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ORIGINAL COMMUNICATION

Prognostic value of amyloid PET scan in normal pressure hydrocephalus

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Abstract Amyloid positron emission tomography ([18F] florbetaben (FBB) PET) can be used to determine concomitant Alzheimer's disease (AD) in idiopathic normal pressure hydrocephalus (iNPH) patients. FBB PET scans and the tap test were performed in 31 patients with clinically suspected iNPH, and amyloid positive (iNPH/FBB+) and negative (iNPH/FBB−) groups were compared with respect to clinical characteristics. We evaluated prognostic value of FBB PET scans by analyzing the response to the tap test using a linear mixed model. We also performed a multivariable regression analysis to investigate whether amyloid PET positivity can predict the positive tap test response independent of other AD biomarkers. The results showed that the iNPH/FBB+ group (7/31, 22.6%) had a higher percentage of *APOE*4 carriers, lower Aβ42, higher CSF t-tau, and p-tau/Aβ42 ratio than the iNPH/FBB− group (24/31, 77.4%), while the two groups did not differ in imaging characteristics. The iNPH/FBB− group had a higher percentage of tap responders and showed a greater improvement in gait scores after the tap test than the iNPH/FBB+ group (group-tap test effect interaction, $p = 0.035$). A multivariable logistic regression analysis showed that amyloid positivity on PET scans (OR 0.03, $p = 0.029$) and CSF p-tau (OR 0.87, $p = 0.044$) were independently associated with the positive tap test response. Among 21 tap responders in the iNPH/FBB− group, 14 patients received shunt surgery and 12/14 (85.7%) patients showed symptom improvement. Our findings suggest that amyloid PET scans can help determine which iNPH patients will benefit from shunt surgery by discriminating concomitant AD.

Keywords Normal pressure hydrocephalus · Alzheimer's disease · Amyloid β · Florbetaben PET · CSF tau

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Introduction

Normal pressure hydrocephalus (NPH) is a syndrome characterized by dilated cerebral ventricles along with the clinical triad of gait disturbance, cognitive impairment, and urinary incontinence. Accurate diagnosis of NPH is imperative because NPH is treatable through shunt surgery. However, despite the diagnostic criteria for NPH [1], diagnosis of NPH, especially idiopathic NPH (iNPH) that does not have the apparent causes of hydrocephalus, is still challenging. Subcortical vascular dementia as well as a variety of neurodegenerative disorders with dementia and parkinsonism can mimic iNPH, and many patients harbor other comorbidities that contribute to NPH symptoms [2].

The most common comorbidity of iNPH may be Alzheimer's disease (AD) since AD pathology is highly prevalent in the brains of elderly adults. Many studies have shown common co-existence of AD and NPH [3–6]. Alzheimer's pathology alone can lead to nonspecific diffuse atrophy, and it is difficult to differentiate whether dilated ventricles are attributable to NPH or cerebral atrophy by visual inspection of MR imaging. What makes the diagnosis even more complicated is the fact that recent studies showed that AD can present with gait impairment more commonly than in normal elderly adults [7], although early motor symptoms are not typical for AD.

Recent studies have shown that a ventriculoperitoneal (VP) shunt cannot improve cognition in patients with NPH combined with AD [8–11]. Therefore, differentiation between pure NPH and NPH with concomitant AD is important for early treatment decisions. Cerebrospinal fluid (CSF) amyloid-β (Aβ) 42 can be useful for the diagnosis of AD [11–14], but the use of this biomarker alone for differentiation between iNPH and AD [9, 15] is not reliable because emerging data show that CSF Aβ42 levels can also be decreased in iNPH [16, 17]. In contrast, amyloid PET has high specificity and sensitivity for detecting amyloid deposition, especially neuritic plaques, in NPH patients [18, 19]. However, only a few studies have investigated iNPH patients using amyloid PET [8, 20–22]. Furthermore, the clinical utility of amyloid PET in the prediction of treatment response in these patients has rarely been studied and only investigated in one study which examined a total of ten patients [8].

In this study, first we conducted [18F] florbetaben (FBB) PET scans to determine concomitant AD pathology in clinically suspected iNPH patients, and compared amyloid positive (iNPH/FBB+) and negative (iNPH/FBB−) iNPH groups in terms of clinical and imaging characteristics. We were especially interested in investigating the prognostic value of FBB PET scan by analyzing its effects on the CSF tap test response, one of the most important tests to predict the outcome of shunt surgery. We also investigated whether amyloid positivity on PET scan can predict the positive tap test response independent of other AD biomarkers such as CSF Aβ42, total tau (t-tau) and phosphorylated tau (p-tau). We hypothesized that compared with iNPH/FBB+, iNPH/FBB− patients are more likely to have typical imaging features of iNPH and have better response to the tap test. We also hypothesized that amyloid positivity on PET scan is an independent predictor of the positive tap test response, and the predictive value would be enhanced when amyloid positivity is combined with CSF biomarker outcomes.

