Clinical significance of CSF biomarkers in Progressive Supranuclear Palsy

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Background

Progressive Sopranuclear Palsy (PSP) is a severe neurodegenerative disease whose neuropathological hallmark is the accumulation of aggregates of modified tau protein. The phenotypic spectrum of PSP is extremely wide, encompassing the classic form of Richardson's Syndrome and many other conditions with prominent movement disorder or cognitive disturbances.

Because of the clinical overlap with other neurological disorders, diagnosis of PSP *in vivo* is still challenging, especially at the early stages. However, in last decade, the assessment of CSF biomarkers gained a crucial role in leading differential diagnosis and predicting prognosis of neurodegenerative diseases. Unfortunately specific CSF biomarkers for PSP have not been identified yet, but other biomarkers of neurodegeneration are available.

Objectives

In this study we measured clinical significance of a panel of CSF biomarkers, including amyloid-beta-42 (Aβ42), total and phosphorylated-181 tau proteins (t-tau and p-tau) in PSP. Specifically, we first provided a comparative analysis of CSF biomarkers among patients with PSP, Parkinson's Disease (PD) and controls aimed at estimating the diagnostic value; then, we correlated biochemical results with clinical parameters of PSP patients to quantify clinical predictive value.

Study population

		PSP	CTL	PD	p
n		39	58	31	-
age	*mean*	70,7	68,4	67,7	no
	st.dev.	5,9	7,3	7,3	
gender	M/F	22 / 17	38 / 20	14 / 17	no
duration	*mean*	2,9	-	3,7	no
	st.dev.	1,7	-	4,4	
PSPRS or UPDRSIII	*mean*	35,7	-	23,0	-
	st.dev.	10,3	-	10,8	
PSP stage	*mean*	2,9	-	-	-
	st.dev.	0,9	-		
MMSE	*mean*	24,4	-	25,5	no
	st.dev.	3,1	-	5,1	

Conclusions

In this study we first defined CSF biomarkers profile of PSP patients, which results as characterized by significant reduction of Aβ42, t-tau and p-tau levels.

We noticed that such a peculiar profile well distinguishes PSP from CTL; moreover, both low Ab42 levels and low p-tau/t-tau ratio support differential diagnosis between PSP and PD. Ab42 seems to be the most reliable biomarker for PSP, indeed we also observed that Ab42 levels may predict clinical impairment of PSP patients, as assessed with PSPRS.

The lowering of Ab42 levels could underlie a major neurodegenerative process with extensive synaptic loss and impaired neurotransmission, providing a plausible explanation for the correlation with disease severity.

Surprisingly, both t-tau and p-tau do not correlate with clinical features. However, either the significant levels reduction with respect to CTL or the lower p-tau/t-tau ratio than PD highlight the existence of taupoathy.

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Experimental Design

Prospective Collection

2013-2016, Unit of Neurology Policlinico Tor Vergata, Rome

- **PSP** patients : NINDS-PSP criteria
- **CTL** : subjects with non-neurodegenerative diseases
- **PD** patients : UK-PDSBB criteria

CSF analysis

- Cito-morpho-chemical analysis
- Biomarkers assay:
  - amyloid-beta-42 (**Aβ42**)
  - total tau (**t-tau**)
  - phosporilated tau (**p-tau**)
  - **Aβ42/p-tau**
  - **p-tau/t-tau**

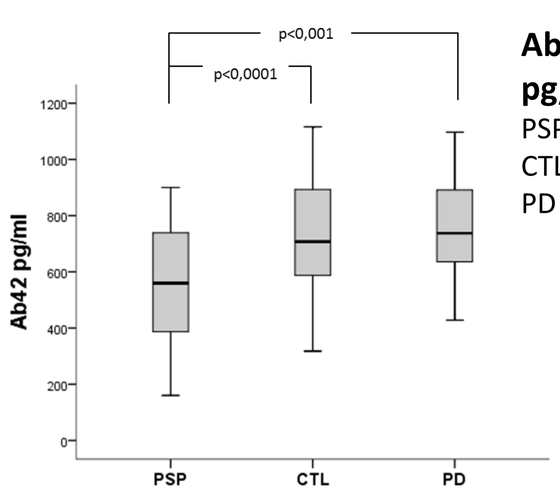
Clinical assesment

- Medical/neurological history and exam.
- PSP patients:
  PSP Rating Scale (**PSPRS**) + MMSE
- PD patients:
  UPDRSIII + MMSE

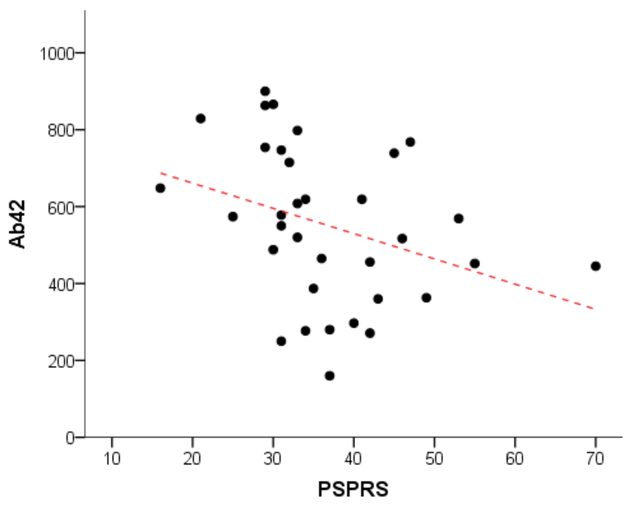
Statistical analysis

- Shapiro-Wilk test
- chi-square test or the one-way ANOVA
- ROC analysis with cut-off point calculation
- Spearman's correlation
- Linear regression

