Cerebrospinal fluid markers for differential dementia diagnosis in a large memory clinic cohort

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ABSTRACT

Objective: To determine how amyloid β 42 (Aβ42), total tau (t-tau), and phosphorylated tau (p-tau) levels in CSF behave in a large cohort of patients with different types of dementia.

Methods: Baseline CSF was collected from 512 patients with Alzheimer disease (AD) and 272 patients with other types of dementia (OD), 135 patients with a psychiatric disorder (PSY), and 275 patients with subjective memory complaints (SMC). Aβ42, t-tau, and p-tau (at amino acid 181) were measured in CSF by ELISA. Autopsy was obtained in a subgroup of 17 patients.

Results: A correct classification of patients with AD (92%) and patients with OD (66%) was accomplished when CSF Aβ42 and p-tau were combined. Patients with progressive supranuclear palsy had normal CSF biomarker values in 90%. Patients with Creutzfeldt-Jakob disease demonstrated an extremely high CSF t-tau at a relatively normal CSF p-tau. CSF AD biomarker profile was seen in 47% of patients with dementia with Lewy bodies (DLB), 38% in corticobasal degeneration (CBD), and almost 30% in frontotemporal lobar degeneration (FTLD) and vascular dementia (VaD). PSY and SMC patients had normal CSF biomarkers in 91% and 88%. Older patients are more likely to have a CSF AD profile. Concordance between clinical and neuropathologic diagnosis was 85%. CSF markers reflected neuropathology in 94%.

Conclusion: CSF Aβ42, t-tau, and p-tau are useful in differential dementia diagnosis. However, in DLB, FTLD, VaD, and CBD, a substantial group exhibit a CSF AD biomarker profile, which requires more autopsy confirmation in the future. ***Neurology*® 2012;78:47–54**

GLOSSARY

Aβ42 = amyloid β 42; **AD** = Alzheimer disease; **BNE** = BrainNet Europe; **CBD** = corticobasal degeneration; **CI** = confidence interval; **CJD** = Creutzfeldt-Jakob disease; **DLB** = dementia with Lewy bodies; **FTLD** = frontotemporal lobar degeneration; **IQR** = interquartile range; **MMSE** = Mini-Mental State Examination; **NINDS** = National Institute of Neurological Disorders and Stroke; **OD** = other types of dementia; **OR** = odds ratio; **p-tau** = phosphorylated tau; **PSP** = progressive supranuclear palsy; **PSY** = psychiatric disorder; **SMC** = subjective memory complaints; **t-tau** = total tau; **VaD** = vascular dementia.

Differential dementia diagnosis is based on clinical criteria and ancillary investigations may provide positive evidence for a specific, nosologic diagnosis. Measurements of biochemical markers in CSF are increasingly used in the diagnostic process of dementia. The sensitivity when using the combination of CSF Aβ42 and total tau (t-tau) for recognition of Alzheimer disease (AD) is high.[1] However, specificity is suboptimal concerning patients with subjective memory complaints (SMC)[2] and other types of dementia.[3,4]

There are several potential explanations for the finding of abnormal markers in patients with other types of dementia. Clinical misdiagnosis or mixed pathology—which is a common finding at autopsy[4]—may explain positive markers. Alternatively, amyloid β and (phosphorylated) tau play also a role in the pathogenesis of other types of dementias. Tau pathology is as well seen in frontotemporal lobar degeneration (FTLD), progressive supranuclear palsy (PSP), corticobasal degeneration (CBD),[5] and prion diseases.[6] Amyloid deposition or disturbance in amyloid metabolism is found in a few patients with FTLD.[7]

CME

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The aim of the present study is to investigate how CSF Aβ42, t-tau, and phosphorylated tau (p-tau) levels behave in a large sample of patients, recruited consecutively at our memory clinic. First, CSF biomarker levels are compared between patients with different types of dementia, patients with subjective memory complaints, and patients with psychiatric disorders. Second, we aim to identify the optimal combination of CSF biomarkers for the discrimination of AD from other types of dementias. For the verification of the clinical diagnosis, we use postmortem diagnosis obtained by autopsy in a subgroup of patients.

