



### **Središnja medicinska knjižnica**

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The 8th International Conference on Alzheimer's and Parkinson's Diseases (AD/PD) took place on March 14-18, 2007, in Salzburg, Austria, and included over 2,200 scientific participants, the largest attendance ever in this series of Alzheimer's disease / Parkinson disease conferences. The book „New Trends in Alzheimer and Parkinson related disorders – ADPD 2007“ contains 46 papers, written by selected authors, who had presented their research at the Meeting.

## **CSF tau proteins in evaluation of patients with suspected dementia**

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### **Summary**

Using commercially available ELISA kits, we evaluated the diagnostic value of CSF total tau protein (t-tau), tau phosphorylated at threonine 181 and serine 199 (p-tau181 and p-tau199) in early Alzheimer's disease (AD) versus healthy controls (HC) and other primary causes of dementia, such as frontotemporal dementia (FTD), vascular dementia (VaD) and dementia with Lewy-bodies (DLB). Mean CSF t-tau and CSF p-tau181 levels were significantly elevated in AD patients compared to FTD, VaD and HC. Discrimination between AD and DLB was maximized by using p-tau181 with a sensitivity of 91% and a specificity of 94%, whereas t-tau was optimal to separate AD from VaD with a sensitivity of 91% and specificity of 95%. P-tau199 showed low specificity of 20-30% in distinguishing AD from other groups when sensitivity was set at 85% or greater. We concluded that p-tau181 and t-tau represent useful biological markers for differentiating early AD from other causes of dementia.

## Introduction

Abnormal hyperphosphorylation of the microtubule-associated protein tau and its incorporation into neurofibrillary tangles are major hallmarks of the pathogenesis of Alzheimer's disease (AD). The cerebrospinal fluid (CSF) levels of phosphorylated tau proteins reflect the phosphorylation state of tau in the brain. Using monoclonal antibodies, different tau phosphoepitopes can be sensitively detected in CSF.

In this pilot study, our objective was to determine the diagnostic value of CSF total tau protein (t-tau), tau protein phosphorylated at threonine 181 and 199 (p-tau181 and p-tau199) in distinguishing early AD from nondemented healthy control subjects (HC) and other types of dementia, such as frontotemporal dementia (FTD), dementia with Lewy bodies (DLB) and vascular dementia (VaD).

## Materials and Methods

A total of 39 subjects were included. We analyzed 26 patients with clinical diagnosis of early AD, FTD, DLB and VaD, and 13 healthy controls (HC). To exclude secondary causes of dementia, during the initial work-up all patients underwent general and neurological examination, Mini Mental State Examination (MMSE), complete blood tests including electrolytes, thyroid function, albumin, levels of vitamin B<sub>12</sub>, VDRL, ECG and neuroimaging (CT or MRI scan of the brain). Patients without secondary causes of dementia finally underwent lumbar puncture for CSF analysis. Among the patients who fulfilled NINCDS-ADRDA criteria for probable AD, those with significant white matter changes on neuroimaging and/or Hachinski ischemic score >4 were excluded from the study. Finally, eleven patients with probable early AD were recruited. None of these patients was under therapy with cholinesterase inhibitors or memantine. Eight selected patients with VaD fulfilled NINCDS-AIREN criteria for VaD, five patients fulfilled clinical criteria for FTD and two for DLB. Control subjects had no evidence of the cognitive decline and were otherwise physically and mentally healthy. Levels of t-tau, p-tau181 and p-tau 199 in the CSF. CSF levels were measured using commercially available ELISA kits (t-tau and p-tau199 from BioSource, Camarillo, CA, USA, and p-tau181 from Innogenetics, Ghent, Belgium). Study was approved by the Ethical Committee and informed consent was obtained from all participants.

## Results

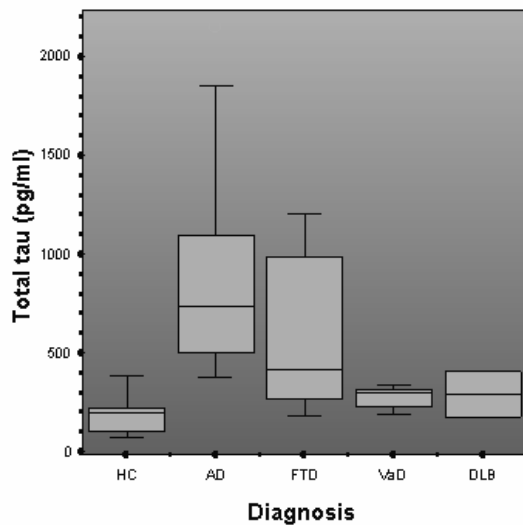
The median levels of the studied t-tau and p-tau181 proteins were significantly elevated in patients with AD compared with other groups (**Table 1** and **Figure 1**).