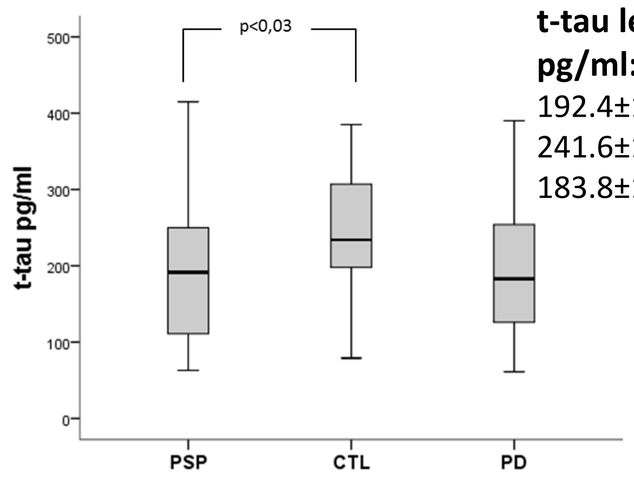
Results



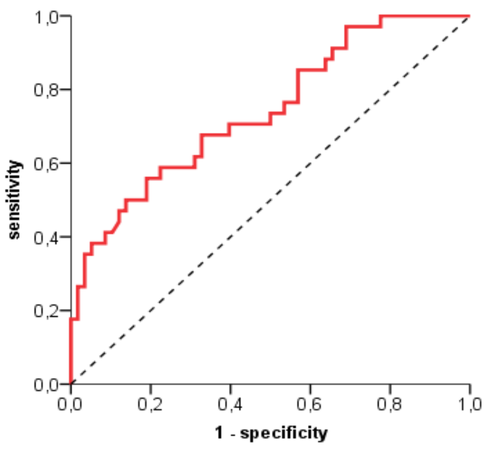
Ab42 levels pg/ml:
PSP= 547.3±34.3
CTL=741.1±25.7
PD =748.2±40.5



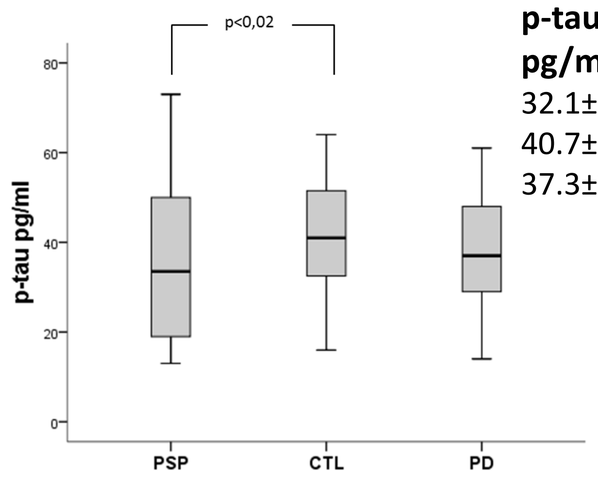
Aβ42 inversely correlates with PSPRS
(R= -0.47,p<0.005)



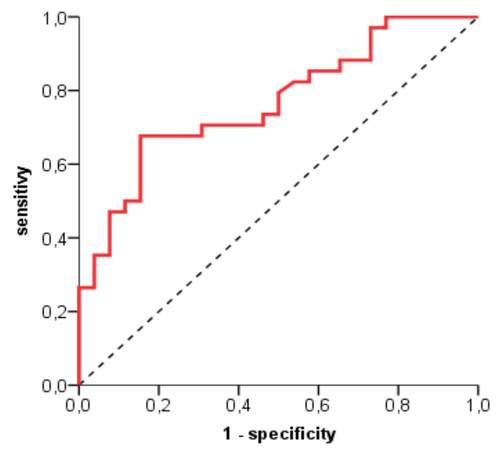
t-tau levels pg/ml:
192.4±14.8
241.6±11.1
183.8±17.4



cut-off Aβ42 = 578.5 pg/ml PSP vs CTL
80%Se, 60% Sp; AUC=0.73, p<0.001



p-tau levels pg/ml:
32.1±2.3
40.7±1.8
37.3±2.8



cut-off Aβ42 = 638 pg/ml PSP vs PD
70%Se, 70% Sp; AUC=0.74, p<0.004

Ab42/p-tau ratio
PSP = 19,6±9,5
CTL =19,5±7,0
PD = 21,6±8,2

p-tau/t-tau ratio
PSP=0,17±0,06
CTL =0,17±0,04
PD=0,2±0,07

* p<0,02