Diagnostic Performance of Cerebrospinal Fluid Total Tau and Phosphorylated Tau in Creutzfeldt-Jakob Disease Results From the Swedish Mortality Registry

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**IMPORTANCE** Identifying a clinical distinction between the invariably lethal prion disease Creutzfeldt-Jakob disease (CJD) and nonprion rapidly progressive dementias is important and sometimes difficult; thus, reliable tools for diagnosis are in great demand.

**OBJECTIVE** To test the diagnostic performance of dementia cerebrospinal fluid (CSF) biomarkers total tau (T-tau), phosphorylated tau (P-tau), and the T-tau to P-tau ratio for CJD by analyzing the results from a large database of routine clinical samples in combination with diagnosis information from the Swedish Mortality Registry.

**DESIGN, SETTING, AND PARTICIPANTS** This was a retrospective cohort study. We cross-referenced the Swedish Mortality Registry with a data set of CSF measurements of T-tau and P-tau performed in routine clinical testing at the Clinical Neurochemistry Laboratory of the Sahlgrenska University Hospital, which serves most of Sweden. The data set consisted of 9765 deceased individuals with CSF measures, including 93 with CJD, with 52 autopsy-verified samples (56%).

**MAIN OUTCOMES AND MEASURES** For each patient, T-tau and P-tau levels in CSF were measured and the T-tau to P-tau ratio was calculated. Biomarker levels (adjusted for age and sex) were analyzed in relation to the recorded cause of death and time of death. We specifically tested a previously defined CJD biomarker profile (T-tau >1400 ng/L and T-tau to P-tau-ratio >25).

**RESULTS** Patients who died of CJD had elevated CSF T-tau levels and T-tau to P-tau ratio, but not elevated CSF P-tau levels, compared with patients who died of Alzheimer disease (AD) and other dementias. The previously defined biomarker profile had a specificity of 99.0%, a sensitivity of 78.5%, and a positive likelihood ratio of 79.9. When tested against common differential diagnoses, the sensitivity, specificity, and positive likelihood ratio of this profile was 78.5%, 99.6%, and 196.6, respectively, in relation to AD and 78.5%, 99.3%, and 109.3, respectively, in relation to other dementias. In CJD individuals (n = 30) with repeated measurements, but not in those with AD (n = 242) or other dementias (n = 258), T-tau levels and T-tau to P-tau ratios increased over time.

**CONCLUSIONS AND RELEVANCE** In this routine clinical setting, the combination of increased T-tau levels and increased T-tau to P-tau ratios in CJD patients has a very high specificity against important differential diagnoses to CJD and may serve as a clinically useful diagnostic test.

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Creutzfeldt-Jakob disease (CJD) is a rare and untreatable prion disease, leading to rapid and invariably lethal neurodegeneration. Distinguishing CJD from other and potentially treatable rapidly progressive encephalopathies is important, and because there is a risk of misdiagnosis due to variation in the symptoms of CJD, reliable tools for diagnosis are in great demand.\(^1,^2\) Periodic sharp-wave complexes in electroencephalography (EEG) are seen in approximately two-thirds of CJD patients, especially in the later stages of the disease, and high signal intensities in the basal ganglia on magnetic resonance imaging (MRI) have been suggested to discriminate CJD from other dementia disorders. However, neither EEG nor MRI has diagnostic accuracy high enough to serve as a sole reliable diagnostic tool.\(^3,^4\) The severe and progressive neuronal loss that is the hallmark sign of this disease leads to protein leakage into the cerebrospinal fluid (CSF), and measuring its biomarker quantities is an important and effective aid in the diagnostic process. The CSF proteins 14-3-3 and total tau (T-tau) reflect neuronal damage and have been of particular interest in this setting, but 14-3-3 has been shown\(^5,^6\) to be less accurate than previously thought, especially regarding diagnostic specificity. Cerebrospinal fluid T-tau levels are believed to correlate with the rate of axonal degeneration across several neurologic diseases.\(^7\) In contrast, CSF levels of tau proteins phosphorylated at specific amino acid residues (P-tau) are increased in Alzheimer disease (AD) but generally not in other progressive neurologic diseases.\(^8\) Predictive values of the T-tau level and the T-tau to P-tau ratio suggest that they are of value, especially in conjunction with other methods in the diagnosis of CJD.\(^9,^{10-12}\) However, previous CSF studies\(^10-14\) that include analysis of the P-tau level and the T-tau to P-tau ratio in CJD are limited by small sample sizes. We wanted to assess the diagnostic performance of T-tau and P-tau levels and the T-tau to P-tau ratio in a large study population by analyzing the results from measurements of biomarkers in CSF taken from a large database of routine clinical samples in combination with diagnosis information from the Swedish Mortality Registry. We hypothesized that patients who died of CJD would show an elevated CSF T-tau level and T-tau to P-tau ratio prior to death, and that a previously defined algorithm using these biomarkers\(^10\) would have high sensitivity and specificity for CJD vs other dementias.