**Table 1.** Median levels of t-tau, p-tau181 and p-tau199 as revealed by ELISA.

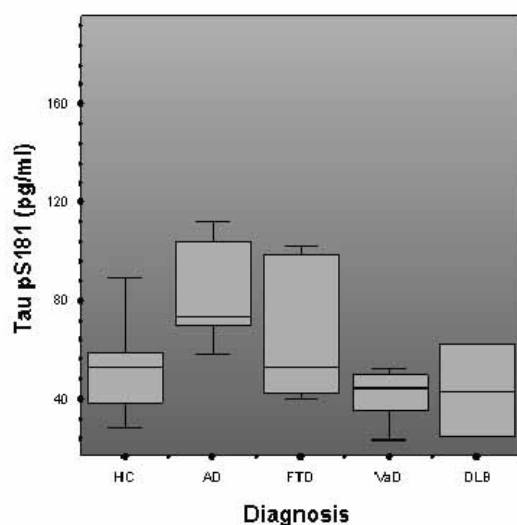
Group (n)	Age, Mean±SD (Range), years	Gender F/M, No	MMSE, Mean±SD (Range)	T-tau, Median (25th - 75th percentile), pg/ml	P-tau181, Median (25th - 75th percentile), pg/ml	P-tau199, Median (25th-75th percentile), pg/ml
AD (11)	66.4 ± 8.5 (51-77)	4/7	16.9 ± 4.5 (10-23)	730.0 (486.0-1200.0)	73.0 (69.0-110.0)	53.0 (50.0-61.0)
VaD (8)	73.2 ± 6.1 (63-81)	4/4	17.4 ± 4.7 (10-23)	290.0 (216.5-315)	44.0 (30.75-50.75)	47.0 (43.25-50.75)
DLB (2)	67.2 ± 5.0 (63-70)	1/1	14 ± 8.5 (8-20)	286.0 (172.0-400.0)	43.0 (24.0-62.0)	59.5 (58.0-61.0)
FTD (5)	65.7 ± 2.5 (62-69)	2/3	22.4 ± 2.1 (19-25)	410.0 (220.0-1092.0)	53.0 (41.0-100.0)	56.0 (47.5-59.0)
HC (13)	60.7 ± 10.0 (45-85)	5/8	29.7 ± 0.7 (28-30)	192 (94.5-215.0)	53.0 (37.5-58.75)	50.0 (46.5-54.75)

**Figure 1.** Boxplots for **a.** CSF t-tau, **b.** p-tau181 and **c.** p-tau199. Boxes represent the median, the 25th and 75th percentiles, bars indicate the range of data distribution. Circles represent outliers (values more than 1.5 box length from the 75th/25th percentile).

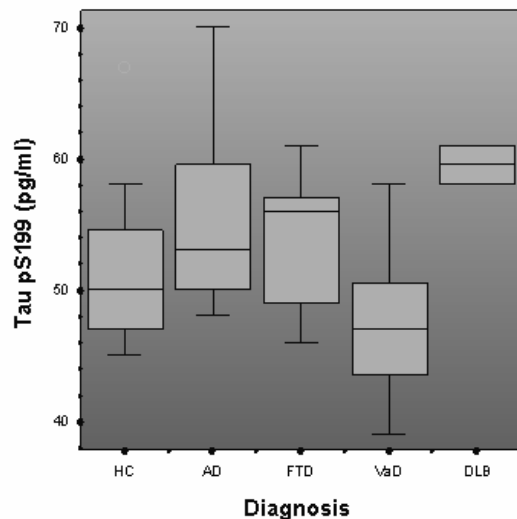
**Fig. 1a.**



**Fig. 1b.**



**Fig. 1c.**



When considered as single markers, t-tau and p-tau181 reached specificity levels greater than 75% between AD and the combined non-AD group when sensitivity was set at 85% or higher. Statistical differences are shown in **Table 2**. Maximal discrimination between AD and dementia with Lewy bodies was obtained using p-tau181 (91% sensitivity and 94% specificity). T-tau separated AD and VaD groups with 91% sensitivity and 95% specificity. P-tau199 showed very low specificity (25-30%) in distinguishing AD from other causes of dementia as well as from healthy controls.

**Table 2.** Specificity of single markers when sensitivity was set at 85% or higher.

<b>AD vs.</b>	<b>t-tau</b>	<b>p-tau181</b>	<b>p-tau199</b>
Non-AD (n=28)	85.2	81.5	29.6
VaD (n=8)	95.0	83.3	25.0
DLB (n=2)	50.0	94.0	0.0
FTD (n=5)	40.0	60.0	20.0
HC (n=13)	100.0	83.3	25.0

### **Conclusions**

Our results largely confirmed earlier observations (refs. 1-5) that t-tau and particularly p-tau181 may be useful biological markers for distinguishing AD from other primary causes of dementia such as DLB and VaD. These findings suggest that CSF examination of tau proteins should become a part of routine diagnostic procedure for patients with suspected dementia.

## References

1. BÜRGER K. et al. Phosphorylated tau predicts rate of cognitive decline in MCI subjects: A comparative CSF study. *Neurology* 65:1502-1503, 2005.
2. DE LEON M.J. et al. MRI and CSF studies in the early diagnosis of Alzheimer's disease. *J Int Med* 256: 205-223, 2004.
3. HAMPEL H. et al. Measurement of phosphorylated tau epitopes in the differential diagnosis of Alzheimer disease. *Arch Gen Psychiat* 61: 95-102, 2004.
4. HANSSON O. et al. Association between CSF biomarkers and incipient Alzheimer's disease in patients with mild cognitive impairment: a follow-up study. *Lancet Neurol* 5: 228-234, 2006.
5. SJÖGREN M. et al. Both total and phosphorylated tau are increased in Alzheimer's disease. *J Neurol Neurosurg Psychiatry* 70:624-630, 2001.
6. VANDERSTICHELE H. et al. Analytical performance and clinical utility of the Innotest phospho-tau181P assay for discrimination between Alzheimer's disease and dementia with Lewy bodies. *Clin Chem Lab Med* 44: 1472-1480, 2006.