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Cerebrospinal fluid amyloid beta and response of cognition to a tap test in idiopathic normal pressure hydrocephalus: a case–control study

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ABSTRACT

Objectives: To examine the relationship between cerebrospinal fluid (CSF) biomarkers of Alzheimer's disease (AD) and tap test response to elucidate the effects of comorbidity of AD in idiopathic normal-pressure hydrocephalus (iNPH).

Design: Case–control study.

Setting: Osaka University Hospital.

Participants: Patients with possible iNPH underwent a CSF tap test.

Measurements: Concentrations of amyloid beta (Aβ) 1–40, 1–42, and total tau in CSF were measured. The response of tap test was judged using Timed Up and Go test (TUG), 10-m reciprocation walking test (10MWT), Mini-Mental State Examination (MMSE), and iNPH grading scale. The ratio of Aβ1–42 to Aβ1–40 ($Aβ_{42/40}$ ratio) and total tau concentration was compared between tap test-negative (iNPH-nTT) and -positive (iNPH-pTT) patients.

Results: We identified 27 patients as iNPH-nTT and 81 as iNPH-pTT. $Aβ_{42/40}$ ratio was significantly lower (mean [SD] = 0.063 [0.026] vs. 0.083 [0.036], p = 0.008), and total tau in CSF was significantly higher (mean [SD] = 385.6 [237.2] vs. 293.6 [165.0], p = 0.028) in iNPH-nTT than in iNPH-pTT. Stepwise logistic regression analysis revealed that low $Aβ_{42/40}$ ratio was significantly associated with the negativity of the tap test. The response of cognition was significantly related to $Aβ_{42/40}$ ratio. The association between $Aβ_{42/40}$ ratio and tap test response, especially in cognition, remained after adjusting for disease duration and severity at baseline.

Conclusions: A low CSF $Aβ_{42/40}$ ratio is associated with a poorer cognitive response, but not gait and urinary response, to a tap test in iNPH. Even if CSF biomarkers suggest AD comorbidity, treatment with iNPH may be effective for gait and urinary dysfunction.

Key words: Idiopathic normal-pressure hydrocephalus, Alzheimer's disease, amyloid beta, total tau, tap test

Introduction

Normal-pressure hydrocephalus (NPH) is a treatable disorder characterized by a triad of symptoms including gait disturbance, cognitive impairment, and urinary dysfunction resulting from an accumulation of cerebrospinal fluid (CSF) (Adams *et al.*, 1965). NPH is classified into idiopathic NPH (iNPH), in which there is no apparent antecedent cause of hydrocephalus, and secondary NPH. In elderly community residents, iNPH is a common disease with a prevalence rate of 2.1–2.8% (Jaraj *et al.*, 2014; Nakashita *et al.*, 2016). Due to its high prevalence rate and treatable nature, iNPH is clinically important for older people.

The symptoms of iNPH are typically relieved following CSF shunt surgery. However, which

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symptoms improve as well as the extent of their improvement varies between patients (Malm *et al.*, 2000; Aygok *et al.*, 2005). Previous studies have observed that having a milder degree and shorter duration of iNPH symptoms before shunt surgery is predictive of a better prognosis after shunt surgery (McGirt *et al.*, 2005; Kazui *et al.*, 2013). These findings suggest that a long duration between symptoms onset and shunt surgery can cause irreversible damage in iNPH patients. Another plausible factor affecting response to a shunt surgery is comorbidity of iNPH with other disorders, particularly Alzheimer's disease (AD). AD-related pathology is prevalent in iNPH patients (Hamilton *et al.*, 2010; Elobeid *et al.*, 2015). In fact, previous studies have demonstrated that the presence of AD pathology suggested by brain biopsy, CSF biomarkers, and amyloid PET predicted poor responsiveness to shunt surgery in iNPH (Hamilton *et al.*, 2010; Tarnaris *et al.*, 2011; Patel *et al.*, 2012; Hiraoka *et al.*, 2015; Nakajima *et al.*, 2015; Kazui *et al.*, 2016; Hamdeh *et al.*, 2019).