METHODS

Patients. Between October 1999 and November 2009, baseline CSF was collected from 1,672 patients from our outpatient memory clinic. CSF was obtained at a median of 2 months (interquartile range [IQR] 1–5 months) after diagnosis. From these 1,672 patients, 1,194 patients were selected: 512 patients with probable AD, 144 patients with FTLD (including patients with behavioral type frontotemporal dementia, semantic dementia, and progressive nonfluent aphasia), 52 patients with dementia with Lewy bodies (DLB), 34 patients with vascular dementia (VaD), 16 patients with CBD, 20 patients with progressive supranuclear palsy (PSP), 6 patients with Creutzfeldt-Jakob disease (CJD), 135 patients with a psychiatric disorder (PSY), and 275 patients with SMC. Patients with mild cognitive impairment (n = 230), patients with possible AD (n = 16), patients with a wide range of other neurologic diseases but no dementia (n = 73), and patients with other unclassified types of dementia (n = 21) were not included, nor were patients whose diagnosis was postponed or unclear (n = 138). All patients underwent a standardized dementia assessment including medical history, informant-based history, physical and neurologic examination, laboratory tests, neuropsychological testing, EEG, and MRI of the brain. Diagnosis was made by consensus in a multidisciplinary meeting, without knowledge of CSF results, and according to clinical diagnostic criteria: National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association criteria for AD,[8] consensus criteria frontotemporal lobar degeneration for FTLD,[9] McKeith criteria for DLB,[10] National Institute of Neurological Disorders and Stroke (NINDS)–Association Internationale pour la Recherche en l'Enseignement en Neurosciences for VaD,[11] CBD according to criteria of Boeve,[12] PSP according to the NINDS–Society for Progressive Supranuclear Palsy criteria,[13] and CJD according to recent criteria.[14] Patients were defined as having a psychiatric disorder (PSY) when based on thorough investigation a neurodegenerative disease seemed unlikely, and clinically there was a suspicion of a psychiatric disorder. Those patients were subsequently referred to a psychiatrist. When clinical investigations yielded normal results (i.e., criteria for MCI not fulfilled), patients were considered to have SMC. Patients with SMC were considered as controls based on normal clinical investigations. Dementia severity was assessed using the Mini-Mental State Examination (MMSE).[15]

Standard protocol approvals, registrations, and patient consents. The study was approved by the ethical review board of the VU University Medical Center. Written informed consent was obtained from all subjects participating in the study.

CSF analysis. CSF was obtained by lumbar puncture between the L3/L4 or L4/L5 intervertebral space, using a 25-gauge needle, and collected in 10-mL polypropylene tubes. Within 2 hours, CSF samples were centrifuged at 2,100 g for 10 minutes at 4°C. A small amount of CSF was used for routine analysis. Aliquots of each sample were immediately frozen at −80°C until further analysis. CSF Aβ42, t-tau, and p-tau phosphorylated at threonine 181 concentrations were determined using commercially available sandwich ELISAs (Innogenetics, Ghent, Belgium).[1] The performance of the assays was monitored with pools of surplus CSF specimens available from an earlier study. Multiple specimens with various concentrations included in 7–18 runs were used for this purpose. The interassay coefficient of variation (mean ± SD) was 11.3 ± 4.9% for Aβ42, 9.3 ± 1.5% for t-tau, and 9.4 ± 2.5% for p-tau-181.[16] The 3 biomarkers were simultaneously analyzed in every CSF sample. CSF Aβ42 data are missing in 4 cases, t-tau data in 13 cases, and p-tau-181 data in 6 cases.

Autopsy. In the 10-year period of CSF sampling, 17 patients underwent autopsy. The neuropathologic diagnosis from these patients was compared to the clinical diagnosis and to the antemortem CSF biomarker profile. For AD, the criteria of Braak were used modified for thin sections[17] and vascular amyloid β deposits were assessed according to BrainNet Europe (BNE) instructions.[18] For FTLD, the Cairns classification was used.[19] For DLB, the Braak criteria were used[20] modified according to the BNE instructions.[21] VaD was classified according to Kalaria et al.,[22] CJD according to Cali et al.,[23] and PSP according to Litvan et al.[24] The neuropathologist was unaware of the CSF biomarker results.

