Plasma Neurofilament Light Chain in memory clinic practice: evidence from a real-life study

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Abstract

**OBJECTIVE:** To explore plasma neurofilament light chain (NfL) as a biomarker for diagnosis and staging of cognitive impairment, in a large cohort with assessments performed in clinical practice.

**METHODS:** Retrospective, cross-sectional, monocentric study, from a tertiary memory clinic. Patients underwent cerebrospinal fluid core Alzheimer’s disease (AD) biomarker evaluation using ELISA or Elecsys methods, and plasma NfL analysis using the single molecule array technology. The patients’ biomarker data were examined for associations with: i/cognitive status ii/presence of neurodegenerative disease and iii/diagnostic groups. Differences in NfL were tested using analysis of variance (ANOVA).

**RESULTS:** Participants (N= 558, mean age= 69.2±8.8, 56.5% women) were diagnosed with AD (n=298, considering dementia and MCI stages), frontotemporal dementia (FTD, n=57), Lewy body disease (LBD, n=40, considering MCI and dementia stages), other neurodegenerative diseases (OND, n=53, e.g Supranuclear Palsy, Corticobasal degeneration), non-neurodegenerative cognitive impairment (NND, n=97, e.g vascular lesions, epilepsy or psychiatric disorders) or neurological controls (NC, n=53). Mean plasma NfL (log, pg/mL) levels were higher in neurodegenerative than non-neurodegenerative disorders (1.35±0.2 vs 1.16±0.23, p<0.001), higher in all diagnostic groups than in NC (1.06 ± 0.23) p<0.001), and associated with the stage of cognitive impairment (p<0.001).

**DISCUSSION:** Plasma NfL may be considered as a clinical-decision support tool, to help distinguish neurodegenerative from non-neurodegenerative disorders.

1. Introduction

Neurofilaments light chain (NfL) are cytoskeletal components of neuronal axons, mainly present in large caliber myelinated axons, known to play a determinant role in the axon radial growth and stability(1). Within the last decade, new assay methods, such as single molecule array (Simoa), allowed ultra-sensitive blood measurements of this cerebral biomarker, unreachable with prior ELISA techniques(2).

Plasma NfL (pNfL) was shown to reflect axonal damage in selected study cohorts of neurodegenerative disorders: Alzheimer’s disease (AD)(3), frontotemporal dementia (FTD)(4–6), or Lewy body disease (LBD) (5, 7), with good accuracy for the discrimination of neurodegenerative diseases from controls(7). However, in daily clinical practice, patients often report unspecific cognitive complaints or clinical symptoms, leading to two unmet needs: 1/to easily differentiate neurodegenerative from non-neurodegenerative disorders (NND), 2/ to help the clinicians refine early preliminary diagnoses, among neurodegenerative conditions. So far, little is known about the discriminating power of plasma NfL in daily clinical practice, in unselected populations with all causes of cognitive impairment, without excluding older patients, or those in advanced stages of dementia.

Our objectives were firstly to compare plasma NfL levels across clinical diagnoses, with regards to the presence or absence of neurodegeneration, in a sample of patients from daily clinical practice and secondly to study plasma NfL levels, across different stages of cognitive impairment.
2. Methods

2.1 Study design and participants

This retrospective, cross-sectional study, included patients with cognitive complaints who had undergone cerebrospinal fluid (CSF) analysis at the Cognitive Neurology Center, Lariboisière (GHU AP-HP.Nord, Paris), between 01/2010 and 02/2021. This department has expertise in diagnosis and care of patients with cognitive disorders and neurodegenerative diseases.

Diagnosis assessment

Patients were assessed by a multidisciplinary team of dementia experts, along three lines. i/ the cognitive status (impaired or not), ii/ the presence of underlying neurodegenerative process. iii/ the final etiological diagnosis. Accordingly, diagnostic groups were established after consideration of the clinical presentation, neuropsychological assessment, neuroimaging and CSF biomarkers, using the most recent diagnostic criteria (8–15). All patients diagnosed with AD were on the AD continuum (Mild Cognitive Impairment (MCI) and dementia) and had a biomarker profile with abnormal Aβ40/42 ratio (16).

