Comparing CSF biomarkers and brain MRI in the diagnosis of sporadic Creutzfeldt-Jakob disease

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Summary

We assessed the diagnostic utility of 3 CSF biomarkers—14-3-3 protein, total tau (T-tau), and neuron-specific enolase (NSE)—from the same lumbar puncture to distinguish between participants with neuropathologically confirmed sporadic Creutzfeldt-Jakob disease (sCJD, $n = 57$) and controls with nonprion rapidly progressive dementia (npRPD, $n = 41$). Measures of diagnostic accuracy, sensitivity, specificity, positive predictive value, and negative predictive value, as well as logistic regression and area under the receiver operator curve (AUC), were used to assess the ability of these CSF biomarkers, alone or concomitantly, to predict diagnosis. In a subcohort with available MRI (sCJD $n = 57$, npRPD = 32), we compared visual assessment of diffusion-weighted imaging MRI sequences to these CSF biomarkers. MRI was the best predictor, with an AUC of 0.97 (confidence interval [CI] 0.92–1.00) and a diagnostic accuracy of 97% (CI 90%–100%). Of the CSF biomarkers, T-tau had a higher diagnostic accuracy (79.6%) than 14-3-3 (70.4%, CI for difference 8.7%, 9.7%; $p = 0.048$) or NSE (71.4%, CI for difference 7.6%, 8.7%; $p = 0.03$).

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CSF levels of 14-3-3 protein were first reported to be useful diagnostic markers for sporadic Creutzfeldt-Jakob disease (sCJD) in 1996.¹ Since then, numerous publications have addressed its utility in the differential diagnosis of sCJD, with variable findings. In the literature, the sensitivity of 14-3-3 has most commonly been reported between 85% and 95%,^{2–8} although it has been reported to range from 53% to 97%.^{1,9,10} Its specificity has been reported to range from 40% to 100%.^{2,4,7,8,11–13} Other CSF protein markers, such as neuron-specific enolase (NSE) and total tau (T-tau), have been used to diagnose CJD; whether these markers are better than 14-3-3 has been a matter of debate. 14-3-3, for example, has been found to have higher accuracy than T-tau in some,² but not all, studies.^{5,13,14} The ratio relationship between T-tau and phosphorylated tau (T-tau/P-tau) has also increasingly been shown to be a useful indicator of disease diagnosis in sCJD, with sensitivities ranging from 75% to 94%^{3,9,15,16} and specificities ranging from 94% to 97%.^{3,9,15,16}

Because of the generally poor sensitivity and specificity of CSF 14-3-3 for sCJD in our rapidly progressive dementia (RPD) cohort,^{10,17,18} and because different CSF markers often yield discordant results in the same patient, we compared the diagnostic utility of CSF 14-3-3, NSE, and T-tau in participants who had all 3 biomarkers tested at the same time. We also compared them with diffusion-weighted imaging (DWI) MRI, which has been shown to be highly sensitive^{19,20} and specific^{e1,e2} for sCJD diagnosis, even early in the course.^{e2} For those patients who also had P-tau assessed, we performed a secondary analysis focusing on the diagnostic utility of T-tau/P-tau.

METHODS

Standard protocol approvals, registration, and patient consents

This study, and the use of human participants, was approved by our institution's Internal Review Board.

Participants

The participants included in this analysis were referred to the University of California San Francisco (UCSF) Memory and Aging Center from March 1, 2005, to April 9, 2012. We queried our database for participants who had 14-3-3, NSE, and T-tau assessed from the same lumbar puncture (LP). In participants with multiple LPs, only the first available sample assessing these 3 CSF biomarkers was used. We restricted sCJD to pathology-proven cases, yielding 57 participants. Fifty-five of 57 participants with sCJD had prion protein gene (*PRNP*) analysis, including codon 129 polymorphism (National Prion Disease Pathology Surveillance Center [NPDPSC], Cleveland, OH); all had no mutation. The 2 remaining participants had no known family history of prion disease or neuropsychiatric illness.

The nonprion RPD (npRPD) cohort was obtained from participants in whom CJD was considered at some point in their disease course; most had a rapidly progressive decline. npRPD participants were included if they had (1) a clearly defined serologic or pathologic diagnosis, (2) a significant clinical improvement, or (3) a total disease duration longer than 3 years^{e3,e4} (supplemental data at Neurology.org/cp), yielding 41 participants. Their clinical diagnoses (5 neuropathologically proven) are detailed in table 1. Thirty (73%) of 41 controls had *PRNP* sequencing (NPDPSC, Cleveland) and were negative for mutations; the remaining 11 had no reported family history of prion disease or similar disorder.

