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CSF-Tau and CSF-Aβ_{1-42} in Posterior Cortical Atrophy

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Key Words

Cognitive disorders · Dementia · Posterior cortical atrophy · Alzheimer's disease · Cerebrospinal fluid · Biomarker · β-amyloid · Tau

Abstract

Objective: Our purpose was to measure Aβ_{1-42}, T-tau and P-tau$_{181}$ in the cerebrospinal fluid (CSF) of patients with posterior cortical atrophy (PCA), a presenile dementia likely to represent a variant of Alzheimer's disease (AD). ***Methods:*** CSF samples from 34 subjects including 9 patients with PCA, 11 age-matched patients with AD and 14 age-matched cognitively healthy controls were analyzed using commercially available ELISA kits. ***Results:*** The Aβ_{1-42}, T-tau and P-tau$_{181}$ levels in PCA patients differed significantly ($p < 0.02$) from those in healthy controls but were indistinguishable from subjects with a clinical diagnosis of AD. ***Conclusion:*** High T-tau and P-tau$_{181}$ and low Aβ_{1-42} levels in PCA – typically observed in AD – indicate that the underlying pathology of PCA is usually AD. If these findings are replicated in PCA patients with autopsy-confirmed AD neuropathology, PCA patients may be eligible for disease-modifying AD treatments.

Posterior cortical atrophy (PCA) is an uncommon early-onset dementia characterized by progressive visuospatial dysfunction [1–3]. Elements of Balint's syndrome, Gerstmann's syndrome, visual agnosia and topographical disorientation are typical manifestations of PCA. Memory and insight remain relatively intact. Alzheimer's amyloid plaques and neurofibrillary tangles in posterior brain regions are the most common underlying pathology, indicating that PCA most often represents a focal, mostly presenile variant of Alzheimer's disease (AD) [4–6]. One of the most sensitive and specific approaches to predict AD in vivo is the analysis of Aβ_{1-42}, T-tau and P-tau in the cerebrospinal fluid (CSF). When combined, the sensitivity and specificity for the diagnosis of AD have been found to be between 80 and 90% [6]. Analysis of these biomarkers may be helpful in predicting Alzheimer's pathology also in PCA. In this study, we postulated that an AD-typical CSF protein profile consisting of low Aβ_{1-42} and high T-tau and P-tau$_{181}$ concentrations would also be observed in PCA patients.

Methods

Selection of Cases

We identified 12 patients with PCA who were evaluated at the Center for Geriatric Medicine and Gerontology, University Hospital Freiburg, Germany, and the Memory Clinic of the Univer-

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Table 1. Clinical characteristics of the patients with PCA (n = 9)

	1	2	3	4	5	6	7	8	9
Elements of Balint's syndrome	+	+	+	+	+	+	+	+	+
Elements of Gerstmann's syndrome	+	+	+	+	+	+	+	+	+
Dressing apraxia	–	(+)	+	–	+	(+)	+	–	–
Environmental disorientation	–	–	+	+	+	+	–	–	–
Pure alexia	–	–	+	–	–	–	+	–	–
Ideomotor apraxia	–	(+)	–	+	+	+	+	+	+
Constructive apraxia	+	+	+	+	+	+	+	+	+
Prosopagnosia	–	–	(+)	–	+	–	–	–	+
Apperceptive agnosia	–	+	+	+	+	–	+	–	+
Visual field deficit	–	+	+	+	–	–	–	(+)	–
Achromatopsia or color agnosia	–	–	–	+	–	–	+	–	–
Extrapyramidal motor signs	–	–	–	–	–	–	–	(+)	(+)

+ = Present; – = absent; (+) = possible.

Table 2. Basic characteristics of the 34 subjects

	PCA (n = 9)	AD (n = 11)	HC (n = 14)	p value
Age at disease onset, years	56.7 (7.6)	58.3 (5.1)	n.a.	0.38
Age at lumbar puncture, years	60.9 (7.7)	61.6 (6.2)	62.6 (5.1)	0.81
Sex (m/f)	4/5	4/7	7/7	0.79
Education, years	11.5 (2.3)	12.0 (2.0)	13.5 (2.8)	0.25
Disease duration, years	4.2 (2.6)	3.4 (2.5)	n.a.	0.49
APOE 4 allele, %	38.9	50.0	14.3	0.48, PCA vs. AD
MMSE score at time of lumbar puncture	17.7 (6.2)	23.6 (3.3)	29.1 (1.2)	0.02, PCA vs. AD