In general, shunt surgery is considered when at least one of the triad symptoms is confirmed to have improved after transient removal of excess CSF (tap test) (Mori *et al.*, 2012). However, the sensitivity of the tap test is not sufficiently high (Mihalj *et al.*, 2016). Similar to the response to shunt surgery, comorbid AD pathology is likely to affect the response to a tap test given its lack of sensitivity. However, there are few studies exploring the association between tap test responsiveness and the presence of AD pathology in patients with iNPH. Therefore, we recruited patients with possible iNPH, divided them into two groups according to their tap test response, and compared CSF AD biomarkers between them to determine the effect of comorbidity of AD on tap test response in iNPH.

Methods

Participants and procedure

In this study, we recruited patients with possible iNPH who underwent a CSF tap test from the neuropsychological clinic of the Department of Psychiatry at the Osaka University Medical Hospital from April 2007 to March 2018. Patients with possible iNPH were examined by geriatric psychiatry and neurology specialists. Patients underwent standard neuropsychological and gait examinations, routine laboratory tests, and neuroimaging. Inclusion criteria for patients with possible iNPH according to Japanese guidelines (Mori *et al.*, 2012) were as follows: (1) 60 years or older; (2) presence of at least one iNPH triad symptom; (3) presence of ventriculomegaly on magnetic resonance (MR) imaging (Evans index > 0.3); (4) absence of other diseases or conditions that could influence clinical symptoms or radiological findings; and (5) no history or evidence of conditions that might cause secondary NPH.

Patients with possible iNPH also underwent a CSF tap test, in which 30 ml of CSF was removed via a lumbar tap. Patients with abnormal CSF contents or pressure were excluded. Patients were divided into two groups; one with positive results in tap tests (iNPH-pTT) and another with negative results in tap tests (iNPH-nTT). A positive result in the tap test was defined as a measurable improvement in symptoms after the lumbar tap.

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. All procedures involving human subjects/patients were approved by the Research Ethical Committee of Osaka University Hospital (Suita, Japan). Written informed consent was obtained from all patients prior to initiating the study procedures.

Tap test

All evaluations were conducted before and after a lumbar puncture by psychiatrists, neurologists, and neuropsychologists, who were blind to the results of CSF analyses. Gait speed was assessed with the Timed Up and Go Test (TUG) (Podsiadlo and Richardson, 1991) and 10-m reciprocation walking test (10mWT) twice a day for 3 consecutive days both before and after tapping, and the best score was used to evaluate the changes of gait disturbances. Cognition was assessed with the Mini-Mental State Examination (MMSE) (Folstein *et al.*, 1975) for general cognition, Frontal Assessment Battery (FAB) (Dubois *et al.*, 2000) for frontal lobe function, immediate, and delayed story recall subtests of the Rivermead Behavioral Memory Test (RBMT) (Wilson *et al.*, 1989) for memory, the Digit Symbol Substitution (DSS) and Block Design (BD) of the Wechsler Adult Intelligence Scale-III for psychomotor speed and visuospatial cognition, respectively, and attention/concentration subtest of the Wechsler Memory Scale – Revised (A/C in WMS-R) for attention. MMSE, FAB, and A/C in WMS-R were conducted before the day after as well as 1-week post tapping, and the best scores after tapping were used to evaluate changes in cognition. RBMT, DSS, and BD were conducted before and 1 week after tapping. Severity of the triad symptoms of iNPH was assessed with the iNPH Grading Scale (iNPHGS) (Kubo *et al.*, 2008).

According to the recommendation of Japanese guidelines (Mori *et al.*, 2012), the tap test response was judged as positive when one or more of the triads improved as follows: improvement of gait defined

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as a reduction of 10% or more in time of TUG or 10mWT, or a decrease of one or more in the gait score of iNPHGS; improvement of cognition defined as an increase of three or more in the MMSE score, or a decrease of one or more in the cognition score of iNPHGS; or improvement of urination defined as a decrease of one or more in the urinary score of iNPHGS.