CSF analysis

CSF 14-3-3 protein testing by Western blot was performed at the NPDPSC, and reported as positive, negative, or ambiguous. For analysis, negative and ambiguous results were grouped as negative, a methodology employed by other studies^{2,4} and supported by our own analysis on our larger 14-3-3 CSF dataset (supplemental data). NSE testing was performed by Mayo Medical Laboratories (Rochester, MN) in 46 sCJD (81%) and 37 (90%) npRPD cases, Quest Diagnostics (San Juan Capistrano, CA) in 10 sCJD (18%) and 4 npRPD (10%) cases, and ARUP Laboratories (Salt Lake City, UT) (1 sCJD case). T-tau testing was performed at the NPDPSC

Supplemental Data

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Table 1 Diagnoses in the nonprion RPD (control) group

Diagnostic category	Diagnosis	No.
Neurodegenerative	Alzheimer disease (5 NINCDS probable, 3 NINCDS possible, 1 <i>PSN1</i> positive)	9
	Dementia with Lewy bodies	6 ^a
	Corticobasal syndrome	1
	Multiple system atrophy	2
	Frontotemporal dementia (1 FTD-ALS and 1 FTLD-TDP)	2 ^a
	Mild cognitive impairment ^b	1
	Progressive supranuclear palsy	1
Autoimmune	Encephalopathy with anti-VGKC-related antibodies	2
	Encephalopathy with anti-Yo antibodies	1
	Encephalopathy with anti-AMPA antibodies	1
	Encephalopathy autoimmune undetermined	1
Vascular	Vascular dementia	2 ^a
Infectious	Echovirus type 17 meningoencephalitis	1 ^a
	Epstein-Barr virus encephalitis (possible)	1
Toxic-metabolic	Extrapontine myelinolysis	1
	Hypoglycemic encephalopathy	1 ^a
Psychiatric	Bipolar disorder	1
	Alcoholism and anxiety	1
Undetermined	Undetermined leukoencephalopathy (1); possible autoimmune encephalopathy (1); seizure disorder of unknown etiology (1); dementia of unknown etiology (3)	6
Total		41

Abbreviations: ALS = amyotrophic lateral sclerosis; AMPAR = α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; FTD = frontotemporal dementia; FTLD-TDP = frontotemporal lobar degeneration with TDP-43 inclusions; NINCDS = National Institute of Neurological and Communicative Disorders and Stroke; RPD = rapidly progressive dementia; VGKC = voltage-gated potassium channel.

^aIncludes 1 participant with neuropathologically confirmed diagnosis.

^bDespite rapid onset of symptoms, this patient still carried a diagnosis of mild cognitive impairment 4 years after onset of symptoms.

in 17 sCJD (30%) and 12 npRPD (29%) cases and Athena Diagnostics (Worcester, MA) in 40 sCJD (70%) and 29 npRPD (71%) cases (supplemental data). P-tau testing was performed in 26 npRPD (63%) and 38 (67%) sCJD cases, all by Athena Diagnostics (supplemental data).

Neuroimaging

MRI scans were obtained on 1.5T or 3T scanners. MRIs classified as definitely or probably CJD based on our previously described criteria^{c1} were considered positive (supplemental data). MRIs were read by neurologists or neuroradiologists in the CJD/RPD research group at UCSF blinded to clinical data, except patient's age and sex. Duration of time from LP to MRI is shown in table 2. Only MRIs performed within ± 45 days of the LP and deemed of adequate quality were used. In 95% of the sCJD and 78% of the npRPD cases, MRI was performed within 1 week of the LP (table 2).

Table 2 Demographics, PRNP codon 129 polymorphism, and general CSF characteristics of the RPD cohort