**Methods**

The Clinical Neurochemistry Laboratory of the Sahlgrenska University Hospital, Gothenburg, Sweden, performs CSF dementia biomarker measurements for all of Sweden and carries out about 15,000 to 20,000 such analyses yearly. Cerebrospinal fluid T-tau and P-tau data generated in routine clinical testing from January 1, 2002, to June 1, 2012, were extracted from the laboratory’s software database. The study was approved by the Regional Ethical Review Board of the University of Gothenburg.

This data set was cross-referenced against the Swedish Mortality Registry using the Swedish 10-digit unique national identification number (personal identity number). The Swedish Mortality Registry is a national registry maintained by the Swedish National Board of Health and Welfare, which maintains complete records on all deaths in Sweden, including causes of death as established by the physician issuing the death certificate using the *International Statistical Classification of Diseases and Related Health Problems* as the standard diagnostic tool. This database was queried for dates and causes of death for the patients in our data set. The inclusion criteria were that test results of both T-tau and P-tau were registered for each patient. The resulting data set contained CSF tests for 9,765 individuals. Ninety-three of these patients were reported to have CJD as a main or underlying cause of death, and 52 of those were verified by autopsy. Thirty of the CJD cases had more than 1 registered sampling of T-tau and/or P-tau in our data set.

A previously suggested neurochemical algorithm was applied to determine a biomarker profile suggestive of CJD.\(^10\) This profile consists of a CSF T-tau concentration greater than 1400 ng/L together with a T-tau to P-tau ratio greater than 25 and was calculated by finding the optimal Youden index\(^10\) for the combination of the biomarkers in a cohort of 9 patients with autopsy-confirmed CJD and a contrast group of 27 patients with clinically suspected CJD that was eventually confirmed as CJD negative, achieving 78% sensitivity and 93% specificity, as described previously.

**Biochemical Measurements**

Cerebrospinal fluid T-tau and P-tau were measured using enzyme-linked immunosorbent assays (human-tau antigen and [\(^{18}S\)P]Phospho-tau; Innogenetics) as previously described.\(^15,16\) The between-assay coefficients of variation for the T-tau and P-tau tests were 10.4% and 10.2%, respectively, as determined by internal control samples during the entire study period (Supplement [eMethods]).

All analyses were performed as part of clinical routine testing by board-certified laboratory technicians. The procedures used were accredited by the Swedish Board for Accreditation and Conformity Assessment.

**Statistical Analysis**

Correlations were calculated using 2-tailed, independent-sample t test, Spearman rank correlation coefficient, and Mann-Whitney test. Statistical hypothesis testing was performed using multiple regression and logistic regression. All statistics, charts, and tables were produced with SPSS, version 20 (IBM). Details on the statistical methods applied in this study can be found in the Supplement (eMethods).

**Results**

**Data Set Description**

Demographics are summarized in Table 1 for CJD patients and non-CJD patients. There was no significant difference in sex distribution between these groups, but CJD patients were significantly younger and had shorter survival compared with non-CJD patients. There were no significant differences \((P > .21)\) in sex, age, time of survival, or biomarker
levels between autopsy-verified and non-autopsy-verified CJD patients. In the whole patient population, age correlated with T-tau level ($R = 0.18; P < .001$) and P-tau level ($R = 0.23; P < .001$). Women had higher levels of T-tau (mean [SD], 736 [2661] vs 631 [1768] ng/L, Mann-Whitney, $1.3 \times 10^7; P < .001$) and P-tau (75 [40] vs 70 [39] ng/L, Mann-Whitney, $1.3 \times 10^7; P < .001$) compared with men.