CSF analysis

CSF samples were collected via a lumbar puncture following removal of the initial 2ml of CSF in the tap test, placed in 10 ml polypropylene tubes. All samples were collected between 10:00 and 12:00 and immediately centrifuged at 1500 rpm. One ml aliquots of the supernatant were placed in 1.5ml polypropylene tubes and stored at – 80 °C until assay. After we had accumulated CSF samples from 20 to 30 patients, we measured levels of amyloid β (Aβ) 1–40, Aβ 1–42, and total tau in 1 batch with commercial enzyme-linked immunosorbent assay kits (Human Amyloid β (1–42) Assay Kit, Human Amyloid β (1–40) Assay Kit (Wako), and Total Tau Human ELISA Kit, Novex, Chertsey, UK).

Statistical analysis

To compare baseline characteristics between iNPH-pTT and iNPH-nTT, we used a Mann–Whitney U test for the continuous and ordinal variables and a χ^2 test for the nominal variables. In each group, changes in scores of clinical assessments were evaluated using the Wilcoxon signed-rank test.

As the primary outcome, the ratio of Aβ 1–42 to Aβ 1–40 ($A\beta_{42/40}$ ratio) and total tau were compared between iNPH-pTT and iNPH-nTT using a Student's *t*-test. In addition, forward stepwise logistic regression analysis was performed to identify the effect of CSF biomarkers on tap test results, which was presented as odds ratio (OR) and the 95% confidence interval (CI), with $A\beta_{42/40}$ ratio and total tau as predictive variables and the tap test result as a dependent variable. When a significant association between the biomarkers and tap test response was found, multivariate logistic regression analyses were also performed with a total score of iNPHGS and duration of iNPH symptoms as covariates to control for the possible confounders of severity and duration of iNPH symptoms.

$A\beta_{42/40}$ ratio, as well as total tau, was also compared between the patients with and without improvement for each respective triad symptom using a Student's *t*-test. Stepwise multiple logistic regression analyses were performed with $A\beta_{42/40}$ ratio and total tau as predictive variables and responsiveness of each triad symptom in the tap test as dependent variables. When a significant association between biomarkers and the tap test result was found, multivariate logistic regression analyses were also performed to control for the potential confounders of degree and duration of iNPH symptoms.

All analyses were performed using SPSS for Mac Version 25.0 (IBM Corp., Armonk, NY, USA). The level of statistical significance was set at $p < 0.05$.

Results

Baseline characteristics

Overall, 108 patients participated in this study; 27 patients responded negatively (iNPH-nTT) while 81 responded positively (iNPH-pTT) to the tap test. There were no significant differences in the baseline characteristics between the two groups (Table 1).

In the iNPH-pTT group, all the clinical measures improved significantly after CSF removal, whereas in the iNPH-nTT group, significant improvements were detected only on the FAB, delayed recall score of a short story of the RBMT, and A/C score in the WMS-R. Among the iNPH-pTT group, gait disturbance, cognitive impairment, and urinary dysfunction significantly improved in 60, 36, and 20 patients, respectively. Among 81 patients in the iNPH-pTT group, 53 patients received shunt surgery and 47 showed a significant improvement. On the other hand, of the 27 patients in the iNPH-nTT group, 4 received shunt surgery and 3 showed a significant improvement.

Tap test response and CSF biomarkers

$A\beta_{42/40}$ ratio was significantly lower (mean [SD] = 0.063 [0.026] vs. 0.083 [0.036], mean difference [95%CI] = –0.020 [–0.035 to –0.005]), and total tau in CSF was significantly higher (mean [SD] = 385.6 [237.2] vs. 293.6 [165.0], mean difference [95%CI] = 91.9 [10.3 to 173.6]) in the iNPH-nTT group compared to the iNPH-pTT group (Table 2). Stepwise logistic regression analysis showed that the $A\beta_{42/40}$ ratio was a significant independent predictor of tap test response (OR per 0.01 units [95% CI] = 1.224 [1.049 to 1.429], Table 3). Multivariate logistic regression analyses showed $A\beta_{42/40}$ ratio was significantly associated with the tap test response even after adjusting for duration of iNPH symptoms (OR per 0.01 units [95% CI] = 1.238 [1.057 to 1.450]), total baseline iNPHGS score (OR per 0.01 units [95% CI] = 1.235 [1.055 to 1.446]), or both (OR per 0.01 units [95% CI] = 1.249 [1.062 to 1.468], Table 3).