Patients were classified as follow: cognitively unimpaired (CU) individuals, with no evidence of neurocognitive disorder; patients with neurodegenerative diseases: AD, FTD, LBD, other neurodegenerative disease (OND) and patients with non-neurodegenerative disease (NND).

In details, the OND group included patients with a diagnosis of dementia related to Creutzfeldt Jakob disease(13), supranuclear palsy(17), corticobasal degeneration(14), non-fluent primary progressive aphasia (18), as well as patients with dementia with evidence of neurodegeneration (defined by atrophy on morphological MRI or hypometabolism on FDG-PET imaging or suspected non amyloid pathology profile on CSF and cognitive decline over follow-up).

The NND group included subjects who i/ presented with an objective cognitive decline ii/ did not fulfil clinical criteria for neurodegenerative dementia (as defined above) ii/ did not meet the criteria for neurodegeneration on Fluorodeoxyglucose Positron Emission Tomography, MRI and CSF biomarkers. The final diagnoses comprised vascular cognitive impairment, sleep apnoea, alcohol-related cognitive impairment, epilepsy, psychiatric disorder (bipolar disorder, depression), traumatic brain injury, infectious diseases (HIV, herpes virus), metabolic (B12 vitamin deficiency, thyroid dysfunction) and toxic (chemotherapy treatment) cognitive impairment.

Neurological Controls (NC) participants, also referred to as CU, regarding the stage of cognitive impairment, reported cognitive complains without evidence for cognitive impairment or neurodegeneration, and might have been included as control subjects, in previous observational research studies. They were classified as CU when a diagnostic of neurocognitive disorder was excluded by the referent physician and they fulfilled the following criteria: i/ the neuropsychological assessment found preserved global cognition (i.e. normative or subnormative scores for age, sex and level of education, ii/ brain MRI did not find significant hippocampal atrophy (Scheltens score ≤ 2), iii/ they displayed a normal CSF biomarker profile.
2.2 Non-inclusion criteria

Patients were not included when no consensual etiological diagnosis was reached or when patients had undergone plasma NfL analysis, after an acute neurological event (traumatic brain injury, stroke).

The flow chart of study participants is presented on Fig. 1.

2.3 Plasma NfL and CSF biomarker measurements

Plasma NfL levels were measured in singlicates using the Simoa platform (Quanterix®, Lexington, MA) in Lariboisière Hospital, and in Neurochemistry Laboratory (Moldnal, Sweden), across 10 analytical runs. Each assay plate included internal quality control samples with high and low plasma NfL concentrations, which were analyzed in duplicate at the beginning and end of the plate. Intra-assay and inter-assay coefficients of variation (CV) were respectively of 3.1% and 11.8%. CV between the two platforms was computed from a subset of 10 samples run on both, and rendered a CV of 7.5%.

CSF Aβ ratio (Aβ42/Aβ40), phosphorylated-tau and total tau measurements were performed in the Biochemistry Unit (Lariboisière Hospital), using Innotest® ELISA (Fujirebio, Gent, Belgium) (2010–2018), and after 2018 using Elecsys® immunoassays on the cobas e601 analyzer (Roche-Diagnostics).

2.4 Statistical analyses

Patients’ data was analyzed along three lines: i/the cognitive status (CU, MCI and dementia) ii/according of the presence of neurodegenerative disease or not and iii/across diagnoses groups: AD, LBD, FTD, OND, NND and NC. Receiver operating characteristic (ROC) analyses were performed according to the presence or absence of neurodegenerative disease, using plasma NfL alone, then plasma NfL, age, MMSE and ApoE status, after logistic regression.

Plasma NfL concentration was log-transformed to achieve normality. Differences in plasma NfL across multiple category variables were tested using analysis of variance (ANOVA), followed by post-hoc test with Bonferroni correction for multiple analyses. Correlation between continuous variables, were analyzed using Spearman or Pearson correlation coefficients. Categorical variables were compared using χ² test. P < 0.05 was considered overall significant. Statistical analyses were performed using IBM SPSS 27.0 and GraphPad Prism 9.1.3.

