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SHORT REPORT

Levels of plasma brain-derived tau and p-tau181 in Alzheimer's disease and rapidly progressive dementias

Fernando Gonzalez-Ortiz[1,2] | **Thomas K. Karikari**[1,3] | **Giuseppe Mario Bentivenga**[4] | **Simone Baiardi**[4] | **Angela Mammana**[5] | **Michael Turton**[6] | **Przemysław R. Kac**[1] | **Andrea Mastrangelo**[4] | **Peter Harrison**[6] | **Sabina Capellari**[4,5] | **Henrik Zetterberg**[1,2,7,8,9,10] | **Kaj Blennow**[1,2] | **Piero Parchi**[4,5]

[1]Department of Psychiatry and Neurochemistry, Institute of Neuroscience and Physiology, The Sahlgrenska Academy at Gothenburg University, Mölndal, Sweden

[2]Clinical Neurochemistry Laboratory, Sahlgrenska University Hospital, Mölndal, Sweden

[3]Department of Psychiatry, University of Pittsburgh, Pittsburgh, Pennsylvania, USA

[4]Department of Biomedical and Neuromotor Sciences (DiBiNeM), University of Bologna, Bologna, Italy

[5]IRCCS Istituto delle Scienze Neurologiche di Bologna, Bologna, Italy

[6]Bioventix Plc, Farnham, Surrey, UK

[7]Department of Neurodegenerative Disease, UCL Institute of Neurology, Queen Square, London, UK

[8]UK Dementia Research Institute at UCL, Queen Square, London, UK

[9]Hong Kong Center for Neurodegenerative Diseases, Science Park, Hong Kong, China

[10]School of Medicine and Public Health, University of Wisconsin-Madison, Madison, Wisconsin, USA

Correspondence
Fernando Gonzalez-Ortiz, Department of Psychiatry and Neurochemistry, Institute of Neuroscience and Physiology, The Sahlgrenska Academy, University of Gothenburg, SE 431 80, Mölndal, Sweden.
Email: Fernando.gonzalez.ortiz@gu.se

Piero Parchi, IRCCS Istituto delle Scienze Neurologiche di Bologna, Ospedale Bellaria, Via Altura 1/8, 40139 Bologna, Italy.
Email: piero.parchi@unibo.it

Abstract

INTRODUCTION: Rapidly progressive dementias (RPDs) are a group of neurological disorders characterized by a rapid cognitive decline. The diagnostic value of blood-based biomarkers for Alzheimer's disease (AD) in RPD has not been fully explored.

METHODS: We measured plasma brain-derived tau (BD-tau) and p-tau181 in 11 controls, 15 AD patients, and 33 with RPD, of which 19 were Creutzfeldt-Jakob disease (CJD).

RESULTS: Plasma BD-tau differentiated AD from RPD and controls ($p = 0.002$ and $p = 0.03$, respectively), while plasma and cerebrospinal fluid (CSF) p-tau181 distinguished AD from RPD ($p < 0.001$) but not controls from RPD ($p > 0.05$). The correlation of CSF t-tau with plasma BD-tau was stronger ($r = 0.78$, $p < 0.001$) than the correlation of CSF and plasma p-tau181 ($r = 0.26$, $p = 0.04$). The ratio BD-tau/p-tau181 performed equivalently to the CSF t-tau/p-tau181 ratio, differentiating AD from CJD ($p < 0.0001$).

DISCUSSION: Plasma BD-tau and p-tau181 mimic their corresponding cerebrospinal fluid (CSF) markers. P-tau significantly increased in AD but not in RPD. Plasma BD-tau, like CSF t-tau, increases according to neurodegeneration intensity.