### Biomarker Levels

We compared the levels of T-tau and P-tau and the T-tau to P-tau ratio between patients with CJD listed as a cause of death and patients with non-CJD diseases listed as causes of death, using continuous biomarker levels. The T-tau level and the T-tau to P-tau ratio were higher in CJD compared with non-CJD patients (Table 1). In contrast, the P-tau level was lower in individuals with CJD. Age and sex were possible confounders for these group differences, but in logistic regression analysis $\log_{10}$ T-tau to P-tau ratio was still a significant predictor of CJD group with age and sex as covariates ($P < .001$; $B = 6.06$; exp $(B) = 429.39$ [95% CI, 226-816]), as was $\log_{10}$ T-tau ($P < .001; B = 6.27$; exp $(B) = 527.67$ [95% CI, 252-1102]), but not $\log_{10}$ P-tau ($P = .17$).

### Sensitivity and Specificity

Using the previously defined biomarker profile (T-tau level $>1400$ ng/L, T-tau to P-tau ratio $>25$), 73 of the 93 individuals with CJD as a cause of death had a positive biomarker profile at their first assessment, resulting in a sensitivity of 78.5%. A total of 9577 of the 9672 patients without CJD as a cause of death had a negative CJD biomarker profile, resulting in a specificity of 99.0%. The positive likelihood ratio (LR+) of this profile was 79.9. Figure 1 shows receiver operating characteristic plots of T-tau level, P-tau level, and T-tau to P-tau ratio as diagnostic predictors in our sample.

### Differences in Age and Survival Between Biomarker-Positive and Biomarker-Negative Patients

We also compared the CJD group with the non-CJD group among the biomarker-positive samples (ie, true-positive vs false-positive) in terms of age at CSF sampling and time of survival. Mann-Whitney tests showed these groups to be significantly different ($P < .001$) both in age and survival. Biomarker-positive CJD patients were younger (median, 66 years; interquartile range [IQR], 61-76) than biomarker-negative non-CJD patients (median, 74 years; IQR, 66-80) and had a shorter survival time (median, 31 days; IQR, 19-76 vs median, 439 days; IQR, 68-1128).

Next, we compared biomarker-positive (true-positive) and biomarker-negative (false-negative) patients within the CJD group. When evaluated by Mann-Whitney tests, these 2 groups differed significantly ($P < .01$) in time of survival but not in age ($P = .26$). The true-positive patients had a shorter survival time (median, 31 days; IQR, 19-76) compared with the false-negative individuals (median, 118 days; IQR, 84-205). Figure 2 shows levels of T-tau and P-tau and the T-tau to P-tau ratio in relation to time to death from sampling for the CJD group and their biomarker profile.

### Relation Between CSF Biomarkers and Survival Time

In the cross-sectional analysis, the level of T-tau and the T-tau to P-tau ratio in CJD increased with disease progression and were at their highest just before the fatal outcome; the