Tap test response in each symptom domain and CSF biomarkers

There were no significant differences in $A\beta_{42/40}$ ratio and total tau between those with and without gait

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Table 1. Baseline characteristics and changes after tapping

	iNPH-nTT ($N = 27$)			iNPH-pTT ($N = 81$)			
	BEFORE TAP	AFTER TAP	P[b]	BEFORE TAP	AFTER TAP	P[b]	P[a]
Sex, male: female	15: 12			49: 32			0.658 [c]
Evans index	0.34 (0.03)			0.34 (0.03)			0.465
Age, years	77.7 (6.2)			76.8 (6.2)			0.546
MMSE	20.0 (6.9)	20.1 (7.2)	0.620	21.2 (5.1)	23.2 (5.0)	<0.001	0.639
FAB	9.7 (4.0)	11.2 (4.1)	0.003	10.4 (3.3)	11.8 (3.4)	<0.001	0.472
IR of RBMT	5.0 (2.9)	5.5 (4.1)	0.637	5.8 (3.7)	6.7 (4.1)	0.021	0.342
DR of RBMT	1.6 (2.6)	2.8 (3.2)	0.021	2.8 (3.4)	4.3 (4.4)	0.001	0.113
DSST	25.9 (17.1)	27.4 (17.6)	0.397	24.9 (14.3)	27.0 (15.5)	0.000	0.920
BDT	14.0 (10.6)	13.6 (9.3)	0.704	17.3 (8.9)	18.7 (9.4)	0.006	0.095
A/C in WMS-R	40.9 (11.3)	43.3 (12.3)	0.030	43.4 (10.3)	45.9 (10.2)	0.001	0.468
TUG, s	15.6 (8.1)	16.6 (11.4)	0.627	16.3 (6.4)	14.3 (6.0)	<0.001	0.173
10mWT, s	26.5 (15.4)	27.7 (20.3)	0.449	34.9 (51.2)	30.9 (47.0)	<0.001	0.156
iNPHGS gait	1.8 (0.9)	1.8 (0.9)	1.000	2.1 (0.6)	1.9 (0.6)	<0.001	0.107
iNPHGS cognition	2.4 (0.7)	2.4 (0.7)	1.000	2.4 (0.7)	2.4 (0.7)	0.034	0.862
iNPHGS urinary	1.5 (1.2)	1.5 (1.2)	1.000	1.8 (1.1)	1.5 (1.1)	<0.001	0.281
mRS	2.6 (0.9)	2.6 (0.9)	1.000	2.7 (0.8)	2.6 (0.8)	0.014	0.717
Number of improvements after tapping							
Gait: cognition: urinary					60: 36: 20		
Gait and cognition					19		
Gait and urinary					15		
Cognition and urinary					4		
All of triad					3		

iNPH-nTT, patients with iNPH with a negative result in the tap test; iNPH-pTT, patients with iNPH with a positive result in the tap test; MMSE, Mini-Mental State Examination; FAB, Frontal Assessment Battery; IR of RBMT, subtest of immediate recall of a short story on the Rivermead Behavioral Memory Test; DR of RBMT, subtest of delayed recall of a short story on the Rivermead Behavioral Memory Test; DSST, digit symbol substitution test; BDT, block design test; A/C in WMS-R, the attention/concentration subtest in the Wechsler Memory Scale – Revised; TUG, Timed Up and Go Test; 10mWT, 10-m reciprocation walking test; iNPHGS, iNPH Grading Scale; mRS, modified Rankin Scale. Data are represented as mean (SD).
[a]Mann–Whitney U test are used to compare the mean values before tap between two groups.
[b]Wilcoxon signed-rank test, [c]χ^2 test.

