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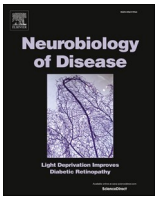

Cerebrospinal fluid neurofilament light chain and total-tau as biomarkers of neurodegeneration in Alzheimer's disease and frontotemporal dementia

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ABSTRACT

Introduction: CSF Neurofilament light chain(NfL) is a promising biomarker of neurodegeneration, but its utility in discriminating between Alzheimer's disease(AD) and frontotemporal dementia(FTD) is limited.
Methods: 105 patients with clinical-biological diagnosis of mild cognitive impairment(MCI) due to AD ($N = 72$) or clinical diagnosis of FTD ($N = 33$) underwent neuropsychological assessment and CSF Aβ42/40, p-tau181, total-tau and NfL quantification. Group comparisons, correlations between continuous variables and ROC curve analysis were carried out to assess NfL role in discriminating between MCI due to AD and FTD, exploring the associations between NfL, ATN biomarkers and neuropsychological measures.
Results: NfL levels were significantly lower in the AD group, while levels of total-tau were higher. In the FTD group, significant correlations were found between NfL, p-tau181 and total-tau, and between NfL and cognitive performances. In the AD group, NfL levels were directly correlated with total-tau and p-tau181; Aβ42/40 ratio was inversely correlated with total-tau and p-tau181, but not with NfL. Moreover, p-tau181 and t-tau levels were found to be associated with episodic memory and lexical-semantic impairment. Total-tau/NfL ratio differentiated prodromal-AD from FTD with an AUC of 0.951, higher than the individual measures.
Discussion & conclusions: The results support that NfL and total-tau levels reflect distinct pathophysiological neurodegeneration mechanisms, independent and dependent of Aβ pathology, respectively, Combining them may enhance both markers reliability, their ratio showing high accuracy in distinguishing MCI due to AD from FTD. Moreover, our results revealed associations between NfL and disease severity in FTD and between tauopathy and episodic memory and lexical-semantic impairment in prodromal-AD.

1. Introduction

Dementia caused by neurodegenerative diseases currently affects >50 million people and, as the world population is aging, this number is expected to increase in the next decades, resulting in considerable burden on individuals and their families and in significant social and economic costs. This challenge has exposed the compelling need for reliable in vivo biomarkers that can recognize or rule out the presence of a neurodegenerative disease in early stages, improve the accuracy of differential diagnosis, predict disease progression, and provide evidence of disease modification.

In recent years, the paradigm shift in the research criteria of Alzheimer's disease (AD) has led to the operationalization of the biomarker-based binary AT(N) classification system, shifting the focus from clinical context to a purely biological definition of the disease, based on underlying pathological processes documented in vivo by biomarkers (Jack Jr et al., 2018). Even if this classification system especially emphasizes the three core CSF biomarkers (namely, amyloid-β, p-tau181 and total-tau), it is expandable to incorporate new biomarkers.

In this context, neurofilament light chain (NfL) has gained

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momentum as a candidate biomarker of neuroaxonal injury and may even be potentially preferable to total-tau (t-tau) as a CSF-based neurodegeneration (N) biomarker (Cousins et al., 2021a), since CSF t-tau and p-tau181 are highly correlated and they do not seem to provide independent information (Mattsson et al., 2017).

NfL is a subunit of neurofilaments, which are structural scaffolding proteins exclusively found in neurons and highly expressed in myelinated axons, where they function as elastic assemblies that confer structural stability and enable radial growth, thereby modulating nerve conduction velocity (Zhu et al., 1997; Yuan et al., 2017). In response to many, if not all, pathological processes which cause central nervous system axonal damage, intracellular neurofilaments are released into the extracellular space, resulting in an increase in their CSF concentration. Additionally, an age-related increase in NfL levels, likely because of a reduced CSF turnover or a slow axonal damage associated with normal aging, has also been investigated (Olsson et al., 2019).