KEYWORDS
Alzheimer's disease, blood biomarkers, brain-derived tau, Creutzfeldt-Jakob disease, rapidly progressive dementia

1 | BACKGROUND

The term "rapidly progressive dementia" (RPD) refers to a group of neurological conditions that develop subacutely over a short time (ie, weeks to months) and that, unlike other types of dementia, can be quickly fatal.[1,2] The RPD definition includes a large and heterogeneous group of non-neurodegenerative and neurodegenerative conditions. The mnemonic VITAMINS (Vascular, Infectious, Toxic, Autoimmune, Malignancies, Non-organic [psychiatric]) is a practical way to summarize some major etiologies of non-neurodegenerative RPD.[2–4] Recently, with the COVID-19 pandemic, the SARS-CoV-2 virus itself has been associated with neurological conditions that might present as RPD, such as encephalopathies, cerebral hemorrhage or thrombosis, and encephalomyelitis.[5] Therefore, COVID-19 infection-associated encephalopathies should also be considered in cases where the cause of RPD is unclear.[5]

Accurate epidemiological data on RPD can be challenging to obtain due to underdiagnosis, misdiagnosis, and limited surveillance systems.[6,7] Creutzfeldt-Jakob disease (CJD), the prototype of human prion disease, is the most common cause of neurodegenerative RPD with an estimated annual incidence of approximately 1 to 2 cases per million population.[8,9] It encompasses several subtypes, including sporadic, familial, iatrogenic, and variant CJD.[10] Sporadic CJD accounts for the majority of cases, presenting predominantly in individuals aged 60 years or older.[2,10]

In contrast to CJD, Alzheimer's disease (AD), characterized by amyloid-beta (Aβ) plaques, tau neurofibrillary tangles composed of phosphorylated tau (p-tau), and neurodegeneration,[11,12] typically has a clinically insidious onset and gradual cognitive decline which is rarely rapid.[13,14] However, unusual presentations can be mistaken for CJD, and several AD cases have been reported in conjunction with cerebral amyloid angiopathy (CAA) and presenting as adult-onset RPD.[2,15] Unlike AD, RPD exhibits an aggressive clinical course with rapid cognitive deterioration.[2] In CJD, rapid progression is linked to the autocatalytic conversion and transcellular propagation of misfolded prion protein (PrP^{Sc}, or prion), resulting in widespread neuronal death.[10] The specific anatomical regions targeted by PrP^{Sc} may vary according to the prion conformation or strain, resulting in heterogeneous clinical phenotypes with distinct cognitive, behavioral, and motor features.[1]

Diagnosing RPD is challenging due to the rapidity of cognitive decline, the complexity of underlying causes, and the overlap of symptoms with other neurodegenerative and non-neurodegenerative conditions.[6,7] More importantly, the prognosis for patients with AD and RPD diverges significantly.[2,15] Accurate differentiation informs clinicians and families about the anticipated course of the disease, enabling them to make informed choices.

The lack of distinctive biomarkers and rapid disease progression is one of the biggest challenges to accurate diagnosis of RPD. Current research has proven the immense value of blood-based tau biomarkers in the evaluation of AD,[11,16–18] but little is known about the value of these biomarkers in RPD. Here, we aimed to investigate the value of established plasma markers for AD in RPD.

2 | METHODS

2.1 | Study cohorts, design, and outcome

Paired plasma and cerebrospinal fluid (CSF) samples from neurochemically defined Aβ+ AD patients (n = 15) and age-matched Aβ− controls (n = 11) were selected from the Sahlgrenska University Hospital, Gothenburg, Sweden. The AD patients were selected based on their core CSF biomarker profile previously reported [16] and had no evidence of other neurological conditions based on routine clinical and laboratory assessments. The control group consisted of selected patients without an AD profile by clinical evaluation and CSF biomarkers.

The RPD samples were provided by the Laboratory of Neuropathology at the Institute of Neurological Sciences of Bologna, a referral Center for prion disease in Italy. The RPD group included patients with a final diagnosis of sporadic CJD (n = 19); autoimmune encephalitis (n = 2); rapidly progressive AD dementia (n = 2); recurrent seizures with dementia (n = 2); rapidly progressive AD dementia with CAA (n = 1); hippocampal infarction with chronic vascular encephalopathy in basal ganglia and thalamus (n = 1); encephalitis (n = 1); dementia with Lewy bodies (n = 1); vascular dementia (n = 1); Wernicke encephalopathy (n = 1); frontotemporal dementia (n = 1); and one patient without a clear neurological history that progressed to respiratory insufficiency and coma of unclear etiology (n = 1). For detailed demographic characteristics, see Table S1.

2.2 | Blood collection and biomarker analysis

Plasma brain-derived tau (BD-tau) and p-tau181 measurements were performed on the Simoa HD-X platform with methods previously described.[16,17] Quality control samples were analyzed in duplicate at the start and the end of each plate to assess precision. These measurements were performed at the Clinical Neurochemistry Laboratory, Sahlgrenska University Hospital, Mölndal, Sweden.

