

Clinical Validation Of Plasma P-217tau In Neurological Diseases



Takeshi Kawarabayashi^{1,2}, Takumi Nakamura², Ryoma Takahashi², Tetsuya Ueda³, Seiji Kinoshita³, Chikage Uchida³, Takashi Sugawara¹, Kentaro Hashimoto¹, Kunihiko Ishizawa¹, Masakuni Amari¹, Kasahara Hiroo², Yoshio Ikeda², Masamitsu Takatama¹, Mikio Shoji^{1,2}.
¹Neurology, Geriatrics Research Institute and Hospital, Maebashi, Japan, ²Neurology, Gunma University Graduate School of Medicine, Maebashi, Japan, ³Analytical Research Center, Mediford Corporation, Tokyo, Japan

ALS and iNPH are two major pitfalls for the clinical application of plasma p-217tau as a biomarker of AD.
Lower motor neuron injury in ALS and cognitive dysfunction in iNPH were associated with elevated plasma p-217tau levels.

INTRODUCTION

Plasma p-217tau was shown to be highly accurate for differentiating AD and AD-related syndromes from other neurological diseases However, increased plasma p-217tau levels have recently been reported in amyotrophic lateral sclerosis (ALS), chronic kidney disease, cardiovascular disease factors, and newborns. For this reason, it is necessary to validate neurological diseases and physical conditions which increase plasma p-217tau levels, to enable the clinical use of the plasma p-217tau level as a specific and sensitive biomarker of AD pathology, and to rule out other pathological conditions. Here, we validated the utility of the plasma p-217tau level as a biomarker of AD by assessing plasma p-217tau levels in 12 other neurological diseases¹.

SUBJECTS

A total of 298 plasma samples, consisting of samples from 81 AD patients, 204 patients with 12 other common neurological diseases, and 13 healthy and cognitively unimpaired control subjects. Patients with high CSF p-181tau levels (>50 pg/mL) were excluded from iNPH, as it was considered as a complication of AD.

Table 1. Patients' profiles, diseases, cognitive function, and plasma p-217tau levels

Disease	N	F/M	Age	MMSE	p-217tau (pg/mL)
AD	81	50/31	69±11	21.6±6.1	\$22.98±14.59
ADD	40	24/17	68±12	18.1±6.3	27.05±14.68
ADMC1	38	24/13	70±9	24.6±3.5	19.70±13.71
ADCU	3	2/1	51±22	29.3±1.2	10.13±7.10
CAA	11	5/6	69±13	20.6±8.2	8.13±8.30
DLB	2	2/0	68, 70	13, 29	7.95, 1.75
FTD	5	1/4	66±7	23.6±2.7	2.89±1.96
CBS	11	5/6	72±6	22.2±5.4	3.92±1.97
PSP	18	6/12	73±7	22.4±5.2	4.54±2.39
PD	32	22/10	67±10	27.2±2.8	3.15±1.35
MSA	21	9/12	67±9	26.2±2.7	3.49±1.74
CCA	5	4/1	56±9	25.0±5.7	3.48±1.62
ALS	40	16/24	68±8	25.9±4.6	*6.82±4.25
iNPH	40	21/19	78±7	20.6±5.5	*8.07±7.19
MS	15	14/1	37±14	n.e.	2.36±0.95
NMOSD	4	3/1	55±24	n.e.	5.15±5.72
HCU	13	3/10	57±16	29.3±1.9	2.80±1.14
Total	298	161/137	67±13	22.9±6.1	10.01±11.68