Since its CSF levels reflect white matter changes (Moore et al., 2018), over the past decades there has been an exponential growth in studies exploring CSF NfL in the context of a wide range of neurological disorders, including inflammatory, traumatic, and neurodegenerative diseases (Olsson et al., 2019; Gaetani et al., 2019). NfL have been identified as an integral component of Lewy bodies in Parkinson's Disease (PD) (Goldman et al., 1983) and they have been found to be potentially useful in differentiating PD from atypical parkinsonian disorders such as progressive supranuclear palsy, multiple system atrophy, or corticobasal degeneration (Olsson et al., 2019; Hall et al., 2012). Moreover, NfL levels have been proposed as a pathologic hallmark of Amyotrophic Lateral Sclerosis, with good diagnostic accuracy for this pathology even in its early stages (Feneberg et al., 2018). They have been also reported to be increased in relapsing multiple sclerosis (MS), in association with relapses and cortical lesions, and in progressive MS, related to T1-hypointense lesion volume (Damasceno et al., 2019). Because of the robust results achieved by NfL in detecting the presence of a variety of CNS diseases and reflecting their dynamic nature, their use as an unspecific screening marker for neurological disorders has recently been proposed (Lambertsen et al., 2020; Gaetani and Parnetti, 2022).

In patients with AD and frontotemporal dementia (FTD), CSF NfL levels are higher than in cognitively unimpaired controls, with high sensitivity in identifying the presence of neurodegenerative processes since their earliest stages. On the other hand, NfL have been considered not disease-specific, having shown limited utility in the differential diagnosis between neurodegenerative diseases (Olsson et al., 2019; Forgrave et al., 2019; Zerr et al., 2018). On this basis, although CSF NfL concentration may be reliable in distinguishing FTD among suspected non-Alzheimer's pathophysiology (Cousins et al., 2021a), its performance in distinguishing AD pathophysiology-positive patients from FTD, especially in prodromal phases, has been found to be unsatisfactory so far (Lista et al., 2017). Therefore, it is not clear whether NFL measurement in AD patients can improve diagnostic efficiency and impact diagnostic decisions.

While previous literature has predominantly focused on exploring the associations between neuropsychological metrics and the three core CSF biomarkers across neurodegenerative diseases, the associations with NfL have been shown to be of interest as well *(*Olsson et al., *2019;* Teitsdottir et al., *2020)*. Although the biological definition of AD was originally intended for research purposes, it has been diffusively incorporated into everyday clinical practice, with the risk of losing sight of cognitive signature. However, a comprehensive evaluation of AD should still require both the presence of cognitive symptoms and a specific biomarker profile (Dubois et al., 2021). It is crucial to clarify the association between neurodegeneration biomarkers and cognition when exploring new diagnostic algorithms for neurodegenerative diseases.

The objectives of this study were: to assess the role of CSF NfL and t-tau as "N" biomarkers and their use in discriminating between mild cognitive impairment (MCI) due to AD and FTD; to explore the different associations between the core CSF AT(N) biomarkers and CSF NfL levels in MCI due to AD and FTD; to investigate the relations between these CSF biomarkers and neuropsychological measures.

2. Methods

2.1. Study population

One hundred and five patients with a clinical-biological diagnosis of MCI due to AD ($N = 72$) (Albert et al., 2011) or a first clinical diagnosis of bvFTD, nfvPPA or svPPA (grouped as FTD, $N = 33$) (Rascovsky et al., 2011; Gorno-Tempini et al., 2011) were enrolled from a consecutive series of native Italian-speaking patients referring to the Neuropsychology Unity – Memory Clinic of the Policlinico A. Gemelli in Rome for diagnostic evaluation of cognitive impairment. All patients underwent a thorough clinical and neurological evaluation, comprehensive of a standard extensive neuropsychological investigation to assess different cognitive domains, routine blood tests, a standard brain magnetic resonance imaging for excluding secondary causes of cognitive impairment, and a lumbar puncture for CSF collection and biomarker analysis. All subjects provided written informed consent before undergoing lumbar puncture. Exclusion criteria were: previous or concomitant neurological diseases (such as, but not limited to: other neurodegenerative disorders, cerebrovascular accidents, tumors, traumatic injury, etc.); major psychiatric disorders; medical conditions potentially able to interfere with cognitive functions (such as, but not limited to: renal or hepatic failure; respiratory diseases, hypothyroidism, vitamin B12 deficiency, etc.); previous participation in trials involving amyloid targeting agents.

