1304–1306.
26. Hamaguchi T, Kitamoto T, Sato T, *et al.* Clinical diagnosis of MM2-type sporadic Creutzfeldt–Jakob disease. *Neurology* 2005;**64**:643–648.

FIGURE LEGENDS

Figure 1 Receiver operating characteristic curves for each display in diagnosis of sporadic Creutzfeldt–Jakob disease. (A) Neurologists. (B) Radiologists. (C) All observers. The true rate (sensitivity) is plotted as a function of the false positive rate (1 - specificity).
DWI, diffusion-weighted imaging; FLAIR, fluid-attenuated inversion recovery; sDWI, standardized DWI; vDWI, variable DWI.

Figure 2 Intraclass correlations for each display. Error bars represent upper limits of 95% confidence intervals.
DWI, diffusion-weighted imaging; FLAIR, fluid-attenuated inversion recovery; sDWI, standardized DWI; vDWI, variable DWI.



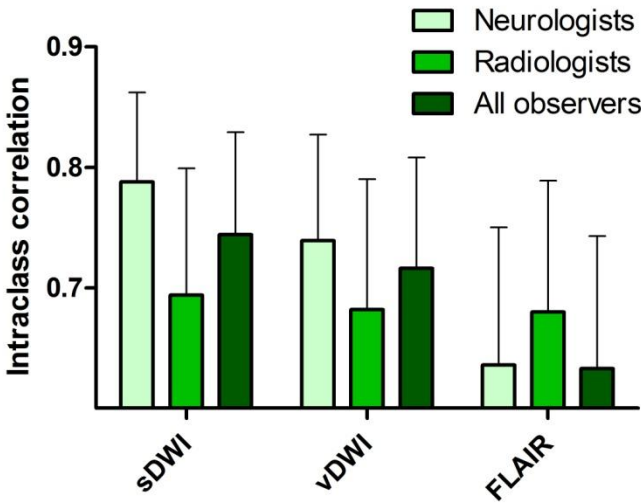


Table 1

Guidelines for Reporting Reliability and Agreement Studies (GRRAS).

page(s)

TITLE AND ABSTRACT	1. Identify in title or abstract that interrater/intrarater reliability or agreement was investigated.	2, 4
INTRODUCTION	2. Name and describe the diagnostic or measurement device of interest explicitly.	7-8
	3. Specify the subject population of interest.	
	4. Specify the rater population of interest (if applicable).	
	5. Describe what is already known about reliability and agreement and provide a rationale for the study (if applicable).	
METHODS	6. Explain how the sample size was chosen. State the determined number of raters, subjects/objects, and replicate observations.	8-13
	7. Describe the sampling method.	
	8. Describe the measurement/rating process (e.g. time interval between repeated measurements, availability of clinical information, blinding).	
	9. State whether measurements/ratings were conducted independently.	
	10. Describe the statistical analysis.	13-17
RESULTS	11. State the actual number of raters and subjects/objects which were included and the number of replicate observations which were conducted.	
	12. Describe the sample characteristics of raters and subjects (e.g. training, experience).	
	13. Report estimates of reliability and agreement including measures of statistical uncertainty.	17-21
DISCUSSION	14. Discuss the practical relevance of results.	
AUXILIARY MATERIAL	15. Provide detailed results if possible (e.g. online)	N.A.

3. Guidelines

The Guidelines for Reporting Reliability and Agreement Studies (GRRAS) are shown in Table 1. They contain issues that should be addressed when reliability and agreement are investigated. The underlying rationale, arguments, or empirical data to support each item are given later. The proposed issues correspond to the headings and order usually used in publications. The items aim to cover a broad range of clinical test scores, classifications or

diagnosis. However, some items are only partly applicable to self-completed questionnaires (e.g., items 4, 6, 11).