RESEARCH IN CONTEXT

1. **Systematic Review**: The authors reviewed the literature using traditional (eg, PubMed) sources and meeting abstracts and presentations. We found 36 publications when using the terms "plasma biomarkers" and "rapidly progressive dementia" (RPD). Most of the publications focused on the diagnosis of Alzheimer's disease (AD) and different clinical presentations of this disease. We did not find publications comparing plasma brain-derived tau (BD-tau) or plasma p-tau181 levels in AD and RPD. In this study, we explored the differences of these two markers in healthy controls, non-prion RPD, prion-RPD and AD.
2. **Interpretation**: Our findings suggest that plasma BD-tau and p-tau181 can provide diagnostic support in cases with rapid cognitive decline and obscure symptomatology. While plasma p-tau181 seems to be strongly associated with amyloid pathology, plasma BD-tau seems to be a neurodegeneration marker modulated by the intensity of the neurodegenerative process. These plasma markers may be potentially used for the first-line screening and monitoring of patients with suspected RPD. They could accurately and inexpensively estimate noninvasively both the degree of neurodegeneration and the presence of AD-related pathology.
3. **Future Directions**: Future research will focus on exploring different types of RPD and evaluating different phosphorylated tau forms, including the resulting BD-tau/p-tau ratios in these conditions.

2.3 | Statistical analysis

Statistical analyses were performed with Prism version 9.3.1 (GraphPad, San Diego, CA, USA). The distributions of data sets were examined for normality using the Kolmogorov-Smirnov test. Non-parametric tests were used for non-normally distributed data. Spearman correlation and the χ^2 test were used for continuous and categorical variables, respectively. Group differences were examined using the Mann-Whitney test (two categories) or the Kruskal-Wallis test with Dunn's multiple comparisons (three or more groups).

3 | RESULTS

3.1 | Plasma BD-tau and plasma p-tau181 perform equivalently to CSF t-tau and p-tau181 respectively when comparing AD dementia and RPD

CSF total tau (t-tau) and plasma BD-tau levels were each highest in the RPD group versus both the Aβ+ AD dementia and Aβ− control groups (Figure 1A,B). Regarding fold increases, plasma BD-tau was slightly higher than CSF t-tau, which could be attributed to increased permeability of the blood-brain barrier in addition to the neurodegenerative process. These results suggest that similar to CSF t-tau, plasma BD-tau levels are not only higher in Aβ+ AD dementia, but they are further increased in individuals with intense neurodegeneration (independently of Aβ status).

Conversely, plasma and CSF p-tau181 levels were significantly higher only in the Aβ+ AD dementia group, while the levels in the Aβ− controls and RPD groups were equivalent (Figure 1). As a result, the fold changes were only modestly increased in the Aβ+ AD dementia group (2.1 for CSF p-tau181 and 2.3 for plasma p-tau181). Importantly, the levels of p-tau181 in blood and CSF in two RPD cases with Aβ+ AD dementia did not differ much from the Aβ+ AD dementia group having similar fold changes.

In terms of correlation, CSF t-tau and plasma BD-tau correlated strongly in the whole cohort (Spearman rho = 0.78, $p < 0.0001$, Figure 1C) while CSF and plasma p-tau181 showed a much weaker correlation (Spearman rho = 0.26, $p = 0.04$, Figure 1F). Interestingly, we observed a group of patients with low levels of CSF t-tau and high plasma BD-tau (Figure 1C), which might explain the higher fold changes in plasma BD-tau compared to CSF t-tau, and speak in favor of an increased permeability of the blood-brain barrier in these patients.

3.2 | Plasma BD-tau, just like CSF t-tau, identifies higher neurodegeneration intensity in CJD versus other RPD

Next, we asked if the plasma biomarker levels differed in the CJD versus other RPD subgroups. Like CSF t-tau levels, the concentrations of plasma BD-tau were significantly higher in the CJD versus the other RPD sub-cohorts ($p = 0.009$, Figure 2A,B). These findings indicate that plasma BD-tau performs as equivalently as CSF t-tau to monitor neurodegeneration intensity, which was higher in CJD than the other RPDs.