2.2. Neuropsychological assessment

Subjects were evaluated using the Mini-Mental State Examination (MMSE) (Folstein et al., 1975; Magni et al., 1996) and an extended version of the Mental Deterioration Battery (Carlesimo et al., 1996), comprehensive of tasks assessing verbal episodic memory (Rey Auditory Verbal Learning Test [RAVLT] immediate free recall, 15-min delayed free recall, target-distractors recognition) (Schmidt, 1996), visuospatial episodic memory (Rey-Osterrieth Complex figure [ROCF] 15-min delayed recall), constructional skills (ROCF copy) (Caffarra et al., 2002a), inhibition (Stroop test) (Caffarra et al., 2002b), visual search (Multiple Features target cancellation [MFTC]) (Gainotti et al., 2001; Marra et al., 2013), short term and working memory (digit span forwards and backwards) (Monaco et al., 2013), abstract reasoning (Raven's Progressive Matrices [PM'47]) (Carlesimo et al., 1996), and language (object naming on picture presentation, phonological verbal fluency task [PVF], category verbal fluency task [CFT]) (Quaranta et al., 2016). The Episodic Memory Score (EMS) was computed by combining the performances obtained on RAVLT subitems and on ROCF delayed reproduction, as described elsewhere (Marra et al., 2016).

2.3. CSF Biomarkers

CSF was collected, stored and processed according to literature recommendation-based (Teunissen et al., 2011; Engelborghs et al., 2017; Hansson et al., 2021) local standardized operating procedures. Lumbar punctures were performed in the morning after an overnight fast, using a 22-gauge Quincke spinal needle. When blood contamination occurred during collection, the first CSF drops were discarded until clear CSF was obtained. The first 2 ml of CSF were directly collected in 15-ml polypropylene Falcon conical centrifuge tubes (catalog number 62.554.001 Sarstedt, Nümbrecht, Germany) and used for routine chemo-diagnostics and cyto-morphometric analysis. Subsequently, 10-ml polypropylene tubes (catalog number 62.610.201; Sarstedt, Nümbrecht, Germany) were used to directly collect 10 ml of CSF for biomarker quantification. This portion of the sample was immediately refrigerated and, within 1 h of collection, centrifugated at 2000 ×g for

10 min. CSF was then immediately aliquoted in 0.5 ml polypropylene vials (catalog number 72.730.006; Sarstedt, Nümbrecht, Germany) and frozen at −80 °C. Levels of CSF Aβ40, Aβ42, total tau (t-tau) and p-tau181 (p-tau) were measured within 30 days using a fully-automated system based on a two-step sandwich chemiluminescent enzyme-immunoassay on the Lumipulse G1200 instrument (Fujirebio), as described by manufacturer (coefficients of variation [CV] - Aβ40: intra-assay ≤4.5%, inter-assay ≤4.5%; Aβ42: intra-assay ≤3.9%, inter-assay ≤4.6%; p-tau: intra-assay ≤5.0%, inter-assay ≤5.1%; t-tau: intra-assay ≤8.3%, inter-assay ≤7.6%), while CSF NfL evaluation was performed with Simple Plex cartridges using the Ella apparatus (ProteinSimple, Bio-techne, Minneapolis, MN, USA), as described by manufacturer (intra-assay CV <5%, inter-assay CV <10%), by laboratory personnel blinded to clinical diagnosis. The CSF Aβ42/40 ratio was calculated and preferred over CSF Aβ42 as a direct marker of amyloid pathology (Janelidze et al., 2016). A cut-off of 0.068 was used for abnormal CSF Aβ42/40 ratio, according to previously determined CSF biomarkers cut-offs for Lumipulse assays (Leitão et al., 2019). The CSF t-tau/NfL ratio was calculated to highlight the differences between the two biomarkers of neurodegeneration and maximize their discriminatory power in distinguishing between MCI due to AD and FTD.