Studies may be conducted with the primary focus on reliability and agreement estimation itself or they may be a part of larger diagnostic accuracy studies, clinical trials, or epidemiological surveys. In the latter case, researchers report agreement and reliability as a quality control, either before the main study or by using data of the main study. Typically, results are reported in just



Multicentre, multiobserver study of diffusion-weighted and fluid-attenuated inversion recovery MRI for the diagnosis of sporadic Creutzfeldt–Jakob disease: a reliability and agreement study



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Research article

Multicentre, multiobserver study of diffusion-weighted and fluid-attenuated inversion recovery MRI for the diagnosis of sporadic Creutzfeldt–Jakob disease: a reliability and agreement study

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Creutzfeldt–Jakob disease (CJD), prion diseases, magnetic resonance imaging (MRI),
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ABSTRACT

Objectives: To assess the utility of the display standardization of diffusion-weighted MRI (DWI) and to compare the effectiveness of DWI and fluid-attenuated inversion recovery MRI (FLAIR) for the diagnosis of sporadic Creutzfeldt–Jakob disease (sCJD).

Design: A reliability and agreement study.

Setting: Thirteen MRI observers comprising 8 neurologists and 5 radiologists at two universities in Japan.

Participants: Data of 1.5-Tesla DWI and FLAIR were obtained from 29 patients with sCJD and 13 controls.

Outcome measures: Standardization of DWI display was performed utilizing b0 imaging. The observers participated in standardized DWI, variable DWI (the display adjustment was observer dependent), and FLAIR sessions. The observers independently assessed each MRI for CJD-related lesions, i.e. hyperintensity in the cerebral cortex or striatum, using a continuous rating scale. Performance was evaluated by the area under the receiver operating characteristics curve (AUC).

Results: The mean AUC values were 0.84 (95% confidence intervals [CI], 0.81–0.87) for standardized DWI, 0.85 (95% CI, 0.82–0.88) for variable DWI, and 0.68 (95% CI, 0.63–0.72) for FLAIR, demonstrating the superiority of DWI ($P <$

0.05). There was a trend for higher intraclass correlations of standardized DWI (0.74; 95% CI, 0.66–0.83) and variable DWI (0.72; 95% CI, 0.62–0.81) than that of FLAIR (0.63; 95% CI, 0.53–0.74), although the differences were not statistically significant.

Conclusions: Standardized DWI is as reliable as variable DWI, and the two DWI displays are superior to FLAIR for the diagnosis of sCJD. We propose that hyperintensity in the cerebral cortex or striatum on 1.5-Tesla DWI but not FLAIR can be a reliable diagnostic marker for sCJD.

ARTICLE SUMMARY

Article focus

- Evaluation of the reliability of diffusion-weighted imaging (DWI) display standardization for the diagnosis of sporadic Creutzfeldt–Jakob disease (sCJD).
- Comparison between DWI and fluid-attenuated inversion recovery (FLAIR) for the diagnosis of sCJD.

Key messages

- Standardized DWI display is as reliable as observer-dependent DWI display.
- DWI is superior to FLAIR for the diagnosis of sCJD.
- Hyperintensity in the cerebral cortex or striatum on 1.5-Tesla DWI but not FLAIR can be a reliable diagnostic marker for sCJD.

Strengths and limitations of this study

- Strength of this study is the large number of physicians who participated in the observer performance study.
- This study was limited by the retrospective nature that may lead to a selection bias.

INTRODUCTION

Reliable detection of Creutzfeldt–Jakob disease (CJD) is imperative for infection control and treatment. Magnetic resonance imaging (MRI) is useful for the early diagnosis of CJD,[1, 2] whereas the utility of electroencephalography (EEG) and conventional cerebrospinal fluid (CSF) tests have been limited.[3]

Diffusion-weighted imaging (DWI) and fluid-attenuated inversion recovery (FLAIR) are key techniques for the diagnosis of sporadic CJD (sCJD) with high sensitivity and specificity when assessed by expert neurologists or neuroradiologists.[1, 4, 5]

However, the utility of MRI for general neurologists or radiologists who are not familiar with diagnosing CJD remains elusive. Moreover, standardization of MRI methodologies, which would be essential for the reproducible assessment of MRI findings of CJD cases, have not been achieved in previous studies.[1, 4, 5] DWI display conditions may particularly vary among institutions or operators,[6] which can give rise to inaccurate assessment of CJD-related lesions, specifically subtle abnormalities in the cerebral cortex. Meanwhile, although DWI seems superior to FLAIR for the detection of CJD lesions,[5] direct comparison of the two sequences is yet to be performed.

