Cerebrospinal fluid tau and amyloid-β_{1-42} in patients with dementia

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Progressive cognitive decline in combination with a cerebrospinal fluid biomarker pattern of low levels of amyloid-β_{1-42} and high levels of total tau and phosphorylated tau is typical of Alzheimer’s disease. However, several neurodegenerative disorders may overlap with Alzheimer’s disease both in regards to clinical symptoms and neuropathology. In a uniquely large cohort of dementia patients, we examined the associations of cerebrospinal fluid biomarkers for Alzheimer’s disease molecular pathology with clinical dementia diagnoses and disease severity. We cross-referenced the Swedish Dementia Registry with the clinical laboratory database at the Sahlgrenska University Hospital. The final data set consisted of 5676 unique subjects with a clinical dementia diagnosis and a complete set of measurements for cerebrospinal fluid amyloid-β_{1-42}, total tau and phosphorylated tau. In cluster analysis, disregarding clinical diagnosis, the optimal natural separation of this data set was into two clusters, with the majority of patients with early onset Alzheimer’s disease (75%) and late onset Alzheimer’s disease (73%) assigned to one cluster and the patients with vascular dementia (91%), frontotemporal dementia (94%), Parkinson’s disease dementia (94%) and dementia with Lewy bodies (87%) to the other cluster. Frontotemporal dementia had the highest cerebrospinal fluid levels of amyloid-β_{1-42} and the lowest levels of total tau and phosphorylated tau. The highest levels of total tau and phosphorylated tau and the lowest levels of amyloid-β_{1-42} and amyloid-β_{1-42}:phosphorylated tau ratios were found in Alzheimer’s disease. Low amyloid-β_{1-42}, high total tau and high phosphorylated tau correlated with low Mini-Mental State Examination scores in Alzheimer’s disease. In Parkinson’s disease dementia and vascular dementia low cerebrospinal fluid amyloid-β_{1-42} was associated with low Mini-Mental State Examination score. In the vascular dementia, frontotemporal dementia, dementia with Lewy bodies and Parkinson’s disease dementia groups 53%, 34%, 67% and 53% of the subjects, respectively had abnormal amyloid-β_{1-42} levels, 41%, 41%, 28% and 28% had abnormal total tau levels, and 29%, 28%, 25% and 19% had abnormal phosphorylated tau levels. Cerebrospinal fluid biomarkers were strongly associated with specific clinical dementia diagnoses with Alzheimer’s disease and frontotemporal dementia showing the greatest difference in biomarker levels. In addition, cerebrospinal fluid amyloid-β_{1-42}, total tau, phosphorylated tau and the amyloid-β_{1-42}:phosphorylated tau ratio all correlated with poor cognitive performance in Alzheimer’s disease, as did cerebrospinal fluid amyloid-β_{1-42} in Parkinson’s disease dementia and vascular dementia. The results support the use of cerebrospinal fluid biomarkers to differentiate between dementias in clinical practice, and to estimate disease severity.
Introduction

Alzheimer’s disease is the most common cause of dementia and a major health concern in the ageing global population, presently affecting more than 20 million people worldwide (Sosa-Ortiz et al., 2012). The hallmark histological signs of Alzheimer’s disease have been known for more than a century and include atrophy of the brain due to neuronal and synaptic/axonal degeneration and loss, extracellular accumulations of amyloid plaques, and intraneuronal neurofibrillary tangles consisting of phosphorylated tau (Blennow et al., 2006). Three core CSF biomarkers for Alzheimer’s disease have been developed, each correlating to one of the key characteristics of Alzheimer’s disease pathology; low levels of CSF amyloid-β1-42 correlate with greater plaque load, high levels of total tau correlate with greater intensity of neuronal degeneration, and high levels of phosphorylated tau correlate with neurofibrillary tangle pathology in Alzheimer’s disease (Blennow et al., 2010). In the context of a clinical presentation consistent with Alzheimer’s disease, the presence of low levels of amyloid-β1-42 in combination with high levels of total tau and phosphorylated tau provide support for the diagnosis with a sensitivity of 80–93% and specificity of 82–90% against cognitively normal controls (Duits et al., 2014). However, other common dementia disorders can overlap with Alzheimer’s disease both in terms of symptoms and CSF profile, and mixed pathologies are common (Zekry et al., 2002; Kertesz et al., 2005; Forman et al., 2006; Schoonenboom et al., 2012; Rosen et al., 2013).

Most studies investigating CSF biomarkers for dementia disorders have been relatively small and have often only included a few different disorders, or have had very strict inclusion and exclusion criteria, which may limit the generalizability of the results. Here we aimed to describe CSF biomarker measurements in clinical practice at the Mölndal site of the Sahlgrenska University Hospital, Sweden from 1 January 2004 to 1 June 2012. We combined two sources of information for this study. The first was a complete set of archived data on CSF amyloid-β1-42, total tau and phosphorylated tau measurements made in clinical practice at the Mölndal site of the Sahlgrenska University Hospital, Sweden from 1 January 2004 to 1 June 2012. The Sahlgrenska University Hospital laboratory handles CSF biomarker measurements for all of Sweden. Only subjects where CSF amyloid-β1-42, total tau and phosphorylated tau had been requested by clinicians were included.