In contrast, CSF and plasma p-tau181 levels did not differ between the CJD and other RPD groups ($p = 0.09$ and $p = 0.25$, respectively, Figure 2C,D), further indicating that these biomarkers do not primarily track the intensity of neurodegeneration.

3.3 | Plasma BD-tau/p-tau181 ratio distinguishes rapidly progressive dementia, independent of amyloid positivity, from AD dementia

We investigated if the plasma BD-tau/p-tau181 ratio could be a surrogate of the established CSF t-tau/p-tau181 ratio to perform the dual function of separating individuals with Aβ+ AD dementia from controls as well as to identify those with a rapidly progressive disease course. The plasma BD-tau/p-tau181 ratio and fold changes were highest in the CJDs, followed by the other RPDs and Aβ+ AD dementia in descending order (Figure 3). Highly similar results were recorded when using the

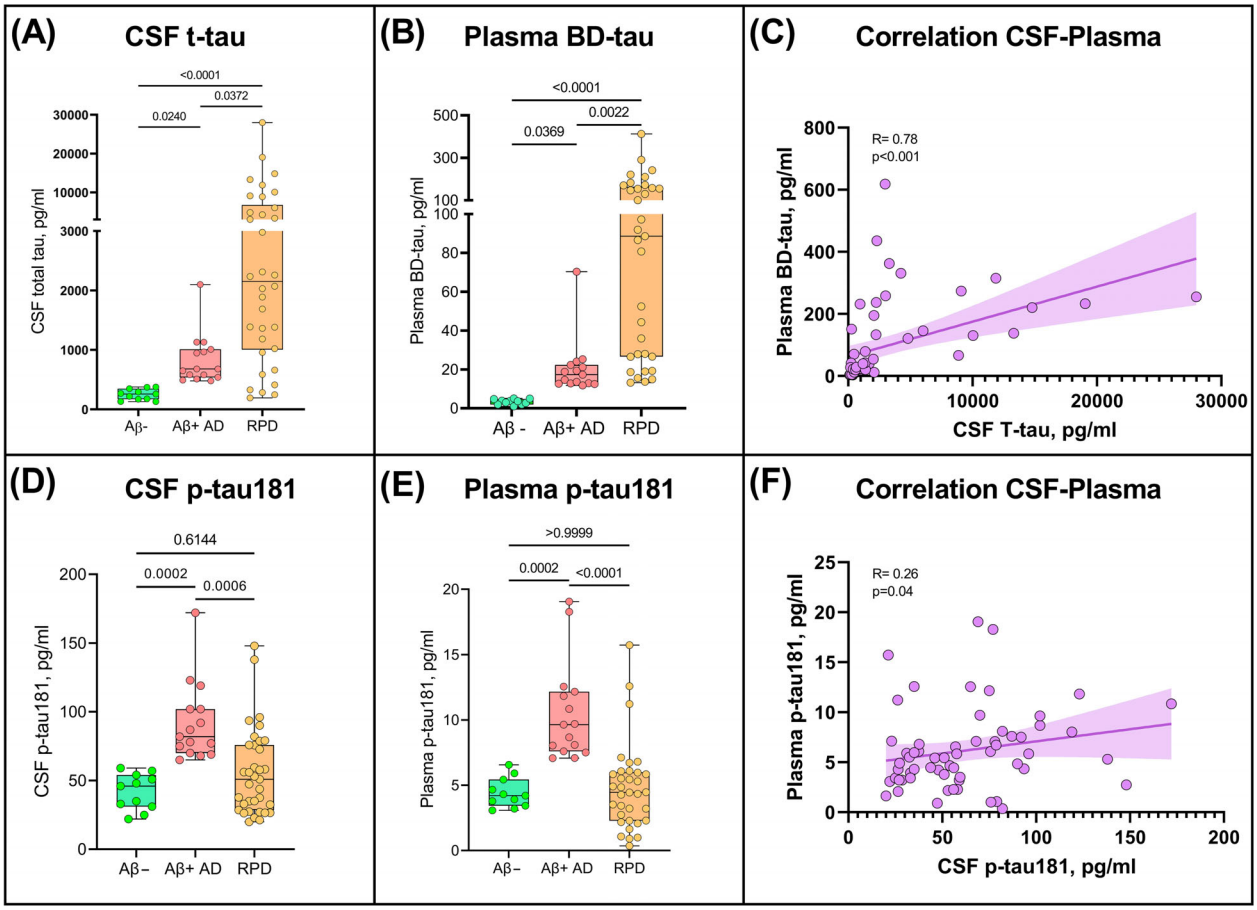

FIGURE 1 Box plots and scatterplots showing the distribution of biomarker concentrations in the different groups. Levels of total tau (t-tau) in CSF (A), and of plasma BD-tau (B), differentiate between the different diagnostic groups. (C) CSF t-tau and plasma BD-tau strongly correlate with each other ($R = 0.78$, $p < 0.001$). CSF p-tau181 (D), and plasma p-tau181 (E), can differentiate AD from controls ($p = 0.0002$ for both) and RPD ($p = 0.0006$ and $p < 0.0001$, respectively), but are unable to distinguish between RPD and controls ($p = 0.61$ and $p > 0.99$, respectively). (F) CSF p-tau181 and plasma p-tau181 show a weak correlation ($R = 0.26$, $p < 0.04$). Aβ, amyloid beta; AD, Alzheimer's disease; BD-tau, brain-derived tau; CSF, cerebrospinal fluid; RPD, rapidly progressive dementias.

CSF t-tau/p-tau181 ratio. Neither the CSF nor the plasma ratio differentiated between controls and AD ($p = 0.21$ and $p = 0.82$, respectively) or non-prion RPD and CJD ($p = 0.09$ and $p = 0.73$, respectively), but both ratios were able to differentiate accurately between Aβ− controls from the RPDs and CJDs ($p < 0.0001$).