2.5 Ethical considerations

All the participants were provided oral and written information about the opportunity to collect additional blood and CSF samples for further research analyses, in the BioCogBank© protocol. They also consented for the anonymous use of their clinical data and the results of their CSF analyses). This study was approved by the local and national Ethics Committees (“Comité d’évaluation et d’Ethique pour la recherche Paris Nord” on 30 May 2016) and the “Commission Nationale Informatique et Libertés” (CNIL).

3. Results
3.1 Characteristics of the study sample

We included 558 participants. Regarding cognitive status, 53 were CU subjects, 218 individuals had MCI and 287 had dementia. Overall, 426 individuals (76.4%) had a neurodegenerative disease; in details AD n = 274, FTD n = 55, LBD n = 40, OND, n = 57, NND, n = 79, NC, n = 53. Plasma NfL was correlated with age (rho = 0.40, p < 0.0001) but not with sex (p = 0.66) nor with APOE ε4 carriership (p = 0.36). The patients’ characteristics and plasma NfL values are displayed in Table 1. The relationship between plasma NfL and the cognitive status, the degenerative or non-degenerative status and the diagnostic groups is illustrated on Fig. 2.

3.2 Plasma NfL regarding cognitive status

Plasma NfL was associated with the severity of cognitive impairment, regardless of the etiology (Table 1). Plasma NfL levels were higher in subjects with MCI or dementia vs CU, p < 0.001). There was also a stepwise increase between patients with MCI and dementia (p < 0.001).

3.3 Plasma NfL regarding degenerative or non-degenerative status

pNfL levels in neurodegenerative patients were higher than in non-neurodegenerative patients (mean ± sd 1.16 ± 0.23 versus 1.35 ± 0.32, pg/mL p < 0.001). In ROC analysis, pNfL discriminated neurodegenerative disorders from NND after logistic regression including age, MMSE and APOE status, with an AUC of 0.84 95% CI=[0.80;0.88].
Table 1  
Characteristics of the study participants

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Overall</th>
<th>NC</th>
<th>NND</th>
<th>AD</th>
<th>FTD</th>
<th>LBD</th>
<th>OND</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=558</td>
<td>N=53</td>
<td>N=79 (14.2)</td>
<td>N=274 (49.1)</td>
<td>N=55</td>
<td>N=40 (7.2)</td>
<td>N=57 (10.2)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Demographics**

<table>
<thead>
<tr>
<th>Age, years, mean (SD)</th>
<th>69.2 ± 8.8</th>
<th>62.2 ± 8.6</th>
<th>66.6 ± 9.9</th>
<th>71.2 ± 8.3</th>
<th>68.0 ± 7.1</th>
<th>68.3 ± 6.3</th>
<th>71.9 ± 7.9</th>
<th>&lt; 0.001*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female, n (%)</td>
<td>314 (56.5)</td>
<td>36 (67.9)</td>
<td>41 (51.9)</td>
<td>161 (59.1)</td>
<td>20 (36.4)</td>
<td>17 (42.5)</td>
<td>39 (68.4)</td>
<td>0.001†</td>
</tr>
<tr>
<td>Education level, yo</td>
<td>11.4 ± 3.5</td>
<td>12.8 ± 3.0</td>
<td>10.6 ± 3.8</td>
<td>11.3 ± 3.5</td>
<td>11.3 ± 3.4</td>
<td>11.5 ± 3.7</td>
<td>11.7 ± 3.1</td>
<td>0.035*</td>
</tr>
<tr>
<td>ApoE4 carriership, n (%)</td>
<td>248 (44.5)</td>
<td>16 (32.6)</td>
<td>14 (18.6)</td>
<td>162 (62.8)</td>
<td>16 (30.2)</td>
<td>20 (51.3)</td>
<td>20 (37.7)</td>
<td>&lt; 0.001†</td>
</tr>
<tr>
<td>MMSE (/30)</td>
<td>24 (19; 27)</td>
<td>27 (25; 29)</td>
<td>25 (22; 27)</td>
<td>21 (17; 26)</td>
<td>24.5 (18; 27)</td>
<td>25 (18.25; 27)</td>
<td>24 (21; 27)</td>
<td>&lt; 0.001‡</td>
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**Cognitive status**

