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Assessment of total tau protein, phospho tau and beta amyloid in cerebrospinal fluid of patients with neurodegenerative disorders, an autopsy correlation study

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Summary
Objective: To evaluate three biomarkers of dementia in cerebrospinal fluid (CSF): Total tau (T-tau), phospho tau (P-tau) and 42 amino acid form of beta amyloid (Aβ-42) in our clinical practice.
Setting: Department of Neurology, Faculty Hospital Motol, Prague.
Material and Methods: Biomarkers of dementia were determined in CSF of neurological patients (N = 155) by immunosorbent assay (ELISA) developed by Innogenetics. Selected subgroups are present: Probable Alzheimer disease (AD; N = 14), minimal cognitive impairment (MCI; N = 8), patients with pathologically confirmed diagnosis (N = 10): Creutzfeldt-Jacob disease (CJD; N = 3), Alzheimer disease (AD; N = 2), Pick disease (N = 1), Progressive supranuclear palsy (PSO; N = 1), Multiple system atrophy (MSA; N = 1), Amyotropic lateral sclerosis + frontotemporal dementia (ALS + FTD; N = 1), Amyotropic lateral sclerosis (ALS; N = 1) and a Control group (N = 37).
Results: Probable AD group: Abnormal values of T-tau were found in all patients (100%), decreased Aβ-42 was detected in 13 patients (92%) and abnormal P-tau in 12 patients (86%). MCI patients Increased P-tau in 2 cases served as prognostic factor for AD. The group with pathologically confirmed diagnosis: CJD patients very high values of T-tau, normal P-tau in 2 patients and slighly increased in one, Aβ-42 was decreased in 1 case. AD patients: High T-tau, increased P-tau and decreased Aβ-42. Pick disease: High T-tau, P-tau was normal, A-42 decreased. PSP: All 3 biomarkers were normal. MSA: All 3 biomarkers were normal. ALS + FTD: Increased T-tau, P-tau and Aβ-42 were normal. ALS: Slightly increased T-tau, P-tau and Aβ-42 were normal. Control group: Normal T-tau and P-tau were found in all patients (100%). In 12 patients (32%) Aβ-42 was decreased.
Conclusion: P-tau is more specific for diagnosis of AD than T-tau and Aβ-42, but it cannot fully replace the other CSF biomarkers especially in CJD or in patients with frontal cognitive impairment. This study confirms a good correlation of CSF biomarkers findings with autopsy based definitive diagnosis AD.
Key words: CSF, total tau protein, phospho tau protein, beta amyloid, dementia.

Introduction

In the last decade there were done many studies on selected biomarkers of dementia. The diagnosis is frequently based on clinical diagnostic criteria (i. e. NINCDS–ADRDA for probable and possible Alzheimer disease), but only minority of studies yielded data on autopsy based definitive diagnosis.

Biomarkers in cerebrospinal fluid (CSF), total tau (T-tau), phospho tau (P-tau) and 42 amino acid form of beta amyloid (Ab-42), are closely related with degeneration of neurons, formation of neurofibrillary tangels and senile plaques and might be of great aid especially in the diagnostic approach to Alzheimer disease (AD). In AD pathology, the concentrations of T-tau and P-tau are increased, while Ab-42 is decreased [1, 2].

T-tau is a general marker of neuronal destruction. It has relatively low power in differentiating AD from other dementing illnesses [3]. The very high levels are found in acute stroke [4] and in Creutzfeldt-Jackob disease (CJD) [5].

P-tau protein more specifically reflects the phosphorylation state of T-tau with subsequent formation of neurofibrillary tangels in AD brain [6, 7, 8].

Low CSF levels of Ab-42 are found in patients with Vascular dementia, Frontotemporal dementia, CJD, Amyotrophic lateral sclerosis (ALS), Multiple systemic atrophy (MSA), in early AD [9] and significantly predict conversion to AD in patients with Minimal cognitive impairment (MCI) with high sensitivity [11].

Material and Methods

Three CSF biomarkers (T-tau, P-tau, Aβ-42 amyloid) were determined by immunosorbent assay (ELISA) developed by Innogenetics. Diagnostic lumbar puncture was performed in patients admitted to our Departement of Neurology (N = 155). Selected subgroups are present: *Probable Alzheimer disease* (AD; N = 14); *Minimal cognitive impairment* (MCI; N = 8); *Patients with pathologically confirmed diagnosis* (N = 10): Creutzfeldt--Jacob disease (CJD; N = 3), Alzheimer disease (AD; N = 2), Pick disease (N = 1), Progressive supranuclear palsy (PSP; N = 1), Multiple system atrophy (MSA; N = 1), Amyotropic lateral sclerosis + Frontotemporal dementia (ALS + FTD; N = 1), Amyotropic lateral sclerosis (ALS; N = 1) and a *Control group* (N = 37) without dementia and without positive inflammatory findings in CSF.

Results

Probable AD (Table 1): Abnormal values of T-tau were found in all subjects (100%). P-tau higher than 60 ng/l was detected in 12 patients (86%) and decreased Aβ-42 was in 13 patients (92 %).