To address these issues, we investigated the utility of a newly proposed

standardization method of DWI display[6, 7] and compared the effectiveness of DWI and FLAIR for the diagnosis of sCJD, particularly for differentiating between abnormal and normal signals by neurologists and radiologists who are not necessarily CJD experts. We conducted a multicentre, multiobserver case-control study and evaluated observer performance with receiver operating characteristics (ROC) analysis.

METHODS

Subjects

Patients diagnosed with sCJD by the CJD Surveillance Committee of Japan[8] from October 2005 to September 2010 were eligible to participate in this study. The accuracy of the diagnosis was defined as follows: definite, i.e. pathologically verified cases; probable, i.e. cases with neuropsychiatric manifestations compatible with sCJD and periodic sharp wave complexes (PSWCs) on EEG without pathological examinations; and possible, i.e. cases with the same findings as probable sCJD, but no PSWCs on EEG.[8, 9] The World Health Organization (WHO) criteria[10] were not applied because the assay of CSF 14-3-3 protein, which is required by the WHO criteria, was standardized only since April 2009 in Japan.[11] The prion protein gene (*PRNP*) was analyzed in the open reading frame after extracting DNA from patients'

blood.[12, 13] For neuropathological examinations, brain sections were stained with routine techniques, and immunohistochemistry was performed using the mouse monoclonal antibody 3F4 (Senetek, MD Heights, MO).[12] For PrP^{Sc} typing, frozen brain tissues were homogenized and analyzed by western blot for proteinase K-resistant PrP using the 3F4 antibody.[14] Assays for CSF γ -isoform of 14-3-3 protein,[11] total tau protein (cut-off value, 1300 pg/ml),[15] and real-time quaking-induced conversion (RT-QUIC)[16] were performed in patients whose CSF samples were available. The following patients were eligible as disease controls: patients who were suspected to have prion disease by primary physicians but were denied to have prion disease by the Committee; or those who were diagnosed with other neurological disorders at Tokushima University Hospital and whose brain MRI showed no abnormal intensity in the cerebral cortex or striatum. We requested physicians who had referred patients to the Committee to provide initial MRI data of eligible patients.

This study was approved by the Medical Ethics Committee of Kanazawa University and the Ethics Committees of the Tokushima University Hospital and Tokyo Medical and Dental University. Written informed consent was obtained from all patients or their families.

Magnetic resonance imaging

DWI, b0, and FLAIR images were converted to the Digital Imaging and Communication in Medicine (DICOM) format. When the DICOM data contained patient information, it was excluded by one of the investigators (M.H.) before the observer performance study. All MRI studies were performed on 1.5-Tesla scanners at each hospital. Quadrature detection head coils or multichannel head coils were used. DWI was performed using the single-shot spin-echo echo planar imaging technique with the following parameters: repetition time, 4000–8000 ms; echo time, 70–100 ms; b value, 1000 s/mm²; slice thickness, 5 mm; matrix size, 128 × 80–128 × 128; field of view, 220–230 mm; 16–20 contiguous axial sections parallel to a line through the anterior and posterior commissures were obtained from each patient. The scanning parameters of FLAIR were as follows: repetition time, 8000–10000 ms; inversion time, 2000–2500 ms; effective echo time, 105–120 ms; matrix size, 256 × 192–320 × 224; field of view, 210–220 mm; slice thickness, 5–6 mm with 1–1.5 mm interslice gaps; and 19–20 slices per patient.

Display methods

Two display methods were used for DWI: standardized and variable. In the

standardized display, the window width and level settings were constant for all evaluations and could not be changed. Details of the standardized display have been reported elsewhere.[6] In brief, the window width and level were as follows: window width = SI_{b0} and window level = $SI_{b0}/2$, where SI_{b0} represents the signal intensity in the normal-appearing subcortical region on b0 imaging.[6] One radiologist (M.H.) manually measured SI_{b0} within a circular region of interest. The calculated window width and level were applied to all images. In the variable display mode, regarded as the most reliable for assessment of DWI, each observer was able to change the window width and level settings on the monitor according to preference. FLAIR was assessed with the variable display method, because no standardized methods are currently available for FLAIR display.

