RESEARCH ARTICLE

Cerebrospinal fluid neurofilament light chain differentiates primary psychiatric disorders from rapidly progressive, Alzheimer's disease and frontotemporal disorders in clinical settings

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Abstract

Introduction

Many patients with cognitive and neuropsychiatric symptoms face diagnostic delay and misdiagnosis. We investigated whether cerebrospinal fluid (CSF) neurofilament light (NfL) and total-tau (t-tau) could assist in the clinical scenario of differentiating neurodegenerative (ND) from psychiatric disorders (PSY), and rapidly progressive disorders.

Methods

Biomarkers were examined in patients from specialist services (ND and PSY) and a national Creutzfeldt-Jakob registry (Creutzfeldt-Jakob disease [CJD] and rapidly progressive dementias/atypically rapid variants of common ND, RapidND).

Results

A total of 498 participants were included: 197 ND, 67 PSY, 161 CJD, 48 RapidND, and 20 controls. NfL was elevated in ND compared to PSY and controls, with highest levels in CJD and RapidND. NfL distinguished ND from PSY with 95%/78% positive/negative predictive value, 92%/87% sensitivity/specificity, 91% accuracy. NfL outperformed t-tau in most real-life clinical diagnostic dilemma scenarios, except distinguishing CJD from RapidND.

Discussion

We demonstrated strong generalizable evidence for the diagnostic utility of CSF NfL in differentiating ND from psychiatric disorders, with high accuracy.

1 INTRODUCTION

There is a great need to improve the timely and accurate diagnosis of neurodegenerative disorders. Despite major advances in clinical neurosciences, many patients with cognitive and neuropsychiatric symptoms still face a significant diagnostic odyssey of several years of multiple assessments, diagnostic uncertainty and delay, misdiagnoses, and imprecise management and prognostication, with significant negative outcomes for patients, families, and health-care systems.[1, 2] These challenges are greater in younger people (onset of symptoms < 65 years of age), for whom atypical presentations are more common, and differential diagnoses are broader.[3-5] Clinical diagnoses of behavioral variant frontotemporal dementia (bvFTD) and Alzheimer's disease (AD) have an appreciable error rate.[6, 7] Multiple factors contribute to the diagnostic odyssey, and even older patients and those with more "typical" presentations that could present less of a diagnostic challenge, often still face delay and misdiagnosis.[1, 8-10] Despite gold-standard; costly; and, at times, invasive multimodal and multidisciplinary assessments, many patients continue to face diagnostic uncertainty.[11] In particular, distinguishing neurodegenerative disorders from primary psychiatric disorders is a frequent diagnostic dilemma. Many patients eventually diagnosed with a neurodegenerative dementia are initially misdiagnosed with psychiatric disorders.[1, 12, 13] Given numerous challenges that patients face to get timely and accurate diagnosis, a biomarker that could assist in the differentiation between neurodegenerative and psychiatric disorders would have significant implications for the care and assessment, and outcomes of patients.

Neurofilament light chain (NfL), an essential component of the neuronal cytoskeleton, has been shown to be a reliable diagnostic marker of neuronal injury and neurodegeneration in diverse neurological and neurodegenerative disorders.[14-22] In our previous work, we found that cerebrospinal fluid (CSF) NfL distinguished ND from primary psychiatric disorders with high accuracy (area under the curve [AUC] 0.94, 87% sensitivity, 90% specificity).[14, 15] Elevated CSF total tau (t-tau) concentrations have also been shown to be a non-specific marker of neuronal injury in a range of conditions such as AD, Creutzfeldt-Jakob disease (CJD), and traumatic brain injury.[23-32] Elevations in CSF t-tau appear to be restricted to AD and CJD, with normal levels in other disorders, including most forms of FTD, progressive supranuclear palsy, and diseases that have a tau-based pathology.[33] NfL and t-tau are markers of neuronal, particularly axonal injury, but are distributed differently in the brain. NfL, although present throughout the neuron, is mainly in larger myelinated axons; t-tau is highly prevalent in thin, cortical interneuron non-myelinated axons.[17, 32] We thus anticipated that NfL and t-tau levels differed between different broad diagnostic groups and subgroups, and potentially demonstrated differential utility.