2.4. Statistical analysis

Statistical analysis was performed using "SPSS" ("Statistical Package for Social Science", IBM SPSS Statistics. Armonk, NY: IBM Corp). The sample was described in its clinical and demographic features using descriptive statistics techniques. Group comparisons were performed by means of the Mann Whitney-*U* test for mean rank and the Chi-squared test. Correlations between CSF biomarkers were examined using Spearman's correlation coefficient. Correlations between neuropsychological scores and CSF p-tau181, t-tau and NfL (Aβ42/40 ratio was excluded by these analyses because of its role in the diagnosis of MCI due to AD) were also performed by means Spearman's correlation coefficient. ROC curve analysis was carried out to assess the diagnostic utility of t-tau, NfL and t-tau/NfL ratio for determination of MCI due to AD versus FTD.

3. Results

The demographic features of the study participants are shown in Table 1. The sample comprised 72 individuals with MCI due to AD (45 female) and 33 individuals with FTD (13 female). The two groups did not differ in terms of age ($p = 0.142$), literacy ($p = 0.873$), while MMSE was lower in the MCI due to AD group ($p = 0.003$).

CSF biomarkers values are shown in Table 2. Consistent with expectations, the values of Aβ42/40 ratio were significantly lower ($p < 0.001$) and p-tau concentration was significantly higher ($p < 0.001$) in the MCI due to AD group; also the levels of t-tau were higher ($p < 0.001$), while CSF levels of NfL were significantly lower ($p = 0.005$) compared to the FLTD group.

CSF NFL Concentration in Relation to Core AT(N) Biomarkers. In both groups, CSF levels of NfL were directly correlated with t-tau and p-tau, as shown in Table 3. Moreover, only in the MCI due to AD group the Aβ42/40 ratio was inversely correlated with t-tau and p-tau levels, but not with NfL levels.

Table 1
Demographic features in MCI due to AD and FTD group.

Demographic Data	MCI due to AD	FTD	*p* value
Female/Male	45/27	13/20	0.027
	Mean ± SD	Mean ± SD	
Age	69.36 ± 6.44	67.21 ± 6.57	0.142
Literacy	13.31 ± 3.58	13.55 ± 3.59	0.873
MMSE	25.63 ± 2.11	27.06 ± 2.28	0.003

Table 2
CSF biomarkers values in MCI due to AD and FTD group.

CSF Biomarkers	MCI due to AD Mean ± SD	FTD Mean ± SD	*p* value
Aβ42/40	0.0432 ± 0.0085	0.0912 ± 0.0099	<0.001
p-tau	128.78 ± 55.19	39.77 ± 17.86	<0.001
t-tau	802.68 ± 341.62	358.15 ± 173.45	<0.001
NfL	1880.13 ± 748.27	3761.53 ± 2908.36	0.005
t-tau/NfL	0.456 ± 0.193	0.141 ± 0.108	<0.001

ROC curve analyses for determination of MCI due to AD versus FTD. In order to find a measure of neurodegeneration which could better distinguish MCI due to AD from FTD, the ratio between t-tau and NfL levels was calculated. As expected, this value was significantly higher ($p < 0.001$) in the MCI due to AD group (0.456 ± 0.193) compared to the FTD group (0.141 ± 0.108) and inversely correlated with the Aβ42/40 ratio ($\rho = -0.666$, $p < 0.001$) in the cohort considered as a whole (Fig. 1).

ROC curve analyses were undertaken in order to address the ability of individual biomarkers of neurodegeneration, as well as their ratio, to differentiate MCI due to AD from FTD (displayed in Fig. 2). CSF NfL and CSF t-tau differentiated MCI due to AD from FTD with an area under the ROC curve (AUC) of 0.671 (95% confidence interval [CI]: 0.54–0.81; $p = 0.005$) and 0.887 (95% CI: 0.83–0.95; $p < 0.001$) respectively, while the t-tau/NfL ratio distinguished MCI due to AD from FTD with an AUC of 0.951 (95% CI: 0.90–1.0; $p < 0.001$), higher than the individual measures. A t-tau/NfL ratio of 0.21 showed a sensitivity of 93.1%, a specificity of 87.9%, a NPV of 85.3%, and a PPV of 94.3% for distinguishing MCI due to AD from FTD.