Observer performance study

Eight neurologists (6–27 years of experience; mean, 12 years; board-certified, 6) and five radiologists (5–25 years of experience; mean, 12.8 years; board-certified, 4; neuroradiologist, 1) participated in the observer performance study at The University of Tokushima Graduate School (persons, 6; neurologists, 3) and Tokyo Medical and Dental University (persons, 7; neurologists, 5 including N.S. and Y.S.). Before the test, the observers were informed that the purpose of the study was to evaluate their

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performance in detecting MRI lesions compatible with CJD, i.e. hyperintensity in the cerebral cortex or striatum, regardless of signal changes in other regions including the thalamus. Three sessions were conducted: standardized DWI, variable DWI, and FLAIR. To reduce the effect of learning, the interval between reading sessions was 1 week or longer. The order of the three sessions was randomized among the observers. Using computer randomization, images of patients with and without sCJD were intermixed. All cases were presented in the same randomized order to the observers in each session. Each observer independently viewed all slices of each MRI study on the same type of monitors (Let'snote, Panasonic, Osaka) using INTAGE Realia Professional (Cubernet, Tokyo) run on Windows XP (Microsoft). The observers were allowed to adjust the window width and level only in variable DWI and FLAIR sessions but not in the standardized DWI session. Observers were blinded to any clinical information including age, sex, and diagnosis.

Each observer used a continuous rating scale of a line-marking method to rate his or her confidence level on the paper format independently. At the left end of the line, a confidence level that lesions compatible with CJD were definitely absent was indicated, whereas at the right end, a confidence level that lesions were definitely present was indicated. Intermediate levels of confidence were indicated by the

different positions on the line between the two ends. The distance between the left end and the marked point was converted to a confidence level that could range from 0 to 100, as described elsewhere.[17]

Statistical Analyses

Observer performance was evaluated using ROC analysis with SPSS version 19 (IBM, Armonk, NY). The ROC curves for each observer indicated the ratio of the true-positive fraction to the false-positive fraction at each confidence level. The area under the ROC curve (AUC) was used to compare observer performance for accurately detecting CJD lesions. Intraclass correlations were calculated in the neurologist group, the radiologist group, and for all observers by two-way random consistency measures using the SPSS software. In all the analyses, P values of less than 0.05 were considered statistically significant.

RESULTS

Patients and controls

MRI data from 85 patients were provided. Of these, 42 subjects from 15 hospitals (including authors' institutions) were eligible for this study after excluding cases that were diagnosed with non-sporadic CJD or lacked the required MRI sequences. This

study cohort included 29 patients with sCJD (men, 11; mean age, 71 years; duration before MRI, 4.4 ± 6.1 months), 3 patients who were suspected of CJD but eventually diagnosed as negative by the Committee, and 10 patients diagnosed with other neurological disorders. Of the 29 sCJD patients, 4 had definite, 24 had probable, and 1 had possible CJD. Twenty-six cases underwent *PRNP* analysis; 24 were homozygous for methionine at codon 129, and 2 were heterozygous with methionine and valine at codon 129. Of the 4 definite cases, PrP^{Sc} was type 1 in two cases, type 1+2 in one case, and type 2 in one case. Eleven of 15 CSF samples from probable sCJD cases were positive for PrP^{Sc} by RT-QUIC (table 1).

Diagnoses for 3 prion-denied patients were immune-mediated encephalopathy, juvenile Alzheimer's disease, and frontotemporal dementia. Other neurological controls were diagnosed with Alzheimer's disease, Parkinson's disease, spinocerebellar degeneration, vascular dementia, old cerebral infarction, benign paroxysmal positional vertigo, dizziness, temporal arteritis, cervical spondylosis, and diabetic neuropathy.

