The combined analysis of CSF t-PrP, t-tau, p-tau and $A\beta_{1-42}$ best distinguishes Creutzfeldt-Jakob disease from Alzheimer disease

Samir Abu Rumeileh[1], Francesca Lattanzio[1], Romana Rizzi[3], Sabina Capellari[1,2], Piero Parchi[1,2].

1Department of Biomedical and Neuromotor Sciences, University of Bologna, Bologna, Italy.
2 IRCCS Institute of Neurological Sciences of Bologna, Bellaria Hospital, Bologna, Italy.
3 Department of Neurology, IRCCS Arcispedale Santa Maria Nuova, Reggio Emilia, Italy.

Background

According to recent studies, the determination of CSF t-tau/phosphorylated tau (p-tau) ratio and total prion protein (t-PrP) levels significantly improves the accuracy of Alzheimer disease (AD) diagnosis in atypical cases with clinical or laboratory features mimicking Creutzfeldt-Jakob disease (CJD) [1,2]. However, this has neither been validated nor tested in series including atypical CJD variants. Furthermore, the added diagnostic value of $A\beta_{1-42}$ remains unclear.

Our aim was to investigate the efficiency of CSF t-PrP levels either alone or in combination with other CSF biomarkers to discriminate CJD from AD.

Methods

We performed a retrospective study on 230 CSF samples that were analyzed for CSF 14-3-3, t-tau, p-tau, and $A\beta_{1-42}$. We measured t-PrP levels in all samples. Based on clinical findings at follow-up, genetic, neuropathological and CSF biomarker data, we identified five groups: 45 typical AD patients, 44 atypical/rapidly progressive AD (a/rp AD) patients, 54 typical CJD patients, 54 atypical CJD patients, and 33 controls.

Results

Histotype classification of CJD cases

	Typical CJD (N=54)	Atypical CJD* (N=54)
Definite sporadic CJD	51	32
MM1	23	6
MM1+2C	8	5
VV2	15	0
MV 2K	5	13
MM 2C	0	5
MM 2T	0	2
VV1	0	1
Definite genetic CJD	1	7
E200K-129MM(V)	1	6
R208K-129VV	0	1
Probable CJD	2	15
MM	0	3
MV	2	12

* The classification of atypical CJD required at least one among: (1) clinical course >2 years, (2) progressive cognitive decline without focal neurological signs (up to the time of CSF analyses), (3) CSF t-tau < 1200 pg/ml, (5) borderline or negative CSF 14-3-3 assay

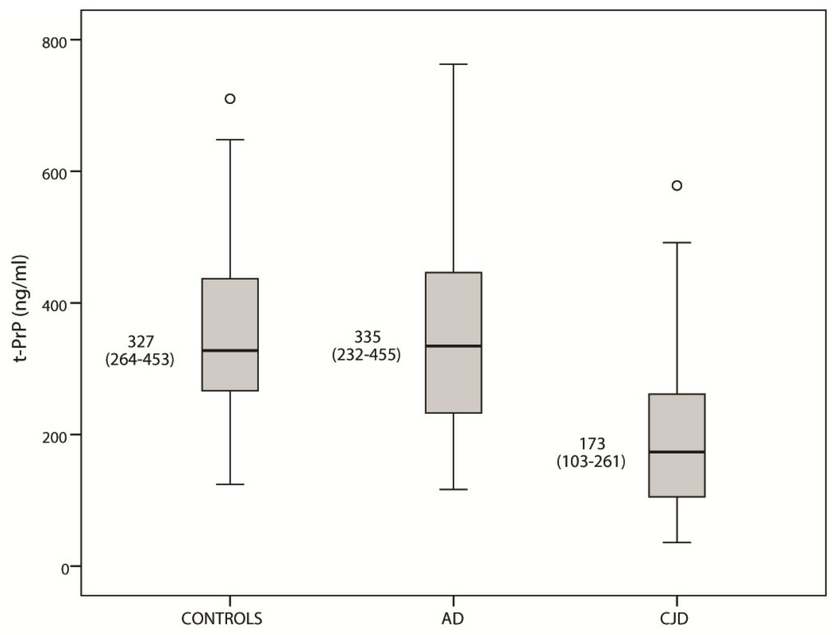
Clinical and biological features of atypical/rapidly progressive AD (N=44)