CSF Biomarkers Concentration in Relation to Neuropsychological Scores. In the FTD group, no significant correlations were found between neuropsychological measures and CSF p-tau or t-tau, while NfL levels were correlated with scores obtained in RAVLT immediate recall ($\rho = -0.535$, $p < 0.005$), delayed recall ($\rho = -0.371$, $p < 0.05$) and target-distractors recognition ($\rho = -0.423$, $p < 0.05$), EMS ($\rho = -0.459$, $p < 0.05$), digit span forwards ($\rho = -0.497$, $p < 0.05$) and number of words produces during both PVF ($\rho = -0.544$, $p < 0.005$) and CFT ($\rho = -0.482$, $p < 0.05$). As expected, similar correlations were found between the t-tau/NfL ratio and several neuropsychological measures (RAVLT immediate recall: $\rho = 0.376$, $p < 0.05$; RAVLT target-distractors recognition: $\rho = 0.370$, $p < 0.05$; EMS: $\rho = 0.443$, $p < 0.05$; digit span forwards: $\rho = 0.484$, $p < 0.05$; PVF: $\rho = 0.551$, $p < 0.005$; Stroop test interference time: $\rho = -0.481$, $p = 0.005$; Stroop test interference errors: $\rho = -0.388$, $p < 0.05$; ROCF copy: $\rho = 0.401$, $p < 0.05$). In the MCI due to AD group, CSF p-tau levels inversely correlated with RAVLT delayed recall ($\rho = -0.239$, $p < 0.05$), and both CSF p-tau and t-tau levels negatively correlated with EMS ($\rho = -0.265$, $p < 0.05$ and $\rho = -0.233$, $p < 0.05$) and the number of words produced during CFT ($\rho = -0.345$, $p < 0.05$ and $\rho = -0.313$, $p < 0.05$), while no significant correlations were found between NfL and neuropsychological measures. Moreover, in this group, the t-tau/NfL ratio values were inversely correlated with MMSE score ($\rho = -0.253$, $p < 0.05$).

4. Discussion

This study confirmed the elevation of NfL concentration in patients with FTD compared with those with MCI due to AD, revealing significant associations of NfL levels with biomarkers of tauopathy, but not with the Aβ42/40 ratio, in both groups. Moreover, the results showed how the changes in concentration of these biomarkers reflect different degrees of cognitive impairments in MCI due to AD and FTD populations and revealed that their combination may be more accurate in discriminating MCI due to AD from FTD than the individual measures.

The findings regarding neurodegeneration biomarkers concentrations in the two groups are consistent with other studies, which have

Table 3
Spearman rank correlation matrix between CSF biomarkers in the FTD group (Table 3A) and in the MCI due to AD group (Table 3B). *$p < 0.05$; **$p < 0.001$.

A)				B)			
FTD	p-tau	t-tau	NfL	MCI AD	p-tau	t-tau	NfL
Aβ42/40	−0.086	−0.017	−0.117	Aβ42/40	−0.350**	−0.366**	−0.154
p-tau		0.862**	0.408*	p-tau		0.955**	0.486**
t-tau			0.604**	t-tau			0.492**