Table 1 Clinical profiles of patients with sporadic Creutzfeldt–Jakob disease

No	Age/ sex	Diagnosis	Codon129/ PrP ^{Sc}	14-3-3/ total tau	RT-QUIC	Pre-MRI duration (months)
1	69/M	Definite	MM/1	+/+	+	–2*
2	77/F	Definite	MM/1	+/+	+	19
3	75/F	Definite	ND/1+2	+/+	+	3
4	65/M	Definite	MM/2	–/–	–	12
5	69/M	Probable	MM	ND	–	0.5
6	72/F	Probable	MM	ND	ND	0.5
7	77/F	Probable	MM	–/–	+	0.5
8	72/M	Probable	MM	ND	ND	1
9	63/M	Probable	MM	+/+	+	1.5
10	88/F	Probable	MM	ND	ND	1.5
11	75/M	Probable	MV	ND	ND	1.5
12	56/M	Probable	MM	+/+	+	2
13	67/M	Probable	MM	+/+	–	2
14	70/M	Probable	MM	+/+	+	2
15	70/F	Probable	MM	+/+	+	2
16	74/F	Probable	MM	+/+	–	2
17	84/F	Probable	MM	+/–	+	2
18	85/F	Probable	MM	–/+	+	2
19	49/F	Probable	ND	+/+	+	2
20	74/F	Probable	MV	+/+	+	2.5
21	54/F	Probable	ND	ND	ND	2.5
22	61/M	Probable	MM	ND	ND	3
23	72/F	Probable	MM	+/–	–	3
24	81/F	Probable	MM	–/–	+	3
25	70/M	Probable	MM	+/+	+	6
26	83/F	Probable	MM	+/+	ND	9
27	67/F	Probable	MM	+/+	–	15
28	84/F	Probable	MM	+/+	–	26
29	57/F	Possible	MM	ND	ND	4

*MRI was obtained two months before the symptom onset.[2]
CJD, Creutzfeldt–Jakob disease; MM, homozygous for methionine; MV, heterozygous with methionine and valine; ND, not done; RT-QUIC, real-time quaking-induced conversion.

Diagnostic performance

We investigated the diagnostic performance of standardized DWI, variable DWI, and FLAIR images assessed by 8 neurologists and 5 radiologists using ROC analysis. Mean AUC values obtained from the 3 sessions were compared within the neurologist group, the radiologist group, and all observers (figure 1, table 2). The AUC values for standardized and variable DWI were not different within each professional group or for the total observer group. On the other hand, AUC values for FLAIR were significantly lower than DWI displayed by either method ($P < 0.05$).

Representative MRI scans are shown in figure 2.

Table 2 Areas under the receiver operating characteristic curves (AUCs)

	Neurologists	Radiologists	All observers
sDWI	0.86 (0.82–0.90)	0.82 (0.77–0.88)	0.84 (0.81–0.87)
vDWI	0.86 (0.82–0.90)	0.83 (0.77–0.89)	0.85 (0.82–0.88)
FLAIR	0.69 (0.63–0.75)	0.66 (0.58–0.73)	0.68 (0.63–0.72)

Means (95% confidence intervals) are indicated.

DWI, diffusion-weighted imaging; FLAIR, fluid-attenuated inversion recovery; sDWI, standardized DWI; vDWI, variable DWI.

Rating agreement

To measure the extent to which the observers agreed when rating the MRI findings, intraclass correlations were calculated. The intraclass correlations of the standardized DWI (0.74; 95% CI, 0.66–0.83) and variable DWI (0.72; 95% CI, 0.62–0.81) tend to be higher than that of FLAIR (0.63; 95% CI, 0.53–0.74), specifically in the neurologist group, although the differences were not significant (figure 3).

DISCUSSION

We demonstrated that standardized DWI was as useful as variable DWI, and that both DWI displays are superior to FLAIR for the diagnosis of sCJD when assessed by multiobservers with various specialty backgrounds.