Table 2. Differences of CSF biomarkers (iNPH-nTT vs. iNPH-pTT)

VARIABLE	iNPH-nTT	iNPH-pTT	MEAN DIFFERENCE (95%CI)	T	P[a]
$A\beta_{42/40}$ ratio	0.063 (0.026)	0.083 (0.036)	− 0.020 (− 0.035 to − 0.005)	− 2.715	0.008
Total tau, pg/ml	385.6 (237.2)	293.6 (165.0)	91.9 (10.3 to 173.6)	2.232	0.028

CSF, cerebrospinal fluid; iNPH-nTT, patients with iNPH with a negative result in the tap test; iNPH-pTT, patients with iNPH with a positive result in the tap test; $A\beta_{42/40}$ ratio, ratio of amyloid β 1–42 to amyloid β 1–40. Data are represented as mean (SD).
[a]Student's *t*-test.

improvement in the tap test. There were also no significant differences in $A\beta_{42/40}$ ratio and total tau between those with and without improvement in the urinary domain.

$A\beta_{42/40}$ ratio was significantly higher for those with improved cognitive functioning in the tap test than for those without (Table 4). Stepwise logistic regression analysis also showed that the $A\beta_{42/40}$ ratio was significantly and independently associated with the cognitive response in the tap test (Table 5). Multivariate logistic regression analyses showed that $A\beta_{42/40}$ ratio was significantly associated with the cognitive response in the tap test after adjusting for duration of iNPH symptoms, total baseline iNPHGS score, or both.

Discussion

The present study demonstrates that the $A\beta_{42/40}$ ratio is significantly lower, and the total tau concentration is significantly higher in the CSF of patients who were negative in the tap test compared to those who were positive. Multiple logistic regression analysis showed a significant and independent association between $A\beta_{42/40}$ ratio and tap test response

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Table 3. Result of multiple logistic regression analysis (iNPH-nTT vs. iNPH-pTT)

		B	SE	WALD	DF	P	ODDS RATIO (95%CI)
Model 0	Aβ1–42/1–40, $\times 10^{-2}$	0.202	0.079	6.602	1	0.010	1.224 (1.049–1.429)
Model 1	Aβ1–42/1–40, $\times 10^{-2}$	0.214	0.081	6.983	1	0.008	1.238 (1.057–1.450)
	Disease duration	− 0.005	0.004	1.553	1	0.213	0.995 (0.988–1.003)
Model 2	Aβ1–42/1–40, $\times 10^{-2}$	0.211	0.081	6.873	1	0.009	1.235 (1.055–1.446)
	iNPHGS total score at baseline	0.198	0.127	2.432	1	0.119	1.219 (0.950–1.563)
Model 3	Aβ1–42/1–40, $\times 10^{-2}$	0.222	0.083	7.232	1	0.007	1.249 (1.062–1.468)
	Disease duration	− 0.005	0.004	1.35	1	0.245	0.995 (0.987–1.003)
	iNPHGS total score at baseline	0.195	0.128	2.348	1	0.125	1.216 (0.947–1.561)

iNPH-nTT, patients with iNPH with a negative result in the tap test; iNPH-pTT, patients with iNPH with a positive result in the tap test; $A\beta_{42/40}$ ratio, ratio of amyloid β 1–42 to amyloid β 1–40; iNPHGS, iNPH Grading Scale. Model 0, stepwise method with $A\beta_{42/40}$ ratio and total tau as predictive variables; Model 1, forced entry method with $A\beta_{42/40}$ ratio (as a predictive variable) and duration of iNPH symptoms (as a potential confounder); Model 2, forced entry method with $A\beta_{42/40}$ ratio (as a predictive variable) and total score of iNPHGS at baseline (as a potential confounder); Model 3, forced entry method with $A\beta_{42/40}$ ratio (as a predictive variable) and both duration of iNPH symptoms and total score of iNPHGS at baseline (as potential confounders).

Table 4. Difference of CSF biomarkers between groups with and without improvement in each triad symptom of iNPH