Importantly, the CSF ratio t-tau/p-tau181 was able to differentiate Aβ+ AD from CJD ($p < 0.0001$) but was unable to distinguish between Aβ+ AD from non-prion RPD ($p = 0.41$), while the plasma BD-tau/p-tau181 ratio was able to differentiate Aβ+ AD from non-prion RPD and CJD ($p = 0.01$ and $p < 0.0001$, respectively, Figure 3B).

Receiver operating characteristic curves showing the performance of the CSF and plasma ratios differentiating AD and RPD can be found in the supplementary material (Figure S1 and Figure S2).

4 | DISCUSSION

The distinct underlying etiologies of RPDs underscore the importance of accurate diagnosis for both patient care and research.[3] An accurate diagnosis of RPD and the initial categorization between neurodegenerative or other etiologies aid in providing appropriate and timely medical interventions, as treatment strategies may differ substantially, and misdiagnosis can lead to ineffective treatments and disease progression.[2,3,6,7]

Several studies have shown the diagnostic value of AD-related CSF markers (Aβ, p-tau, and t-tau) in the identification of AD etiology in patients with suspected RPD.[19,20] Moreover, CSF surrogate markers of neurodegeneration, including proteins t-tau and 14-3-3, remain fundamental and widely used to support the diagnosis of CJD in patients with RPDs despite the recent introduction of the prion RT-QuIC, a specific CSF assay for the detection of PrP^{Sc}.[20]

Since plasma p-tau is strongly associated with amyloid pathology,[11,21] and plasma BD-tau with the intensity of neurodegeneration and cortical injury,[17,22] we hypothesized that the combined use of plasma BD-tau and p-tau181 may also provide valuable information in patients with RPD. Here, we have investigated the value of these novel tau-specific plasma biomarkers in the RPD diagnosis compared to established CSF markers. We observed that plasma

