CSF phospho-tau levels at Parkinson's disease onset predict the risk for development of motor complications

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Background and Objective

Motor complications (MC) represent a disabling milestone of the Parkinson's disease (PD) course. While rearrangement of motor circuits due to prolonged abnormal dopaminergic signaling plays a key role in MC pathophysiology (1), the early neuropathological substrate has not been outlined yet. However, recent evidence has highlighted the significant impact of brain co-pathologies on the clinical and pathological progression of PD (2) We therefore investigated whether the biological profile at the PD onset, as defined through a panel of CSF biomarkers, may predispose to the subsequent development of MC.

Materials and Methods

We conducted a dual-center retrospective longitudinal study involving 131 de novo (DN) PD patients. At baseline, patients were evaluated by standard motor and non-motor scores, and the measurement of CSF total α- synuclein (α-syn), total and phosphorylated-181 tau (t-tau, p-tau), amyloid- β42 and amyloid-β40 (Aβ42, Aβ 40) levels, p-tau/t-tau, Aβ42/ Aβ40, and p-tau/ Aβ42 ratios. According to the successive development of MC, patients were classified as "with MF" (wMC) or "without MC" (noMC). A control group of 107 controls was also collected. Variables were compared between the groups, adjusting for main covariates; ROC and Cox regression analyses were run to estimate their predictive values.

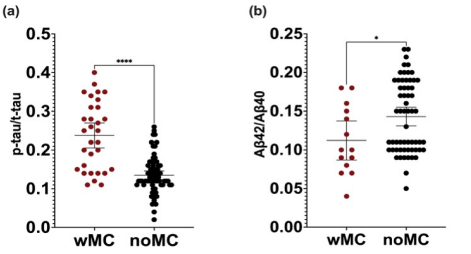

Figure1. Scatter plots of CSF phosphorylated-181 tau/total tau (p-tau/t-tau) and amyloid- β42/amyloid-β40 (Aβ42/Aβ40) values in patients with motor complications (wMC) and without motor complications (noMC), with median and 25th-75th interquartile range. *p < 0.05. (a) CSF p-tau/t-tau values comparison. Black dots represent noMC cohort; red dots represent wMC cohort. (b) CSF Aβ42/Aβ40 values. Black dots represent noMC cohort; red dots represent wMC cohort.

	wMC (n=38)	noMC (n=93)	significance
Demographic parameters			
Sex (m/f)	27/11	67/26	n.s.
Age (y)	60.65 ± 8.703 (41 - 73)	62.04 ± 10.932 (32 - 81)	n.s.
FU (mo)	51.38 ± 15.77 (22 - 85)	61.01 ± 19.99 (27 -127)	n.s.
Clinical parameters			
Disease Duration (y)*	1.51 ± 0.98 (0 - 5.0)	1.51 ± 1.05 (0 - 7.0)	n.s.
Time to MC onset (mo)	48.67 ± 14.53 (22 - 79)	\	\
LEDD at MC onset/end FU (mg/day)	667.98 ± 291.83 (150 - 1300)	416.173 ± 173.04 (150 - 925)	**p < 0.001**
MDS-UPDRS part-III	22.52 ± 9.62 (5 - 46)	23.37 ± 11.25 (5 - 47)	n.s.
HY	1.93 ± 0.56 (1.0 - 3.0)	1.93 ± 0.56 (1.0 - 3.0)	n.s.
MMSE	28.06 ± 1.80 (25.00 - 30.00)	27.95 ± 2.30 (19.00 - 30.00)	n.s.
MoCA	23.30 ± 5.35 (12 - 30)	25.50 ± 3.22 (12 - 30)	n.s.
NMSS *total score*	43.50 ± 37.50 (0 - 140)	34.55 ± 27.31 (0 - 123)	n.s.
CSF biomarkers			
α-synuclein (pg/ml)[a]	952.85 ± 307.07 (475 - 1620)	914.73 ± 326.91 (238 - 1646)	n.s.
Aβ42 (pg/ml)	816.43 ± 308.18 (285 - 1729)	928.30 ± 353.13 (195 - 1807)	n.s.
Aβ40 (pg/ml)[b]	7882.34 ± 2469.51 (1497 - 11833)	7395.00 ± 3148.55 (2853 - 16532)	n.s.
Aβ42/Aβ40[b]	0.12 ± 0.092 (0.04 - 50)	0.1310 ± 0.046 (0.05 - 23)	**p = 0.014**
total tau (pg/ml)	202.22 ± 130.90 (60 - 806)	206.27 ± 75.85 (39.00 - 377)	n.s.
phosphorylated-181-tau (pg/ml)	39.59 ± 20.78 (8 - 124)	27.75 ± 12.44 (5.00 - 59.00)	**p < 0.001**
phosphorylated-181-tau/ total tau	0.22 ± 0.087 (0.11 - 0.40)	0.1371 ± 0.048 (0.02 - 0.26)	**p < 0.001**
phosphorylated-181-tau/ Aβ42	0.056 ± 0.039 (0.02 - 0.19)	0.033 ± 0.023 (0.00 - 0.21)	**p < 0.001**