Materials and methods

We combined two sources of information for this study. The first was a complete set of archived data on CSF amyloid-β1-42, total tau and phosphorylated tau measurements made in clinical practice at the Mölndal site of the Sahlgrenska University Hospital, Sweden from 1 January 2004 to 1 June 2012. The Sahlgrenska University Hospital laboratory handles CSF biomarker measurements for all of Sweden. Only subjects where CSF amyloid-β1-42, total tau and phosphorylated tau had been requested by clinicians were included.
The second source of data was SveDem, the Swedish Dementia Registry, which was started in May 2007 to improve the quality of the diagnostic work-up, treatment and care for patients with dementia throughout Sweden (Religa et al., 2012; Wimo et al., 2013), and which presently covers 95% of all memory clinics and 70% of all primary care units in Sweden (SveDem, 2013). From SveDem all information on clinical diagnosis, date of diagnosis and Mini-Mental State Examination (MMSE) score was drawn. In SveDem, each patient is registered when diagnosed with dementia in clinical practice. The registered diagnosis is assigned to a diagnostic group out of nine preset options in the report form: early onset Alzheimer’s disease (onset <65 years of age); late onset Alzheimer’s disease (onset ≥65 years of age); frontotemporal dementia; dementia with Lewy bodies; Parkinson’s disease dementia; vascular dementia; mixed Alzheimer’s disease; and vascular dementia; dementia not otherwise specified; and a group for the collected remainders of named dementia diagnoses called ‘other dementias’, including corticobasal syndrome, alcohol-related dementias, and other rare diagnoses. Reporting clinicians are instructed to follow diagnostic guidelines as specified in ICD-10 to secure a unified basis for diagnosis (Sorbi et al., 2012). In addition, the McKeith criteria (The Lund and Manchester Groups, 1994) are used for dementia with Lewy bodies, the Lund-Manchester criteria for frontotemporal dementia (McKeith et al., 2005) and the Movement Disorder Society Task Force criteria for Parkinson’s disease dementia (Martinez-Martin et al., 2011). In a survey conducted in 2015, reporting physicians (n=40, representing 76% of the regions that report into SveDem) answered a call to specify their means of setting Alzheimer’s disease and vascular dementia diagnoses. Ninety-seven per cent stated that they used the McKhann et al. (1984) criteria, with slight or no variations, for Alzheimer’s disease diagnosis. The remaining 3% stated that they used variants of newly proposed research criteria (McKkhan et al., 2011; Dubois et al., 2014). Eighty per cent stated that they used the NINDS-AIREN (Roman et al., 1993) criteria for diagnosing vascular dementia and 18% stated that they used NINDS-AIREN but that they would also diagnose vascular dementia without focal neurologic deficits if there was imaging evidence of cerebrovascular disease, including small vessel disease. A majority of the patients included in this study (>70%) received their diagnosis by dementia specialists at memory, neurology or geriatric centres. Primary care units are instructed to only report cases with a clear diagnosis, and to refer more complicated cases or rare conditions to specialist care units. Eighteen percent of the 75–85 year olds, 30% of the 65–74 year olds and 49% of the patients under 65 years of age had been exposed to extended testing by neuropsychologists (SveDem, 2013). In the annual follow-ups of patients with dementia diagnoses in SveDem, <5% have had their diagnosis changed (SveDem, 2013). The two data sources were cross-referenced using the Swedish personal identity number. When multiple CSF analyses were available for the same individual, the measurements closest to the date of diagnosis were used. Subjects with CSF analyses performed more than 3 years before or after the diagnosis were excluded. Five thousand six hundred and seventy-six unique subjects with a complete set of measurements for amyloid-β1-42, total tau and phosphorylated tau were matched and used for this study.

**Clinical monitoring**

To ensure a high quality standard of the reported data in SveDem clinical monitoring is performed continually. A report from SveDem is published annually to inform medical and care professionals as well as political and administrative decision-makers about the current quality of diagnostics, treatment and care of patients with dementia disorders in Sweden. Monitoring is performed by a research nurse who visits units all over the country and randomly selects 10% of the reported medical record and verifies if the data in SveDem correspond to the original data in patients’ medical records. At the time of publication of the 2013 SveDem annual report, 76% of the specialist care units had been monitored, and 25% of the primary care units (SveDem, 2013).

**Biochemical measurements**

CSF total tau and phosphorylated tau were measured using enzyme-linked immunosorbent assays (ELISAs) [INNOTEST® hTAU Ag and PHOSPHO-TAU (181P); Innogenetics] as previously described (Blennow et al., 1995; Vanmechelen et al., 2000). CSF amyloid-β1-42 was measured using a sandwich ELISA [INNOTEST® β-amyloid1-42], specifically constructed to measure amyloid-β containing both the first and 42nd amino acids, as previously described (Andreasen et al., 1999). The between-assay coefficients of variation (CV) for the total tau, phosphorylated tau and amyloid-β1-42 tests were 10.35%, 10.19% and 10.21%, respectively (as determined by internal control samples during the entire study period).

All CSF analyses were performed by board-certified laboratory technicians using procedures accredited by the Swedish Board for Accreditation and Conformity Assessment (SWEDAC). Longitudinal stability in the measurements over the study period was ascertained using an elaborate system of internal quality control samples and testing of incoming reagents (Supplementary material). More details about the CSF procedures can be found in the Supplementary material.

**Classification**

For statistical analysis, we used cut-offs for amyloid-β1-42 (<530 ng/l), total tau (>350 ng/l) and phosphorylated tau (>60 ng/l), previously defined in a longitudinal study at the Sahlgrenska University Hospital laboratory, to classify all subjects according to presence of biochemical evidence of Alzheimer’s disease pathology (Hansson et al., 2006). In accordance with the newly proposed IWG-2 criteria (Dubois et al., 2014), a pathologic amyloid-β1-42 in combination with a pathologic level of either total tau or phosphorylated tau was considered an Alzheimer’s disease-like pathologic profile.

**The amyloid-β1-42:phosphorylated tau ratio**

In previous studies, the amyloid-β1-42:phosphorylated tau ratio has been shown to add discriminatory power over solitary amyloid-β1-42, phosphorylated tau and total tau measurements in separating Alzheimer’s disease from controls and other disorders (Frankfort et al., 2008; Duits et al., 2014). We therefore
included it for analysis in this paper, and used a cut-off (<6.5) as defined by Hansson et al. (2006).

**Statistics**

We tested associations between diagnostic group and potential confounding factors (age, sex and MMSE scores) using ANOVA, ANCOVA and chi-square analysis. ANOVA was used to test for differences in age, and ANCOVA was used to test for differences in MMSE scores between diagnostic groups. The main part of the analysis was logically divided into four steps. First, we tested for differences in biomarker levels between diagnostic groups, using ANCOVA. Second, we calculated the percentage of patients in different diagnostic groups with an Alzheimer’s disease biomarker profile. Third, we tested for associations between CSF biomarkers and MMSE, within diagnostic groups, using linear regression. Fourth, we tested for natural classifications of the data, using the SPSS TwoStep algorithm for data clustering. In the cluster analysis, the Schwarz Bayesian Criterion was used to choose between competing models, for determining the optimal cluster count. The main outcome of the clustering algorithm, or the silhouette measure, ranges from −1 to 1, where 1 is a perfect fit, and averages each record’s distance to the nearest cluster centre that it does not belong to. Age, MMSE scores, biomarker and sex distribution across clusters was analysed by Mann-Whitney U and chi-square statistics.

Natural logarithmic transformations were used to fit the significantly skewed amyloid-β1-42, total tau and phosphorylated tau data for ANCOVA and regression. For all ANCOVAs Bonferroni corrections for multiple comparisons was used. All ANCOVAs and linear regression models were adjusted for age and sex. Statistical significance was determined at \( P < 0.05 \). All statistics, charts and tables were produced in SPSS version 20 (IBM, New York).

**Ethics**

All patients in SveDem were informed about their participation in the registry and had the right to decline participation. This study was approved by the regional ethical committee at the University of Gothenburg.