Table 1. Results of CSF tests in Probable Alzheimer disease group (n = 14)

Age	T-tau	P-tau	Aß-42
	[ng/l]		
76	841.2	107.5	282.0
77	498.6	63.9	241.5
69	912.7	108.0	274.0
66	428.6	63.8	430.0
55	561.2	56.7	222.7
65	680.0	76.0	440.0
73	900,0	160.0	320.0
65	>2700.0	198.0	315.0
56	1050.0	134.0	445.0
72	>2700.0	134.2	244.0
72	980.0	114.6	200.0
57	240.0	57.0	210.0
72	540.0	155.0	305.0
70	1040.0	110.0	570.0

MCI patients (Table 2): increased T-tau and P-tau was in 2 patients. Aβ-42 was normal in the whole group.

Table 2. Results of CSF tests in Minimal congnitive impairment group (n = 8)

Age	T-tau	P-tau	Aß-42
	[ng/l]		
72	490.0	74.0	365.0
53	80.0	16.0	510.0
81	274.5	43.0	528.0
62	226.9	44.0	1187.0
60	135.0	43.0	710.0
52	60.0	23.0	630.0
72	195.0	85.0	580.0
79	420.0	47.0	862.0

Autopsy confirmed diagnosis (Table 3): **CJD** (N = 3): Very high T-tau, slightly increased P-tau was only in 1 patient, Aβ-42 was decreased in 1 case. **AD** (N = 2): High T-tau, increased P-tau and decreased Aβ-42. **Pick disease** (N = 1): High T-tau, normal P-tau and decreased Aβ-42. **PSP** (N = 1): All 3 biomarkers were normal. **MSA** (N = 1): All 3 biomarkers were normal. **ALS + FTD** (N = 1): Increased T-tau, P-tau and Aβ-42 were in normal values. **ALS** (N = 1): Slightly increased T-tau, P-tau and Aβ-42 were normal.

Table 3. Results of CSF tests in Autopsy confirmed diagnosis group (n = 10)

Diagnosis	Age	T-tau	P-tau	Aß-42
		[ng/l]		
CJD	49	>2700,0	89.4	501.0
CJD	69	>2700.0	52.0	655.0
CJD	59	>2700.0	25.9	422.0
AD	78	>2700.0	225.0	310.0
AD	79	874.0	95.9	285.0
Pick disease	58	1850.0	36.0	380.0
PSP	71	385.0	58.0	550.0
MSA	68	185.0	37.9	586.0
ALS + FTD	58	569.0	44.5	616.0
ALS	47	370.0	61.0	600.0

Control group (Table 4): Normal concentrations of T-tau and P-tau were found in all patients (100%). In 12 patients (32%) Aβ-42 was decreased.

Table 4. Results of CSF tests in Control group (N = 37)

Age	T-tau	P-tau	Aß-42
	[ng/l]		
43	120.0	36.0	450.0
55	215.0	37.0	520.0
61	135.0	41.0	580.0
53	150.0	39.0	460.0
58	95.0	24.0	270.0
44	40.0	24.0	365.0
62	55.0	24.0	320.0
40	275.0	44.0	575.0
57	215.0	25.5	530.0
60	200.0	53.0	305.0
49	55.0	23.0	1020.0
51	86.1	20.0	272.2
57	254.2	43.6	789.8
53	294.8	50.3	518.7
76	280.0	35.4	523.4
55	187.3	35.3	438.2
76	354.9	46.8	830.2
52	190.6	32.6	493.5
64	279.0	24.6	584.4
51	250.1	38.7	927.2
53	215.8	40.4	715.4
57	191.0	37.0	628.6
55	284.2	44.4	697.4
76	241.2	41.8	732.8
55	195.7	34.3	719.9
79	245.7	38.4	567.0
51	276.2	45.8	566.0
61	289.5	42.6	490.1
55	204.5	42.1	609.8
70	227.2	40.5	784.3
63	265.4	40.1	980.7
52	247.1	35.4	755.5
60	232.7	36.4	493.5
55	236.1	38.1	523.4
64	153.8	26.5	474.6
61	317.1	47.9	796.9
52	299.4	49.4	870.8

Discussion

Increased T-tau was found in all patients with probable AD, but it is true that the range of normal values for this marker is very wide. Abnormal T-tau was found in 69 patients out of 155, while P-tau was increased only in 26 patients out of the whole group, mostly with AD diagnosis. Increased P-tau in 2 MCI patients served as prognostic factor for AD [10]. It was interesting,

that we did not find reduced Aβ-42 in MCI group as we expected [12, 13, 14, 15, 16, 17]. On the contrary Aβ-42 was abnormal in 32% of patients in our control group.

Conclusion

We belive that P-tau is more specific for diagnosis of AD than T-tau and Aβ-42 but it cannot fully replace the other CSF biomarkers especially in CJD or in patients with frontal cognitive impairment. Our experience suggests a limited value of Aβ-42 in differential diagnosis of dementia. This study confirms a good correlation of CSF biomarkers findings with autopsy based definitive diagnosis AD.

Explanatory notes:
CSF – cerebrospinal fluid
CJD – Creutzfeldt-Jacob disease
AD – Alzheimer disease
PSP – progressive supranuclear palsy
MSA – multiple system atrophy
ALS – amyotropic lateral sclerosis
FTD – frontotemporal dementia
MCI – minimal cognitive impairment
OND – other neurological diagnosis

Normal values of CSF biomarkers in ng/l (Innogenetics)
T-tau protein
AD below 60 years: 229.8 ± 84.9
AD older than 60 years: 425.7 ± 244.3
OND below 60 years: 202.9 ± 184.9
OND older than 60 years: 173.2 ± 108.3
P-tau protein: < 61
Aβ-42 protein: > 500

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