a Data are available for 18 wMC patientsts and 40 NoMC
b Data are available for 22 wMC patients and 80 NoMC
**from motor symptoms onset to diagnosis*

Table2. Demographic and clinical characteristics of wMC and noMC cohorts. Values are given in mean ± standard deviation (range). Statistical significance is marked in **bold**.

Results

The DN PD cohort was followed for 57 (±18) months, with 38 (29%) patients developing MC. At baseline, patients showed lower CSF total α-syn and t-tau levels than controls. Patients with MC had higher p-tau, p-tau/t-tau, and p-tau/Aβ42 ratios than those without MC (**Figure1**). ROC curves for p-tau, p-tau/Aβ42, p-tau/t-tau showed an area under the curve (AUC) of 0.68, 0.75, and 0.78, respectively (**Figure2**). We implemented the analysis considering covariates for p-tau/t-tau ratio, obtaining an AUC of 0.79; with a cutoff value of 0.148, resulting in an 81% sensitivity and 61% specificity. PD patients with a p-tau/t-tau ratio ≥ 0.148 were 2.6 times more likely to develop MF, with a mean time of onset of 69 months (vs. 86 months) (**Figure3**)

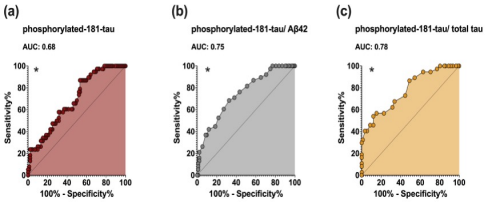

Figure2. Receiver operating characteristic (ROC) curves of CSF phosphorylated-181 tau levels (p-tau), phosphorylated-181 tau/ amyloid-β42 (p-tau/Aβ42), and phosphorylated-181 tau/total tau (p-tau/t-tau). *p < 0.05. (a) ROC curve of cerebrospinal fluid p-tau levels to discriminate wMC and noMC groups (red). (b) ROC curve of cerebrospinal fluid p-tau/Aβ42 values to discriminate wMC and noMC groups (grey). (c) ROC curve of cerebrospinal fluid p-tau/t-tau values to discriminate wMC and noMC groups (yellow).

Discussion

Our results showed that patients who developed MC had higher CSF levels of p-tau and increased p-tau/t-tau and p-tau/Aβ42 ratios at PD onset, suggesting a contribution of tau pathology in driving motor trajectories of disease progression. Amyloid-β-pathology could also be involved, albeit marginally, to MC risk, supporting, in general, the role of Alzheimer's Disease (AD) co-pathology in shaping the motor phenotype of PD. Conversely, data from α-synuclein seem to downsize its role in the pathophysiology of MC.

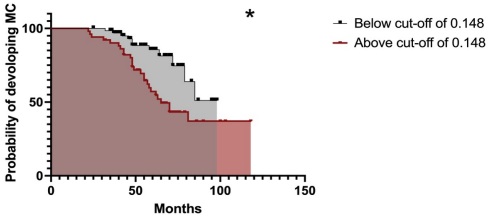

Figure3. Survival curve for the onset of motor complications during follow-up. The groups for the Kaplan–Meier estimates were determined by maximizing the Youden index for adjusted p-tau/t-tau values. The cutoff value shows a highly significant difference in motor complications onset for the resulting groups (p = 0.007). Groups below the cutoff are depicted in grey and above the cutoff in red.

Conclusions

Elevated CSF p-tau/t-tau ratios in DN PD patients indicate a higher risk for MC development along the disease course, supporting using CSF biomarkers to stratify patients at PD onset. These findings also suggest the relevance of Alzheimer's disease co-pathology, especially tauopathy, in determining the motor trajectory of PD since the earliest disease stages.

Full article:

Bibliography

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