**Results**

**Age, sex and MMSE**

Data on age, sex and MMSE scores are presented in Table 1. Patients with early onset Alzheimer’s disease and frontotemporal dementia were younger than the other diagnostic groups \( (P < 0.05) \), while patients with mixed Alzheimer’s disease and vascular dementia were older than all other groups \( (P < 0.001) \). The frontotemporal dementia group had higher MMSE scores than all other groups \[ \text{frontotemporal dementia versus early onset Alzheimer’s disease mean difference (MD) = 2.3, } P < 0.001; \text{ versus late onset Alzheimer’s disease MD = 1.2, } P = 0.009; \text{ versus dementia with Lewy bodies MD = 2.0, } P = 0.001; \text{ versus mixed Alzheimer’s disease and vascular dementia MD = 1.5, } P = 0.001; \text{ versus dementia not otherwise specified MD = 1.9, } P < 0.001; \text{ versus Parkinson’s disease dementia MD = 2.3, } P = 0.010; \text{ versus vascular dementia MD = 1.7, } P < 0.001; \text{ versus other dementias MD = 1.9, } P = 0.005, \text{ adjusted for age and sex.} \]

**Total onset Alzheimer’s disease** had higher MMSE scores than the early onset Alzheimer’s disease group \( (MD = 1.0, P = 0.020) \). There were no other significant group differences in MMSE.

**Amyloid-β1-42**

Figure 1A shows the unadjusted distribution of amyloid-β1-42 across all diagnostic groups. When adjusted for age and sex (Table 2), early onset Alzheimer’s disease and late onset Alzheimer’s disease did not differ significantly from each other or from the mixed Alzheimer’s disease and vascular dementia group, but had significantly lower levels than all other groups. Frontotemporal dementia had significantly higher levels than all other groups. Dementia with Lewy bodies had lower levels than most other non-Alzheimer’s disease groups.

**Total tau**

Figure 1B shows the unadjusted distribution of total tau across all diagnostic groups. When adjusted for age and sex (Table 2), early onset Alzheimer’s disease had the highest levels of total tau, followed by late onset Alzheimer’s disease and mixed Alzheimer’s disease and vascular dementia. Parkinson’s disease dementia and dementia with Lewy bodies had the lowest levels.

**Phosphorylated tau**

Figure 1C shows the unadjusted distribution of phosphorylated tau across all diagnostic groups. As for total tau, in an age- and sex-adjusted analysis (Table 2), the highest levels of phosphorylated tau were found in early onset Alzheimer’s disease, followed by late onset Alzheimer’s disease and mixed Alzheimer’s disease and vascular dementia. Parkinson’s disease dementia and dementia with Lewy bodies had the lowest levels.

**Amyloid-β1-42:phosphorylated tau ratio**

Figure 1D shows the unadjusted distribution of amyloid-β1-42:phosphorylated tau ratio across all diagnostic groups. When adjusting for age and sex (Table 2), early onset Alzheimer’s disease had the significantly highest levels of the amyloid-β1-42:phosphorylated tau ratio, followed by late onset Alzheimer’s disease and mixed Alzheimer’s disease and vascular dementia. Frontotemporal dementia had significantly lower levels than all other groups, except Parkinson’s disease dementia and vascular dementia.
Prevalence of pathologic patterns per diagnosis group

By applying the cut-offs for amyloid-β1-42, total tau and phosphorylated tau (see ‘Materials and methods’ section), we classified all subjects according to presence of biomolecular evidence of Alzheimer’s disease pathology. In the vascular dementia, frontotemporal dementia, dementia with Lewy bodies and Parkinson’s disease dementia groups 83%, 81% and 71%, respectively, had a pathologic amyloid-β1-42 levels, 89%, 89% and 83% had abnormal total tau levels, and 86%, 84% and 75% had abnormal phosphorylated tau levels (Fig. 2). In these groups 83%, 81% and 71%, respectively, had a pathologic amyloid-β1-42:phosphorylated tau ratio.

Disease severity and biomarker levels

We investigated the relationship between CSF biomarkers and disease severity, using MMSE score as a proxy. Figure 3 shows how amyloid-β1-42 (Fig. 3A), total tau (Fig. 3B), phosphorylated tau (Fig. 3C) and the amyloid-β1-42:phosphorylated tau ratio (Fig. 3D) vary with MMSE score. Figure 3 shows how amyloid-β1-42 levels, total tau levels, and phosphorylated tau levels vary with MMSE score in late onset Alzheimer’s disease. As previously mentioned, biomarker levels might have influenced the Alzheimer’s disease diagnosis.

Table 1 Demographics of study population

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Count</th>
<th>Sex</th>
<th>Age at sampling</th>
<th>MMSE</th>
<th>Amyloid-β1-42 (ng/l)</th>
<th>Total tau (ng/l)</th>
<th>Phosphorylated tau (ng/l)</th>
<th>Amyloid-β1-42:phosphorylated tau ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>5676</td>
<td>54.8%</td>
<td>45.2%</td>
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<tr>
<td>Early onset Alzheimer’s disease</td>
<td>383</td>
<td>61.1%</td>
<td>38.9%</td>
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<tr>
<td>Late onset Alzheimer’s disease</td>
<td>2231</td>
<td>63.4%</td>
<td>36.6%</td>
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<tr>
<td>Mixed Alzheimer’s disease</td>
<td>982</td>
<td>53.0%</td>
<td>47.0%</td>
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<tr>
<td>Vascular dementia</td>
<td>759</td>
<td>54.1%</td>
<td>45.9%</td>
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<tr>
<td>Frontotemporal dementia</td>
<td>232</td>
<td>51.7%</td>
<td>48.3%</td>
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<tr>
<td>Dementia with Lewy bodies</td>
<td>206</td>
<td>29.6%</td>
<td>70.4%</td>
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<tr>
<td>Parkinson’s disease dementia</td>
<td>79</td>
<td>29.1%</td>
<td>70.9%</td>
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<tr>
<td>Other</td>
<td>150</td>
<td>46.0%</td>
<td>54.0%</td>
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<tr>
<td>Dementia not otherwise specified</td>
<td>644</td>
<td>50.9%</td>
<td>49.1%</td>
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</tbody>
</table>

All sex differences are significant at P < 0.05 level, except mixed Alzheimer’s disease and vascular dementia versus frontotemporal dementia, dementia not otherwise specified and other. Other versus vascular dementia, dementia not otherwise specified and frontotemporal dementia, Lewy body dementia versus Parkinson’s disease dementia, early onset Alzheimer’s disease versus late onset Alzheimer’s disease and frontotemporal dementia versus dementia not otherwise specified.