This study, part of The Markers in Neuropsychiatric Disorders Study (The MiND Study), aimed to extend our earlier pilot work in a large, diverse cohort of individuals presenting with cognitive and neuropsychiatric symptoms, in which the differential diagnoses included psychiatric and neurological/neurodegenerative disorders. The primary aim was to compare CSF NfL and t-tau levels in patients with neurodegenerative and psychiatric disorders, and control participants. We included patients with neurodegenerative disorders (ND) and psychiatric disorders (PSY) seen in a clinical neuropsychiatry service, and patients referred to a national CJD registry who had post mortem diagnostic confirmation. This second group included patients diagnosed with CJD and patients diagnosed with other rapidly progressive ND (RapidND) disorders. Secondary aims included assessing

the diagnostic utility of NfL and t-tau in differentiating between ND, PSY, and CJD/RapidND groups, and between specific diagnoses within these groups.

2 METHODS

This study included retrospective and prospective data collected between January 2009 and August 2020, from patients (1) referred for diagnostic assessment of a possible ND to a clinical neuropsychiatry service, and neurology/neuropsychiatry clinical trials; (2) with symptoms of a rapidly progressive dementia whose CSF samples were sent to the Australian National Creutzfeldt-Jakob Disease Registry (ANCJDR) for suspected CJD and where there was a post mortem diagnosis; and (3) control participants.

RESEARCH IN CONTEXT

Systematic Review: We reviewed the literature on PubMed on neurofilament light chain (NfL). There is extensive data on NfL in neurodegenerative disorders (ND), including recent comprehensive reviews. However, there is limited literature on primary psychiatric disorders (PSY), and especially on NfL assisting in the common clinical diagnostic dilemma of differentiating PSY from ND.

Interpretations: Our findings significantly extend the literature and provide strong evidence for the diagnostic utility of NfL in real-world clinical settings, to distinguish broad ranges of PSY from diverse ND, including rapidly progressive ND.

Future Directions: We are building on these findings, investigating diagnostic, clinical, and health economic utility of blood NfL, in a range of specialist and primary care settings, aiming for clinical translation: a simple test to reduce diagnostic delay and misdiagnosis, and dramatically improve the assessment and care for patients with cognitive and psychiatric symptoms, and outcomes for them, their families, clinical trials, and health-care systems.

Neuropsychiatry is a tertiary clinical service in Melbourne, Australia, providing diagnostic input to people with a range of neuropsychiatric presentations, including younger onset dementia.11 Patients received comprehensive multidisciplinary and multimodal investigations (e.g., magnetic resonance imaging (MRI) and single photon emission computed tomography/positron emission tomography (SPECT/PET) brain, neuropsychiatry, neurology, neuropsychology, CSF analysis) and received gold standard consensus diagnosis based on established diagnostic criteria, such as National Institute on Aging–Alzheimer's Association (NIA-AA) criteria for AD dementia, and international consensus criteria for bvFTD.34, 35 One hundred and twenty-eight participants from our previous study were included (77 ND and 31 PSY from neuropsychiatry, 20 controls).14

ANCJDR is the national CJD surveillance center, to which patients with a rapidly progressive dementia (including atypically rapid presentations/variants of more common ND such as AD, Lewy body dementia), and a suspicion of CJD, are referred for CSF biomarker analysis and diagnosis. ANCJDR

operational and surveillance methods, and methods of reviewing clinical criteria have been previously described.36, 37 We included all patients with a post mortem diagnosis during the study period who had remnant CSF specimens after diagnostic 14-3-3 testing.

Control data were accessed from the Australian Imaging, Biomarker & Lifestyle (AIBL) study of aging.38 Inclusion criteria included age < 70; no neurological or active psychiatric disorder diagnosis at time of CSF; no recent diagnosis (within 18 months of CSF) of neurological disorder, stroke, transient ischemic attack, traumatic brain injury, or psychiatric disorder; negative amyloid PET; and normal CSF amyloid beta (Aβ)42, t-tau and phospho-tau levels.