Statistical analysis. For statistical analysis, SPSS, version 16.0, was used. As all variables, except for age, were not normally distributed, nonparametric analyses (Kruskal-Wallis followed by the Mann-Whitney *U* test) were used to compare groups. Post hoc, the different groups were compared with AD and SMC only. For categorical data, we used the χ^2 test. Correlations are estimated with the Spearman method. Patients with CJD were omitted from the statistical analyses when comparing groups, because of their small number. Logistic regression analysis with backward stepwise selection was used to estimate the simultaneous impact of the continuous variables CSF Aβ42, t-tau, and p-tau on the diagnosis AD compared to controls and compared to the pooled groups of other types of dementia. SMC and PSY are pooled as controls, based on the comparability of their biomarker results. Patients with other types of dementia are collectively defined other dementias (OD). An optimal cutoff line was calculated comparing AD vs OD. Based on the cutoff line the percentage of patients with a CSF AD profile was calculated. Age, MMSE, and disease severity were compared between patients with and without a CSF AD profile. Statistical significance was set at $p < 0.05$.

RESULTS

Patients. Baseline characteristics are shown in table 1. Age differed among groups, with patients with VaD, DLB, and AD being oldest, and PSY, SMC, and CBD being youngest. There are also sex differences among groups, with an overrepresentation of men in DLB and VaD.

Table 1 Clinical and biomarker data by diagnostic group[a]

	Age, y	Female	MMSE	Duration, y	Aβ42, pg/mL	Tau, pg/mL	p-tau, pg/mL
AD (n = 512)	67 (60–74)[b]	264 (52)	21 (18–24)[b]	3 (2–4)	447 (365–535)[b]	604 (419–860)[b]	83 (63–112)[b]
FTLD (n = 144)	62 (58–68)[b,c]	57 (40)[c]	26 (22–28)[b,c]	3 (2–5)[b]	741 (500–959)[b,c]	350 (250–496)[b,c]	47 (36–63)[c]
DLB (n = 52)	69 (63–78)[b,c]	12 (23)[b,c]	23 (19–26)[b,c]	3 (2–4)	638 (467–790)[b,c]	305 (222–510)[b,c]	52 (40–69)[b,c]
VaD (n = 34)	69 (61–77)[b]	9 (27)[b,c]	23 (19–27)[b]	2 (2–3)	627 (432–862)[b,c]	238 (166–430)[c]	35 (27–56)[b,c]
CBD (n = 16)	59 (55–73)	6 (38)	25 (21–27)[b,c]	2 (1–4)	681 (435–998)[c]	262 (226–352)[c]	50 (35–69)[c]
PSP (n = 20)	68 (65–75)[b]	15 (75)[b,c]	26 (21–28)[b,c]	3 (2–4)	767 (563–963)[c]	203 (167–407)[c]	36 (27–47)[c]
CJD (n = 6)[d]	61 (52–66)	5 (83)	17 (14–20)	1 (0.4–1)	755 (705–886)	2,060 (1,884–4,920)	54 (40–102)
PSY (n = 135)	57 (51–63)[b,c]	62 (46)	28 (27–29)[b,c]	3 (2–5)[b,c]	906 (756–1,041)[c]	213 (167–310)[c]	41 (33–58)[c]
SMC (n = 275)	59 (52–66)[c]	124 (45)	29 (28–30)[c]	2 (1–4)	863 (691–1,045)	245 (179–318)	45 (36–57)

Abbreviations: Aβ42 = amyloid β 42; AD = Alzheimer disease; CBD = corticobasal degeneration; CJD = Creutzfeldt-Jakob disease; DLB = dementia with Lewy bodies; FTLD = frontotemporal lobar degeneration; MMSE = Mini-Mental State Examination; PSP = progressive supranuclear palsy; PSY = psychiatric disorder; p-tau = phosphorylated tau; SMC = subjective memory complaints; VaD = vascular dementia.