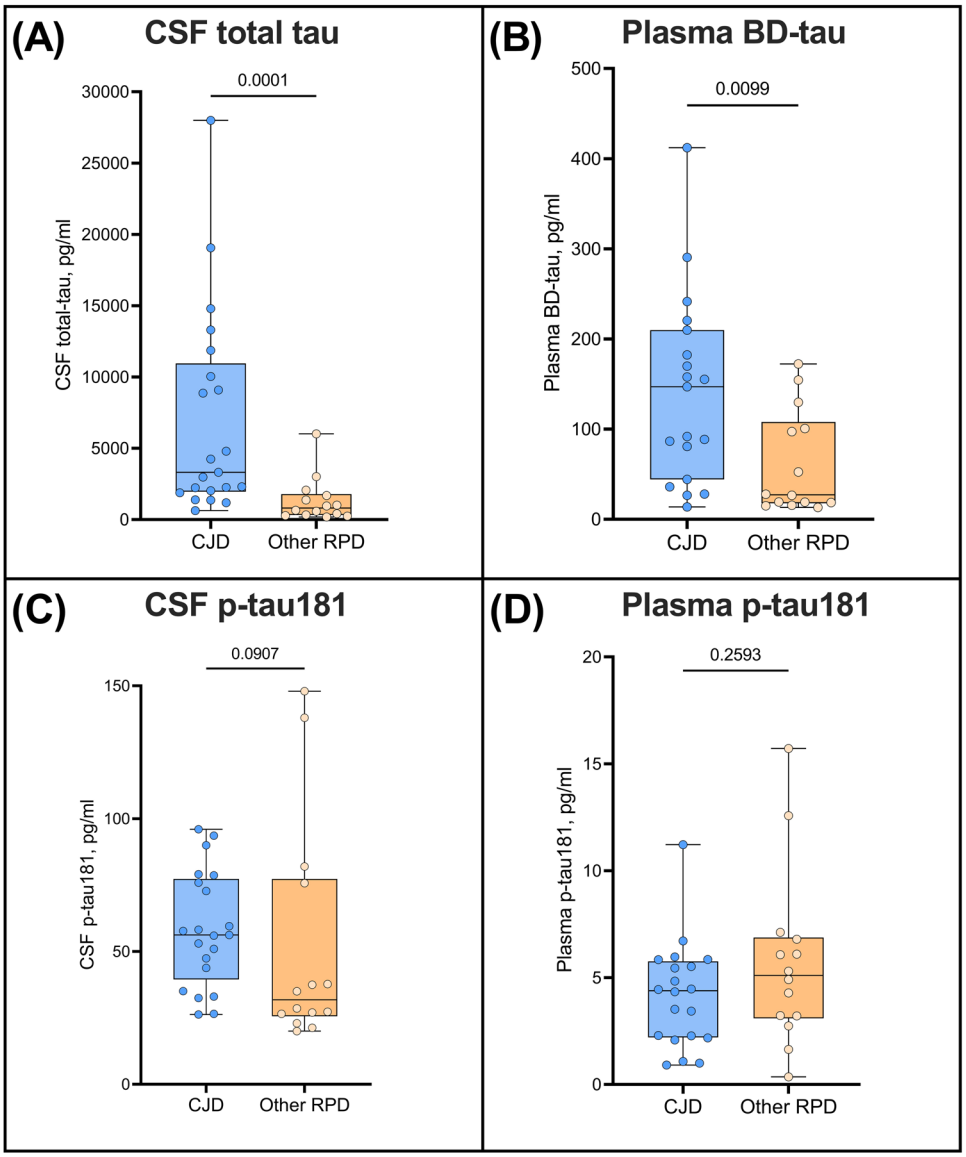

FIGURE 2 Box plots showing the distribution of biomarker concentrations in CJD and non-prion RPD (other RPD). CSF total-tau (A) and plasma BD-tau (B) differentiate between CJD and other RPD ($p = 0.0001$ and $p = 0.009$, respectively). CSF p-tau181 (C) and plasma p-tau181 (D) are unable to distinguish between RPD of prion origin from RPD of non-prion origin ($p = 0.09$ and $p = 0.25$, respectively). BD-tau, brain-derived tau; CJD, Creutzfeldt-Jakob disease; CSF, cerebrospinal fluid; RPD, rapidly progressive dementias.

p-tau181 and BD-tau mimic CSF p-tau and t-tau, respectively. While plasma and CSF p-tau only increase significantly in the AD group, CSF t-tau and BD-tau increase in both AD and RPDs proportionally to the intensity of neurodegeneration. Our results also suggest that p-tau is a very AD-specific marker, not capable of differentiating controls from non-AD RPDs, including CJD. Consequently, the combination of plasma p-tau and BD-tau in a biomarker ratio may also help in discriminating between AD-related RPDs and RPDs due to other etiologies.

Taken together, our results indicate that these novel tau-related plasma markers might be useful tools to help clinicians to estimate non-invasively both the degree of neurodegeneration and the presence of AD-related pathology with relatively low cost and have a potential application for the first-line screening and monitoring of a broad patient population with suspected RPD. The results of the present study show that the combined use of plasma BD-tau and p-tau181 provide very valuable information in patients with rapid cognitive decline and obscure symptomatology. The availability of plasma biomarkers performing similarly to CSF may allow a faster, noninvasive approach for the early screening of these patients, and for their longitudinal monitoring of clinical progression and response to therapies.