	No. sCJD/npRPD	sCJD group	npRPD group	p Value
Age at onset, y	57/41	61, 62 ± 10 (37-81)	60, 59 ± 11 (35-80)	0.18
Female, %	57/41	44	48	0.63
Time from onset to first LP, wk	57/41	34.9, 44.0 ± 35.1 (3.4-156.6)	68.6, 102.5 ± 89.2 (1.3-379.9)	0.0002 ^a
Disease duration, mo ^b	57/41 ^b	13.8, 16.2 ± 11.9 (1.7-57.7)	43.6, 47.3 ± 27.5 (2.2-107.6) ^b	<0.0001 ^a
PRNP codon 129 polymorphism, %	55/30			
MM		43.6	33.3	0.51
MV		36.4	36.7	
VV		20.0	30.0	
CSF leukocytes/ μ L	56/40	1.0, 1.0 ± 1.2 (0-6)	1.0, 1.5 ± 2.4 (0-12)	0.26
CSF glucose, mg/dL	54/40	65.5, 67.1 ± 8.6 (51-99)	63.0, 69.4 ± 22.9 (43-151)	0.92
CSF protein, mg/dL	53/41	44.0, 50.2 ± 22.0 (20-149)	41.0, 44.8 ± 20.6 (24-137)	0.23
CSF IgG index	48/36	0.5, 0.53 ± 0.06 (0.4-0.7)	0.5, 0.73 ± 0.79 (0.4-4.7)	0.19
CSF 14-3-3, n (%)	57/41			
Positive		29 (50.88)	1 (2.44)	<0.0001 ^a
Ambiguous		23 (40.35)	12 (29.27)	
Negative		5 (8.77)	28 (68.29)	
CSF NSE levels, ng/mL	57/41	36.3, 51.3 ± 43.4 (7-207)	13.7, 16.6 ± 12.8 (1-78)	<0.0001 ^a
CSF total tau levels, pg/mL	55 ^c /41	2,021.0, 4,335.3 ± 4,756.9 (152.1-21,264.0)	211.2, 794.0 ± 2,714.2 (0-17,585.6)	<0.0001 ^a
Time from LP to MRI, d	57/32	1, 2 ± 3 (0-14)	1, 6 ± 10 (0-41)	0.04 ^a

Abbreviations: IgG = immunoglobulin G; LP = lumbar puncture; npRPD = nonprion rapidly progressive dementia; NSE = neuron-specific enolase; RPD = rapidly progressive dementia; sCJD = sporadic Creutzfeldt-Jakob disease.

Values displayed as median, mean ± SD (range) unless indicated otherwise.

^aSignificant.

^bDate of death was known for 7/41 npRPD participants. Date of last contact was used to determine disease duration in the other 34 participants. For the 7 npRPD participants in whom date of death was known, the median, mean ± SD, and range in months for disease duration was 58.7, 44.8 ± 32.0, and 2.2-80.4, respectively.

^cFor 2 participants with sCJD, tau levels were reported only as >1,200 pg/mL, which allowed for their classification as positive using the analyzing laboratory's cutoff, but not for their inclusion in a continuous analysis of group differences between the 2 disease cohorts.

As NSE and T-tau were assayed in different laboratories, and MRIs performed on different scanners, we used standard meta-analysis techniques^{es} to assess heterogeneity across sites. We did not find that the variability of results was greater than might be expected by chance (supplemental data).

Neuropathology

Neuropathologic assessment was done through the NPDPS or UCSF in 55 sCJD cases. Two sCJD autopsies were performed at other medical centers (supplemental data).

Statistical analysis

We compared demographic and clinical data using χ^2 , *t* tests, or Mann-Whitney tests, depending on data type and normality. The diagnostic utility of each isolated biomarker, as well as multiple biomarkers in combination, was quantified using estimates of sensitivity, specificity,

positive predictive value (PPV), negative predictive value, accuracy, and area under receiver operating characteristic (ROC) curves (AUC) accompanied by 95% confidence intervals (CIs). Their predictive ability was compared based on DeLong's test for 2 ROC curves accompanied by permutation.⁶⁶ CIs are inferred based on 1,000 bootstrap samples.⁶⁷

Because length of time from symptom onset to LP has been shown to have an effect on some CSF biomarkers,^{4,10,13} we controlled for duration from symptom onset to time of LP (duration to LP) in ancillary analyses. In most cases, date of symptom onset was based on extensive interviews with the patient, his or her family, or his or her friends,⁶⁸ as well as outside medical records. In these analyses, the diagnostic utility of logistic regression (LR) models in which all 3 of the CSF biomarkers were included was examined based on a score derived from coefficients representing weights of CSF biomarkers in predicting diagnosis. Statistical analyses were performed in SAS (v 9.2; SAS Institute, Cary, NC) or the R package for statistical computing (R Development Core Team).

RESULTS

The 2 cohorts did not differ significantly in sex, age at disease onset, or general CSF findings (table 2). sCJD participants had shorter duration to LP and disease duration, and a longer interval between LP and MRI (table 2). The distribution of sCJD molecular subtypes is shown in table e-3.