[a] Data are expressed as median (interquartile range) or n (%). Statistical analyses were performed using Kruskal-Wallis followed by Mann-Whitney *U* tests and χ^2 tests. Post hoc, all groups were compared to AD and SMC.

[b] $p < 0.05$ compared to SMC.

[c] $p < 0.05$ compared to AD.

[d] Statistics were not performed on the small group of patients with CJD.

CSF analysis. ***CSF levels of Aβ42, t-tau, and p-tau.*** Median CSF levels of the 3 biomarkers by diagnostic group are shown in table 1. Table 2 summarizes the behavior of the CSF biomarkers in each diagnostic group as compared to SMC. In FTLD, (moderately) decreased levels of CSF Aβ42 and (moderately) increased levels of CSF t-tau are found compared to SMC subjects, while CSF p-tau levels were normal. In DLB, CSF levels of Aβ42 are slightly decreased and CSF t-tau and p-tau levels are increased. In VaD, CSF Aβ42 is decreased but CSF t-tau and p-tau are normal. In CBD there is a trend toward a decreased CSF Aβ42 ($p = 0.06$) at a normal CSF t-tau and p-tau (although the latter with remarkable overlap). Patients with CJD exhibit an extremely high CSF t-tau, while CSF p-tau is relatively less elevated and CSF Aβ42 levels are normal. In PSP and PSY, CSF levels of Aβ42, t-tau, and p-tau are comparable to SMC subjects.

Table 2 Summary of CSF biomarkers by diagnostic group as compared to patients with SMC[a]

	Aβ42	Tau	p-tau
SMC	Ref	Ref	Ref
AD	↓↓	↑↑	↑↑
FTLD	↓	↑	=
DLB	↓	↑	↑
VAD	↓	=	=
CBD	↓	=	=
CJD	=	↑↑↑	↑
PSP	=	=	=
PSY	=	=	=

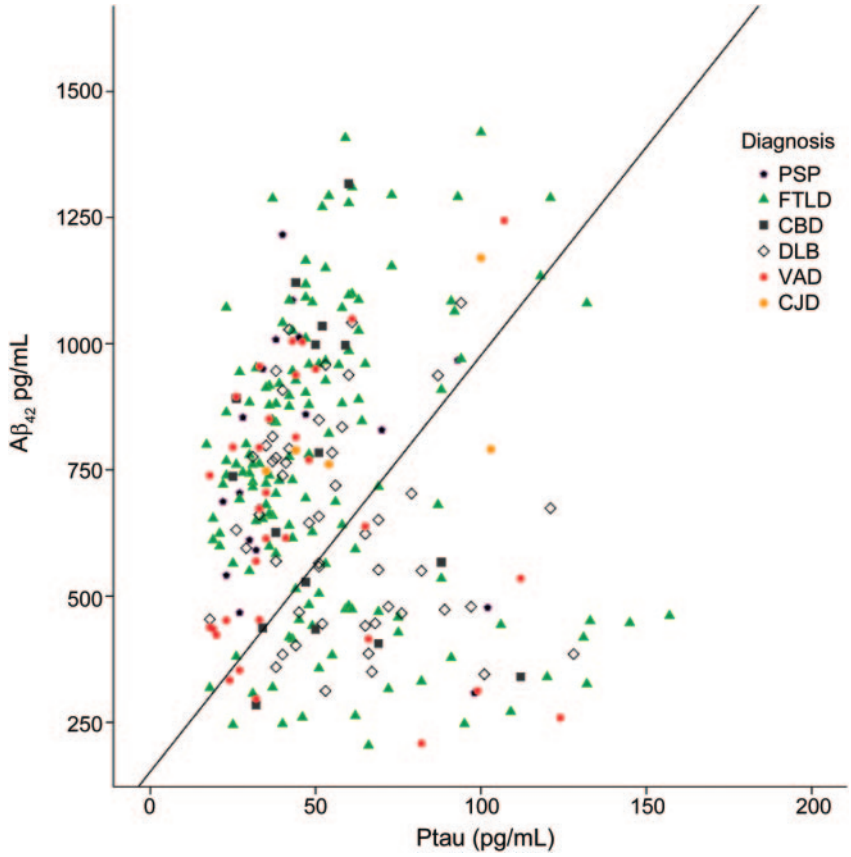
Abbreviations: Aβ42 = amyloid β 42; AD = Alzheimer disease; CBD = corticobasal degeneration; CJD = Creutzfeldt-Jakob disease; DLB = dementia with Lewy bodies; FTLD = frontotemporal lobar degeneration; p-tau = phosphorylated tau; PSP = progressive supranuclear palsy; PSY = psychiatric disorder; SMC = subjective memory complaints; VaD = vascular dementia.

