CSF Tau in diagnosis of Amyotrophic Lateral Sclerosis: relation with clinical features.

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Background

Amyotrophic Lateral Sclerosis (ALS) is a motorneuron disease characterized by a progressive and fatal course, consequence of neurodegeneration of both upper (UMN) and lower motorneuron (LMN). The discover of a reliable biomarker would be an important hallmark in the study of the pathology but today only the neurofilaments have been proven to have a potential prognostic role in ALS. Several studies focused their attention on the tau protein with conflicting results.

Methods

We included 66 incident patients with possible, probable and definite ALS and 175 patients defined as control group (n.126 Alzheimer Disease –AD- and n.49 patients with other non-neurodegenerative diseases –ONND- mainly polyneuropathies and some migraines). Patients were enrolled in a period from March 2009 to April 2016 and ALS patients followed up till April 2017. Comparisons between groups were performed with Kruskal-Wallis test followed by Dunn's post-hoc test. Correlations were evaluated with Spearman rank test. Receiver Operating Curve (ROC) was used to calculate an optimal cut-off concentration of CSF Tau, p-Tau and p-Tau/Tau ratio to discriminate patients with ALS from ONND. Kaplan-Meier estimator was used for the analysis of survival, followed by Cox hazard ratio model .

Results 1

AD patients had the highest CSF tau and PTau levels among the three groups, whereas ALS patients had higher CSF Tau and lower pTau/tau than ONND (Table 1).

	ALS (n.66)	AD (n.126)	p	ONND (n.49)	p
Tau Protein (pg/mL)	191,24 ± 105,32	320,49 ± 232,76	<0.001	127,08 ± 77,16	<0.001
pTau Protein (pg/mL)	35,24 ± 13,13	52,18 ± 28,77	<0.001	32,47 ± 14,10	n.s.
Ratio (pTau/tau)	0,20 ± 0,07	0,18 ± 0,06	n.s.	0,31 ± 0,27	<0.001

Table 1 – CSF Tau, pTau and Ratio levels in ALS, AD and ONDD patients.

Results 2

ROC analysis revealed a sensibility of 80,3% and specificity of 61,2% for these markers (AUC: 0,73) in discriminating between ALS and ONND patients (Figure 1).

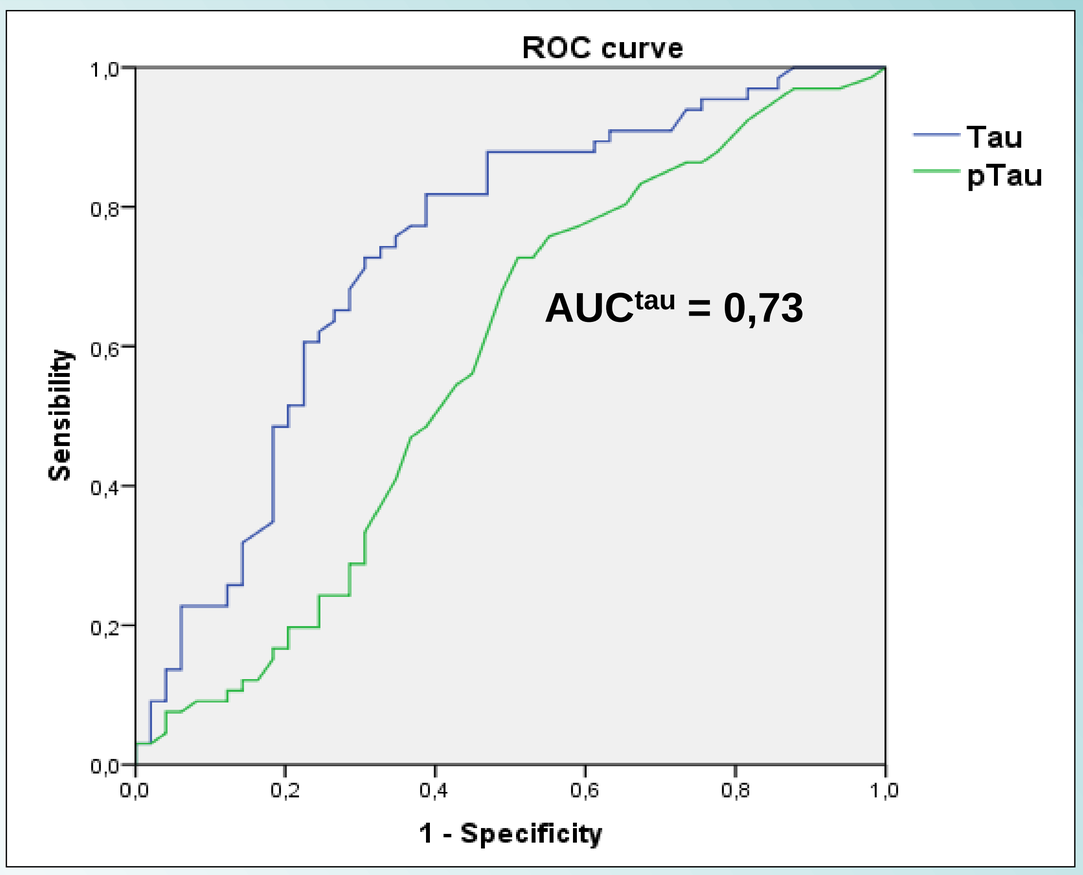

FIGURE 1 – ROC curve of specificity and sensibility of Tau and pTau in discriminating between ALS and ONND.