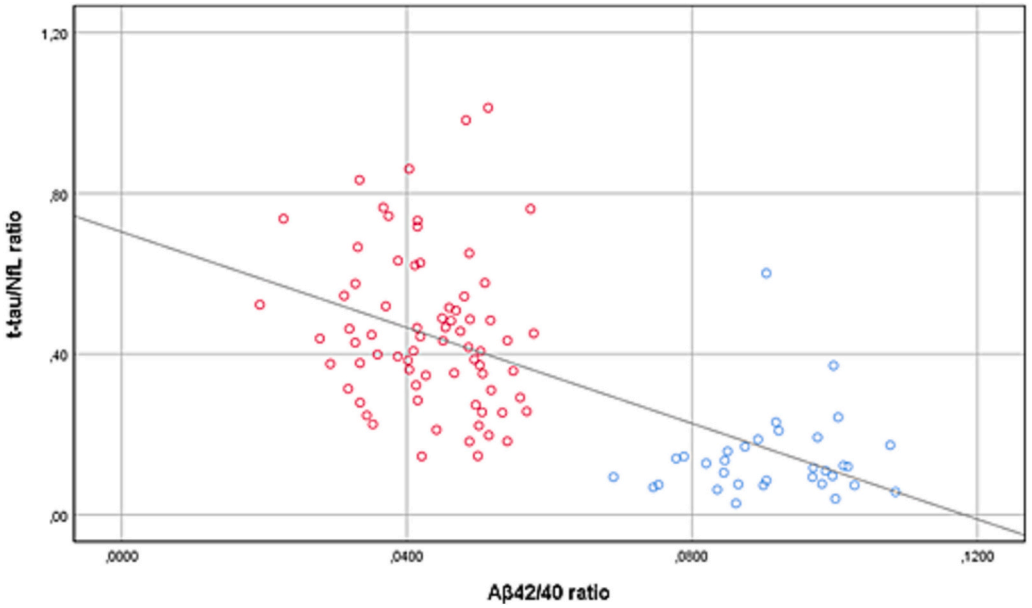

Fig. 1. Scatterplot distribution and linear correlation of t-tau/NfL ratio and Aβ42/40 ratio in the two groups MCI due to AD (red) and FTD (blue). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

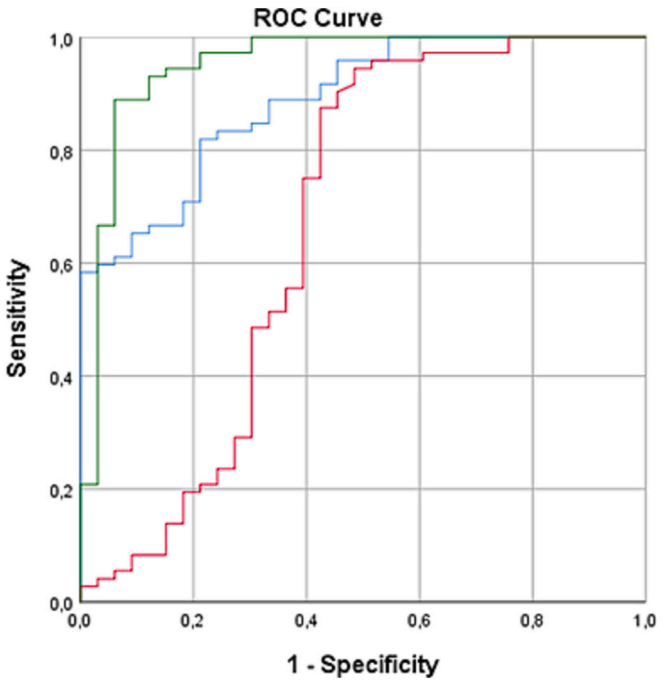

Fig. 2. ROC analyses: performance of t-tau/NfL ratio (green line), t-tau (blue line) and NfL (red line) in distinguishing MCI due to AD from FTD. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