Figures are means with standard deviations in parentheses.
MMSE = Mini-Mental State Examination (0–30).

sity Hospital Basel, Switzerland, between 2005 and 2007. Inclusion criteria for PCA were applied according to proposed clinical criteria [2]. Required are all of the following: (1) insidious onset and gradual progression; (2) presentation with visual complaints despite intact primary visual functions; (3) evidence of predominant complex visual disorder on examination; (4) proportionally less impaired memory and verbal fluency, and (5) relatively preserved insight with or without depression. It was possible to collect CSF in 9 of these 12 patients with PCA. The clinical features of these 9 patients are summarized in table 1. All subjects and their next of kin gave written informed consent for research participation. The study was approved by the local ethics committee.

Selection of Controls

Fourteen cognitively healthy individuals from a longitudinal ageing study were matched with the PCA group according to age, gender and education. Eleven early-onset AD patients served as disease controls. These AD cases were sporadic, i.e. there was no evidence of an autosomal-dominant mode of inheritance in any patient. All subjects underwent detailed neurological and neuropsychological examination, brain imaging (MRI or CT, CBF-SPECT in selected cases), and routine blood tests.

CSF Analysis

From each subject 14 ml of CSF were collected in polypropylene tubes, transferred on ice and stored at –80°C within 1 h. $A\beta_{1-42}$, T-tau and P-tau_{181} were measured in duplicates unknown to the analyst using a commercial sandwich ELISA kit (Innogenetics®, Belgium).

Statistics

The statistical analysis was done with SPSS for Windows (SPSS Inc., Chicago, Ill., USA). To test for differences between the groups we used the Mann-Whitney U and Kruskal-Wallis tests, since the assumptions of normality were not met. Gender and APOE 4 differences between the groups were analyzed with the χ^2 test.

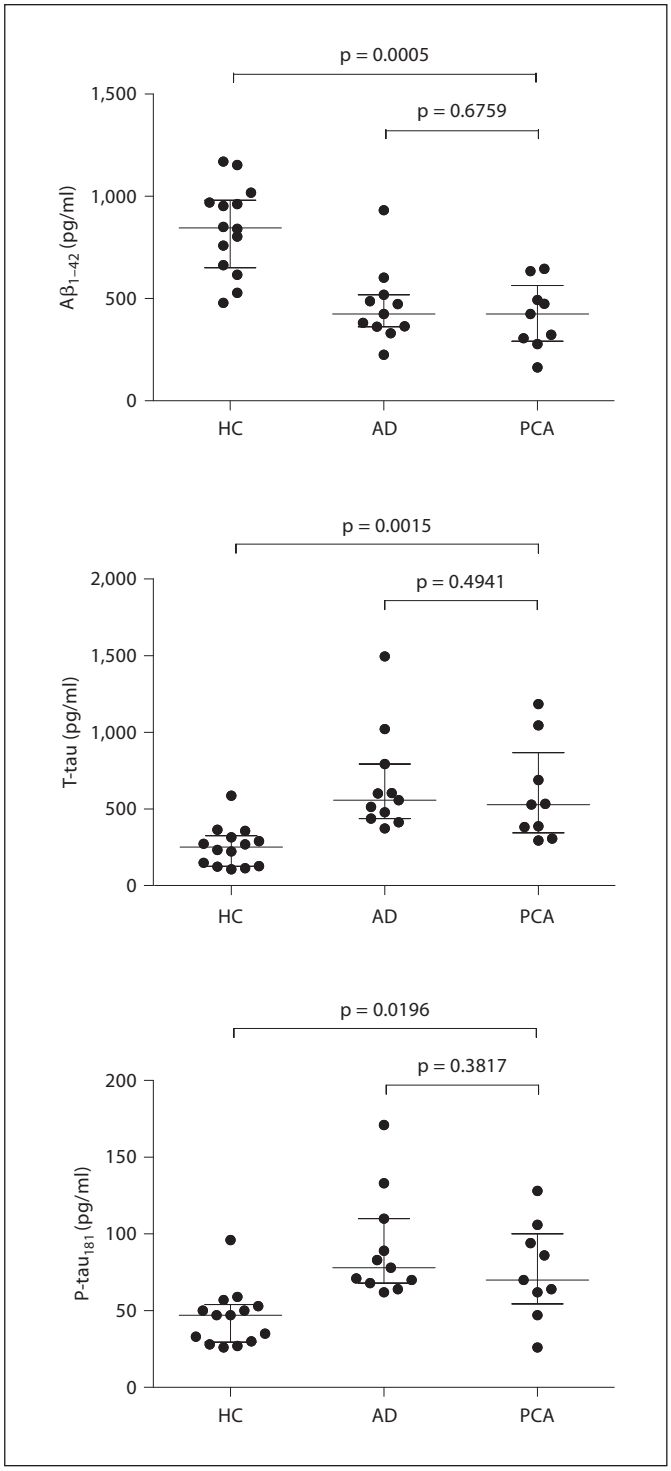

Fig. 1. $A\beta_{1-42}$, T-tau, and P-tau_{181} concentrations in CSF (medians and interquartile ranges).