[a] ↓↓, Strongly decreased, compared to SMC and patients with other types of dementia (OD); ↑↑, strongly increased, compared to SMC and OD; ↓, decreased compared to SMC; ↑, increased compared to SMC; =, comparable with SMC; ↑↑↑, extremely increased, compared to all other groups.

CSF biomarkers, age, and dementia severity. In patients with FTLD, DLB, VaD, PSY, and SMC, CSF tau and p-tau levels are higher in older patients (CSF t-tau; FTLD: $r = 0.34$, DLB: $r = 0.43$, VaD: $r = 0.42$, PSY: $r = 0.36$, SMC: $r = 0.40$, all $p < 0.05$; CSF p-tau; FTLD: $r = 0.40$, DLB: $r = 0.36$, VaD: $r = 0.50$, PSY: $r = 0.32$, SMC: $r = 0.36$, all $p < 0.05$). In DLB and SMC CSF Aβ42 is lower in older patients (DLB: $r = -0.37$; SMC: $r = -0.19$, $p < 0.05$). Furthermore, lower MMSE is associated with lower CSF Aβ42 levels in AD, FTLD, DLB, with a trend in CBD (AD: $r = 0.12$, FTLD: $r = 0.21$, DLB: $r = 0.37$ [all $p < 0.05$]; CBD: $r = 0.41$, $p = 0.10$).

Combination of biomarkers. Logistic regression analysis with diagnosis AD vs controls (SMC + PSY) as dependent variable and CSF Aβ42, t-tau, and p-tau as independent variables result in correct classification of 465 out of 508 patients with AD (92%) and 355 out of 405 controls (88%), with an overall correct percentage of 90%, using a combination of CSF Aβ42 (odds ratio [OR] = 0.994; 95% confidence interval [CI] = 0.993–0.995) and t-tau (OR = 1.006; 95% CI = 1.005–1.007). In this model CSF p-tau does not contribute significantly to the dis-

Figure Scatterplot of CSF amyloid β 42 (Aβ42) and phosphorylated tau (p-tau) in other dementias



The equation of the line for optimal separation is Aβ42 = 152 + 8.25 × p-tau (obtained from logistic regression analysis comparing Alzheimer disease with the pooled group of other dementias). CBD = corticobasal degeneration; CJD = Creutzfeldt-Jakob disease; DLB = dementia with Lewy bodies; FTLD = frontotemporal lobar degeneration; PSP = progressive supranuclear palsy; VAD = vascular dementia.

crimination of patients with AD from controls. Logistic regression analysis with AD vs OD results in correct classification of 171 out of 259 patients with OD (66%), with an overall correct classification of 83%, using CSF Aβ42 (OR = 0.996; 95% CI = 0.995–0.997) and CSF p-tau (OR = 1.033; 95% CI = 1.026–1.041); i.e., 66% of the patients with OD have normal CSF Aβ42 and normal p-tau levels. In this model CSF t-tau does not contribute significantly to the differentiation of AD from OD. In the figure, CSF Aβ42 and p-tau are plotted for AD vs OD with the cutoff line Aβ42 = 152 + 8.25 × p-tau for optimal separation (based on the results of the logistic regression analysis). In table 3 the percentages of patients with a CSF AD profile—defined as a score below 1, calculated with the formula Aβ42/152 + 8.25 × p-tau—are shown for each diagnostic group. FTLD, DLB, VaD, SMC, and PSY subjects with a CSF AD profile are older and have a lower MMSE in FTLD, DLB, and AD than patients with a non-AD (or normal) CSF AD profile. In AD, this is reverse: younger patients are more likely to have a CSF AD profile. There is no difference in disease severity between the groups.

