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A novel diagnostic tool: Measurement of CSF total prion protein levels for distinguishing CJD from Alzheimer's disease*

» INTRODUCTION

Although typical forms of Alzheimer disease (AD) and Creutzfeldt-Jakob disease (CJD) are clinically distinguishable, atypical AD phenotypes remain a diagnostic challenge. The current clinical diagnostic criteria for identifying CJD, 14-3-3 protein in cerebrospinal fluid (CSF), is unfortunately characterized by a diagnostic specificity of only 71 % for CJD.

» AIMS

These study addresses relevance of determining the total prion protein (t-PrP) level in CSF for differential biological diagnosis. Therefore the **BetaPrion® HUMAN EIA** was used additionally to other relevant biomarker determination such as total Tau and P-tau$_{181}$ protein.

» STUDY DESIGN

A retrospective study of an autopsy-confirmed cohort of 82 patients was performed to distinguish 30 definite cases AD from 52 definite cases CJD by evaluation of CSF t-PrP levels. Furthermore CSF t-PrP was measured in a cohort of 104 patients including 55 patients with portable AD, 26 with portable sporadic CJD and 23 control patients. 46 patients diagnosed as having portable AD presented atypical phenotypes.

» CSF ANALYSIS

CSF t-PrP was measured for all patients using Analytik Jenas **BetaPrion® HUMAN EIA**. The ratio of total Tau protein and P-tau$_{181}$ (INNOTEST htau-Ag and INNOTEST phophorylated Tau$_{181}$, Innogenetics/Fujirebio) was calculated and diagnostic accuracy of each biomarker alone or in combination was determined. Then misclassification rate for each biomarker that corresponded to the percentage of patients within the group of atypical AD phenotypes wrongly classified as CJD was calculated.

RESULTS

CSF Biomarker Values in Definite and Probable AD and CJD groups

As shown in **Figure 1** t-PrP levels were significantly higher in definite AD than in definite CJD. Where as no difference was found between typical probable AD and definite AD, a significant difference was shown between probable and definite CJD. The comparison of the typical AD groups with CJD groups yielded a significant difference in t-PrP levels. The control population showed significantly lower t-PrP levels than the typical AD group and significantly higher values than CJD groups.
The cutoff of 263 µg/L t-PrP was determined to distinguish between AD and CJD with 82.0 % sensitivity and specificity, whereas T-tau/t-PrP ratio discriminates with 98.6 % sensitivity and 97.7 % specificity.
As displayed in receiver operating characteristics curve comparison analyses **(Figure 2)**, T-tau levels (cutoff: 1128 ng/l) distinguish typical AD from CJD groups with 91.3 % sensitivity and 92.9 % specificity. For P-tau$_{181}$ (cutoff: 63ng/l) a sensitivity of 69.0 % and 82.4 % specificity was observed. A T-tau/P-tau$_{181}$ value higher than 13.2 yielded 94.2 % sensitivity and 98.9 % specificity.

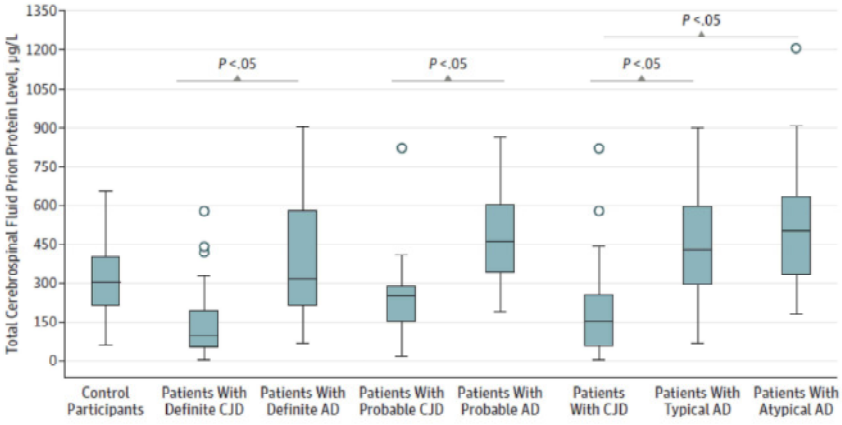

Figure 1 | Total Cerebrospinal Fluid Prion Protein in Control, AD and CJD populations. Typical AD indicates definite AD and portable AD; and CJD, definite CJD and portable CJD.

CSF Biomarkers in Atypical Probable AD compared with CJD and Typical AD Groups

The cutoff value of 263 µg/l for t-PrP distinguished CJD and atypical AD with 82.1 % sensitivity and 93.1 % specificity. **Table 1** represents the misclassification rates of patients with atypical AD when using each relevant biomarker for CJD diagnosis. The misclassification rate of atypical AD phenotypes decreased from 43.5 % when considering p14-3-3 results, to only 4.3 % when calculating the ratio of Tau total/(p$_{181}$Tau x t-PrP).

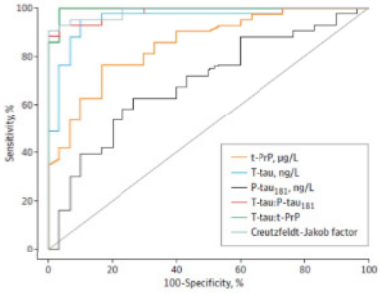

Figure 2 | Comparison of receiver operating characteristics curves for different CSF biomarkers for differential diagnosis between AD and CJD. The corresponding areas under the curve are 0.996 (T-tau/t-PrP), 0.995 (CJD factor), 0.994 (T-tau/P-tau$_{181}$), 0.964 (T-tau), 0.886 (t-PrP), and 0.803 (P-tau$_{181}$).

Parameters and Cutoff Values for Differential Diagnosis of CJD vs Typical AD	Patients Diagnosed as Having CJD, %	
	a-AD (n = 46)	CJD (n = 78)
p14-3-3 Test results (trace or positive)	43.5	96.2
T-tau, >1128 ng/L	65.2	91.3
T-tau:P-tau$_{181}$, >13.2	13.0	94.2
t-PrP, ≤263 µg/L	8.7	82.4
T-tau:t-PrP, >5.30	6.5	98.8
Creutzfeldt-Jakob factor, >0.054	4.3	95.7

Table 1 | Classification of a-AD and Patients with CJD with each relevant biomarker for CJD diagnosis.

CONCLUSIONS

In this study evidence was provided to introduce CSF t-PrP measurements as a new biomarker to help clinicians exclude CJD in the setting of AD when suspicion of CJD increases owing to unusual presentation, evolution, and/or biological profile ambiguity. Combining CSF t-PrP with Tau proteins into the so-called **Creutzfeldt-Jakob factor (Tau total/(p$_{181}$Tau x t-PrP)** differentiates CJD and atypical AD with 100 % sensitivity and 95.7 % specificity.
The use of CSF t-PrP levels may be beneficial in clinical practice in addition to the current classic biomarkers.

Reference:
* Dorey A, Tholance Y, Vighetto A, Perret-Liaudet A, Lachman I, Krolak-Salmon P, Wagner U, Struyfs H, De Deyn PP, El-Moualij B, Zorzi W, Meyronet D, Streichenberger N, Engelborghs S, Kovacs GG, Quadrio I. (2015) Association of Cerebrospinal Fluid Prion Protein Levels and the Distinction Between Alzheimer Disease and Creutzfeldt-Jakob Disease. JAMA Neurol. doi: 10.1001/jamaneurol.2014.4068.

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