4.1 | Strengths and limitations

Strengths of this study include the variety of conditions in the RPD group. Limitations include the lack of longitudinal data and analysis of the diagnostic performance in the clinical setting. In addition, the

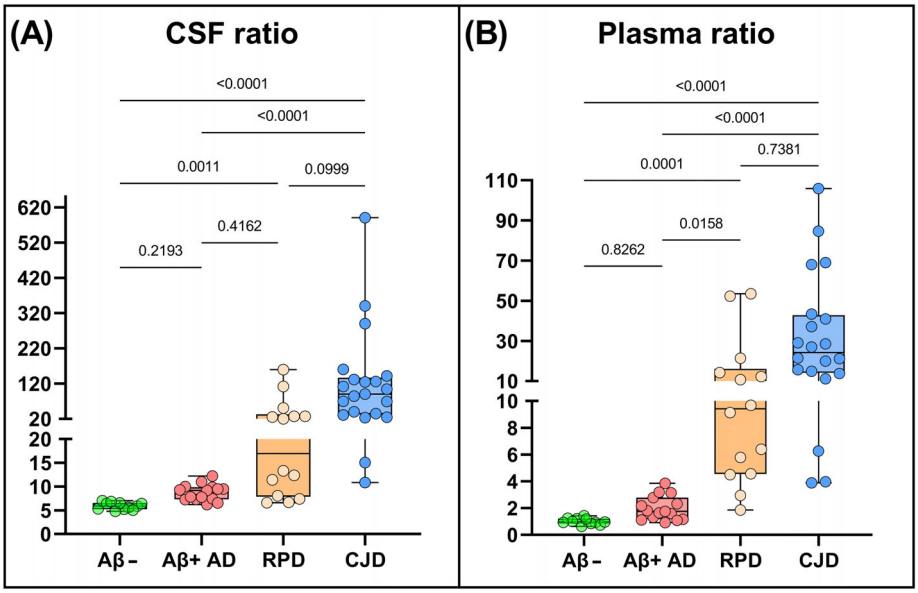

FIGURE 3 Comparison of the ratio total-tau/p-tau181 in CSF (A), with the ratio BD-tau/p-tau181 in plasma (B). Both the CSF and plasma ratios performed similarly, distinguishing controls from RPD and CJD, and AD from CJD, but, interestingly, only the plasma ratio distinguished AD from non-prion RPD ($p = 0.01$). Aβ, amyloid beta; AD, Alzheimer's disease; BD-tau, brain-derived tau; CJD, Creutzfeldt-Jakob disease; CSF, cerebrospinal fluid; RPD, rapidly progressive dementias.

non-prion RPD group consisted of a heterogeneous group of pathologies with a limited number of cases for each condition.

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CONFLICT OF INTEREST STATEMENT

M.T. and P.H. are employees of Bioventix Plc. H.Z. has served a scientific advisory boards and/or as a consultant for AbbVie, Alector, Annexon, Artery Therapeutics, AZTherapies, CogRx, Denali, Eisai, NervGen, Pinteon Therapeutics, Red Abbey Labs, Passage Bio, Roche, Samumed, Siemens Healthineers, Triplet Therapeutics, and Wave, and has given lectures in symposia sponsored by Cellectricon, Fujirebio, AlzeCure, Biogen, and Roche. K.B. has served as a consultant and at advisory boards for Acumen, ALZPath, BioArctic, Biogen, Eisai, Lilly, Moleac Pte. Ltd, Novartis, Ono Pharma, Prothena, Roche Diagnostics, and Siemens Healthineers; has served at data monitoring committees for Julius Clinical and Novartis; has given lectures, produced educational materials and participated in educational programs for AC Immune, Biogen, BioArctic, Celdara Medical, Eisai and Roche Diagnostics. H.Z. and K.B. are co-founders of Brain Biomarker Solutions in Gothenburg AB, a GU Ventures-based platform company at the University of Gothenburg. The other authors declare no competing interest. Author disclosures are available in the supporting information.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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