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**Table 1. Demographic Characteristics**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>CJD</th>
<th>Non-CJD</th>
<th>Total</th>
<th>P Valuea</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, No.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>50</td>
<td>4615</td>
<td>4665</td>
<td>.25b</td>
</tr>
<tr>
<td>Male</td>
<td>43</td>
<td>5057</td>
<td>5100</td>
<td></td>
</tr>
<tr>
<td>Age at sampling, y</td>
<td>67 (10)</td>
<td>74 (9)</td>
<td>74 (9)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>66 (61-74)</td>
<td>76 (70-81)</td>
<td>76 (69-81)</td>
<td></td>
</tr>
<tr>
<td>Age at death, y</td>
<td>67 (10)</td>
<td>78 (9)</td>
<td>78 (9)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>66 (61-74)</td>
<td>79 (73-84)</td>
<td>79 (73-84)</td>
<td></td>
</tr>
<tr>
<td>Time to death at sampling, d</td>
<td>78 (89)</td>
<td>1265 (854)</td>
<td>1254 (858)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>40 (22-102)</td>
<td>1154 (555-1864)</td>
<td>1143 (541-1857)</td>
<td></td>
</tr>
<tr>
<td>T-tau level, ng/L</td>
<td>9794 (19 994)</td>
<td>594 (676)</td>
<td>681 (2240)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>4300 (2200-9960)</td>
<td>490 (310-730)</td>
<td>490 (320-740)</td>
<td></td>
</tr>
<tr>
<td>P-tau level, ng/L</td>
<td>61 (31)</td>
<td>73 (40)</td>
<td>73 (40)</td>
<td>.006</td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>59 (38-73)</td>
<td>64 (45-91)</td>
<td>64 (45-91)</td>
<td></td>
</tr>
<tr>
<td>T-tau to P-tau ratio</td>
<td>155 (280)</td>
<td>8.4 (7.8)</td>
<td>9.8 (31.6)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>101 (34-170)</td>
<td>7.3 (6.2-8.6)</td>
<td>7.3 (6.2-8.7)</td>
<td></td>
</tr>
</tbody>
</table>

**Abbreviations:** CJD, Creutzfeldt-Jakob disease; IQR, interquartile range; P-tau, phosphorylated tau; T-tau, total tau.

**A 2-tailed, independent samples t test was used to determine group mean differences.**  
**b Determined using Pearson $\chi^2$ test.**
Figure 1. Discriminatory Power of Total (T)-Tau and Phosphorylated (P)-Tau Levels and the T-Tau to P-Tau Ratio

Receiver operating characteristic (ROC) plot displaying the discriminatory power of T-tau and P-tau levels and the T-tau to P-tau ratio in patients with Creutzfeldt-Jakob disease (CJD) compared with those without CJD (A), with Alzheimer disease (AD) (B), and with other dementias (C). The combination of biomarkers in the T-tau to P-tau ratio has better performance than do T-tau and P-tau level individually. Areas under the curve for T-tau and P-tau levels and the T-tau to P-tau ratio were 0.949, 0.584, and 0.982 in CJD vs non-CJD; 0.923, 0.766, and 0.985 vs AD; and 0.951, 0.593, and 0.984 vs other dementias, respectively.

Figure 2. Survival in Relation to Biomarker Levels in Creutzfeldt-Jakob Disease (CJD)

Days of survival and biomarkers of disease intensity for patients with CJD. Levels of both total (T)-tau and the T-tau to phosphorylated (P)-tau ratio show a clear trend of higher values prior to death. P-tau levels decline with disease progress. Markers are color coded as being CJD biomarker profile positive or negative. The solid lines are local regression fits. The dashed lines show cutoff values for the biomarker profile.
P-tau level decreased and was at its lowest level at that time (Figure 2). Separate multiple regression analyses were conducted to predict log $T_{-}\text{tau}$, log $P_{-}\text{tau}$, and log $T_{-}\text{tau}$ to $P_{-}\text{tau}$ ratio from sex, age (years), and time of survival (days). These variables significantly predicted log $T_{-}\text{tau}$, but only time of survival ($P < .001; \beta = 0.51$) added significantly to the prediction. They also significantly predicted log $T_{-}\text{tau}$ to $P_{-}\text{tau}$ ratio ($F_{3,89} = 10.3; P < .001; R^2 = 0.26$), but only time of survival ($P < .001; \beta = -0.51$) added significantly to the prediction. The prediction of log $P_{-}\text{tau}$ ($F_{3,89} = 13.28; P < .001; R^2 = 0.31$), but again only time of survival ($P < .001; \beta = -0.26$) to $P_{-}\text{tau}$ ratio as a first diagnostic gate and assessing only by age at sampling ($P = 0.2; \beta = 0.02$).