All age differences are significant at P < 0.05 except late onset Alzheimer’s disease versus vascular dementia, dementia with Lewy bodies versus dementia not otherwise specified, dementia with Lewy bodies versus Parkinson’s disease dementia and other versus Parkinson’s disease dementia.

SD = standard deviation; Mdn = median.

Abnormal amyloid-β1-42 levels, 89%, 89% and 83% had abnormal total tau levels, and 86%, 84% and 75% had abnormal phosphorylated tau levels (Fig. 2). In these groups 83%, 81% and 71%, respectively, had a pathologic amyloid-β1-42:phosphorylated tau ratio. As previously mentioned, biomarker levels might have influenced the Alzheimer’s disease diagnosis.
**Figure 1 Biomarker distribution for all diagnoses.** Medians marked by red and 95% confidence interval (CI) by yellow lines. Cut-offs for amyloid-$\beta_{1-42}$ (530 ng/L), total tau (350 ng/L) and phosphorylated tau (60 ng/L) used in this study marked by green lines. *P*-values are given in Table 2. (A) CSF amyloid-$\beta_{1-42}$ is low in Alzheimer’s disease and dementia with Lewy bodies. The early onset Alzheimer’s disease, late onset Alzheimer’s disease and mixed Alzheimer’s disease and vascular dementia groups have the lowest levels of amyloid-$\beta_{1-42}$ followed by dementia with Lewy bodies. The frontotemporal dementia group has the highest levels. (B) CSF total tau is high in Alzheimer’s disease. Subjects in the early onset Alzheimer’s disease, late onset Alzheimer’s disease and mixed Alzheimer’s disease and vascular dementia groups have higher levels of total tau than patients with other dementias. (C) CSF phosphorylated tau is high in Alzheimer’s disease. Phosphorylated tau levels are higher in the Alzheimer’s disease groups (early onset Alzheimer’s disease, late onset Alzheimer’s disease and mixed Alzheimer’s disease and vascular dementia) than in other dementias. (D) CSF amyloid-$\beta_{1-42}$:phosphorylated tau ratio is low in Alzheimer’s disease. In early onset Alzheimer’s disease, late onset Alzheimer’s disease and mixed Alzheimer’s disease and vascular dementia amyloid-$\beta_{1-42}$:phosphorylated tau ratios are lower than in all other groups. The frontotemporal dementia group shows the highest levels.

(continued)
(B = 1.21, β = 0.10, R² = 0.02, P < 0.001), Parkinson’s disease dementia (B = 3.46, β = 0.27, R² = 0.08, P = 0.022) and vascular dementia (B = 0.98, β = 0.11, R² = 0.03, P = 0.002). Log(total tau) and log(phosphorylated tau) were associated with MMSE only in late onset Alzheimer’s disease (B = −1.13, β = −0.12, R² = 0.02, P < 0.001; B = −0.57, β = −0.05, R² = 0.01, P = 0.024). The log(amyloid-β₁₋₄₂:phosphorylated tau) ratio was associated with MMSE in frontotemporal dementia (B = 1.34, β = 0.15, R² = 0.06, P = 0.024), late onset Alzheimer’s disease (B = 0.84, β = 0.10, R² = 0.02, P < 0.001) and vascular dementia (B = 0.67, β = 0.09, R² = 0.03, P = 0.012). The B-values in this analysis can be interpreted as the change in MMSE for each one unit increase on a logarithmic scale of the biomarker level. These associations were adjusted for age and sex.

Among the patients with a clinical diagnosis of Alzheimer’s disease, the IWG-2 positive patients, i.e. those
Table 2 ANCOVA analyses of biomarker levels across diagnosis groups, adjusted for age and sex

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Early onset Alzheimer’s disease</th>
<th>Late onset Alzheimer’s disease</th>
<th>Dementia not otherwise specified</th>
<th>Frontotemporal dementia</th>
<th>Dementia with Lewy bodies</th>
<th>Mixed Alzheimer’s disease and vascular dementia</th>
<th>Other</th>
<th>Parkinson’s disease dementia</th>
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<tbody>
<tr>
<td>Amyloid-β₁₋₄₂</td>
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<tr>
<td>Late onset Alzheimer’s disease</td>
<td>0.043 (1.000)</td>
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<tr>
<td>Dementia not otherwise specified</td>
<td>-0.279 (&lt; 0.001)</td>
<td>-0.235 (&lt; 0.001)</td>
<td>-0.231 (&lt; 0.001)</td>
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<tr>
<td>Frontotemporal dementia</td>
<td>-0.510 (&lt; 0.001)</td>
<td>-0.466 (&lt; 0.001)</td>
<td>-0.204 (&lt; 0.001)</td>
<td>0.075 (1.000)</td>
<td>0.306 (&lt; 0.001)</td>
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<tr>
<td>Dementia with Lewy bodies</td>
<td>-0.091 (0.118)</td>
<td>-0.047 (0.208)</td>
<td>0.188 (&lt; 0.001)</td>
<td>0.419 (&lt; 0.001)</td>
<td>0.113 (0.032)</td>
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<tr>
<td>Mixed Alzheimer’s disease and vascular dementia</td>
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<tr>
<td>Other</td>
<td>-0.296 (&lt; 0.001)</td>
<td>-0.253 (&lt; 0.001)</td>
<td>-0.214 (&lt; 0.001)</td>
<td>-0.092 (1.000)</td>
<td>-0.205 (&lt; 0.001)</td>
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<tr>
<td>Parkinson’s disease dementia</td>
<td>-0.320 (&lt; 0.001)</td>
<td>-0.277 (&lt; 0.001)</td>
<td>-0.041 (1.000)</td>
<td>0.190 (0.035)</td>
<td>-0.116 (1.000)</td>
<td>0.229 (&lt; 0.001)</td>
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<td>Vascular dementia</td>
<td>-0.337 (&lt; 0.001)</td>
<td>-0.293 (&lt; 0.001)</td>
<td>-0.214 (&lt; 0.001)</td>
<td>-0.133 (0.004)</td>
<td>-0.246 (&lt; 0.001)</td>
<td>-0.041 (10.000)</td>
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<td>Total tau</td>
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<tr>
<td>Late onset Alzheimer’s disease</td>
<td>0.149 (&lt; 0.001)</td>
<td>0.555 (&lt; 0.001)</td>
<td>0.038 (1.000)</td>
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<tr>
<td>Dementia not otherwise specified</td>
<td>0.704 (&lt; 0.001)</td>
<td>0.593 (&lt; 0.001)</td>
<td>0.214 (&lt; 0.001)</td>
<td>0.176 (0.015)</td>
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<tr>
<td>Frontotemporal dementia</td>
<td>0.742 (&lt; 0.001)</td>
<td>0.676 (&lt; 0.001)</td>
<td>-0.423 (&lt; 0.001)</td>
<td>-0.636 (&lt; 0.001)</td>
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<tr>
<td>Dementia with Lewy bodies</td>
<td>0.918 (&lt; 0.001)</td>
<td>0.132 (&lt; 0.001)</td>
<td>0.088 (0.289)</td>
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<tr>
<td>Mixed Alzheimer’s disease and vascular dementia</td>
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<tr>
<td>Other</td>
<td>0.691 (&lt; 0.001)</td>
<td>0.542 (&lt; 0.001)</td>
<td>-0.013 (1.000)</td>
<td>-0.051 (1.000)</td>
<td>-0.227 (0.002)</td>
<td>0.410 (&lt; 0.001)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parkinson’s disease dementia</td>
<td>0.936 (&lt; 0.001)</td>
<td>0.787 (&lt; 0.001)</td>
<td>0.232 (0.006)</td>
<td>0.194 (0.155)</td>
<td>0.018 (1.000)</td>
<td>0.655 (&lt; 0.001)</td>
<td>0.245 (0.024)</td>
<td></td>
</tr>
<tr>
<td>Vascular dementia</td>
<td>0.845 (&lt; 0.001)</td>
<td>0.696 (&lt; 0.001)</td>
<td>0.141 (&lt; 0.001)</td>
<td>0.103 (0.367)</td>
<td>-0.073 (1.000)</td>
<td>0.564 (&lt; 0.001)</td>
<td>0.154 (0.034)</td>
<td>-0.091 (1.000)</td>
</tr>
<tr>
<td>Phosphorylated tau</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Late onset Alzheimer’s disease</td>
<td>0.120 (&lt; 0.001)</td>
<td>0.485 (&lt; 0.001)</td>
<td>0.088 (0.289)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dementia not otherwise specified</td>
<td>0.606 (&lt; 0.001)</td>
<td>0.573 (&lt; 0.001)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frontotemporal dementia</td>
<td>0.694 (&lt; 0.001)</td>
<td>0.573 (&lt; 0.001)</td>
<td>0.088 (0.289)</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