Autopsy. In table 4, patients who went to autopsy are shown, including the clinical diagnosis, antemortem CSF biomarker levels, and neuropathologic diagnosis obtained at autopsy. In 15 out of 17 (85%) patients, clinical diagnosis corresponded with the neuropathologic diagnosis. The CSF–neuropathologic concordance is comparable: the CSF biomarker profile correctly classifies during life 15 out of 17 patients (85%) as AD or non-AD. This is even higher (16 out of 17, 94%) if additional AD pathology is taken into account. Patient 17 has a clinical diagnosis of CBD, while the neuropathologic diagnosis reveals PSP with Braak stage 3b. The CSF profile exhibits a high CSF p-tau (88 pg/mL) and t-tau (604 pg/mL), at a borderline CSF Aβ42 (567 pg/mL). It should be noted that this patient was 80 years old at autopsy.

In 6 out of 7 patients with clinically diagnosed AD, a CSF AD profile was found, except for patient 6, who has a CSF profile congruent with non-AD

Table 3 CSF AD profile, age, and disease severity

	CSF AD profile, %[a]	Age, y[b]	MMSE[b]
AD	90	67 vs 69[c]	21 vs 23[d]
FTLD	28	66 vs 62[c]	24 vs 26[c]
DLB	47	73 vs 67[c]	20 vs 24[d]
VAD	27	75 vs 65[c]	23 vs 23
CBD	38	61 vs 58	26 vs 25
PSP	10	69 vs 68	26 vs 26
PSY	9	63 vs 57[c]	28 vs 28
SMC	12	67 vs 58[c]	29 vs 29

Abbreviations: Aβ42 = amyloid β 42; AD = Alzheimer disease; CBD = corticobasal degeneration; DLB = dementia with Lewy bodies; FTLD = frontotemporal lobar degeneration; MMSE = Mini-Mental State Examination; p-tau = phosphorylated tau; PSP = progressive supranuclear palsy; PSY = psychiatric disorder; SMC = subjective memory complaints; VaD = vascular dementia.

[a] CSF AD profile: score below 1 using the formula CSF Aβ42/152 + 8.25 × p-tau, obtained from the cutoff line for optimal separation of Alzheimer disease vs other types of dementias (see also the figure).

[b] Age and MMSE (median values) are compared between patients with a CSF AD profile vs patients with a CSF non-AD profile using Mann-Whitney *U* test.

[c] $p < 0.05$.

[d] Trend; $p < 0.1$.

and a neuropathologic diagnosis of DLB. Revision of the clinical data reveals a change in diagnosis to probable PSP instead of AD. Patient 12 has an ambiguous clinical diagnosis with both FTLD and alcohol abuse, and neuropathologically hippocampal sclerosis, which fits both clinical diagnoses. CSF Aβ42 is decreased in this patient (418 pg/mL), while CSF p-tau is normal (42 pg/mL), resulting in a borderline CSF AD profile. Because of the hippocampal sclerosis plaques or tangles could not be well characterized in this patient.

DISCUSSION In the current study, we evaluate CSF biomarker results in a very large cohort of carefully characterized memory clinic patients with a variety of diagnoses. For the differential diagnosis of patients with AD vs patients with other types of dementia, the combination of CSF Aβ42 and p-tau yields the best diagnostic accuracy. Sensitivity is high for AD, but specificity for other types of dementias is moderate. In DLB almost half of the patients fall into the category AD according to their CSF biomarker profile. Also in FTLD, VaD, and CBD, a substantial proportion of patients have a CSF AD profile. Patients with CJD and PSP can be separated from AD based on the combination of CSF biomarkers. In PSY and SMC a CSF AD profile, based on the cutoff line comparing AD with OD, is uncommon.