Results

Mean age at disease onset and disease duration were similar in PCA and AD (56.7 vs. 58.3 years, p = 0.38, and 4.2 vs. 3.4 years, p = 0.49). The MMSE score was lower in PCA compared with AD (mean = 17.7 vs. 23.6, p = 0.02; table 2). CSF data are shown in figure 1. PCA and AD had lower $A\beta_{1-42}$ levels compared with healthy controls (HC; median = 424 and 424 pg/ml vs. 845 pg/ml; p = 0.0004 and p = 0.0005). The T-tau values were higher in PCA and AD compared to HC (median = 528 and 557 pg/ml vs. 251 pg/ml; p = 0.0001 and p = 0.0002). The P-tau_{181} concentrations were higher in PCA and AD compared with HC (median = 70 and 78 pg/ml vs. 47 pg/ml; p = 0.0015 and p = 0.0196). No differences were found between PCA and AD for $A\beta_{1-42}$ (p = 0.6759), T-tau (p = 0.4941) and P-tau_{181} (p = 0.3817).

Discussion

Our results indicate that CSF $A\beta_{1-42}$, T-tau and P-tau_{181} findings characteristic of AD are also observed in PCA. In all 9 PCA patients at least 1 of these 3 markers was outside the published normal range [7]. To the best of our knowledge, this is the first study to report detailed CSF protein findings in a group of PCA patients and to provide another line of evidence for a close pathophysiological link between PCA and AD. Recently, low $A\beta_{1-42}$ and high CSF P-tau_{199} values were reported in a patient with PCA [8] using the same ELISA test as in this study. However, as in another PCA case report [9], no interpretation of the findings was given. Predicting the underlying Alzheimer pathology in focal atrophy syndromes such as PCA is of high clinical interest as soon as disease-modifying treatments for AD become available. In 2 recent PCA case studies, increased uptake of C11-labeled Pittsburgh Compound B in the occipital cortex indicated that imaging of fibrillary amyloid in PCA is feasible in vivo [6, 9]. However, the costs of amyloid PET scans are high, and their availability is limited. In contrast, CSF analysis is inexpensive and well tolerated in the elderly [11]. A combination of CSF $A\beta_{1-42}$, T-tau and P-tau_{181} has been shown to be sensitive and specific for the diagnosis of AD [6]. CSF protein analysis may therefore be more suitable for detecting AD-specific protein abnormalities with atypical presentation of AD such as PCA, progressive mixed aphasia, progressive nonfluent aphasia or corticobasal syndrome. A recent autopsy study suggested that plaques and tangles are the underlying pathology in

a substantial number of these patients (46–100%) [4]. In a study on focal cerebral atrophies, all 7 subjects with PCA showed Alzheimer pathology at autopsy and none had alternative published histopathology such as corticobasal degeneration, Creutzfeldt-Jakob disease, dementia with Lewy bodies or progressive subcortical gliosis [5, 12]. Should our CSF results be confirmed in a larger cohort of PCA patients with autopsy-confirmed amyloid plaques and tau aggregates in posterior brain regions, patients with PCA syndrome and AD-typical CSF findings may be candidates for AD trials targeting at the modification of $A\beta_{1-42}$ or tau protein. The limitations of this study include the small number of PCA cases and the probability of a more advanced disease stage in the PCA group compared to the AD group. The disease duration was longer and the MMSE scores were significantly lower in the PCA group. However, data from the literature indicate that alterations in tau and $A\beta_{1-42}$ occur early in the disease course and do not ($A\beta_{1-42}$) or only slightly (T-tau) change over time [13]. Moreover, we found no correlations between the CSF biomarkers (tau, P-tau_{181}, $A\beta_{1-42}$) and the MMSE scores either in the PCA group, in the AD group or in the combined group (AD and PCA). It is therefore unlikely that higher MMSE scores in the PCA group would have altered the interpretation of our data.

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