VARIABLE	NEGATIVE IN GAIT (*N*=48)	POSITIVE IN GAIT (*N*=60)	MEAN DIFFERENCE (95%CI)	T	P[a]
$A\beta_{42/40}$ ratio	0.075 (0.033)	0.080 (0.035)	− 0.004 (− 0.017 to 0.009)	− 0.618	0.538
Total tau, pg/ml	348.6 (212.9)	291.0 (164.4)	57.6 (− 14.4 to 129.6)	1.587	0.116
VARIABLE	NEGATIVE IN COGNITION (*N*=72)	POSITIVE IN COGNITION (*N*=36)	MEAN DIFFERENCE (95%CI)	T	P[a]
$A\beta_{42/40}$ ratio	0.073 (0.034)	0.087 (0.033)	− 0.014 (− 0.028 to − 0.000)	− 2.034	0.044
Total tau, pg/ml	327.4 (190.4)	295.2 (186.3)	32.2 (− 44.3 to 108.7)	0.835	0.406
VARIABLE	NEGATIVE IN URINARY (*N*=88)	POSITIVE IN URINARY (*N*=20)	MEAN DIFFERENCE (95%CI)	T	P[a]
$A\beta_{42/40}$ ratio	0.078 (0.034)	0.078 (0.034)	− 0.001 (− 0.018 to 0.016)	− 0.112	0.911
Total tau, pg/ml	318.2 (197.1)	309.9 (151.0)	8.3 (− 84.9 to 101.4)	0.176	0.861

CSF, cerebrospinal fluid; iNPH-nTT, patients with iNPH with a negative result in the tap test; iNPH-pTT, patients with iNPH with a positive result in the tap test; $A\beta_{42/40}$ ratio, ratio of amyloid β 1–42 to amyloid β 1–40. Data are represented as mean (SD).
[a] Student's *t*-test.

Table 5. Result of multiple logistic regression analysis (positive vs. negative in cognition after tapping)

		B	SE	WALD χ^2	DF	P	ODDS RATIO (95%CI)
Model 0	Aβ1–42/1–40, $\times 10^{-2}$	0.121	0.061	3.879	1	0.049	1.128 (1.001–1.272)
Model 1	Aβ1–42/1–40, $\times 10^{-2}$	0.121	0.061	3.889	1	0.049	1.128 (1.001–1.272)
	Disease duration	0	0.004	0.009	1	0.925	1.000 (0.992–1.007)
Model 2	Aβ1–42/1–40, $\times 10^{-2}$	0.122	0.061	3.953	1	0.047	1.130 (1.002–1.274)
	iNPHGS total score at baseline	0.058	0.116	0.245	1	0.621	1.059 (0.843–1.330)
Model 3	Aβ1–42/1–40, $\times 10^{-2}$	0.122	0.061	3.961	1	0.047	1.130 (1.002–1.274)
	Disease duration	0	0.004	0.007	1	0.934	1.000 (0.992–1.007)
	iNPHGS total score at baseline	0.057	0.116	0.243	1	0.622	1.059 (0.843–1.330)

$A\beta_{42/40}$ ratio, ratio of amyloid β 1–42 to amyloid β 1–40; iNPHGS, iNPH Grading Scale. Model 0, stepwise method with $A\beta_{42/40}$ ratio and total tau as predictive variables; Model 1, forced entry method with $A\beta_{42/40}$ ratio (as a predictive variable) and duration of iNPH symptoms (as a potential confounder); Model 2, forced entry method with $A\beta_{42/40}$ ratio (as a predictive variable) and total score of iNPHGS at baseline (as a potential confounder); Model 3, forced entry method with $A\beta_{42/40}$ ratio (as a predictive variable) and both duration of iNPH symptoms and total score of iNPHGS at baseline (as potential confounders).

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after adjusting for the degree and duration of iNPH symptoms. In addition, among the triad symptoms of iNPH, the response in the cognitive domain, but not in the gait or urination domains, was significantly associated with $A\beta_{42/40}$ ratio.