What could cause the overlap in CSF AD profile between the different types of dementias? First, misdiagnosis cannot be ruled out. In the present study clinical diagnosis is used as gold standard. This diagnosis is based on a large battery of investigations and on expert opinion after consensus in a multidisciplinary team. Most subjects are followed for years, increasing our confidence in baseline diagnosis. The small sample of patients with diagnosis at autopsy reveals a reasonable clinico-pathologic concordance. Moreover, there is a good concordance between CSF biomarker classification and neuropathologic diagnosis. Remarkably, the agreement between neuropathologic diagnoses vs CSF biomarker profile is in the same order of magnitude as the agreement between clinical diagnoses vs CSF biomarker profile, which strengthens our opinion that CSF biomarkers give a good reflection of the neuropathology, even in cases with clinical doubt or mixed pathology.[4,25]

A second explanation for the overlap in CSF AD profile is that mixed dementias is a common finding at autopsy.[26] Pure forms of (early onset) AD or other types of dementias are a minority in the whole spectrum of dementias.[26–29] Our findings of overlap in CSF Aβ42 and CSF (p)t-tau between the different dementias are thus not that surprising. In most studies low sensitivity and specificity figures of clinical diagnosis are found in autopsy confirmed cases.[30] Furthermore, synergistic mechanisms between major pathologic proteins (amyloid β, tau, α-synuclein, TDP-43) suggest common pathogenic mechanisms.[31]

In DLB and VaD mixed pathology is often found,[28,32] and our findings of low CSF Aβ42 correspond with earlier studies.[3] In DLB AD-related pathology is found especially in patients with more severe cognitive impairment.[33] We find an association between MMSE and age with CSF Aβ42 in DLB, which suggests the presence of plaques in the brain of the patients with the most severe dementia and aged patients with DLB.[34] The decrease of CSF Aβ42 and increase of CSF (p)t-tau in FTLD could be due to inclusion of patients with progressive nonfluent aphasia in this group, exhibiting plaques and tangles in the brain as in AD.[27]

The moderately decreased CSF levels of Aβ42 and increased p-tau levels in CBD are not surprising as this type of dementia is linked with a number of pathologies, including AD pathology.[35] Decreased CSF Aβ42 levels in CBD have been shown before, as well as increased CSF p-tau.[36] The increase of CSF p-tau in some of the patients with CBD could be attributed to cerebral tau depositions, either as a characteristic of CBD pathology (classified as tauopathy) or as a result of AD pathology, which is more likely as p-tau is increased in CSF and not t-tau.

Table 4 Clinical-CSF-neuropathologic concordance[a]

Patient no./sex/age at diagnosis, y	Clinical diagnosis	CSF biomarker profile	Neuropathologic diagnosis
1/F/57	AD	AD	AD, Braak 6c
2/F/56	AD	AD	AD, Braak 6b
3/M/58	AD	AD	AD, Braak 6c
4/M/72	AD	AD	AD, Braak 6c
5/F/85	AD	AD	AD, Braak 5c
6/M/74	AD	AD	Braak 6c
7/M/51	AD-PSP	Non-AD	DLB
8/M/55	FTLD	Non-AD	FTLD, TDP-43
9/F/66	FTLD	Non-AD	FTLD, TDP-43, Braak 2c
10/M/57	FTLD	Non-AD	FTLD, TDP-43
11/F/67	FTLD	Non-AD	FTLD, TDP-43, Braak 1a
12/M/68	FTLD/alcohol abuse	AD	Hippocampal sclerosis, Braak 2–3
13/F/67	FTLD	Non-AD	FTLD, TDP-43
14/F/41	CJD	Non-AD	CJD
15/F/55	CJD	Non-AD	CJD
16/M/59	DLB	Non-AD	DLB, Braak 2a
17/F/80	CBD	AD	PSP, Braak 3b

Abbreviations: Aβ42 = amyloid β 42; AD = Alzheimer disease; CBD = corticobasal degeneration; CJD = Creutzfeldt-Jakob disease; DLB = dementia with Lewy bodies; FTLD = frontotemporal lobar degeneration; p-tau = phosphorylated tau; PSP = progressive supranuclear palsy.

[a] CSF biomarker profile: AD: score <1 using formula CSF Aβ42/152 + 8.25 × p-tau, obtained from logistic regression analysis; non-AD: score >1 using formula CSF Aβ42/152 + 8.25 × p-tau.