(continued)
## Table 2 Continued

**Phosphorylated tau**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Early onset Alzheimer's disease</th>
<th>Late onset Alzheimer's disease</th>
<th>Dementia not otherwise specified</th>
<th>Frontotemporal dementia</th>
<th>Dementia with Lewy bodies</th>
<th>Mixed Alzheimer's disease and vascular dementia</th>
<th>Other</th>
<th>Parkinson's disease dementia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dementia with Lewy bodies mixed Alzheimer's disease and vascular dementia</td>
<td>0.725 (&lt;0.001)</td>
<td>0.605 (&lt;0.001)</td>
<td>0.119 (0.016)</td>
<td>0.031 (10.000)</td>
<td>-0.440 (&lt;0.001)</td>
<td>-0.472 (&lt;.001)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>0.627 (&lt;0.001)</td>
<td>0.507 (&lt;0.001)</td>
<td>0.021 (1.000)</td>
<td>-0.066 (1.000)</td>
<td>-0.098 (1.000)</td>
<td>0.374 (&lt;0.001)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parkinson's disease dementia</td>
<td>0.770 (&lt;0.001)</td>
<td>0.650 (&lt;0.001)</td>
<td>0.164 (0.043)</td>
<td>0.076 (1.000)</td>
<td>0.045 (1.000)</td>
<td>0.517 (&lt;0.001)</td>
<td>0.143 (0.608)</td>
<td></td>
</tr>
<tr>
<td>Vascular dementia</td>
<td>0.721 (&lt;0.001)</td>
<td>0.600 (&lt;0.001)</td>
<td>0.115 (&lt;0.001)</td>
<td>0.027 (1.000)</td>
<td>-0.004 (1.000)</td>
<td>0.467 (&lt;0.001)</td>
<td>0.094 (0.558)</td>
<td>-0.049 (1.000)</td>
</tr>
</tbody>
</table>

**Amyloid-β1-42:phosphorylated tau ratio**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Early onset Alzheimer's disease</th>
<th>Late onset Alzheimer's disease</th>
<th>Dementia not otherwise specified</th>
<th>Frontotemporal dementia</th>
<th>Dementia with Lewy bodies</th>
<th>Mixed Alzheimer's disease and vascular dementia</th>
<th>Other</th>
<th>Parkinson's disease dementia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Late onset Alzheimer's disease</td>
<td>-0.167 (0.001)</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dementia not otherwise specified</td>
<td>-0.887 (&lt;0.001)</td>
<td>-0.720 (&lt;0.001)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frontotemporal dementia</td>
<td>-10.204 (&lt;0.001)</td>
<td>-10.037 (&lt;0.001)</td>
<td>-0.317 (&lt;0.001)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dementia with Lewy Bodies</td>
<td>-0.931 (&lt;0.001)</td>
<td>-0.764 (&lt;0.001)</td>
<td>-0.044 (1.000)</td>
<td>0.273 (&lt;0.001)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mixed Alzheimer's disease and vascular dementia</td>
<td>-0.348 (&lt;0.001)</td>
<td>-0.181 (&lt;0.001)</td>
<td>0.540 (&lt;0.001)</td>
<td>0.856 (&lt;0.001)</td>
<td>0.583 (&lt;0.001)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>-0.926 (&lt;0.001)</td>
<td>-0.759 (&lt;0.001)</td>
<td>-0.039 (1.000)</td>
<td>0.278 (0.001)</td>
<td>0.005 (1.000)</td>
<td>-0.578 (&lt;0.001)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parkinson's disease dementia</td>
<td>-10.092 (&lt;0.001)</td>
<td>-0.926 (&lt;0.001)</td>
<td>-0.205 (0.202)</td>
<td>0.111 (1.000)</td>
<td>-0.162 (1.000)</td>
<td>-0.745 (&lt;0.001)</td>
<td>-0.166 (1.000)</td>
<td></td>
</tr>
<tr>
<td>Vascular dementia</td>
<td>-10.060 (&lt;0.001)</td>
<td>-0.893 (&lt;0.001)</td>
<td>-0.173 (&lt;0.001)</td>
<td>0.144 (0.084)</td>
<td>-0.129 (0.310)</td>
<td>-0.712 (&lt;0.001)</td>
<td>-0.134 (0.635)</td>
<td>0.033 (1.000)</td>
</tr>
</tbody>
</table>

Each cell contains adjusted mean difference (columns–rows) for logarithmic biomarker values and P-value for differences. Significant differences in bold.
with an Alzheimer’s disease-like biomarker pattern, had significantly lower MMSE scores ($P < 0.001$) than those who were IWG-2 negative. To exclude that the biomarker-negative Alzheimer’s disease patients, i.e. patients who may have been misdiagnosed with Alzheimer’s disease, were driving the correlations of CSF biomarkers with MMSE, we tested the regression models for late onset Alzheimer’s disease in only the biomarker-positive group. The correlations to MMSE remained significant ($P < 0.01$) for amyloid-$\beta_{1-42}$, total tau, and the amyloid-$\beta_{1-42}$:phosphorylated tau ratio, but not for phosphorylated tau ($P = 0.1$).