Our standardization method of DWI display was originally proposed as an easy-to-use way to decide the window width and level for DWI even in emergency settings.[6] Indeed, this method was demonstrated as useful for detecting acute ischemic lesions on DWI.[7] Results of the present study shows the standardization method is also reliable for diagnosis of sCJD, in which DWI is one of the key sequences. We suggest some advantages of standardized DWI over variable DWI although there was no statistical difference between the two methods. First,

standardized DWI can be helpful for physicians who can refer only to hardcopies, but not softcopies. Second, even for doctors who can readily refer to softcopies and thus variable DWI, the standardization method can simplify assessment procedure without any disadvantages. Third, the standardization can facilitate direct comparison of DWI findings from different CJD patients.

DWI and FLAIR have been reported as useful markers for the diagnosis of CJD. Of these, DWI has been assumed to be the most sensitive, although without direct evidence.[1, 5, 18] Hyperintensity in the cerebral cortices, the striatum or both indicate the diagnosis of CJD. The striatum hyperintensity is anterior-dominant at early stages of the disease.[19] MRI lesion profiles reportedly differ among molecular subtypes of sCJD,[20, 21] which was not reproduced in a recent study.[5] Zerr et al. proposed that high signal abnormalities in caudate nucleus and putamen or at least two cortical regions (temporal, parietal, or occipital lobes) either in DWI or FLAIR, together with typical clinical signs can be diagnostic for probable sCJD.[4] Based partly upon their report, “high signal in caudate/putamen on MRI brain scan” has been used as one of the laboratory findings in the diagnostic criteria for probable sCJD in the European CJD Surveillance System (EUROCJD) since January 2010.[22] However, their criteria did not distinguish DWI and FLAIR, thereby

maintaining ambiguity about the diagnostic values of MRI in situations where DWI is not available. Our data indicate that FLAIR without DWI is unreliable for the diagnosis of sCJD. On the other hand, high signals in the cerebral cortex have not been regarded as diagnostic in the EUROCD criteria, probably because cortical abnormalities are less reliable on conventional MRI. Our results suggest that, using standardized or variable DWI but not FLAIR, cortical signals can also be utilized as a diagnostic marker.

Meanwhile, Young et al. reported that the sensitivity and the specificity of DWI and FLAIR for the diagnosis of CJD are 91% and 95%, respectively.[23] More recently, Vitali et al. reported that hyperintensity greater on DWI than FLAIR is diagnostic for sCJD, whereas hyperintensity greater on FLAIR than DWI is characteristic for non-prion rapidly progressive dementia.[5] Furthermore, reduction of apparent diffusion coefficient in subcortical (striatum) hyperintensity regions on DWI is supportive for sCJD.[5, 24, 25] These findings can be greatly helpful for differentiating sCJD from other rapidly progressive dementia. However, assessment of FLAIR lesions tends to vary among physicians, particularly among neurologists, as shown by the present study, and standardized methods for FLAIR or apparent diffusion coefficient map have not been established until date. Therefore, clinical

criteria which require DWI but not necessarily FLAIR or apparent diffusion coefficient will be more readily applicable.

As many as 13 neurologists and radiologists from different institutions participated in the observer performance study, although the sample size of patients was relatively small. Notably, the observers had various specialty backgrounds such as stroke neurologists, neurophysiologists, experts in dementia or prion disease, and general and neuroradiologists. This variety simulates practical situations in which the diagnosis of suspected CJD cases may be made by physicians who do not necessarily specialize in prion disease.

This study has some limitations. First, we did not evaluate patterns of cortical involvement suggestive of sCJD[4, 5] because we had to address whether DWI or FLAIR is suitable for detecting cortical lesions in the first place. Second, we did not assess the difference among sCJD subtypes[21] because majority of our cases had a typical phenotype and were homozygous for methionine; thus, they were compatible with MM1 sCJD. Until date, MM2 thalamic-type sCJD remains a diagnostic challenge in MRI-based assessment; thalamic hypoperfusion or hypometabolism on SPECT or PET can be useful.[26] Third, majority of the control patients were not

those who were suspected to have CJD. However, the principle aim of the present study was to establish a display method which reliably distinguishes potentially CJD-associated signals from normal signals. Thus, our results provide a practical foundation for utilizing DWI as a general diagnostic marker of sCJD when combined with previous findings.[1, 4, 5]