reported the performance of both CSF and blood NfL in identifying neurodegenerative diseases, though highlighting how their levels provide limited information in separating specific disorders which cause cognitive impairment (Forgrave et al., 2019; Ashton et al., 2021; Cousins et al., 2021b). While previous literature has inconstantly reported correlations between increased CSF NfL and decreased in CSF Aβ42 (Zetterberg et al., 2016) and there has been a debate on whether CSF NfL correlates with Aβ pathology, there is evidence suggesting that changes in CSF NfL concentration are independent of Aβ pathology (Jin et al., 2019; Dhiman et al., 2020) and correlate better with tau pathology in both AD and non-AD neurodegenerative disorders (Zetterberg et al., 2016; Jin et al., 2019; Dhiman et al., 2020; Alawode et al., 2022). On the other hand, the increase in t-tau, whilst included in the AT(N) as a general biomarker of neurodegeneration and neuronal injury, does indeed reflect AD pathology when combined with raised p-tau. (Alawode et al., 2021). In fact, while higher t-tau levels with lower p-tau levels could be found in a wide range of neurological conditions (such as stroke, Creutzfeldt-Jakob disease, and other neurodegenerative diseases) as a direct result of massive neuronal death, it has been suggested that CSF tau production rate in AD positively correlates with amyloidosis and tau aggregation, and that increased tau levels in AD subjects could be a response to amyloid-β pathology rather than reflect actual neurodegeneration (Mattsson-Carlgren et al., 2020; Sato et al., 2018).

Regarding the association between CSF biomarkers concentration and neuropsychological impairment in the two groups, the finding of correlations between NfL concentration and cognitive disturbances in FTD (but not in MCI due to AD) is consistent with previously reported associations between higher CSF NfL levels and disease severity in bvFTD, nfvPPA, and svPPA (Meeter et al., 2019; Scherling et al., 2014; Verde et al., 2021). To our knowledge, those findings have seldom been

replicated in prodromal AD; indeed, some studies have reported significant correlations between CSF NfL concentration and global cognition assessed by MMSE among AD patients, but not among patients with MCI (Olsson et al., 2019; Zetterberg et al., 2016). On the other hand, CSF p-tau increases have been shown to strongly correlate with cognitive measures in prodromal AD (Nelson et al., 2012), as observed in our cohort. It is worth noting that the tasks whose scores were found to be associated with p-tau and t-tau levels were those assessing episodic memory (EMS) and semantic memory impairment (CFT). Despite episodic memory impairment having been classically considered the main and most precocious clinical hallmark of hippocampal dysfunction, degradation of semantics has been recently described to be an independent indicator of AD (Venneri et al., 2019). Semantic memory impairment may be a specific cognitive marker of early degeneration in prodromal AD (Barbeau et al., 2012) and measuring it may be helpful in discriminating healthy aging from prodromal AD and predicting disease progression (Vita et al., 2014; Marra et al., 2021). These considerations support the general idea that in prodromal AD, p-tau, and partially t-tau, mainly drive the cognitive symptoms, while NFL correlate with a global measure of cognitive decline (MMSE) mainly in the later stages of the disease. This is reinforced by the inverse correlation observed between the t-tau/NFL ratio and MMSE score in our MCI due to AD cohort. Our findings also suggest that not only episodic memory, but also semantic memory is a cognitive marker of underlying p-tau pathology.

The finding that in the FTD group NfL correlates with several neuropsychological measures evaluating memory, semantics, executive functions, and language mainly suggest a different relationship between pathological processes and cognitive impairment in FTD and AD.

While CSF NfL concentration is a promising biomarker for the identification of neurodegenerative processes as an underlying cause of cognitive symptoms and can reliably distinguish AD from healthy controls with reasonably high sensitivity and specificity, this increase is not disease-specific and does not seem to be associated with either amyloid pathology or episodic or semantic memory impairment in prodromal AD patients. CSF t-tau and NfL may reflect two distinct and only partially overlapped pathophysiological neurodegeneration mechanisms (dependent and independent of Aβ pathology, respectively). The high accuracy demonstrated by the combination of these two biomarkers in telling apart MCI due to AD from FTD may be an expression of such different processes, making t-tau and NfL not interchangeable as (N) biomarkers. Based on this, the t-tau/NfL ratio may have the potential to accurately capture the impact of the different pathophysiological mechanisms of neurodegeneration, complementing the existing diagnostic markers.

