SUPPLEMENTARY FILE

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## TABLE S1 - Clinical details of patients excluded from the study

|  |  |  |  |
| --- | --- | --- | --- |
| Age/sex | Initial Diagnosis | CSF NfL concentration (pg/mL) | Exclusion reason |
| 36F | Unclear | 421 | Lost to follow-up |
| 55M | Unclear | 670 | Lost to follow-up |
| 65F | PPA | 1238 | Lost to follow-up |
| 52F | Schizoaffective disorder | 514 | Lost to follow-up |
| 77M | Probable dementia with Lewy bodies | 1026 | Died within 1 year |
| 65F | Probable AD | 1369 | Lost to follow-up |
| 55F | Dissociative disorder | 469 | Lost to follow-up |
| 44F | Somatoform disorder | 345 | Lost to follow-up |
| 53M | Probable AD | 1272 | Lost to follow-up |
| 48M | Functional cognitive disorder | 761 | Lost to follow-up |
| 55M | Psychogenic non-epileptic seizure | 416 | Lost to follow-up |
| 71F | Probable AD | 1436 | Died within 1 year |
| 69M | Progressive supranuclear palsy | 2969 | Died within 1 year |
| 68M | Unclear | 1003 | Lost to follow-up |
| 59F | Delusional disorder | 32437 | Lost to follow-up |
| 43F | Unclear | 1497 | Lost to follow-up |
| 63F | Probable AD | 414 | Lost to follow-up |
| 64F | Multifactorial, not neurodegenerative | 609 | Lost to follow-up |
| 60M | Probable AD | 901 | Lost to follow-up |

AD – Alzheimer’s disease, CSF NfL – cerebrospinal neurofilament light

## Table S2 - Clinical details of patients with a final diagnosis of neurodegenerative disorder where CSF NfL was inaccurate

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Age/Sex | Age of Symptom Onset  | Psychiatric History | Baseline diagnosis | Final diagnosis | Time until final diagnosis(months) | CSF NfL(pg/mL) | Possible explanation for CSF NfL inaccuracy |
| 73M | 70 | agitated depression with suicidal ideation since 2006 | Unclear – PDD vs bvFTD vs pseudodementia  | mixed dementia - AD and VD | 80 | 521 | Follow-up period 80 months; AD proteins indeterminate, mild-mod small vessel ischaemia |
| 50F | 49 | Depression 7 years prior due to husband’s death | Dementia NOS | Parkinson's disease & depression | 47 | 413 | Final Dx PDD |
| 68F | 67 | Anxiety & depression diagnosed ~10 years prior  | Major depressive disorder | bvFTD  | 109 | 441 | Follow-up period = 109 months |
| 52M | 50 | Schizoaffective disorder diagnosed 15 years prior | Schizoaffective disorder | bvFTD | 91 | 514 | Follow-up period = 91 months |
| 51M | 48 | Depression & anxiety diagnosed 3 years prior  | Possible bvFTD | bvFTD | 79 | 531 | Follow-up period = 79 months  |
| 58M | 48 | Depression diagnosed 6 years prior | Dementia NOS ?MCI vs early AD | Parkinson's disease & late onset psychosis | 78 | 504 | Final Dx = PDD |
| 54F | 52 | Anxiety & depression diagnosed 20+ years prior | AD PCA | AD PCA | 26 | 387 | Low T-tau, P-tau |
| 55M | 48 |  Nil | Possible bvFTD | Dementia NOS | 38 | 414 | Dx certainty = possible |

## Table S3 - Clinical details of patients with a final diagnosis of primary psychiatric disorder where CSF NfL was inaccurate