MRI analyses

Concomitant MRI within ± 45 days of the LP was available in all 57 sCJD cases and in 78% (32/41) of npRPD participants. LR analyzing MRI individually showed it to be the most robust predictor, with an AUC of 0.97 (CI 0.92–1.00) and diagnostic accuracy of 97% (CI 90%–100%), significantly higher than any of the CSF determinants considered, or any permutation thereof (table 3). We did not find that duration to LP significantly influenced the predictive ability of this measure (table 4). Fifteen participants with sCJD (26%; $p < 0.001$) had a negative 14-3-3, NSE, and T-tau result. In 14/15 of these cases, MRI predicted the correct diagnosis.

CSF biomarker analyses

The diagnostic accuracy for T-tau in our cohort was 79.6%, higher than the accuracy for 14-3-3 (70.4%, CI for difference between T-tau and 14-3-3 7.6%–8.7%; $p = 0.04$) or NSE (71.4%, CI for difference between T-tau and NSE 7.6%–8.7%; $p = 0.045$).

There was discordance among 14-3-3, NSE, and T-tau (one test did not agree with the other two) in 18 (32%) participants with sCJD. When discordant, T-tau was positive (correct) in 15, NSE in 6, and 14-3-3 in 5 observations (supplemental data). Only 1 participant with npRPD, with AMPAR limbic encephalopathy, had discordant results (positive T-tau, negative 14-3-3 and NSE). We performed multiple analyses to determine the optimal combination of the CSF biomarkers in our primary analysis for prediction of sCJD diagnosis (table 3). Although some inclusive combinations, such as a positive NSE or a positive T-tau result being considered as diagnostic for sCJD, yielded slightly higher diagnostic accuracies and AUCs, these were not significantly higher than T-tau alone. Duration to LP did not significantly influence the utility of any of the 3 CSF biomarkers, either individually or concomitantly (table 4). In the subcohort of patients for whom we had available P-tau data, we found that the diagnostic accuracy for T-tau/P-tau was 75% (CI 64%–86%), the sensitivity was 63% (CI 46%–78%), the specificity was 92% (CI 75%–99%), and the AUC was 0.78 (CI 0.68–0.87).

DISCUSSION

This study was designed to directly compare 14-3-3, NSE, and T-tau with each other and with MRI in the diagnosis of sCJD using a control cohort of participants with npRPD initially referred with suspected prion disease. MRI had far better diagnostic utility than any individual CSF biomarker or combination thereof.

Table 3 Diagnostic characteristics of CSF biomarkers and MRI in an RPD cohort

Biomarker	Sensitivity, % (95% CI)	Specificity, % (95% CI)	PPV, % (95% CI)	NPV, % (95% CI)	Accuracy, ^a % (95% CI)	AUC
14-3-3^b	50 (37, 64)	98 (87, 100)	97 (83, 100)	59 (46, 71)	70 (62, 80)	0.74 (0.67, 0.81)
NSE^b	53 (39, 66)	98 (87, 100)	97 (83, 100)	60 (47, 72)	71 (61, 80)	0.75 (0.68, 0.82)
T-tau^b	68 (55, 80)	95 (83, 99)	95 (83, 99)	68 (55, 80)	80 (70, 87)	0.82 (0.75, 0.89)
MRI^c	98 (91, 100)	94 (79, 99)	97 (88, 100)	98 (83, 100)	97 (90, 100)	0.97 (0.92, 1.00)
14.3.3 or NSE^b	61 (48, 74)	98 (87, 100)	97 (85, 100)	65 (51, 76)	77 (67, 85)	0.79 (0.73, 0.86)
14.3.3 or T-tau^b	70 (57, 82)	95 (80, 100)	95 (84, 99)	70 (56, 81)	81 (71, 88)	0.83 (0.76, 0.89)
NSE or T-tau^b	72 (58, 83)	95 (83, 100)	95 (84, 99)	71 (57, 83)	82 (73, 89)	0.84 (0.77, 0.90)
14.3.3 or NSE or T-tau^b	74 (60, 84)	95 (83, 100)	95 (85, 89)	72 (58, 84)	83 (74, 90)	0.84 (0.78, 0.91)
14.3.3 and NSE^b	42 (29, 56)	98 (87, 100)	96 (80, 100)	55 (43, 66)	65 (55, 75)	0.70 (0.63, 0.77)
14.3.3 and T-tau^b	49 (36, 63)	98 (87, 100)	97 (82, 100)	58 (45, 70)	69 (59, 78)	0.73 (0.66, 0.80)
NSE and T-tau^b	49 (36, 63)	98 (87, 100)	97 (82, 100)	58 (45, 70)	69 (59, 78)	0.73 (0.66, 0.80)
14.3.3 and NSE and T-tau^b	36 (29, 56)	98 (87, 100)	96 (80, 100)	55 (43, 66)	65 (55, 75)	0.70 (0.63, 0.77)