Clinical presentation	
Cognitive decline	44/44
Extrapyramidal signs	9/44
Pyramidal signs	3/44
Myoclonus	5/44
Cerebellar signs	2/44
Biomarkers Data	
t-tau>1200 pg/ml	22/44
Positive 14-3-3	7/44
Genetic features	
APOE gene allele frequency§	ε4 - 30% ε4/4 13%
FAD Mutations** (APP, PSEN1, PSEN2)	2/13 (both in PSEN1)

§ patients (n=31) with available DNA / informed consent for genetic analyses

**patients (n=13) with early onset AD (<65 years) and/or a positive family history

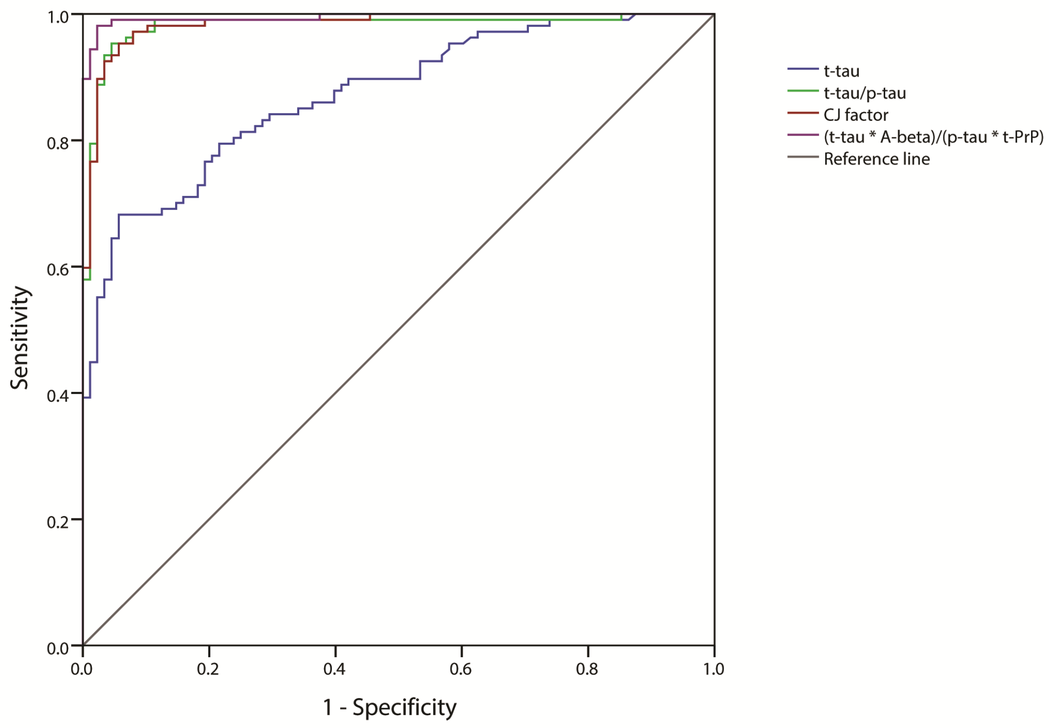
CJD patients showed significantly lower CSF t-PrP levels than controls ($p<0.001$) and AD patients ($p<0.001$). Atypical CJD was associated with lower t-PrP levels in comparison to typical CJD ($p=0.005$; see table below).