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Age/Sex | Age of Symptom Onset  | Psychiatric History | Baseline diagnosis | Final diagnosis | Time until final diagnosis(months) | CSF NfL(pg/mL) | Possible explanation for CSF NfL inaccuracy |
| 75M | 75 | BPAD diagnosed 3 years prior | Mood disorder | Mood disorder | 33 | 683 | IHD, hypertension, hypercholesterolaemia, AF, overweight; mild chronic small vessel ischaemia |
| 61M | 61 | Nil | Late-onset BPAD | BPAD | 27 | 714 | Multiple FLAIR white matter hyperintensities on MRI-B 2019 |
| 59M | 56 | Anxiety diagnosed 10 years prior | Unclear | bvFTD phenocopy | 21 | 783 | mild white matter hyperintensities & OSA |
| 74F | 74 | Postnatal depression diagnosed 45 years prior | Depression | Depression | 29 | 647 | Moderate chronic small vessel ischemic change on MRI-B 2019 |
| 62M | 57 | First episode psychosis in 2018 | Schizophrenia | Schizophrenia with negative symptoms  | 13 | 609 | borderline NfL; Mild and age-appropriate patchy WMH suggestive of chronic small vessel ischaemia, |
| 59M | 55 | Late onset psychosis | Delusional disorder/Late onset psychosis | Schizophrenia | 17 | 689 | Hypertension, hypercholesterolaemia, obese, IHD, smoker, periventricular white matter |
| 71M | 63 | Depression diagnosed 11 years prior | bvFTD phenocopy | bvFTD phenocopy | 14 | 864 | Hypertension, hypercholesterolaemia, obese, IHD, smoker, periventricular white matter |
| 54M | 52 | PTSD since early 20s | Delusional disorder | Delusional disorder | 12 | 594 | borderline NfL; Hypertension, hypercholesterolaemia, with mild cerebral small vessel disease |

| Table S4 – ATN classification based on CSF samples |
| --- |
|  | **Dx\_99cat** |
| **DH** | **MCI/other non-progressive** |  **ND** | **PSY** |
| A+T+N+ |  | 0 |  | 39 |  | 0 |  |
| A+T+N- |  | 0 |  | 1 |  | 1 |  |
| A+T-N- |  | 5 |  | 32 |  | 25 |  |
| A+T-N+ |  | 0 |  | 4 |  | 1 |  |
| A-T+N+ |  | 5 |  | 9 |  | 2 |  |
| A-T+N- |  | 1 |  | 0 |  | 1 |  |
| A-T-N+ |  | 0 |  | 5 |  | 0 |  |
| A-T-N- |  | 10 |  | 23 |  | 27 |  |
| Missing |  | 0 |  | 8 |  | 11 |  |
|  |

 MCI = mild cognitive impairment, ND = neurodegenerative disorder, PSY = primary psychiatric disorder

## Table S5a – Sensitivity/specificity table comparing NfL performance against ND + MCI/other vs PSY

|  |  |  |
| --- | --- | --- |
|  | ND/MCI/other +ive | ND/MCI/other -ive |
| NfL +ive | 129 | 10 |
| NfL -ive | 15 | 58 |

Sensitivity = 129/144 = 89.6%

Specificity = 58/68 = 85.3%

PPV = 129/139 = 92.8%

NPV = 58/73 = 79.5%

## Table S5b - Sensitivity/specificity table comparing NfL performance against ND vs PSY only

|  |  |  |
| --- | --- | --- |
|  | ND +ive | ND -ive |
| NfL +ive | 114 | 10 |
| NfL -ive | 8 | 58 |

Sensitivity = 114/122 = 93.4%

Specificity = 58/68 = 85.3%

PPV = 114/124 = 91.9%

NPV = 58/66 = 87.9%

ND = neurodegenerative disorder

NfL = neurofilament light level

MCI/other = mild cognitive impairment and other non-progressive neurological disorders

PSY = primary psychiatric disorder

|  |
| --- |
| Table S6 – General linear model comparison of CSF NfL (Log10 transformed) between final diagnostic groups with age as covariate |
| Dependent Variable: CSF\_NfL\_1\_log10  |
| Final diagnosis category A | Final diagnosis category B | Mean Difference of CSF NfL (log 10) |  |
| p | 95% Confidence Interval |
| Lower | Upper |
| MCI/other | PSY | .206 | .003 | .098 | .333 |
| ND | -.184 | .003 | -.280 | -.056 |
| ND | PSY | .390 | <.001 | .327 | .454 |
| a. Unless otherwise noted, bootstrap results are based on 1000 bootstrap samples |

ND = neurodegenerative disorder

NfL = neurofilament light level

MCI/other = mild cognitive impairment and other non-progressive neurological disorders

PSY = primary psychiatric disorder

## Figure S1 - Boxplot of NfL levels (log 10) in diagnostic groups