### Biomarker Profile Validity and Optimization

In the analyses described above, we used the Blennow et al. biomarker profile. We also generated a new profile by applying the Youden index strategy to our data set. The optimal individual cutoff level for $T_{-}\text{tau}$ was calculated as 1350 ng/L (Youden index, 0.81) and for the $T_{-}\text{tau}$ to $P_{-}\text{tau}$ ratio, 17 (Youden index, 0.90). Applying this new biomarker profile increased the sensitivity from 78.5% to 85.0%; the specificity decreased only from 99.0% to 98.6% and the LR+ decreased from 79.9 to 61.8. An algorithmic approach was also tested using the $T_{-}\text{tau}$ to $P_{-}\text{tau}$ ratio as a first diagnostic gate and assessing only the individual $T_{-}\text{tau}$ value if the $T_{-}\text{tau}$ to $P_{-}\text{tau}$ ratio surpassed the optimal cutoff point at 17. A new Youden index calculation was made using the data in our patients that passed the first gate, and a $T_{-}\text{tau}$ value of 2100 ng/L (Youden index, 0.56) was determined as the optimal cutoff point. This was the best profile in terms of having the least absolute number of misdiagnosed CJD cases (false-positive + false-negative = 96) and had a sensitivity of 77.4%, a specificity of 99.2%, and an LR+ of 99.8. The results of the performance testing of all biomarker profiles are detailed in Table 2.

### Biomarker Diagnostic Performance and Differential Diagnoses

We also tested the accuracy of the biomarkers for CJD against contrast groups consisting of patients whose cause of death was AD ($n = 2004$) or other dementias ($n = 2645$) by calculating the sensitivity and specificity of the original CJD biomarker profile (defined by a $T_{-}\text{tau}$ cutoff level of 1400 ng/L in combination with a $T_{-}\text{tau}$ to $P_{-}\text{tau}$ ratio $> 25$). When compared with the AD group, the sensitivity, specificity, and LR+ in the

### Table 2. Biomarker Profile Performance

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>T-Tau &gt;1400 ng/L, T-Tau to P-Tau Ratio &gt;25</th>
<th>T-Tau &gt;1350 ng/L, T-Tau to P-Tau Ratio &gt;17</th>
<th>T-Tau to P-Tau Ratio &gt;17</th>
<th>T-Tau &gt;2100 ng/L, T-Tau to P-Tau Ratio &gt;17</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Non-CJD cases, No.</td>
<td>9577</td>
<td>95</td>
<td>9539</td>
<td>133</td>
</tr>
<tr>
<td>CJD cases, No.</td>
<td>20</td>
<td>73</td>
<td>14</td>
<td>79</td>
</tr>
<tr>
<td>Sensitivity, %</td>
<td>78.5</td>
<td>85.0</td>
<td>93.6</td>
<td>77.4</td>
</tr>
<tr>
<td>Specificity, %</td>
<td>99.0</td>
<td>98.6</td>
<td>97.1</td>
<td>99.2</td>
</tr>
<tr>
<td>Correctly diagnosed cases</td>
<td>9650</td>
<td>9618</td>
<td>9479</td>
<td>9669</td>
</tr>
<tr>
<td>Misdiagnosed cases</td>
<td>115</td>
<td>147</td>
<td>286</td>
<td>96</td>
</tr>
<tr>
<td>Positive likelihood ratio</td>
<td>7.9</td>
<td>61.8</td>
<td>32.3</td>
<td>99.8</td>
</tr>
</tbody>
</table>

Abbreviations: CJD, Creutzfeldt-Jakob disease; $P_{-}\text{tau}$, phosphorylated $\text{tau}$; $T_{-}\text{tau}$, total $\text{tau}$.