$A\beta_{42/40}$ ratio was significantly lower and total tau was significantly higher in those that did not show an improvement in the tap test compared to those who did. Decreased $A\beta_{42/40}$ ratio and increased total tau in CSF have both been established as useful biomarkers for the diagnosis of AD (Sunderland *et al.*, 2003; Hansson *et al.*, 2019). Our results suggest that iNPH patients with concomitant AD pathology are less responsive to the tap test, which is similar to the association between shunt unresponsiveness and the presence of AD pathology in iNPH (Hamilton *et al.*, 2010; Tarnaris *et al.*, 2011; Patel *et al.*, 2012; Hiraoka *et al.*, 2015; Nakajima *et al.*, 2015; Kazui *et al.*, 2016; Hamdeh *et al.*, 2019). A previous study with 31 iNPH patients reported that the ratio of phosphorylated-tau to Aβ 1–42, which is an established biomarker for AD diagnosis, was significantly higher in tap test nonresponders than in tap test responders (Kang *et al.*, 2014). Additionally, another study in iNPH patients showed that the rate of amyloid positivity via amyloid positron emission tomography was significantly higher in tap test nonresponders than in tap test responders (Jang *et al.*, 2018). Our results are consistent with these previous studies and confirm the influence of concomitant AD pathology on tap test responsiveness in iNPH with a significantly larger sample size. In addition, this is the first study to show an association between tap test responsiveness and the presence of AD pathology in patients with iNPH even after adjusting for disease duration and symptomatic severity, which have been reported as prognostic predictors after shunt surgery (McGirt *et al.*, 2005; Kazui *et al.*, 2013).

In the stepwise logistic regression analysis, only the $A\beta_{42/40}$ ratio, but not total tau, was selected for the model. One plausible reason for this would be that only the more influential biomarker was selected for the model in the stepwise regression analysis. Several previous studies have reported that total tau levels in the CSF of patients with iNPH are comparable (Santangelo *et al.*, 2017; Manniche *et al.*, 2019) or even reduced (Jeppsson *et al.*, 2019) relative to healthy elderly patients, despite the higher frequency of complications of AD pathology that should generally increase total tau in the CSF of patients with iNPH (Hamilton *et al.*, 2010; Elobeid *et al.*, 2015). It is likely that factors other than AD mediate the concentration of total tau in the CSF of patients with iNPH. Importantly, the concentration of total tau in CSF has been reported to be elevated in neurodegenerative diseases other than AD and is therefore not specific to AD (Otto *et al.*, 1997; Green *et al.*, 1999; Urakami *et al.*, 2001).

Interestingly, among the triad symptoms of iNPH, the $A\beta_{42/40}$ ratio was not associated with a response in the gait or urination domains in the tap test but was associated with a response in the cognitive domain. These results suggest that the presence of AD pathology affects responsiveness only in the cognitive domain, but not in the gait or urination domain. As AD does not cause gait disturbances or urinary dysfunctions until it's in the advanced stage, it is plausible that gait and urination would respond to CSF removal in patients with iNPH regardless of AD pathology comorbidity. This is consistent with findings in previous studies demonstrating that the presence of AD pathology affected the improvement of cognition, but not of gait disturbance after shunt surgery (Hiraoka *et al.*, 2015; Kazui *et al.*, 2016).

Even in the iNPH-nTT group, improvement was detected in some of the cognitive measures, including scores of FAB, delayed story recall of RBMT, and A/C in WMS-R, which were not used to judge the response to the tap test in the present study. Both the FAB and A/C in the WMS-R assess frontal lobe function, which is affected more in iNPH than in AD (Ogino *et al.*, 2006; Saito *et al.*, 2011). The change of FAB and A/C in the WMS-R seen even in the iNPH-nTT group might reflect an improvement in a portion of the cognitive functions affected by iNPH rather than AD. This means that to properly evaluate the response of the tap test or shunt surgery in iNPH patients with comorbid AD pathology, assessments of frontal lobe dysfunction may be useful. A small but significant improvement was also observed in the delayed story recall of the RBMT in the iNPH-nTT group. As the performance on a memory test is affected by not only memory but also attention, an improvement in attention after CSF removal might affect the performance on RBMT. This also suggests that more detailed memory tests would be helpful in evaluating the improvement in memory after the tap test, especially in iNPH patients with suspected AD pathology comorbidity. Among 27 patients in the iNPH-nTT group, 4 patients received shunt surgery and 3 of them showed a significant improvement in the present study. Therefore, the current method for judging the result of a tap test may have a high false-negative rate. Detailed tests such as FAB, A/C in WMS-R, and the RBMT may be helpful in improving tap test accuracy.