Group categorization (according to most recent diagnosis on longitudinal follow up) was made blinded to the NfL levels.

CSF was stored at –80°C, and NfL and t-tau levels measured at the National Dementia Diagnostic Laboratory (NDDL), Melbourne, according to manufacturers' protocols, described previously.14, 15, 39 NfL was measured using a commercial enzyme-linked immunosorbent assay (ELISA; NF-light; UmanDiagnostics, Sweden). Diluted CSF 1+1 and reconstituted standards were added to the plate in duplicate, incubated, and washed. Samples displaying concentrations above the highest standard point were further diluted and re-assayed. T-tau was measured using an INNOTEST ELISA. CSF, ready-to-use calibrators, and run validation controls were added to the plate in duplicate, incubated, and washed. Two internal controls of pooled CSF were included in each NfL and t-tau plate. Mean intra-assay coefficient for NfL and t-tau were 6.2% and 4% respectively; inter-assay coefficient of variation 11.3% and 8.4%, respectively.

Consent was not necessary, but where appropriate, participants provided informed consent. This study was approved by Human Research Ethics Committees at Melbourne Health (2016.038, 2017.090, 2018.371, 2020.142), University of Melbourne (1341074), St. Vincent's Hospital (028-06), and Florey Institute of Neurosciences and Mental Health (1648441.1).

2.1 Statistical analysis

Statistical analyses were performed using IBM SPSS 27. General linear models (GLM) were estimated to examine relationships between NfL and clinical variables. Age at CSF was included as a covariate where appropriate, given its strong correlation with NfL.16, 40 Receiver operator characteristic (ROC) curves were computed to AUC, sensitivity, and specificity of NfL and t-tau in distinguishing ND from PSY, and between various subgroups. Optimal cut-off was determined using Youden's (1959) method. Paired-sample area difference under the curve determined differences in biomarker performance. As normality of sampling distribution could not be assumed for all variables, robust statistical methods were used for all analyses. Inference was performed using bias-corrected and accelerated (BCa) confidence intervals, computed for all GLMs via nonparametric bootstrapping (1000 replicates). Statistical significance was defined as any confidence interval not capturing the null hypothesis value (at the 95% level). These robust statistical methods were selected because they mitigate the effects of distributional violations, including presence of outliers.

3 RESULTS

3.1 Study cohort details

A total of 498 participants were included, mean age 63 years, 49% female. Diagnostic groups (Table 1) were neurodegenerative disorders (ND; n = 197), primary psychiatric disorders (PSY; n = 67), ANCJDR cohort (n = 161), mild cognitive impairment (MCI; n = 5), and controls (n = 20).

ND included: older-onset AD (OlderAD, n = 52), younger-onset AD (YoungerAD, n = 59), bvFTD (n = 33), and other ND disorders (OtherND, n = 53). PSY were all patients referred to a specialist service for diagnostic assessment of a possible ND, and ultimately diagnosed with PSY: schizophrenia (n = 17), major depressive disorder (MDD; n = 16), bipolar affective disorder (BPAD; n = 12), and other psychiatric disorders (OtherPSY; n = 22). ANCJDR consisted of: CJD (n = 161), and other severe/rapidly progressive ND disorder (RapidND, n = 48). As detailed in Table 2, RapidND included many atypically rapid variants/presentations of more common ND (such as AD [n = 13], and Lewy body dementia [n = 7]), where CJD was suspected clinically due to the aggressive presentation.

ND patients were older than PSY (62 vs. 49 years; mean difference [Mdiff] = 13, 95% confidence interval [CI]: [10, 16]) and controls were older than PSY (66 vs. 49 years; Mdiff = 17, 95% CI: [11, 23]).

3.2 CSF NfL and T-tau in ND, primary psychiatric, and control groups

As demonstrated in Table 1 and Figure 1, CSF NfL levels were elevated in ND (mean, M = 1528pg/mL) compared to PSY (M = 435pg/mL), and controls (M = 523pg/mL). Adjusting for age, the difference between NfL levels in ND and PSY groups was large (GLM, Mdiff = 1089, 95% CI: [640, 1539]), as was the difference between ND and controls (GLM Mdiff = 1007, 95% CI: [653, 1359]). There was no difference between PSY and controls, after adjusting for age (GLM Mdiff = 82, 95% CI: [–174, 338]). The spread of NfL levels in PSY was much narrower than in ND, and no patients in PSY had an NfL level > 802 pg/mL (Figure 1).