Longitudinal Data

To explore how the levels of biomarkers develop with disease progression, longitudinal biomarker levels were analyzed in the subset of CJD patients with more than 1 CSF sample registered ($n = 30$). Their individual changes in $T_{-}\text{tau}$ and $P_{-}\text{tau}$ levels and in $T_{-}\text{tau}$ to $P_{-}\text{tau}$ ratio are plotted in Figure 3. Higher values of both $T_{-}\text{tau}$ level and $T_{-}\text{tau}$ to $P_{-}\text{tau}$ ratio were seen at later stages in the disease for most measurements (85% for $T_{-}\text{tau}$ level and 93% for $T_{-}\text{tau}$ to $P_{-}\text{tau}$ ratio). The greatest increases in $T_{-}\text{tau}$ level and $T_{-}\text{tau}$ to $P_{-}\text{tau}$ ratio were seen closest to death. The $P_{-}\text{tau}$ level had a variable longitudinal pattern, with 54% of patients having increasing values and 46% having decreasing values. The same clear trend of rising $T_{-}\text{tau}$ level and $T_{-}\text{tau}$ to $P_{-}\text{tau}$ ratio was not seen in the groups with AD or other dementias listed as cause of death. Of 242 patients with AD who had multiple measurements, increasing $T_{-}\text{tau}$ levels were documented in 46% of the sample and increasing $T_{-}\text{tau}$ to $P_{-}\text{tau}$ ratios were noted in 58%. Of 258 patients with other dementias, increasing $T_{-}\text{tau}$ levels were observed in 48% of the sample and increasing $T_{-}\text{tau}$ to $P_{-}\text{tau}$ ratios were noted in 56% (Figure 3).

In evaluation of the diagnostic performance of $T_{-}\text{tau}$ level and $T_{-}\text{tau}$ to $P_{-}\text{tau}$ ratio using the test results at the time point closest to death, 7 additional CJD patients were classified as biomarker positive, resulting in a sensitivity of 86.0% and an LR+ of 87.6 compared with the original sensitivity of 78.5% and LR+ of 79.9 obtained when the first test results were used. The specificity remained unchanged.

### Discussion

In this study, we explored a large data set of dates and causes of death from the Swedish Mortality Registry, cross-referenced with a data set of CSF measurements of $T_{-}\text{tau}$ and $P_{-}\text{tau}$ performed in routine clinical testing. Our hypothesis that patients whose cause of death was CJD would show an elevated CSF $T_{-}\text{tau}$ level and $T_{-}\text{tau}$ to $P_{-}\text{tau}$ ratio prior to death...
was confirmed, with the CJD-indicative biomarker profile (T-tau >1400 ng/L and T-tau to P-tau ratio >25) having a specificity of 99.0%, a sensitivity of 78.5%, and an LR+ of 79.9 in this dataset of 9675 deceased individuals in contrast to 93 CJD patients. In groups of common differential diagnoses to CJD, the sensitivity, specificity, and LR+ were 78.5%, 99.6%, and 196.6, respectively, in relation to AD and 78.5%, 99.3%, and 109.3, respectively, in relation to other dementias. Furthermore, the patients with false-negative test results (CJD diagnosis but negative biomarker profile) had a longer survival time than did those with a true-positive diagnosis, possibly indicating that the test was performed at an earlier stage of the disease, therefore displaying lower levels and a negative profile because of the shorter time of progression. The subset of CJD

Figure 3. Longitudinal Biomarker Assessments and Survival in Creutzfeldt-Jakob Disease (CJD)

Spaghetti plots of how biomarker levels develop over time in the CJD cases with more than 1 recorded biomarker assessment. Most CJD cases show increasing levels of total (T)–tau (A) and T-tau to phosphorylated (P)–tau (B) ratio as survival days diminish, but P-tau levels have a heterogeneous development (C). Patients with Alzheimer disease (AD) and those with other dementias do not show the same pattern of increasing T-tau level and T-tau to P-tau ratio close to death (A and B). The x-axis is cut at 1500 days for visual clarity.
patients in our data set with longitudinal data showed rising T-tau levels and T-tau to P-tau ratios, further corroborating this hypothesis. The sensitivity of the biomarker profile increased to 86.0% when the latest biomarker measurement was taken into account for this group of patients, which suggests that, in cases in which clinical presentation and/or other investigations support a diagnosis of CJD, repeated CSF samplings may be of value.