	all AD (N=89)	typical AD (N=45)	a/rp AD (N=44)	all CJD (N=108)	typical CJD (N=54)	atypical CJD (N=54)
t-PrP (ng/ml) Median (IQR)	335 (234-455)	334 (281-455)	345 (224-469)	173 (103-261)	209 (131-288)	141 (83-208)
t-tau (pg/ml) Median (IQR)	822 (582-1223)	697 (509-846)	1223 (703-1668)	2489 (1389-7344)	7284 (3022-10004)	1390 (914-2086)
p-tau (pg/ml) Median (IQR)	104 (77-140)	90 (74-115)	122 (81-151)	49 (37-68)	55 (41-72)	46 (34-65)
$A\beta_{1-42}$ (pg/ml) Median (IQR)	358 (266-465)	371 (279-469)	326 (250-442)	527 (366-747)	553 (353-773)	498 (370-738)
14-3-3 N° positive	7/89	0/45	7/44	68/108	54/54	14/54
t-tau/p-tau Median (IQR)	7.67 (6.76-10.06)	7.13 (6.38-7.98)	9.08 (7.35-11.27)	59.30 (27.03-110.78)	110.71 (64.52-198.34)	32.19 (20.58-52.11)
$A\beta_{1-42}$ × t-tau/p-tau Median (IQR)	2870 (2143-3938)	2615 (2010-3373)	3089 (2344-4661)	27675 (13490-59655)	55348 (30720-121296)	15176 (9099-27420)
CJ factor Median (IQR)	0.024 (0.018-0.037)	0.022 (0.018-0.031)	0.032 (0.019-0.045)	0.370 (0.161-0.778)	0.637 (0.238-1.345)	0.223 (0.131-0.460)
(t-tau × $A\beta_{1-42}$) / (p-tau × t-PrP) Median (IQR)	8.63 (6.02-12.62)	7.64 (5.68-10.56)	10.88 (6.06-14.80)	155.05 (82.86-400.74)	262.58 (133.62-682.16)	103.84 (69.94-204.80)

T-tau, 14-3-3 or t-PrP alone yielded, respectively, 80.6, 63.0 and 73% sensitivity and 75.3, 92.1 and 75% specificity in distinguishing AD from CJD.

On Receiver Operating Characteristic (ROC) curve analyses of biomarker combinations, the (t-tau × $A\beta_{42}$)/(p-tau × t-PrP) ratio achieved the best accuracy, with 98.1% sensitivity and 97.7% specificity overall (see figure below), and 96.2% sensitivity and 95.5% specificity for the "atypical" disease groups.



Discussion

- We confirm the previously described decrease of t-PrP CSF levels in CJD, which may reflect the extent of abnormal PrP deposition in CJD brains like so CSF $A\beta_{1-42}$ levels inversely correlates with amyloid burden in AD.
- Atypical CJD variants such as MV2 and MM2 are usually associated with a relatively high amount of PrP^{Sc} accumulation involving major areas of the brain. This could explain the higher reduction of t-PrP levels in atypical CJD cases.
- In our CJD population, $A\beta_{1-42}$ CSF levels were highly heterogeneous, with several cases of both typical and atypical CJD groups showing a lower than cut-off value. Whether this result simply reflects the burden of associated AD pathology or also depends on a pathogenic interaction between PrP and Aβ1-42 remains to be seen.
- While individually none of the major CSF proteins that reflect the specific molecular pathology of AD (p-tau and Aβ42) and CJD (PrP) or the associated neuronal damage (t-tau, 14-3-3) distinguish the two disorders with sufficient accuracy, various combinations of these markers significantly increase the diagnostic power. Among, them the (t-tau × $A\beta_{1-42}$)/(p-tau × t-PrP) ratio best distinguishes CJD from AD patients and is especially recommended in the diagnostic work-up of patients presenting with atypical clinical features that are compatible with both diseases.

References

1 Skillbäck T, Rosén C, Asztely F, Mattsson N, Blennow K, Zetterberg H. Diagnostic performance of cerebrospinal fluid total tau and phosphorylated tau in Creutzfeldt-Jakob disease: results from the Swedish Mortality Registry. JAMA Neurol. 2014 Apr;71(4):476-83.

2 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. Association of cerebrospinal fluid prion protein levels and the distinction between Alzheimer disease and Creutzfeldt-Jakob disease. JAMA Neurol. 2015 Mar;72(3):267-75.