As far as we know, this is the largest single center sample thus far reported. This large sample size makes our data robust, especially in view of the inclusion of patients with other types of dementia.[4,30] However, there are a few limitations to this study. First, we included patients with SMC instead of healthy controls, and consider them as the "worried well" of our memory clinic population, based on their normal clinical investigations. Our SMC population show normal CSF biomarker levels in 88%, comparable with the prevalence in a previously published population-based sample without cognitive complaints (i.e., 12% CSF AD profile).[37] We are currently performing follow-up studies to study the predictive value of CSF biomarkers in SMC. Second, our study group is relatively young. Pathology differs between young and old patients with AD, patients with dementia, and patients without dementia.[38] Our study clearly shows that patients with different types of dementia and older patients with SMC are more prone to have a CSF AD profile. In line with former studies, older individuals are more likely to have AD-like biomarkers.[16,39] Conversely, this implies that CSF biomarkers may be most informative in younger patients, which should be taken into account for use in clinical practice. Third, we have neuropathologic data only in a small subgroup of patients, forming an unintended selection of the more complex patients. In this selected group the clinico-neuropathologic-CSF biomarker concordance is high, but prospective studies would reveal whether this is also the case in unselected patients. A recent study showed low sensitivity for DLB comparing clinical with autopsy diagnosis, especially in patients with more severe dementia.[40] Clinical diagnosis is the gold standard in the present study. To date, pathology remains the true gold standard for diagnosing the presence of biological disease, although this can also be debated, as postmortem information is by definition post hoc, mostly years after the diagnosis was first made.

Our data support the value of CSF biomarkers for confirmation of the clinical diagnosis of AD, or to exclude AD with high degree of certainty. Further studies need to focus on the discovery of more specific biomarkers as well as on comparing CSF biomarkers with autopsy to understand the overlap between different types of dementias and the heterogeneity of AD.

AUTHOR CONTRIBUTIONS

Dr. Schoonenboom wrote the manuscript and analyzed the data. Dr. Reesink assisted in writing and analyzing the data and contributed equally to this work. Dr. Verwey critically read the manuscript and assisted in writing. Dr. Kester critically read the manuscript and assisted in writing. Dr. Teunissen supervised laboratory examinations and critically read the manuscript. Dr. van de Ven advised and assisted in statistics. Dr. Pijnenburg critically read the manuscript and assisted in writing. Dr. Blankenstein supervised laboratory examinations and critically read the manuscript. Dr. Rozemuller provided background information about the neuropathological data and critically read the manuscript. Dr. Scheltens critically read the manuscript and assisted in writing. Dr. Van der Flier provided the data and assisted in statistics and writing.

DISCLOSURE

Dr. Schoonenboom, Dr. Reesink, Dr. Verwey, and Dr. Kester report no disclosures. Dr. Teunissen serves on a scientific advisory board for Innogenetics and has a patent pending re: Biomarkers for Alzheimer disease. Dr. Van de Ven and Dr. Pijnenburg report no disclosures. Dr. Blankenstein has received speaker honoraria from Abbott and Ferring and serves as an Associate Editor for *Annals of Clinical Biochemistry*. Prof. Rozemuller has received research support from the EU FP6 and the International Foundation for Alzheimer Research (ISAO). Dr. Scheltens serves on scientific advisory boards for Danone, Wyeth/Elan Corporation, Bristol-Myers Squibb, Genentech, Inc., Pfizer Inc, and GE Healthcare; has received funding for travel or speaker honoraria from Lundbeck Inc.; served as an Associate Editor of the *Journal of Neurology, Neurosurgery & Psychiatry*; serves a Book Review Editor for *Alzheimer's Disease and Associated Disorders* and on the editorial board of *Dementia Geriatric Cognitive Disorders*; serves as a consultant for Pfizer Inc, GE Healthcare, Avid Radiopharmaceuticals, Inc./Eli Lilly and Company, Genentech, Inc., and Janssen AI; and receives research support from Alzheimer Nederland, the Alzheimer Center, and Stichting VUmc fonds. Dr. Van der Flier reports no disclosures.

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