Optimization of the diagnostic biomarker profile proposed by Blennow et al. using Youden index calculation in our material suggested that a lower cutoff point for the T-tau to P-tau ratio was more optimal in the present cohort. For T-tau, the cutoff levels identified in the present study were well aligned with previously suggested values. The best-performing biomarker profile in the present study was acquired with an algorithmic approach using a T-tau to P-tau ratio threshold as a first diagnostic gate and then applying a second test of a T-tau threshold only to data passing the first gate. This method yielded the highest specificity (99.2%), the lowest number of misdiagnosed patients (96), and the highest LR+ (99.8) but a lower sensitivity (77.4%). An LR+ of 99.8 could be regarded as diagnostically reliable because values exceeding 10 are generally considered satisfactory. The exact cutoff values of these algorithms and profiles might not be directly transferable for use at other laboratories and clinical centers because of differences in laboratory equipment, assays, routines, and patient cohorts. Also, as for any diagnostic test, the ultimate clinical usefulness of these biomarkers is influenced by the disease prevalence in the tested cohort.

There are several sets of diagnostic criteria for CJD in clinical settings, the most commonly used being those of the World Health Organization; University of California, San Francisco (UCSF) and the European Magnetic Resonance Imaging Creutzfeldt-Jakob Consortium. These criteria all rely on clinical symptoms and presentation as a basis and can be backed up by typical EEG findings or CSF analysis of 14-3-3 protein as confirmatory tests or by MRI characteristics in the European MRI-CJD and UCSF criteria, but none of these sets of criteria includes CSF levels of T-tau or the T-tau to P-tau ratio. The validity and performance of these sets of diagnostic criteria have been examined, and some concerns have emerged. Periodic sharp-wave complexes in EEG have a poor sensitivity (40%-67%) but high specificity, are usually positive in certain molecular subtypes, and can be mimicked by other conditions. Cerebrospinal fluid 14-3-3 protein detection in CSF was initially thought to be both highly specific and highly sensitive for CJD diagnosis but was later found to be released into the CSF in many other nonprion conditions characterized by extensive neuronal loss, such as stroke, multiple sclerosis, and meningoccephalitis, lowering its credibility as a disease-specific marker. The high value of MRI as a diagnostic tool has been demonstrated relatively recently but is sometimes lacking in sensitivity and might not be appropriate in late-stage disease, and defining MRI criteria has proven to be a challenging task. Tau levels in CSF reflect various neurodegenerative processes and are usually very high in CJD, and the T-tau to P-tau ratio discriminates CJD from AD and frontotemporal dementia. Furthermore, a CSF biomarker profile is an objective and easily achievable means of substantiating a clinical suspicion of CJD as opposed to the more subjective nature of MRI and EEG evaluation. In the present study, we showed that a CJD biomarker profile effectively distinguished CJD from many other conditions, specifically AD and other dementias. More studies directly comparing different diagnostic modalities for diagnosing CJD vs other dementias are needed.

The main strength of the present study was the large size of the data set used for analysis, which included complete records of registered causes and dates of death in concert with CSF measurements of T-tau and P-tau for all patients who had undergone a diagnostic lumbar puncture with measurements of dementia markers in clinical routine at the Clinical Neurochemistry Laboratory of the Sahlgrenska University Hospital between 2002 and 2012.

There are several limitations to this study, the most important being the lack of autopsy confirmation in 44% of the CJD cases, as this is the only definitive way of correctly diagnosing CJD. However, because no statistically significant differences were found between autopsy-confirmed and clinically diagnosed cases, we believe that this limitation did not influence our results. Furthermore, in Sweden, reporting CJD cases to the Swedish Institute for Infectious Disease Control is mandatory, and the specific regulations of this report demand strong evidence for a CJD diagnosis, probably minimizing the risk of false-positive diagnoses in this material. Finally, because all diagnoses in our data were taken from the Swedish Mortality Registry, we could be treating CJD-positive cases as negatives if CJD was not listed as a cause of death. Again, this is unlikely because it is mandatory to follow through and report clinically suspected CJD cases in Sweden.

Conclusions

The combination of increased T-tau levels and increased T-tau to P-tau ratios in patients with CJD has a very high specificity against important differential diagnoses to CJD. In the routine clinical setting, this combination may serve as a useful diagnostic test.
Total vs Phosphorylated Tau in Creutzfeldt-Jakob

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