Results 3

CSF Tau and pTau did not differ between ALS patients stratified for clinical/anamnestic features such as occupational exposure to working toxicants; cognitive impairment; site of onset (bulbar/spinal and UMN/LMN). Furthermore, these markers did not correlate with age at onset, onset-diagnosis interval, ALSFRS-r, MMT, progression rate, time to generalization. Kaplan Meier curve showed a shorter survival (event as death/tracheostomy) in ALS patients with higher CSF tau (p=0.03) (Figure 2) with a 3-fold higher risk of death/tracheostomy during follow up (range: 4.7-125 months) in patients with high CSF tau levels.

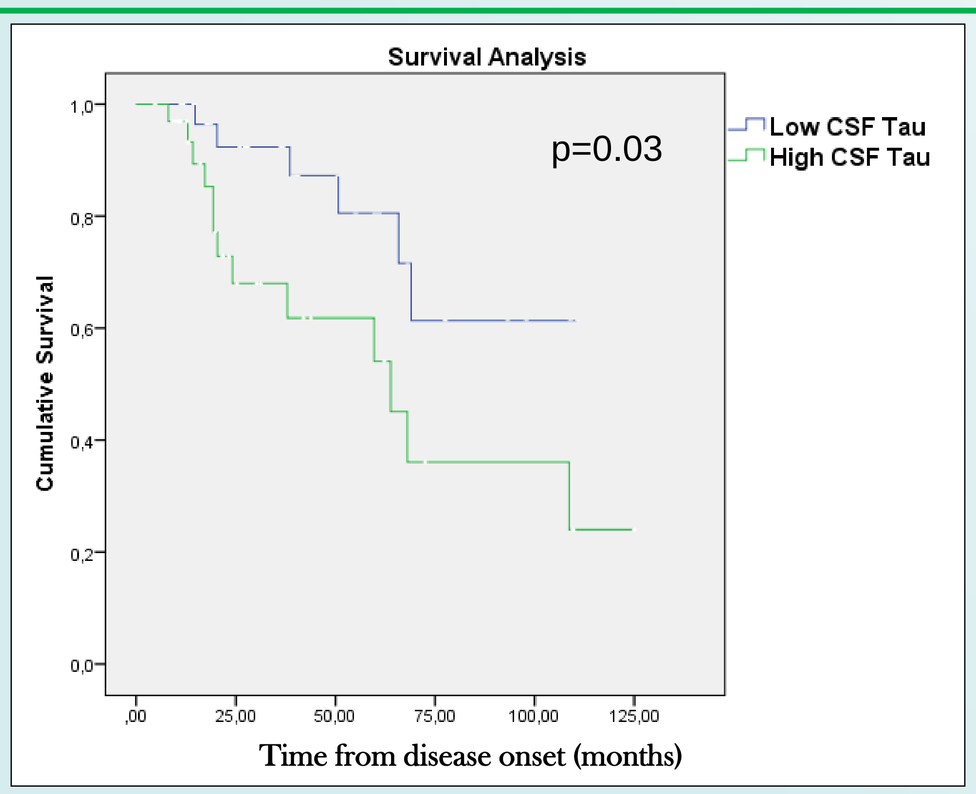

FIGURE 2 – Analysis of survival. Median time from disease onset to death/tracheostomy in patients with high CSF tau levels: 21,73 months. Median time from disease onset to death/tracheostomy in patients with low CSF tau levels: 39,3 months

Discussion

- CSF tau levels and ptau/tau ratio at diagnosis were significantly higher in ALS patients than ONND , reflecting the burden of neurodegeneration that characterizes ALS. On the other hand, their lower levels than in AD suggest a less extensive neurodegeneration.
- The low specificity and sensibility of those biomarkers makes them an unreliable diagnostic tool for ALS. Similarly the lack of relations between CSF tau and Ptau levels and clinical features limits their prognostic role on the progression of the disease.
- High levels of CSF Tau, even if independent of the ALS clinical features, are related to a shorter survival.

In ALS CSF Tau and pTau proteins cannot be considered as a diagnostic biomarker. The possible role of survival predictor has to be confirmed in studies in larger cohorts.

References

1) Tarasiuk J, Kulakowska A, Drozdowski W, Kornhuber J, Lewczuk P. CSF markers in amyotrophic lateral sclerosis. J Neural Transm (Vienna). 2012 Jul;119(7):747-57.

2) Grossman M, Elman L, McCluskey L, McMillan CT, Boller A, Powers J, Rascovsky K, Hu W, Shaw L, Irwin DJ, Lee VM, Trojanowski JQ. Phosphorylated tau as a candidate biomarker for amyotrophic lateral sclerosis. JAMA Neurol. 2014 Apr;71(4):442-8.

3) Wilke C, Deuschle C, Rattay TW, Maetzler W, Synofzik M. Total tau is increased, but phosphorylated tau not decreased, in cerebrospinal fluid in amyotrophic lateral sclerosis. Neurobiol Aging. 2015 Feb;36(2):1072-4.