CSF t-tau was significantly elevated in ND (M = 514 pg/mL), compared to PSY (M = 157 pg/mL; Mdiff = 250, 95% CI: [190, 309]), and controls (M = 182 pg/mL; Mdiff = 370, 95% CI [233, 507]), Table 1 and Figure 2. There was no difference between PSY and controls (Mdiff = 120, 95% CI: [–37, 389])

NfL at the 582 pg/mL cut-off distinguished ND from PSY with a 95% positive predictive value (PPV), 78% negative predictive value (NPV), 6.8 positive likelihood ratio (LR+ve), 0.09 negative likelihood ratio (LR–ve), accurately classifying 91% (239/264) of patients, diagnostic odds ratio of 73 (Table 4). NfL performed better than t-tau, which at a cut-off of 198 pg/mL was associated with 94% PPV, 60% NPV, 4.8 LR+ve, 0.22 LR–ve, 82% accuracy, diagnostic odds ratio of 22.

As demonstrated in Table 3 and supporting information, NfL performed better at distinguishing RapidND from ND, compared to t-tau. NfL and t-tau were not significantly different in distinguishing RapidND from PSY. NfL and t-tau both distinguished CJD from PSY with extremely high accuracy. Combining all ND disorders in our cohort (i.e., CJD, RapidND from ANCJDR, and ND from Neuropsychiatry) into a combined “CJD+RapidND+ND” group, improved the diagnostic performance of NfL and t-tau in differentiating from PSY (compared to ND [without ANCJDR] vs. PSY).

3.4 CSF NfL and t-tau levels in diagnostic subgroups

To reflect real-life clinical diagnostic dilemma scenarios, NfL and t-tau levels and diagnostic performance were compared between a range of combinations of diagnostic subgroups (Table 3 and supporting information). NfL levels in all ND, and each ND subgroup (OlderAD, YoungerAD, bvFTD, OtherND), were higher than levels in all PSY, and each PSY subgroup (schizophrenia, MDD, BPAD, and OtherPSY). NfL levels in CJD and RapidND were higher compared to ND, ND subgroups, PSY, PSY subgroups. No differences were found between YoungerAD and OlderAD, between ND subgroups, between PSY subgroups, or between all PSY subgroups and controls.

CSF t-tau was not consistently elevated in ND subgroups, compared to PSY subgroups. T-tau levels were not different between bvFTD and several PSY subgroups (schizophrenia, OtherPSY, MDD, and BPAD), and bvFTD and controls (Table 3 and supporting information). Furthermore, t-tau levels were not different between OtherND and MDD, OtherND and BPAD, and OtherND and controls. There were no differences in t-tau between PSY subgroups.

As demonstrated in Table 3 and supporting information, NfL was superior to t-tau in distinguishing: ND from PSY, bvFTD from PSY, bvFTD from schizophrenia, bvFTD from bipolar disorder, bvFTD from depression, and RapidND from ND. T-tau performed better than NfL in distinguishing CJD from RapidND, and CJD from ND.

4 DISCUSSION

Our findings in a large cohort of patients from real-world clinical settings showed that CSF NfL levels distinguished diverse neurodegenerative disorders (ND) from psychiatric disorders (PSY), with high accuracy. CSF NfL levels can assist the clinician in the common, clinical challenge of distinguishing ND from PSY, leading to earlier, accurate diagnosis. These findings confirm and extend our previous work.14 A significant strength and substantial contribution to the literature is that data were derived from real-world Australian tertiary and quaternary services and clinical settings, to which patients presented with diverse clinical presentations and diagnostic uncertainty. Additional strengths included longitudinal follow-up for most patients, consistent gold-standard multimodal and multidisciplinary assessments, diagnoses based on established diagnostic criteria, and broad types of ND and PSY.