**Natural classification**

Cluster analysis identified a division using log(total tau) and log(amyloid-$\beta_{1-42}$:phosphorylated tau) that optimally separated our data into two groups (average silhouette = 0.6). The first cluster ($n = 2851$) contained large proportions (91%) of the vascular dementia, frontotemporal dementia, Parkinson’s disease dementia and dementia with Lewy bodies groups, while Cluster 2 ($n = 2825$) contained the majority of patients with late onset Alzheimer’s disease (73%) and early onset Alzheimer’s disease (75%) (Fig. 4). The patients with late onset Alzheimer’s disease in Cluster 1 were significantly younger ($P = 0.03$), had significantly higher MMSE scores ($P < 0.001$) and had a larger share of males ($P = 0.01$) than the patients with late onset Alzheimer’s in Cluster 2. They also had significantly higher amyloid-$\beta_{1-42}$ ($P < 0.001$), lower total tau ($P < 0.001$) and lower phosphorylated tau levels ($P < 0.001$). The patients with early onset Alzheimer’s disease in the two clusters did not differ significantly in terms of age, MMSE scores and sex ($P = 0.58$, $P = 0.99$, $P = 0.06$, respectively), but the Cluster 2 patients had significantly lower amyloid-$\beta_{1-42}$ ($P < 0.001$), higher total tau ($P < 0.001$) and higher phosphorylated tau levels ($P < 0.001$).

If Cluster 2 is considered the Alzheimer’s disease-like pathology cluster, the cluster analysis result classified 74% in accordance with clinical diagnosis. When applying current reference limits, 76% of the early and late onset Alzheimer’s disease had a biomarker profile in accordance with clinical diagnosis.

**Discussion**

This large study reports CSF biomarkers for Alzheimer’s disease pathology measured in clinical practice at the Sahlgrenska University Hospital neurochemistry laboratory in combination with clinical data from SveDem. As expected, we found the most clear-cut Alzheimer’s disease-like biomarker pattern in patients diagnosed with Alzheimer’s disease. Large proportions of the other groups also had an Alzheimer’s disease-like profile, but this was seen less often in the frontotemporal dementia group. CSF amyloid-$\beta_{1-42}$, total tau, phosphorylated tau and the amyloid-$\beta_{1-42}$:phosphorylated tau ratio all correlated with disease severity in Alzheimer’s disease, and low CSF amyloid-$\beta_{1-42}$, but not high CSF total tau or
phosphorylated tau, correlated with poor cognitive performance in Parkinson’s disease dementia and vascular dementia. A low amyloid-β_{1-42}:phosphorylated tau ratio also correlated with low MMSE performance in frontotemporal dementia and vascular dementia. Using cluster analysis, we identified a natural division of all our subjects into two groups, where one group included most Alzheimer’s disease (late onset Alzheimer’s disease, early onset Alzheimer’s disease and mixed Alzheimer’s disease and vascular dementia) patients (70%), and the other contained most non-Alzheimer’s disease patients (86%).

As the CSF biomarkers were analysed in clinical practice they were expected to have influenced the diagnosis of Alzheimer’s disease, and it was therefore not surprising to find high levels of total tau and phosphorylated tau, and low levels of amyloid-β_{1-42} and amyloid-β_{1-42}:phosphorylated tau ratios in subjects with a clinical Alzheimer’s disease diagnosis. Patients with Alzheimer’s disease also had the largest share of patients with pathologic amyloid-β_{1-42}, total tau and phosphorylated tau levels of all the diagnosis groups in this study. The risk of circular reasoning precludes firm conclusions from these findings. In the other diagnostic groups (where the specific diagnoses are less likely to have been influenced by the CSF biomarkers), high levels of total tau and phosphorylated tau, and low levels of amyloid-β_{1-42} and the amyloid-β_{1-42}:phosphorylated tau ratio were seen in a proportion of subjects, suggesting concomitant Alzheimer’s disease pathology. Frontotemporal dementia had the lowest levels of total tau and phosphorylated tau, and the highest levels of amyloid-β_{1-42}, which is in concordance with the lack of cerebral β-amyloidosis in this disease and suggests that only few patients with frontotemporal dementia had Alzheimer’s disease pathology (Cairns et al., 2007; Galimberti and

Figure 3 Biomarkers and MMSE scores in Alzheimer’s disease (late onset Alzheimer’s disease, early onset Alzheimer’s disease and mixed Alzheimer’s disease and vascular dementia). Plot markers are binned according to legend for visual clarity. Trend lines were computed using linear regression. (A) Amyloid-β_{1-42} levels in CSF decrease with low MMSE scores (B = 3.15). (B) Total tau increase with lower MMSE scores (B = −8.22). (C) Phosphorylated tau levels increase with lower MMSE scores (B = −0.42). (D) Amyloid-β_{1-42}:phosphorylated tau ratios decrease with lower MMSE scores (B = 0.05).
A recent study showed that patients fulfilling clinical criteria for behavioural variant FTD in fact had evidence of Alzheimer’s disease pathology at post-mortem examination, possibly indicating that the share of patients with a more Alzheimer’s disease-like biomarker pattern amongst the frontotemporal dementia patients in this study could be misdiagnosed Alzheimer’s disease patients (Mendez et al., 2013). In agreement with previous studies (Sjogren et al., 2000), frontotemporal dementia patients also had the highest percentage of subjects with no pathologic levels of any of the tested biomarkers. It is unknown why CSF tau markers are relatively unaltered in frontotemporal dementia, in which a significant proportion of patients have tauopathies. However, the correlation between CSF phosphorylated tau and tau tangles has been weak in several studies with autopsy confirmation, even in Alzheimer’s disease (Buerger et al., 2006; Engelborghs et al., 2007). One possibility is that the tau pathology seen in frontotemporal dementia may be reflected by other tau fragments in CSF that escape the current ELISA method, which is based on three monoclonal antibodies directed against the mid-region of tau (Blennow et al., 1995). Tau is present in CSF as several different N-terminal and mid-domain fragments (Meredith et al., 2013), and it is possible that specific tau isoforms are increased in CSF in non-Alzheimer’s disease tauopathies. Another possibility is that increased CSF tau levels are related to specific patterns or mechanisms of neurodegeneration. In some previous CSF biomarker studies, frontotemporal dementia has shown slightly elevated CSF levels of tau as compared to neurologically healthy controls, but with phosphorylated tau at normal levels, while other studies have shown normal levels of all mentioned biomarkers (Sjogren et al., 2000; Hampel et al., 2004; Bian and Grossman, 2007; van Harten et al., 2011; Irwin et al., 2013). Importantly, frontotemporal dementia is a heterogenic condition with varying underlying neuropathology (including tau tangle pathology, ubiquitin/TDP-43 pathology, and different patterns of brain atrophy), clinical presentation (including behavioural variant, semantic dementia, and progressive non-fluent aphasia), and different CSF biomarker patterns (often dominated by increased CSF neurofilament light protein) (Riemenschneider et al., 2002; Kapaki et al., 2008; Irwin et al., 2013; Scherling et al., 2014).