Despite established core CSF ATN biomarkers having been known for years to well distinguish AD from other neurodegenerative diseases, the reliability showed by a combination of two neurodegeneration biomarkers expressing different quality and origins may be of some interest. The possibility to obtain in the near future a panel of multiple biological markers not only devoted to recognizing AD, but also able to identify the peculiarity within any single neurodegenerative process, is a stimulating challenge in the present scenario. In this context, future studies should focus on the diagnostic and prognostic potential of associations between multiple fluid biomarkers reflecting distinct neuropathological processes and multiple neuropsychological measures expressing the impairment of specific cognitive domains. Assessing the relationship between CSF biomarkers and neuropsychological measures of cognitive decline can be of great interest in the elaboration of diagnostic algorithms for neurodegenerative diseases, which should focus on both cognitive symptoms and biochemical profiles.

Our study has several limitations that should be addressed in future research. The relatively small sample size prevents generalization, and the absence of autopsy-confirmed diagnoses could be a confounding factor. The lack of a control group composed by healthy subjects with normal values of neurodegeneration biomarkers poses a relevant limitation to the interpretation of the results and, while this study focused on comparing individuals with mild cognitive impairment due to different neurodegenerative diseases to investigate on a common diagnostic challenge in clinical practice, further investigation is needed to also assess the influence of disease stage on the discriminatory ability of the t-tau/NfL ratio. Moreover, the lack of longitudinal data does not allow to determine how biomarkers of neurodegeneration and tauopathy could predict the trajectory of cognitive decline over time. Longitudinal studies with larger cohorts are warranted to explore the relationship between these biomarkers and cognitive decline over time, providing valuable insights into their predictive value and their potential as markers of disease progression.

Our findings could prompt further investigation into the practical applications and clinical relevance of the t-tau/NfL ratio, considering its potential value in capturing the impact of distinct pathophysiological mechanisms of neurodegeneration. Future studies could validate these results in larger cohorts and examine its diagnostic value in distinguishing AD from other neurodegenerative disorders which can cause cognitive impairment, such as PD and atypical parkinsonian disorders, as well as from healthy subjects with normal values of neurodegeneration biomarkers. Moreover, the potential usefulness of the t-tau/NfL ratio may be investigated in studies including subjects with overlapping pathologies or phenotypes, trying to disentangle the relative contribution of each mechanism in determining the disease. Furthermore, considering the different association between these biomarkers of neurodegeneration and impairment in specific cognitive domains, investigating whether their combination can predict regional atrophy specific to AD would be of great interest. Conducting such research endeavors would provide valuable insights into the field and contribute to the development of improved diagnostic and prognostic approaches for neurodegenerative diseases.

5. Conclusions

In summary, these findings reveal the different relations between CSF NfL, the three core AT(N) biomarkers and cognitive decline in patients with FTD and MCI due to AD, highlighting the associations between NfL concentration and disease severity in FTD and between tauopathy and early and specific cognitive changes such as episodic memory decline and lexical-semantic impairment in prodromal AD. These results indicate how NfL and t-tau levels reflect distinct pathophysiological mechanisms of neurodegeneration (independent and dependent of Aβ pathology, respectively) and suggest that combining a non-disease specific neurodegeneration biomarker such as NfL with a disease-specific neurodegeneration biomarker such as t-tau may strengthen the reliability in distinguishing MCI due to AD from FTD.

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CRediT authorship contribution statement

Guido Maria Giuffrè: Conceptualization, Data curation, Formal analysis, Investigation, Writing – original draft, Methodology. **Davide Quaranta:** Conceptualization, Formal analysis, Resources, Supervision, Writing – review & editing. **Emanuele Maria Costantini:** Conceptualization, Data curation, Investigation, Methodology. **Salvatore Citro:** Data curation, Investigation. **Noemi Martellacci:** Data curation, Investigation. **Grazia De Ninno:** Data curation, Investigation, Methodology. **Maria Gabriella Vita:** Supervision, Resources, Writing – review & editing. **Valeria Guglielmi:** Supervision, Resources, Writing – review & editing. **Paolo Maria Rossini:** Supervision, Resources, Writing – review & editing. **Paolo Calabresi:** Supervision, Resources, Writing – review & editing. **Camillo Marra:** Supervision, Resources, Writing – review & editing, Conceptualization, Project administration, Funding

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Declaration of Competing Interest

None.

Data availability

Data will be made available on request.

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