Given the PPV of 95%, an elevated CSF NfL in a patient with an initial neuropsychiatric presentation reduces the likelihood of a primary psychiatric misdiagnosis, and indicates need for further investigation. In a patient with an existing primary psychiatric diagnosis, an elevated NfL level would prompt further investigation for an ND diagnosis. Conversely, a low level could reassure that an ND is unlikely, reinforce the need for psychiatric treatment, and reduce the need for further investigations and referrals to specialist services. Caution and close clinical monitoring would still be warranted, given the NPV of 78% and that a low NfL does not entirely rule out a neurodegenerative disorder.

Our study adds important data to the literature on the high accuracy of NfL in assisting in a broad range of frequently faced, specific clinical diagnostic dilemmas (Table 3), especially in younger people. Distinguishing bvFTD from PSY can be particularly challenging; bvFTD is associated with

greater diagnostic delay and rates of psychiatric misdiagnoses.6 Recent expert consensus recommendations highlighted the potential role of biomarkers such as NfL.6 Our study included patients with bvFTD and PSY referred explicitly with a question of whether the clinical picture was due to a primary psychiatric or ND condition, unlike previous studies that included patients from general psychiatric services for which there was no clear suspected or differential diagnosis of bvFTD, or excluded patients with comorbidities (e.g., substance abuse, head injuries). Despite relatively small numbers of patients with bvFTD, our findings, demonstrating high accuracy in this challenging clinical scenario, provide evidence for the real-world diagnostic utility of NfL in distinguishing bvFTD from PSY. Given the often non-diagnostic neuroimaging findings, and lack of diagnostic biofluid markers, a strong case can be made for NfL as a first-tier test.6 As a single biofluid biomarker for the distinguishing AD from PSY, NfL has superior AUC, sensitivity, and specificity, compared to MRI to distinguish AD from controls.41 Further clinical utility and health economic analysis studies are needed to determine whether NfL (especially plasma NfL) has a place as a first-tier routine test for all patients and differential diagnoses, or is best reserved for specific situations.

A recent study of 162 patients referred for evaluation of cognitive disorders investigated the diagnostic utility of CSF NfL and t-tau.42 For differentiating ND from PSY, this study found AUCs of NfL/t-tau of 0.877/0.857 respectively, sensitivity 76.6%/93.8%, specificity 86.4%/67%. This contrasts with our larger, younger cohort, in which NfL differentiated ND from PSY with superior AUC, sensitivity, specificity, PPV, and NPV. We found NfL outperformed t-tau in distinguishing ND from all PSY, and even more so for distinguishing ND+CJD+RapidND from all PSY. Also, we found no benefit for a combination of NfL and t-tau, or sequential use (except for differentiating CJD from RapidND).

Patients were referred to a tertiary neuropsychiatry service, most commonly by neurologists and psychiatrists, for diagnostic assessment and clarification. The referral reason in most cases was to assist with distinguishing ND from psychiatric differential diagnoses. CSF analysis was performed where clinically indicated, and not routinely if other assessments were clearly diagnostic. This study thus focuses on a clinical population that is more “atypical” and complex than may be seen in routine practice. However, not every such patient gets referred, nor do most places in the world have access to such tertiary services. Patients in other clinical settings and with less complexity, also face diagnostic dilemmas. Therefore, even though our study builds definitive evidence for diagnostic utility in tertiary and quaternary services, it is of relevance to secondary specialist (e.g., neurology, psychiatry, geriatrics) and other clinical settings in which most patients with cognitive and neuropsychiatric symptoms are assessed. Further study to confirm generalizability to less specialized and lower prevalence settings are needed, and are under way.