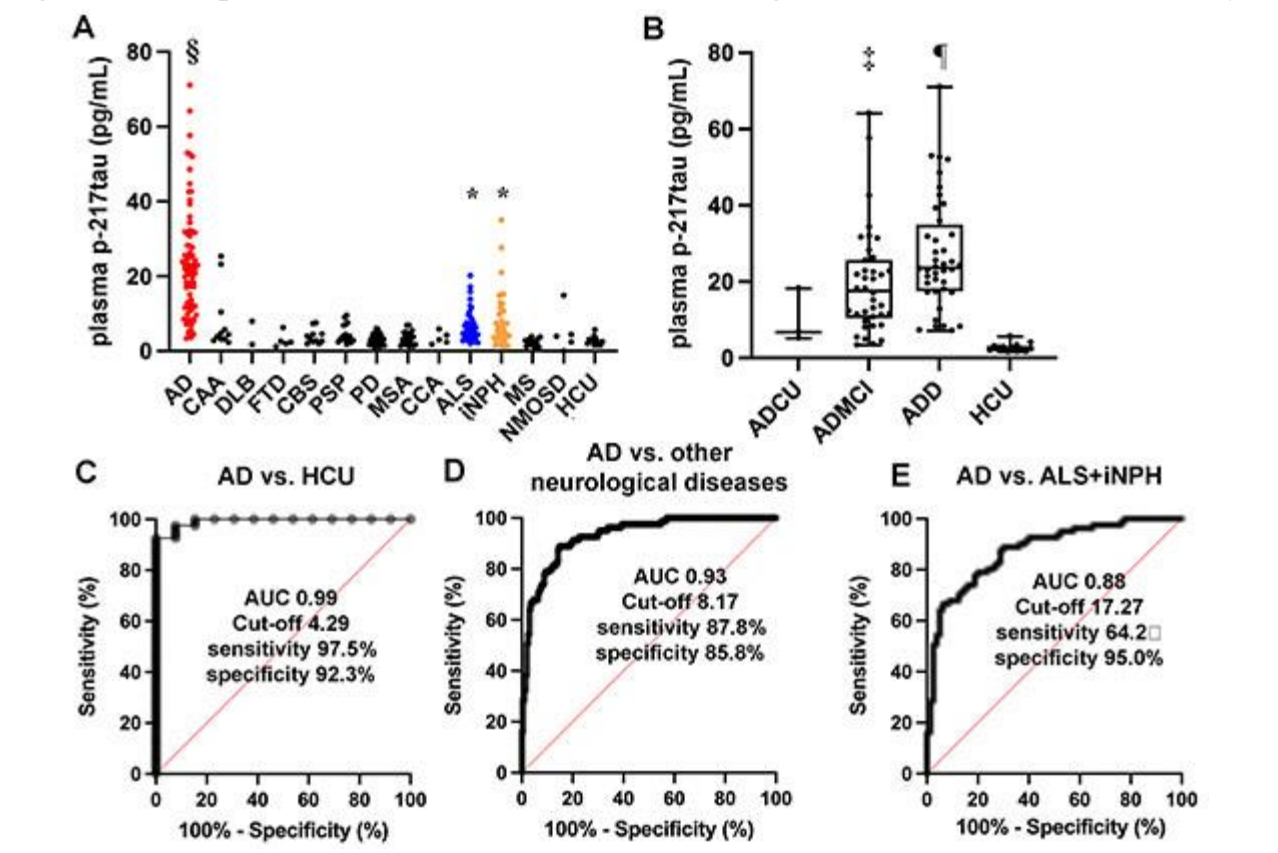
§ p<0.0001, * p<0.05, n.s.: not significant, n.e.: not examined

METHODS

Plasma p-217tau levels were measured using an electrochemiluminescence assay from Meso Scale Diagnostics, LLC, Rockville, MD (S-PLEX; Cat No: K151APFS)². CSF t-tau, p-181tau, and p-217tau levels were measured using ELISA assays that we developed^{3,4}. CSF Aβ1-40 and Aβ1-42 were measured with an enzyme immunoassay using the Human Amyloid (1–40) ELISA Kit Wako II and the Human/Rat Amyloid (1–42) ELISA Kit Wako High-Sensitive (Wako, Pure Chemical Industries, Ltd., Osaka, Japan), respectively.

RESULTS

Fig1. Plasma p-217tau levels in various neurological diseases and ROC analysis



(A) Plasma p-217tau levels in various neurological diseases. (B) Plasma p-217tau levels of ADCU, ADMCI, and ADD patients compared with those of the HCU. (C-E) ROC analysis of the utility of the plasma p-217tau level for differentiating AD patients from the HCU (C), patients with other neurological diseases (D), and ALS and iNPH patients (E). ‡ p<0.001, † p<0.01, * p<0.05.