Figure 4 Cluster analysis reveals a separation into one Alzheimer’s disease-dominated cluster (Cluster 2) and one cluster dominated by other dementias (Cluster 1). Each segment is labelled with subject count in absolute numbers.

The α-synucleinopathies Parkinson’s disease dementia and dementia with Lewy bodies are clinically similar but have been shown to differ in biomarker pattern in a previous study (Kaerst et al., 2014). In comparison to dementia with Lewy bodies, Parkinson’s disease dementia showed more normal levels of all biomarkers represented in this study. In dementia with Lewy bodies, amyloid-β1-42 levels were markedly decreased, with 71% of the subjects at pathologic amyloid-β1-42 levels, reflecting the common occurrence of cerebral β-amyloidosis in this condition. Total tau levels were increased in a relatively small proportion of subjects with dementia with Lewy bodies (28%), and might in these cases reflect general neurodegeneration, comorbidity with Alzheimer’s disease pathology or clinical misdiagnosis (Kasuga et al., 2010; Kaerst et al., 2014). For Parkinson’s disease dementia, 53% had pathologic amyloid-β1-42 levels potentially indicating mixed pathology or misdiagnosis. However, there were no significant differences in biomarker levels between the dementia with Lewy bodies and Parkinson’s disease dementia groups.

Vascular dementia is often seen together with Alzheimer’s disease in mixed dementia, a condition that is often difficult
to discriminate from its constituent parts (Engelborghs, 2013). We found lower levels of total tau and phosphorylated tau, and higher amyloid-$\beta_{1-42}$ and amyloid-$\beta_{1-42}$:phosphorylated tau ratios in vascular dementia than in Alzheimer’s disease, corroborating earlier studies and the potential of these biomarkers as distinguishing factors between Alzheimer’s disease and vascular dementia (de Jong et al., 2006; Tang et al., 2014). However, 56% of the subjects with vascular dementia had reduced amyloid-$\beta_{1-42}$ levels. One interpretation of this finding is that concomitant cerebellar $\beta$-amyloidosis is common in clinically diagnosed vascular dementia cases (Zekry et al., 2002). The biomarker pattern of the mixed Alzheimer’s disease and vascular dementia group more closely resembled that of the patients with Alzheimer’s disease in this study, with low amyloid-$\beta_{1-42}$, and high total tau and phosphorylated tau, although all of these biomarkers were at intermediate levels between Alzheimer’s disease and vascular dementia. In cluster analysis most mixed Alzheimer’s disease and vascular dementia subjects grouped with early onset Alzheimer’s disease and late onset Alzheimer’s disease, suggesting significant Alzheimer’s disease pathology in this group.

We further tested how CSF amyloid-$\beta_{1-42}$, total tau, phosphorylated tau and the amyloid-$\beta_{1-42}$:phosphorylated tau ratio were associated with disease severity, as measured by MMSE, an area in which conclusive data have been missing so far (McGhee et al., 2014). We found several significant correlations in our material, but it should be noted that all were very weak. In late onset Alzheimer’s disease, all tested biomarkers individually correlated with MMSE. This association was not driven by biomarker-negative, potentially misclassified Alzheimer’s disease patients as it remained when also examining biomarker-positive Alzheimer’s disease patients only.

The finding that the CSF amyloid-$\beta_{1-42}$ correlation with MMSE score was of the same magnitude as for the tau markers in this group, who were all in the clinical phase of Alzheimer’s disease, contradicts previously suggested models of biomarker development in Alzheimer’s pathology where the amyloid load remains stable during the clinical phase of Alzheimer’s disease (Jack et al., 2013), and also previous studies where tau markers have been more correlated with cognitive measures that amyloid-$\beta_{1-42}$ (Stefani et al., 2006; van der Vlies et al., 2009). In the other diagnostic groups, significant correlations between MMSE score and biomarker levels in CSF were rare. This could in part be attributed to a lower number of study subjects, the analysed biomarkers’ specific link to Alzheimer’s disease pathology, and the design of the MMSE test, mainly reflecting Alzheimer’s disease symptoms (Mathuranath et al., 2000; Prieto et al., 2011). Another explanation could be that the high number of included subjects made even a weak correlation significant in late onset Alzheimer’s disease, which would also explain the lack of correlations in early onset Alzheimer’s disease. Of note, subjects in the Parkinson’s disease dementia group showed a weak indication of lower amyloid-$\beta_{1-42}$ levels with decreasing MMSE score, corroborating previous studies linking Parkinson’s disease dementia to amyloid-\(\beta\) plaque pathology (Alves et al., 2014; Compta et al., 2014). In the vascular dementia group both amyloid-$\beta_{1-42}$ and the amyloid-$\beta_{1-42}$:phosphorylated tau ratio were abnormal, confirming previous studies where vascular dementia has been shown to exhibit, like Alzheimer’s disease, increased levels of total tau and decreased levels of amyloid-$\beta_{1-42}$ but normal levels of phosphorylated tau (Kærst et al., 2013). Amyloid-$\beta_{1-42}$ and the amyloid-$\beta_{1-42}$:phosphorylated tau ratio also correlated with cognitive deficiency in vascular dementia. For frontotemporal dementia, the amyloid-$\beta_{1-42}$:phosphorylated tau ratio weakly but significantly correlated with MMSE. This result is somewhat difficult to interpret as MMSE score is not a reliable measure of disease progression in frontotemporal dementia (Mathuranath et al., 2000; Prieto et al., 2011), and that the amyloid pathology is thought to be minimal in frontotemporal dementia (Galimberti and Scarpini, 2010). These correlations may stem from cases where frontotemporal dementia was mixed with Alzheimer’s disease, or where Alzheimer’s disease was misdiagnosed as frontotemporal dementia. In previous studies, mixed frontotemporal dementia and Alzheimer’s disease pathology has been shown to be present in a significant number of cases (Toledo et al., 2012, 2013). Further, frontal variant Alzheimer’s disease could be mistaken for frontotemporal dementia as it presents with personality change and executive dysfunction similar to that seen in behavioural variant frontotemporal dementia (Blennervassett et al., 2014).