<table>
<thead>
<tr>
<th>Cognitively unimpaired</th>
<th>53 (9.5)</th>
<th>53 (100)</th>
<th>0 (0)</th>
<th>0 (0)</th>
<th>0 (0)</th>
<th>0 (0)</th>
<th>0 (0)</th>
<th>&lt; 0.001†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild cognitive impairment</td>
<td>218 (39.1)</td>
<td>0 (0)</td>
<td>63 (79.7)</td>
<td>95 (34.7)</td>
<td>12 (21.8)</td>
<td>19 (47.5)</td>
<td>29 (50.9)</td>
<td></td>
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<tr>
<td>Dementia</td>
<td>287 (51.4)</td>
<td>0 (0)</td>
<td>16 (20.3)</td>
<td>179 (65.3)</td>
<td>43 (78.2)</td>
<td>21 (52.5)</td>
<td>28 (49.1)</td>
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**Core CSF biomarkers**

<table>
<thead>
<tr>
<th>A-T-N-</th>
<th>191 (34.2)</th>
<th>53 (100)</th>
<th>61 (77.2)</th>
<th>0(0)</th>
<th>36 (65.5)</th>
<th>22 (55.0)</th>
<th>20 (35.1)</th>
<th>&lt; 0.001†</th>
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<tbody>
<tr>
<td>A- with T + or N+</td>
<td>67 (12.0)</td>
<td>0 (0)</td>
<td>17 (21.5)</td>
<td>0 (0)</td>
<td>19 (34.5)</td>
<td>8 (20.0)</td>
<td>23 (40.4)</td>
<td></td>
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<tr>
<td>A + T-N-</td>
<td>37 (6)</td>
<td>0 (0)</td>
<td>1 (1.3)</td>
<td>18 (6.6)</td>
<td>0 (0)</td>
<td>6 (15.0)</td>
<td>12 (21.1)</td>
<td></td>
</tr>
<tr>
<td>A + T-N+</td>
<td>16 (2.9)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>13 (4.7)</td>
<td>0 (0)</td>
<td>1 (2.5)</td>
<td>2 (3.5)</td>
<td></td>
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<tr>
<td></td>
<td>Overall</td>
<td>NC</td>
<td>NND</td>
<td>AD</td>
<td>FTD</td>
<td>LBD</td>
<td>OND</td>
<td>p</td>
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<tr>
<td>N</td>
<td>558</td>
<td>53</td>
<td>79</td>
<td>274</td>
<td>55</td>
<td>40</td>
<td>57</td>
<td></td>
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<tr>
<td>(mean (SD))</td>
<td>(9.5)</td>
<td></td>
<td>(14.2)</td>
<td>(49.1)</td>
<td>(9.9)</td>
<td>(7.2)</td>
<td>(10.2)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>A + T + N-</td>
<td>10</td>
<td>0</td>
<td>9</td>
<td>0</td>
<td>8</td>
<td>0</td>
<td></td>
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<tr>
<td></td>
<td>(1.8)</td>
<td></td>
<td>(3.3)</td>
<td>(3.3)</td>
<td>(20.0)</td>
<td>(0.0)</td>
<td>(0.0)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>A + T + N+</td>
<td>237</td>
<td>0</td>
<td>234</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td></td>
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<tr>
<td></td>
<td>(42.5)</td>
<td></td>
<td>(85.4)</td>
<td>(85.4)</td>
<td>(0.0)</td>
<td>(5.0)</td>
<td>(0.0)</td>
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<tr>
<td>pNfL</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<td></td>
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<tr>
<td>pNfL (pg/mL, mean (SD))</td>
<td>23.7 ± 15.1</td>
<td>13.3 ± 7.9</td>
<td>20.4 ± 17.4</td>
<td>24.8 ± 11.8</td>
<td>32.2 ± 22.1</td>
<td>18.0 ± 7.5</td>
<td>28.5 ± 18.8</td>
<td>&lt; 0.001*</td>
</tr>
<tr>
<td>Log pNfL (pg/mL)</td>
<td>1.31 ± 0.24</td>
<td>1.06 ± 0.23</td>
<td>1.22 ± 0.26</td>
<td>1.35 ± 0.19</td>
<td>1.43 ± 0.25</td>
<td>1.21 ± 0.20</td>
<td>1.38 ± 0.26</td>
<td>&lt; 0.001*</td>
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*ANOVA test† χ²squared test. † Kruskall-Wallis test. Multiple comparison adjustment with Bonferroni's method. P < 0.05 for comparison of i/ AD and NC, NND, OND, ii/ NC and all groups