Although neuropathological confirmation of the diagnosis of sCJD was obtained in few cases, we performed RT-QUIC, a newly established CSF PrP^{Sc} amplification assay which achieved greater than 80% sensitivity and 100% specificity for CJD.[16]

Overall, 15 of 29 cases (51.7%) were pathologically proven or confirmed by RT-QUIC to have CJD. **There were no significant differences in MRI findings between sCJD patients with and without positive results of CSF 14-3-3 protein, total tau protein, or RT-QUIC.** It will be important to further evaluate accurate diagnostic ability (sensitivity and specificity) of DWI in a prospective cohort of suspected CJD patients, i.e. consecutive patients registered to the CJD surveillance who will also undergo CSF confirmation tests or neuropathological analyses.

In conclusion, we suggest that hyperintensity in the cerebral cortex or striatum assessed on the standardized or variable DWI scanned with 1.5-Tesla machines can

be a reliable first-line, on-site diagnostic marker for sCJD.

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Patient consent Obtained.

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REFERENCES

1. Shiga Y, Miyazawa K, Sato S, *et al.* Diffusion-weighted MRI abnormalities as an early diagnostic marker for Creutzfeldt–Jakob disease. *Neurology* 2004;**63**:443–449.
2. Satoh K, Nakaoke R, Nishiura Y, *et al.* Early detection of sporadic CJD by diffusion-weighted MRI before the onset of symptoms. *J Neurol Neurosurg Psychiatry* 2011;**82**:942–943.
3. Chitravas N, Jung RS, Kofskey DM, *et al.* Treatable neurological disorders misdiagnosed as Creutzfeldt–Jakob disease. *Ann Neurol* 2011;**70**:437–444.
4. Zerr I, Kallenberg K, Summers DM, *et al.* Updated clinical diagnostic criteria for sporadic Creutzfeldt–Jakob disease. *Brain* 2009;**132**:2659–2668.
5. Vitali P, Maccagnano E, Caverzasi E, *et al.* Diffusion-weighted MRI hyperintensity patterns differentiate CJD from other rapid dementias. *Neurology* 2011;**76**:1711–1719.

6. Sasaki M, Ida M, Yamada K, *et al.* Standardizing display conditions of diffusion-weighted images by using concurrent b0 images: a multivendor multi-institutional study. *Magn Reson Med Sci* 2007;**6**:133–137.
7. Hirai T, Sasaki M, Meada M, *et al.* Diffusion-weighted imaging in ischemic stroke: effect of display method on observers' diagnostic performance. *Acad Radiol* 2009;**16**:305–312.
8. Nozaki I, Hamaguchi T, Sanjo N, *et al.* Prospective 10-year surveillance of human prion diseases in Japan. *Brain* 2010;**133**:3043–3057.
9. Masters CL, Harris JO, Gajdusek DC, *et al.* Creutzfeldt–Jakob disease: patterns of worldwide occurrence and the significance of familial and sporadic clustering. *Ann Neurol* 1979; **5**:177–188.
10. WHO. Global surveillance, diagnosis and therapy of human transmissible spongiform encephalopathies: report of a WHO consultation. In: *World Health Organization: Emerging and Other Communicable Diseases, Surveillance and Control*. Geneva:WHO;1998
11. Satoh K, Tobiume M, Matsui Y, *et al.* Establishment of a standard 14-3-3 protein assay of cerebrospinal fluid as a diagnostic tool for Creutzfeldt–Jakob disease. *Lab Invest* 2010;**90**:1637–1644.
12. Kitamoto T, Shin RW, Doh-ura K, *et al.* Abnormal isoform of prion proteins