Disregarding clinical diagnoses, we identified a natural division of subjects using a cluster-based analysis of the biomarker data in the entire data set. The division into two groups using the amyloid-$\beta_{1-42}$:phosphorylated tau ratio and total tau yielded two clusters of patients with one group displaying evidence of Alzheimer’s disease-like pathology with high total tau levels in combination with low amyloid-$\beta_{1-42}$:phosphorylated tau ratios, and another group of subjects with relatively low total tau levels and high amyloid-$\beta_{1-42}$:phosphorylated tau ratios. The clinical diagnoses applied to the subjects in these groups largely complied with these patterns, with the majority of patients with early onset Alzheimer’s disease (75%) and late onset Alzheimer’s disease (73%) assigned to the Alzheimer’s disease-like cluster and the vascular dementia (91%), frontotemporal dementia (94%), Parkinson’s disease dementia (94%) and dementia with Lewy bodies (87%) to the other cluster. The mixed Alzheimer’s disease and vascular dementia group also mainly expressed an Alzheimer’s disease-like pattern (61%), while the dementia not otherwise specified subjects did not (23%). The presence of subjects without clear biomarker signs of Alzheimer’s disease-like pathological processes who still received an Alzheimer’s disease diagnosis could indicate that they received their diagnosis relatively early in the disease process, where the biomarker profile is not yet as distinguished. The facts that they were younger and had higher MMSE scores...
support this notion. Patients with Alzheimer’s disease in Cluster 1 also had more pathological levels of all biomarkers measured here, potentially suggesting that current clinical reference limits need to be adjusted. This has also been suggested in previous studies (Palmqvist et al., 2014; Zwan et al., 2014). However, the cluster analysis did not perform better than current cut-points in distinguishing patients with Alzheimer’s disease according to clinical diagnosis, which speaks against changing them. Another explanation for the lack of biomarker evidence in a share of patients with a clinical diagnosis of Alzheimer’s disease could be that there is an overdiagnosis of the disease, but such a statement would need to be confirmed by histopathological evaluation.

Strengths and limitations

The main strengths of this study are the very large number of included study subjects from a broad referral base, and the wide spread of dementia diagnoses. This study had several limitations, the main one being that the CSF measurements were performed in clinical practice, and might have influenced the clinical diagnostic process, introducing a risk of circular reasoning. Although biomarkers are not yet part of the diagnostic criteria for any of the disease entities studied here, they may influence the diagnostic thinking. These biomarkers are mainly used to identify Alzheimer’s disease-like pathology, by gathering support for an Alzheimer’s disease diagnosis, or by ruling in or out Alzheimer’s disease as a differential diagnosis. The risk of circular reasoning in this study must thus be taken into account in the interpretation of the analyses that include Alzheimer’s disease subjects. However, as discussed earlier, when comparing non-Alzheimer’s disease groups to each other, the risk of circular reasoning is much less evident as the biomarkers investigated here are not generally used to differentiate between non-Alzheimer’s disease diagnoses. A limitation in the analysis of biomarker levels in correlation to disease severity was that the MMSE test is designed to mainly focus on cognitive abilities linked to hippocampal function, and is not an ideal test for severity in frontotemporal dementia, dementia with Lewy bodies and Parkinson’s disease dementia (Hodges et al., 1999; Mathuranath et al., 2000; Palmqvist et al., 2009; Prieto et al., 2011). We did not have access to any other neuropsychological assessment of the study participants. The lack of detailed clinical information in our data set is also a limitation, as is the lack of post-mortem histopathological confirmation of the diagnoses, although both are mitigated to some extent by the size of the study population.

The results in this study should be interpreted with caution as samples for all participants in this study were analysed in one central laboratory with expert knowledge on these types of measurements and high sample throughput (Mattsson et al., 2013), reducing obstacles such as issues with standardization across labs and other potentially confounding analytical factors. It has been shown that there is a large variability in measurements of the core Alzheimer’s disease biomarkers between clinical centres and laboratories (Mattsson et al., 2011, 2013), but progress is currently being made in the quest to overcome these issues, by implementing reference measurement procedures for amyloid-β1-42, total tau and phosphorylated tau in CSF, unified detailed pre-analytical and analytical protocols, as well as external quality control programs (Carrillo et al., 2013; Mattsson et al., 2013; Korecka et al., 2014; Leinenbach et al., 2014).

Conclusion

Comparing several different dementias, subjects with frontotemporal dementia had a CSF biomarker profile most distinct from Alzheimer’s disease. CSF levels of amyloid-β1-42, total tau, phosphorylated tau and the amyloid-β1-42:phosphorylated tau ratio all correlated weakly with disease severity in Alzheimer’s disease, as approximated by MMSE score, as did low amyloid-β1-42 in several non-Alzheimer’s disease groups. We also found CSF biomarker evidence of Alzheimer’s disease-like pathological processes in a considerable proportion of subjects without an Alzheimer’s disease diagnosis. This study demonstrates the feasibility of applying CSF biomarker studies to very large populations, and demonstrates the potential clinical utility of CSF biomarkers to differentiate between dementias. Further studies with determined clinical phenotypes and neuropathology are required to confirm these findings.

Acknowledgements

The authors are grateful to SveDem (www.svedem.se) for providing data for this study and to all participants in SveDem (patients, caregivers and staff).

Funding

This study was supported financially by the Knut and Alice Wallenberg Foundation, the Swedish Brain Power network, the Swedish association of local authorities and regions, the Stockholm County Council, the Swedish Research Council, the Swedish Society of Medicine, the EU Joint Programme – Neurodegenerative Disease Research (BIOMARKAPD) the Alzheimer Foundation, the Gothenburg Medical Society, the NIHR UCL/H Biomedical Research Centre and Queen Square Dementia BRU, the Wolfson Foundation, ARUK, the Torsten Söderberg Foundation and the Innovative Medicines Initiative Joint Undertaking under EMIF grant agreement nº 115372, resources of which are composed of financial contribution from the European Union’s Seventh Framework Programme (FP7/2007-2013) and EFPIA companies’ in kind contribution.
Supplementary material

Supplementary material is available at Brain online.

References