Figure 2. Plasma NfL levels across diagnostic groups, cognitive stages and neurodegenerative status

3.4 Plasma NfL regarding diagnostic groups

Plasma NfL levels were higher in all diagnostic groups compared with NC. Although displaying the higher levels in our study, plasma NfL levels from individuals with FTD did not differ statistically from AD or OND. However, plasma NfL was higher in FTD than in NND or LBD. LBD patients’ plasma NfL levels were lower than individuals with AD (p < 0.01), FTD (p < 0.0001) or OND (p < 0.01) but did not differ from subjects with NND (Fig. 1). The levels of plasma NfL between patients with MCI vs dementia in FTD were significantly different (1.28 ± 0.21 vs. 1.48 ± 0.24, respectively p < 0.001 after age-adjustment), whereas the difference was not significant in MCI vs. dementia due to AD.

4. Discussion

This analysis of 558 patients from daily clinical practice highlighted the potential interest of plasma NfL as a biomarker, along the diagnostic process. First, plasma NfL accurately reflected the stage of cognitive impairment, regardless of the diagnosis; plasma levels were higher in subjects with dementia than in those with MCI, and higher in MCI patients than in NC. Second, plasma NfL was higher in patients with neurodegenerative disorders than in those with NND. Third, patients with FTD showed the highest plasma NfL concentration, which differed significantly from individuals diagnosed with LBD, NC and NND, but not from those with OND or AD. In a recent publication, Wilke et al. reported that plasma NfL progressively increased in conversion stages of genetic forms of FTD(19). The absence of difference between patients
with FTD and AD might be explained by the inclusion of early-stage FTD subjects in our sample(20). We confirmed the results of prior publications(5, 7) showing that patients with LBD presented higher levels of plasma NfL than NC, but also lower levels than patients with AD, FTD or OND.

To the best of our knowledge, only two other studies assessed the role of plasma NfL in cognitively impaired individuals with different diagnostic groups. Last year, Ashton et al. established optimal cutpoints for plasma NfL in 2269 individuals with various neurodegenerative or NND, achieving the correct classification of most individuals with FTD, progressive supranuclear palsy, multiple system atrophy, or amyotrophic lateral sclerosis(5). However, in this study, participants came from two multicenter cohorts (KCL in UK and BioFINDER in Sweden). Because of stringent inclusion and exclusion criteria, such as thresholds of MMSE for MCI and dementia staging, the population of this study did not completely reflect the daily clinical practice settings and concerns. Willemse et al. highlighted the interest of plasma NfL, as a biomarker of neurodegenerative diseases, in a smaller sample (n = 109) of younger patients (mean age 63 ± 9) from clinical practice, especially in the youngest half of their study population(21). Consistent with the results of these two studies, plasma NfL in our population proved accuracy to distinguish neurodegenerative from NND, but brought limited information for indicating specific etiologies of cognitive disorders. Therefore, plasma NfL may be used as a first-line screening test, to support a neurodegenerative hypothesis, for example to rule out a psychiatric condition(20).

Plasma NfL levels modifications in neurodegenerative disorders are related to chronic and progressive neuronal death(22). Thus, unlike in brain injuries (stroke, meningitis), plasma NfL levels progressively increase over the course of the disease, reflecting the dynamic process of neurodegeneration. This dynamic profile of plasma NfL was confirmed in clinical studies assessing the therapeutic response and disease activity in patients with multiple sclerosis(23). Our results also suggest the potential use of this dynamic biomarker in clinical practice, for the monitoring of unselected patients, as a “neurologist troponin”(24).