Although the results of the logistic regression analyses showed that lower $A\beta_{42/40}$ ratio affected poorer tap test response, it is difficult to evaluate the effect size. Logistic regression analysis calculates the OR for a one-unit increase in the continuous variable, and the OR changes if the unit of input

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variable changed. In the present study, we planned to calculate the OR per 0.01 units for $A\beta_{42/40}$ ratio because it is not reasonable to assume that $A\beta_{42/40}$ ratio changes by one unit. However, it is not unclear which units were suitable to evaluate the effect size of $A\beta_{42/40}$ ratio. In the present study, low Aβ42/40 ratio was associated with poor tap test response especially in cognition, but improvement in the detailed cognitive tests was shown after tapping even in iNPH-nTT. The effects of comorbidity with AD on tap test response were significant but may be small in iNPH. Therefore, irrespective of the comorbidity with AD, the tap test should be considered in iNPH.

Our study has several strengths compared to previous reports. First, the number of subjects was over 100. A few previous studies have reported an association between AD pathology and tap test responsiveness in iNPH, but the sample size was too small to allow for multiple comparison adjustment or multivariate analysis. Second, CSF was sampled and measured in a uniform manner at a single institution. Finally, the Aβ42/40 ratio was assessed. Previous studies on the association between tap test reactivity and AD pathology used concentrations of Aβ1–42 in CSF (Kang *et al.*, 2014; Jang *et al.*, 2018), but the Aβ42/40 ratio has been suggested to be a superior measure for the identification of AD pathology compared to concentrations of Aβ1–42 alone (Hansson *et al.*, 2019).

There are some limitations to this study. First, we used the $A\beta_{42/40}$ ratio and total tau in CSF as biomarkers of AD pathology. However, the concentration of proteins in CSF, including Aβ and total tau, has been reported to be different between iNPH patients and healthy subjects (Chen *et al.*, 2017). Thus, the concentration of Aβ and total tau in the CSF of iNPH patients may not be the best biomarker for AD pathology in these patients. In addition, we did not have the cutoff values of CSF biomarkers to detect AD pathology in our institution and therefore the results should be carefully interpreted. Second, the effect of CSF removal is generally larger in a shunt surgery than in a tap test. Even in the iNPH-nTT group, improvement may be seen after shunt surgery, as in this study, a shunt surgery was performed in a small proportion of the patients from this group and was effective. As a tap test is intended to predict the prognosis of shunt surgery, it will be important to follow the results of shunting even in the iNPH-nTT group to evaluate the accuracy of the tap test.

Conclusions

In the present study, we found that the Aβ42/40 ratio in CSF was decreased in patients with possible iNPH without improvement after the tap test, even after adjusting for symptom duration and severity, which have been reported to be predictors of short-term prognosis after shunt surgery. Therefore, comorbidity with AD may be one of the factors that mediate a negative response to the tap test in patients with iNPH. Among the iNPH triad of symptoms, improvement of cognition, but not gait or urination, was related to a CSF Aβ42/40 ratio. Therefore, irrespective of the comorbidity with AD, the tap test should be considered, as there was no association between CSF biomarkers and the response in gait or urination and therefore it may still provide an improvement in these symptoms. In addition, the effect of comorbidity with AD on tap test response in cognition was significant but may be small, and the detailed neuropsychological tests for memory and frontal lobe function revealed a significant improvement even in those whom the MMSE failed to detect an improvement. Thus, a detailed cognitive test battery may be a useful tool in evaluating the cognitive response to a tap test, although the degree of improvement in cognition may be small in iNPH patients with low CSF $A\beta_{42/40}$ ratio.

Conflict of interest

H. Kazui received donations from the 15th Japan Congress of Normal Pressure Hydrocephalus, the chairman of which was H. Kazui, and a speaker's honoraria from Johnson & Johnson K.K., Medtronic Inc., and Nihon Medi-Physics Co., Ltd. E. Mori received a speaker's honoraria from Medtronic Inc. and Nihon Medi-Physics Co., Ltd. The remaining authors have no conflicts of interest to declare.

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Authors' contributions

H. Kanemoto designed the study and wrote the initial draft of the manuscript. E. Mori, M. Ikeda, and M. Hashimoto contributed to the analysis and interpretation of data and assisted in the preparation

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of the manuscript. T. Tanaka contributed to the analysis of CSF biomarkers. All authors have contributed to data collection, reviewed the manuscript, approved the manuscript, and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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