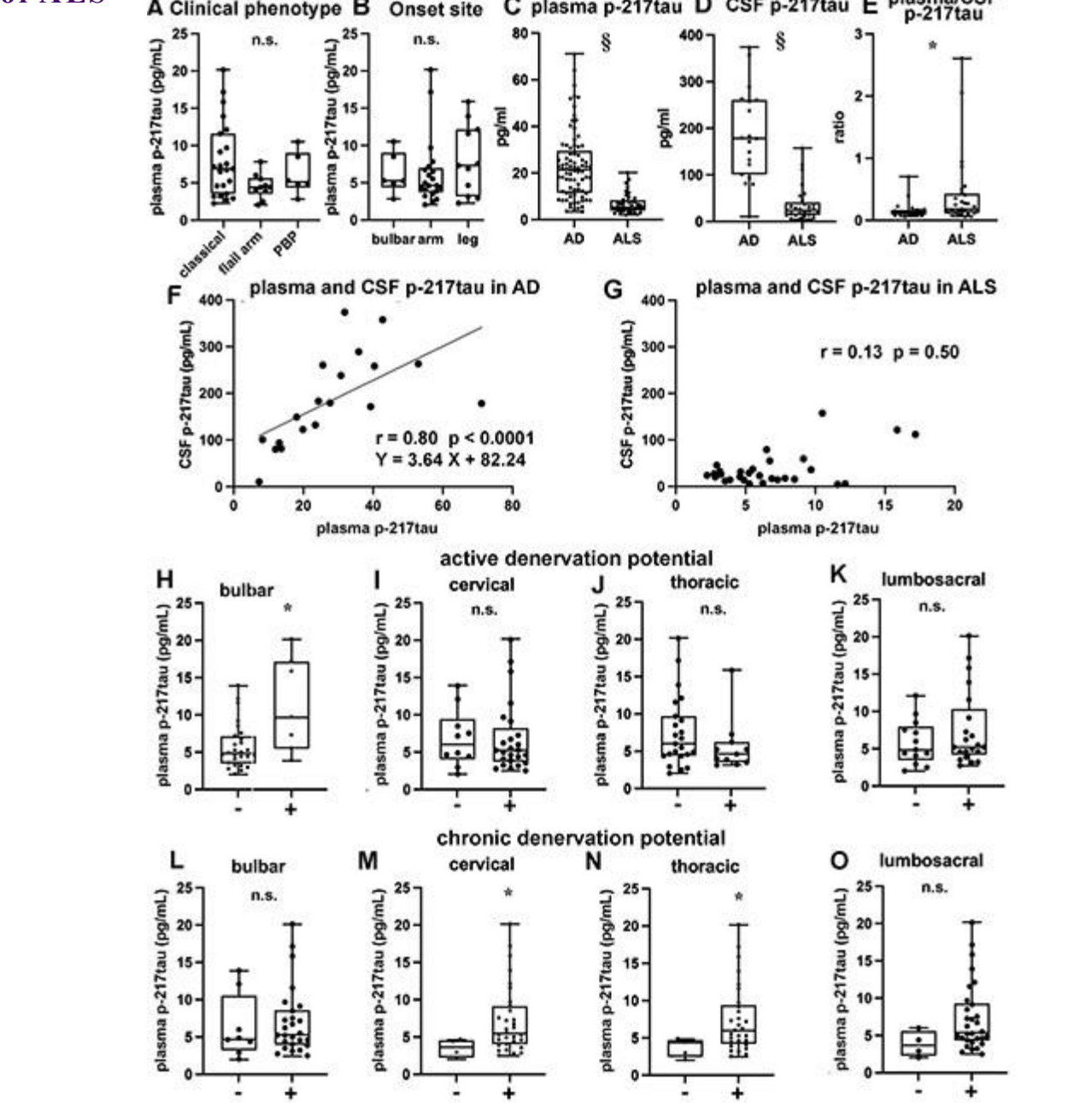
Table 2. CSF biomarker levels in AD, ALS, and iNPH

CSF biomarker (pg/mL)	AD	ALS	iNPH
p-217tau	185.4±97.8 n=19	36.7±37.1 n=29	n.e.
p-181tau	76.5±31.2 n=43	54.4±37.3 n=29	23.9±17.8 n=40
t-tau	710.9±292.0 n=43	653.3±256.9 n=29	178.2±96.3 n=40
Aβ1-42	546.0±271.3 n=62	n.e.	630.1±294.5 n=40
Aβ1-40	9244±3758 n=62	n.e.	5731±2416 n=40
Aβ1-40/Aβ1-42 ratio	18.87±7.89 n=62	n.e.	9.50±2.48 n=40

§ p<0.0001, * p<0.05, n.s.: not significant, n.e.: not examined

RESULTS

Fig2. Associations between plasma p-217tau and the clinical findings of ALS



(A, B) The clinical phenotype and affected sites at onset did not affect the plasma p-217tau level. (C, D) The mean plasma and CSF p-217tau level of the ALS patients compared to AD patients was 31%, and 20%, respectively. (E) The mean plasma p-217tau/CSF p-217tau ratio was significantly higher in ALS than in AD (F, G) Plasma p-217tau levels were strongly correlated with CSF p-217tau levels in AD (F), however, they were not correlated in ALS (G). (H-O) In the EMG analysis, the existence of active denervation potentials in the bulbar region, and chronic denervation in the cervical, thoracic, or lumbosacral region were found to be associated with higher plasma p-217tau levels. n.s.: not significant, *p<0.05 +: positive, -: negative

Table 3. Correlation study: plasma p-217tau and CSF biomarkers and clinical factors in ALS

Subject	Correlation coefficient (r)	Probability value (p)
CSF p-217tau	0.13	0.50
CSF p-181tau	0.34	0.07
CSF t-tau	0.030	0.88
Age at onset	0.25	0.12
Time since onset	0.16	0.32
MRC score	-0.21	0.20
UMN score	0.003	0.99
ALSFRS-R score	-0.17	0.29
ALSFRS-R progression rate	0.17	0.29
MMSE	-0.13	0.59
PaCO ₂	*0.39	*0.03
PaO ₂	0.042	0.82
%VC	-0.14	0.44