- accumulates in the synaptic structures of the central nervous system in patients with Creutzfeldt–Jakob disease. *Am J Pathol* 1992;**140**:1285–1294.
13. Kitamoto T, Ohata M, Doh-ura K, *et al*. Novel missense variants of prion protein in Creutzfeldt–Jakob disease or Gerstmann–Sträussler syndrome. *Biochem Biophys Res Commun* 1993;**191**:709–714.
14. Shimizu S, Hoshi K, Muramoto T, *et al*. Creutzfeldt–Jakob disease with florid-type plaques after cadaveric dura mater grafting. *Arch Neurol* 1999;**56**:357–362.
15. Satoh K, Shirabe S, Eguchi H, *et al*. 14-3-3 protein, total tau and phosphorylated tau in cerebrospinal fluid of patients with Creutzfeldt–Jakob disease and neurodegenerative disease in Japan. *Cell Mol Neurobiol* 2006;**26**:45–52.
16. Atarashi R, Satoh K, Sano K, *et al*. Ultrasensitive human prion detection in cerebrospinal fluid by real-time quaking-induced conversion. *Nat Med* 2011;**17**:175–178.
17. Hirai T, Korogi Y, Arimura H, *et al*. Intracranial aneurysms at MR angiography: effect of computer-aided diagnosis on radiologists' detection performance. *Radiology* 2005;**237**:605–610.
18. Kallenberg K, Schulz-Schaeffer WJ, Jastrow U, *et al*. Creutzfeldt–Jakob disease: comparative analysis of MR imaging sequences. *Am J Neuroradiol*

- 2006;**27**:1459–1462.
19. Murata T, Shiga Y, Higano S, *et al.* Conspicuity and evolution of lesions in Creutzfeldt–Jakob disease at diffusion-weighted imaging. *Am J Neuroradiol* 2002;**23**:1164–1172.
20. 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.
21. Meissner B, Kallenberg K, Sanchez-Juan P, *et al.* MRI lesion profiles in sporadic Creutzfeldt–Jakob disease. *Neurology* 2009;**72**:1994–2001.
22. Diagnostic criteria for sporadic CJD from 1 January 2010. In: National Creutzfeldt–Jakob Disease Surveillance Diagnostic Criteria [online]. Available at: www.cjd.ed.ac.uk/criteria.htm. Accessed October 3, 2011.
23. Young GS, Geschwind MD, Fischbein NJ, *et al.* Diffusion-weighted and fluid-attenuated inversion recovery imaging in Creutzfeldt–Jakob disease: high sensitivity and specificity for diagnosis. *Am J Neuroradiol* 2005;**26**:1551–1562.
24. Lin YR, Young GS, Chen NK, *et al.* Creutzfeldt–Jakob disease involvement of rolandic cortex: a quantitative apparent diffusion coefficient evaluation. *Am J Neuroradiol* 2006;**27**:1755–1759.
25. Fujita K, Nakane S, Harada M, *et al.* Diffusion tensor imaging in patients with

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Creutzfeldt–Jakob disease. *J Neurol Neurosurg Psychiatry* 2008;**79**:1304–1306.

26. Hamaguchi T, Kitamoto T, Sato T, *et al*. Clinical diagnosis of MM2-type sporadic

Creutzfeldt–Jakob disease. *Neurology* 2005;**64**:643–648.

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FIGURE LEGENDS

Figure 1 Receiver operating characteristic curves for each display in diagnosis of sporadic Creutzfeldt–Jakob disease. (A) Neurologists. (B) Radiologists. (C) All observers. The true rate (sensitivity) is plotted as a function of the false positive rate (1 - specificity).
DWI, diffusion-weighted imaging; FLAIR, fluid-attenuated inversion recovery; sDWI, standardized DWI; vDWI, variable DWI.

Figure 2 Representative MRI of a sporadic Creutzfeldt–Jakob disease patient (case 17). Abnormal hyperintensity in the cerebral cortex is evident on standardized diffusion-weighted imaging (A, arrow) but obscure on fluid-attenuated inversion recovery (B, arrow).

Figure 3 Intraclass correlations for each display. Error bars represent upper limits of 95% confidence intervals.
DWI, diffusion-weighted imaging; FLAIR, fluid-attenuated inversion recovery; sDWI, standardized DWI; vDWI, variable DWI.