Abbreviations: AUC = area under the receiver operator characteristic curve; CI = confidence interval; npRPD = nonprion rapidly progressive dementia; NPV = negative predictive value; NSE = neuron-specific enolase; PPV = positive predictive value; RPD = rapidly progressive dementia; sCJD = sporadic Creutzfeldt-Jakob disease; T-tau = total tau.

^aAccuracy = Number of true positives and true negatives/all cases.

^bsCJD n = 57, npRPD n = 41.

^csCJD n = 57, npRPD n = 32.

One reason 14-3-3, NSE, and T-tau are not as helpful as MRI is that they are nonspecific markers of rapid neuronal injury.^{7,e9,e10} Other studies have combined different CSF markers for increased accuracy in the diagnosis of sCJD.^{2,4,5} Although this is a reasonable approach, one of the issues often faced in clinical practice is that those tests might yield conflicting results, so determining which CSF biomarker is the most likely to predict a correct diagnosis is important. In this cohort, 18/57 sCJD (but only 1 npRPD) participants had discordant 14-3-3, NSE, and T-tau results; when there was discordance, T-tau was correct much more commonly than 14-3-3 or NSE. In our statistical analysis, T-tau had greater diagnostic accuracy than 14-3-3 or NSE, and performed statistically as well as any permutation of CSF biomarkers in either inclusive or exclusive scenarios of diagnostic determination. Our findings might be particularly useful when trying to interpret conflicting results, and indicate that prioritizing the T-tau result is advisable. This is not to suggest, however, that NSE, 14-3-3, or other CSF biomarkers should not be tested when sCJD is a possible diagnosis. In the proper statistical framework, they have been shown to be very helpful in refining the differential when prion disease is suspected.^{e11} Elevated 14-3-3 does not, however, equate with CJD. Although it is interesting to note that T-tau/P-tau had a lower AUC and diagnostic accuracy than T-tau alone, since we did not perform a formal validation comparing this measure to the others tested, we cannot comment on its diagnostic utility in this cohort.

The sensitivities of the CSF biomarkers were lower and the specificities similar or higher in our cohort than has been reported by others.^{2,4,5,13,14,e12} The reason for this is not entirely clear, but could be due to disparities in sample size or referral biases across centers. As a major referral center for prion disease, our cohort had a high proportion of sCJD cases. Based on our larger RPD cohort consisting of patients who did not have all 3 CSF biomarkers tested from the same LP, we suspect that by including more npRPD cases, the PPV would significantly decrease for CSF biomarkers and not change significantly for MRI. Conversely, many

Table 4 Logistic regression models and areas under ROC curves for CSF markers and brain MRI, with and without controlling for duration to LP (controlling for duration to LP does not significantly influence biomarker AUC result)

	No. sCJD/npRPD	AUC	95% CI	p Value
CSF markers				
14-3-3	57/41	0.74	0.67, 0.81	0.47
14-3-3^a	57/41	0.78	0.69, 0.87	
NSE	57/41	0.75	0.68, 0.82	0.45
NSE^a	57/41	0.79	0.71, 0.88	
T-tau	57/41	0.82	0.75, 0.89	0.46
T-tau^a	57/41	0.86	0.78, 0.93	
14-3-3^b; NSE; T-tau	57/41	0.84	0.77, 0.91	0.42
14-3-3^{a,b}; NSE; T-tau	57/41	0.85	0.78, 0.91	
MRI				
MRI	57/32	0.97	0.92, 1.00	0.19
MRI^a	57/32	0.98	0.96, 1.00	

Abbreviations: AUC = area under the receiver operator characteristic curve; CI = confidence interval; LP = lumbar puncture; npRPD = nonprion rapidly progressive dementia; NSE = neuron-specific enolase; ROC = receiver operator characteristic; sCJD = sporadic Creutzfeldt-Jakob disease; T-tau = total tau.

^aLogistic regression performed controlling for duration to LP.