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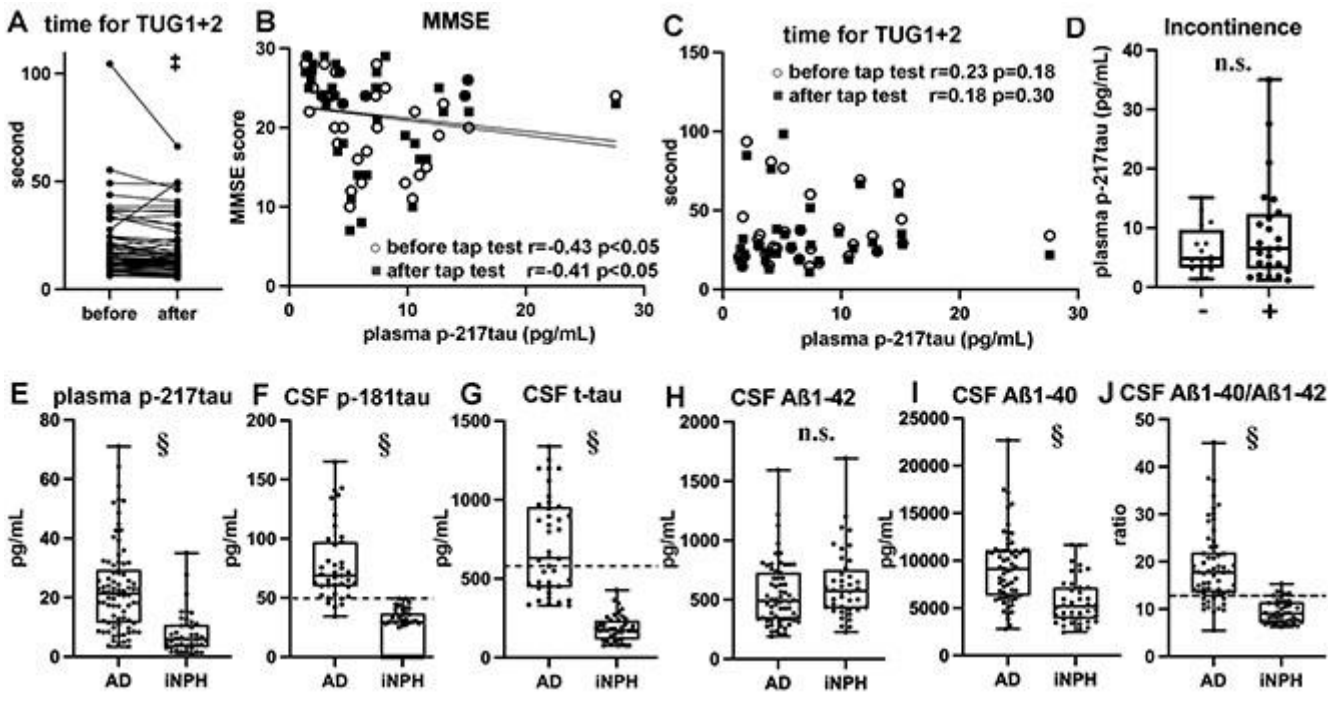
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Fig3. Plasma p-217tau and clinical factors and other CSF biomarkers in iNPH



(A) The mean time for the TUG1+2 conducted before the tap test was significantly worse than those for the TUG1+2 conducted after the tap test. (B) The plasma p-217tau level and MMSE score were negatively correlated before (○) and after (●) the tap test. (C) Gait disturbance, as assessed by the time for the TUG, was not correlated with the plasma p-217tau level before (○) or after (●) the tap test. (D) Plasma p-217tau levels did not differ between the patients that were negative and positive for urinary incontinence. Plasma p-217tau (E), CSFp-181tau (F), and CSF t-tau (G) levels were significantly higher in the AD patients than in those with iNPH. (H) CSF Aβ1-42 levels did not differ significantly between AD and iNPH. (I) CSF Aβ1-40/Aβ1-42 ratio (J) were significantly lower in the iNPH patients than in the AD patients. n.s.: not significant; The dashed lines represent the threshold levels for the HCU. § p<0.0001, ‡ p<0.001

CONCLUSIONS

Plasma p-217tau is an excellent biomarker for identifying AD pathology; however, ALS and iNPH are two major pitfalls for the clinical application of plasma p-217tau as a specific biomarker of AD.
LMN injuries in ALS and cognitive dysfunction in iNPH are both contributing factors for increased plasma p-217tau levels.
In clinical evaluations of plasma p-217tau levels, it is important to be aware that plasma p-217tau levels may be increased by mechanisms unrelated to AD pathology.

CONTACT

tkawara@ronenbyo.or.jp

ALZHEIMER'S ASSOCIATION

AAIC 26