Extremely high CSF NfL levels were seen in CJD, consistent with other studies.43 Similarly elevated levels were seen in RapidND (such as encephalitis, rapidly progressive presentations of AD and dementia with Lewy bodies [DLB]), suggesting NfL is a marker not only of neurodegeneration, but also of the severity and rate of progression in these presentations. This contrasts with similar studies that found lower NfL in comparable RapidND groups (which also included disorders such as AD, DLB).43, 44 This could possibly reflect more severe cases in our cohort. Our findings suggest that t-tau may help differentiate CJD from RapidND with a suspicion of CJD. These findings extend the literature on CJD biomarkers.26, 31, 43-48 As our RapidND group consisted mostly of atypically rapid/aggressive variants of more common ND disorders, further study is needed on NfL and t-tau in

a broader range of rapidly progressive and rarer dementias. Further study is also needed on NfL, t-tau and specific tests such as real-time quaking-induced conversion (RT-QuIC) in CJD and RapidND, and to determine whether NfL could act as a screening test in the earliest stages of CJD, in particular in less common instances of psychiatric presentations and differentials, and prior to the onset of frank neurological signs.

Limitations of our study include its retrospective nature, reliance on clinical diagnosis, lack of pathological or genetic confirmation in the ND group (all AD cases were sporadic). A significant limitation is the small number of controls, and the older, narrow age range in this group. Younger ND still had greater NfL levels than controls, demonstrating much greater increases in NfL levels due to neurodegeneration, relative to well-known age-related increases.16 The older controls may have reduced our ability to find a difference from younger PSY. Patients recruited later in the study period had 8 to 12 months of follow-up information, and potentially less certainty based on time and serial assessments, compared to earlier patients. Although people with MCI seemed to have intermediate NfL levels (between ND and PSY), the very small number in this group limited any comparisons and interpretations. It is important to note that t-tau levels were incorporated into the clinical diagnoses (compared to NfL levels, which were blinded to clinical diagnoses and diagnostic categorization), therefore it is likely that t-tau performance was overestimated. This is particularly likely to be the case in AD diagnoses where CSF Aβ42, t-tau and phosphorylated tau were incorporated into diagnostic decisions as per diagnostic criteria for AD. The overall study cohort when viewed as a whole can appear unbalanced, given the large CJD group relative to other groups. We focused on distinguishing between ND and PSY groups (comparable or larger than similar studies in clinical settings), and between specific NDs and PSYs, considering these as the most generally clinically relevant distinctions. Data on one of the largest post mortem confirmed cohorts of CJD and RapidND in which CJD was suspected clinically, demonstrated important biomarker performance findings in, and comparisons between, an even more extended and diverse set of presentations.

This study demonstrated the diagnostic utility of CSF NfL to distinguish a broad range of neurodegenerative disorders from primary psychiatric disorders and controls, in real-world, generalizable clinical settings, with high accuracy. NfL performed well in a range of commonly faced clinical diagnostic dilemmas, such as differentiating bvFTD from a range of primary psychiatric disorders, where this was an explicit clinical question. A patient with a significantly elevated NfL level could quickly dismiss primary psychiatric disorder differentials, and lead to appropriate, tailored investigations and referrals. An extremely high NfL level (with or without an elevated t-tau) would prompt urgent investigations and assessments, and even hospitalization. Conversely, a low NfL could reduce the chance of a misdiagnosis of a neurodegenerative disorder, support investigations and a treatment of a primary psychiatric disorder, and reduce unnecessary investigations and referrals. Stability of levels on serial testing could offer further reassurance. An added potential of NfL as a "first-tier" test for neurodegeneration could be to help facilitate research and precision use of more specific tests (e.g., phosphorylated tau for AD).

Given CSF and plasma NfL levels correlate strongly,16, 22 the availability of a blood test could dramatically alter the care, assessment, diagnosis, and treatment of patients. A plasma NfL level could form a part of a "dementia blood screen" ordered by a general practitioner. The level could inform and guide initial clinical management, referrals, and triaging. We are building on our findings,

investigating the diagnostic and health economic utility of plasma NfL in specialist and primary care settings, with the aim of developing an inexpensive blood test which can act as a “CRP” for the brain, that could significantly reduce diagnostic delay and misdiagnosis, and improve outcomes for patients, families, and health-care systems.