^bLogistic regression model includes all listed predictors and shows the contribution of each to the predictive value of the model.

national CJD surveillance centers screen dementia populations using these CSF biomarkers, and referrals are based on positive results. This might result in higher sensitivity and lower specificity.^{13,e13–e15}

The sensitivity of these biomarkers has been reported to be influenced by factors such as age at onset,^{2,4,9} duration of disease,^{4,9} timing of LP,^{2,e16} or molecular subtype (based on *PRNP* codon 129 polymorphism and prion protein isoform).^{e17} There is some evidence that serial LPs are more likely to yield positive CSF biomarkers in CJD,⁴ and that participants with longer disease courses and duration to LP are more likely to have negative biomarkers.^{9,10,13} The median disease duration in our sCJD cohort was 13.8 months, which is longer than typically reported in the literature.^{e18} This might in part be explained by the fact that we query patients, their family, and their caregivers extensively regarding first symptoms and often find that the earliest indicators of disease can occur months before the first symptoms reported in the medical records, or initially by the family. We accounted for duration of disease to LP in ancillary analyses, however, and did not find that it significantly influenced the predictive value of any of the LR models for MRI, or CSF biomarkers individually or concomitantly. Our lower CSF biomarker sensitivity also might be explained by our under-representation of classic (MM1/MV1) sCJD cases.⁴ Our finding that the general CSF profiles between the sCJD and npRPD cohorts were similar is not inconsistent with the literature.^{e19}

Although we found brain MRI to be the best test for the diagnosis of sCJD, it is not perfect and is dependent on a reader familiar with typical CJD findings,^{e20,e21} and others have reported different results. One recent study found T-tau to have identical diagnostic accuracy to MRI (93%), in part because there was higher T-tau sensitivity (80%) and no false-positive T-tau results.^{e12} This difference might be due to the small sample size, not all of whom had MRI or T-tau testing.

Our findings might be particularly useful when trying to interpret conflicting results, and indicate that prioritizing the T-tau result is advisable.

We had 1 false-negative and 2 false-positive MRIs in our cohort. The false-negative scan was in a patient with the MM2 molecular subtype who also had no positive CSF biomarkers in the sample tested. The 2 false-positive MRIs were in npRPD participants with seizures (one of these epileptic participants, who also had hypoglycemia, had the highest level of T-tau observed in the entire cohort as well as a positive 14-3-3 and a very elevated NSE result). Recent seizures, particularly if prolonged, are a well-described cause of DWI cortical ribboning and can even cause basal ganglia hyperintensity.^{e22} Therefore, one should be cautious diagnosing sCJD based on a positive DWI MRI in this setting. Once the seizures are controlled, however, these DWI abnormalities should remit within days or weeks.^{e22,e23}

There were some limitations to our study. First, the sample size is relatively small. Replicating our results in a large and independent cohort is necessary. Our distribution of certain sCJD molecular subtypes differed from those reported by other groups, with fewer MM1/MV1 cases.¹³ Additionally, the CSF biomarker results were obtained from different laboratories, and the MRIs on different scanners, which could potentially influence our results. This, however, reflects general clinical experience in the United States, where diagnostic information is culled from numerous sources. Additionally, we did not find that the variability of results, either between laboratories or between scanners, was greater than that which might be expected by chance. Ideally, however, the same laboratories and reagent kits would have been used for analysis of the various CSF biomarkers, and the same scanner for the acquisition of the MRI data.

One advantage of this study is our inclusion of npRPD participants in whom CJD was considered in the differential diagnosis, even if they were not pathology-proven. Restricting the control cohort to pathology-proven cases would miss many of the participants referred to our center whom were initially suspected of having prion disease, but ultimately were found to have other etiologies and either survived a long time or improved with or without treatment, and better replicates general clinical experience. Despite the stringent inclusion criteria applied to the npRPD cohort, our diagnostic certainty for these participants is not as high as that for the sCJD group.

These data suggest that brain MRI acquisition, including fluid-attenuated inversion recovery, DWI, and apparent diffusion coefficient sequences, should be a mainstay of the assessment of patients with suspected sCJD, particularly in atypical cases or when CSF testing shows conflicting or negative results. In this cohort, T-tau was a better diagnostic measure of sCJD than 14-3-3 or NSE, but much less accurate than MRI. It is important to stress that MRI should always be interpreted within the clinical context, however, and expertise in interpreting CJD MRIs is required. False-positives and false-negatives, although rare, do occur,^{17,e22} and MRIs in sCJD are often misread by radiologists.^{e20,e21}

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