The main strength of our work is the large-sampled evaluation of plasma NfL assay, in multidisciplinary-evaluated patients, from clinical practice. The NND group comprised various diagnoses, reflecting the diversity of patients from a memory clinic. All the analyses were adjusted for age, which was associated with plasma NfL levels. There are some limitations of this study. The monocentric design is leading to a lack of external validity. Although our sample was large, the number of patients who were diagnosed with FTLD or LBD as compared with AD was rather small, which oversized the effect of extreme values of plasma NfL in these groups. This discrepancy may represent the consequence of a selection bias for research in the field of neurocognitive disorders, as patients are frequently referred by their physicians to tertiary memory centers with the perspective of participation to clinical trials. Moreover, this was a cross-sectional analysis with only one plasma NfL measurement by participant. Thus, there are uncertainties regarding the evolution of plasma NfL in our participants over the years of follow-up.

5. Conclusion
Plasma NfL appeared as an accurate biomarker for discriminating degenerative from non-degenerative causes of cognitive disorders, and could be regarded as a first-line biomarker along the diagnostic process. Precise thresholds should be defined in future works, before its implementation in clinical practice. The relationship of plasma NfL to other progression biomarkers, such as neuroimaging abnormalities, also deserves further investigation.

Declarations

Ethical authorizations and consent to participate

All the participants were provided oral and written information about the opportunity to collect additional blood and CSF samples for further research analyses, in the BioCogBank© protocol. They also consented for the anonymous use of their clinical data and the results of their CSF analyses. The “Comité d'Evaluation de l'Ethique des projets de Recherche Biomédicale (CEERB) Paris Nord” (Institutional Review Board-IRB 00006477-of HUPNVS, Paris 7 University, AP-HP), has reviewed and approved the research project entitled «Clinico-biological database of cognitive disorders» (Dr Dumurgier, principal investigator) on May 30, 2016, and the “Commission Nationale Informatique et Libertés” (CNIL).

Consent for publication

Not applicable

Availability of data and material

The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request.

Competing interest

KB has served as a consultant, at advisory boards, or at data monitoring committees for Abcam, Axon, BioArctic, Biogen, JOMDD/Shimadzu. Julius Clinical, Lilly, MagQu, Novartis, Ono Pharma, Pharmatrophix, Prothena, 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, outside the work presented in this paper. The other authors report no conflict of interest.

Funding

None

Authors’ contribution

KG, ML and CP designed the study and processed the data of participants. KG, AV and ML drafted the manuscript. KG and AV performed the NfL measurements; MM, EBA, and FML supervised the procedure.
JH, JD, EC, FML, EBA, KB, HZ, CP and ML critically reviewed and edited the manuscript and contributed to the discussion.

Acknowledgment

Not applicable

References


Figures

Patients between 06/01/2010 and 19/02/2021 diagnosed with CSF biomarkers and with plasma sample available

\[ N = 658 \]

Not included: \( N = 97 \)
- Multiple assessments: \( N = 16 \)
- No consensual diagnosis: \( N = \)

Included patients
\[ N = 558 \]

Analyzer
\[ N = 558 \]

AD  \( N = 274 \)
LBD  \( N = 40 \)
FTD  \( N = 55 \)
OND  \( N = 57 \)
NND  \( N = 97 \)
NC   \( N = 53 \)

Figure 1

Flow chart of study participants
Figure 2

Plasma NfL levels across diagnostic groups, cognitive stages and neurodegenerative status

For each figure, mean levels, first and third quartiles are represented inside the box, with the mean plasma NfL level on the right. Plasma NfL levels were compared unadjusted using ANOVA and adjusted for age using ANCOVA (adjusted P-values are shown between brackets). P-values were corrected for multiple comparisons using Bonferroni’s method.

Figure 2A. Plasma NfL levels across cognitive impairment stages
Figure 2B. Plasma NfL levels in neurodegenerative and non-neurodegenerative groups

Figure 2C. Plasma NfL across diagnostic groups. NC had lower rates of plasma NfL compared with all groups (p<0.001 for all groups but LBD, p=0.002)

Figure 2D. Plasma NfL levels in subgroups of AD and FTD, according to cognitive impairment stage. NC had lower rates of plasma NfL compared with all groups (p<0.001 for all groups, but FTD MCI, p=0.004