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CONFLICTS OF INTEREST

Piero Perucca has received speaker honoraria or consultancy fees to his institution from Chiesi, Eisai, LivaNova, Novartis, Sun Pharma, Supernus, and UCB Pharma. He is an associate editor for Epilepsia Open. Henrik Zetterberg has served on scientific advisory boards for Eisai, Denali, Roche Diagnostics, Wave, Samumed, Siemens Healthineers, Pinteon Therapeutics, Nervgen, AZ Therapies, and CogRx; has given lectures in symposia sponsored by Cellectricon, Fujirebio, Alzecure, and Biogen; and is a co-founder of Brain Biomarker Solutions in Gothenburg AB (BBS), which is a part of the GU Ventures Incubator Program. Mark Walterfang has received research funding, speaker honoraria, and has served on advisory boards for Pfizer, Glaxo SmithKline, Eli Lilly, Actelion, Vtesse, and Biomarin pharmaceuticals. KB has served as a consultant, on advisory boards, or on data monitoring committees for Abcam, Axon, Biogen, JOMDD/Shimadzu, Julius Clinical, Lilly, MagQu, Novartis, Roche Diagnostics, and Siemens Healthineers, and is a co-founder of Brain Biomarker Solutions in Gothenburg AB (BBS), which is a part of the GU Ventures Incubator Program, all unrelated to the work presented in this paper. Dennis Velakoulis has received consultancy fees from TEVA pharmaceuticals. Oskar Hansson has acquired research support (for the institution) from AVID Radiopharmaceuticals, Biogen, Eli Lilly, Eisai, GE Healthcare, Pfizer, and Roche. In the past 2 years, he has received consultancy/speaker fees from AC Immune, Alzpath, Biogen, Cerveau, and Roche. Samantha M. Loi received grant funding from the National Health and Medical Council Early Career Fellowship. Christiane Stehmann is supported by the ANCJDR which is funded by the Australian Government, Department of Health, and received $400 as invited speaker and organizer from the inaugural Taiwan-Australia CJD conference 2021. Alexander Santillo received grant funding from Lund University, Region Skåne, MULTIPARK, Sweden, and, held a leadership or fiduciary role in The Sjöbring Foundation and The Bundy Academy, Sweden. Shorena Janelidze received grant funding

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AUTHOR CONTRIBUTIONS

Dhamidhu Eratne: study design and coordination, data collection, data analysis and interpretation, literature search, statistical analysis, creating figures, writing manuscript. Samantha M. Loi: data interpretation, manuscript editing. Qiao-Xin Li: data collection and interpretation, manuscript review. Christiane Stehmann: data collection, data interpretation, manuscript editing. Charles B. Malpas: statistical analysis, manuscript review. Alexander Santillo: data interpretation, manuscript editing. Shorena Janelidze: data interpretation, manuscript editing. Claire Cadwallader: data collection and interpretation, manuscript editing. Nirbaanjot Walia: data collection and interpretation, manuscript editing. Blair Ney: data collection and interpretation, manuscript editing. Victoria Lewis: data collection and interpretation, review of manuscript. Matteo Senesi: data collection, manuscript review. Christopher Fowler: data collection, manuscript review. Amelia McGlade: data collection, manuscript review. Shiji Varghese: data collection, manuscript review. Parsa Ravanfar: manuscript editing. Sarah Farrand: manuscript editing. Michael Keem: manuscript editing. Matthew Kang: manuscript editing. Anita M. Y. Goh: manuscript editing. Kunal Dhiman: data collection and interpretation, manuscript editing. Veer Gupta: data collection and interpretation, manuscript editing. Rosie Watson: data interpretation and manuscript editing. Nawaf Yassi: data interpretation and manuscript editing. Cath Kaylor Hughes: study recruitment design, manuscript editing. Richard Kanaan: manuscript editing. Piero Perucca: manuscript editing. Hannah Dobson: manuscript editing. Lucy Vivash: study design, sample and data collection, manuscript editing. Rashida Ali: sample processing, data collection, manuscript editing. Terence J. O'Brien: study design, sample and data collection, manuscript editing. Oskar Hansson: data interpretation, manuscript editing. Henrik Zetterberg: data interpretation, manuscript editing. Kaj Blennow: data interpretation, manuscript editing. Mark Walterfang: manuscript editing. Colin L. Masters: data interpretation, manuscript editing. Samuel F Berkovic: data interpretation, manuscript editing, supervision of Dr. Eratne. Steven

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