Methods

Subjects

We enrolled 31 possible NPH patients from our memory disorder clinic at Samsung Medical Center between October 2015 and November 2016. All the patients were diagnosed with possible iNPH by neurologists and only those who met the following inclusion criteria were recruited in our study: (1) age ≥ 60 years; (2) gait disturbance plus more than one of the following two symptoms: cognitive impairment and urinary incontinence; (3) ventricular dilation (Evans' index > 0.3); (4) above-mentioned clinical symptoms that could not be completely explained by other neurological or non-neurological diseases; (5) no obvious preceding diseases possibly causing ventricular dilation including subarachnoid hemorrhage, meningitis, head injury, congenital hydrocephalus, and aqueductal stenosis. All patients underwent FBB PET scans and were divided into iNPH/FBB+ and iNPH/FBB− groups according to their PET results. Tap tests were also performed in all patients. The Institutional Review Board of Samsung Medical Center approved this study. Although the requirement for informed consent was waived for the analysis of clinical data, written informed consent was obtained from all patients before PET scans and lumbar punctures after a detailed explanation of the study.

Clinical assessments

The triad symptoms of NPH were evaluated with the iNPH grading scale (iNPHGS) [23]. The iNPHGS assessed gait disturbance [0 = normal, 1 = complaints of dizziness of drift and dysbasia but no objective gait disturbance, 2 = unstable but independent gait, 3 = walking with any support, 4 = walking not possible], cognitive impairment [0 = normal, 1 = complaints of amnesia or inattention but no objective memory and attentional impairment, 2 = existence of amnesia or inattention but no disorientation of time and place, 3 = existence of disorientation of time and place but conversation is possible, 4 = disorientation for the situation or meaningful conversation impossible], and urinary

disturbance [0 = normal, 1 = pollakiuria or urinary urgency, 2 = occasional urinary incontinence (1–3 or more times per week but less than once per day), 3 = continuous urinary incontinence (1 or more times per day), 4 = bladder function is almost or completely deficient], which are rated based on observations and interviews with the patients and their caregivers. Gait was also assessed at least three times with the Timed Up & Go Test (TUG) [24] that measures the time (in seconds) taken by a patient to stand up from a standard arm chair, walk a distance of 3 meters, turn, walk back to the chair, and sit down again. The best measurement was recorded by an independent neurologist. Cognition was assessed with the Mini-Mental State Examination (MMSE) [25], and the global disability was measured by the modified Rankin Scale (mRS) [26]. In addition, 26 of the 31 patients underwent detailed neuropsychological tests at baseline using a standardized battery called Seoul Neuropsychological Screening Battery [27]. Out of these tests, scorable tests included digit span (forward and backward), the Korean version of the Boston Naming Test (K-BNT), the Rey–Osterrieth Complex Figure Test (RCFT; copying, immediate, and 20-min delayed recall, and recognition), the Seoul Verbal Learning Test (SVLT; three learning-free recall trials of 12 words, a 20-min delayed recall trial for these 12 items, and a recognition test), and the phonemic and semantic Controlled Oral Word Association Test (COWAT). For imaging parameters, the Evans' index and presence of the Disproportionately Enlarged Subarachnoid Space Hydrocephalus (DESH) sign were evaluated. We also rated the extent of periventricular hyperintensity (PVH) and deep white matter hyperintensity (DWMH) according to the modified Fazekas scale [28], and excluded patients with severe ischemia defined as periventricular WMH ≥ 10 mm and deep WMH ≥ 25 mm. Additionally, *APOE* genotyping was done for patients who agreed to perform this test.

[18F] Florbetaben PET acquisition and imaging processing

All participants underwent FBB PET using a Discovery STe PET/CT scanner (GE Medical Systems, Milwaukee, WI) or a Biograph mCT PET/CT scanner (Siemens Medical Solutions, Malvern, PA) in 3D scanning mode that examined 35 slices of 4.25-mm thickness spanning the entire brain. A 20-min emission PET scan in dynamic mode (consisting of 4 × 5 min frames) was performed 90 min after a bolus mean dose of 381 MBq was injected into an antecubital vein. Trained experts visually assessed regional cortical tracer uptake in the frontal, lateral temporal, posterior cingulate/precuneus, and parietal regions. The presence of increased uptake in any of the four brain regions was regarded as amyloid positivity [29]. For a sensitivity analysis, we also quantified the global and regional FBB uptake using the cerebral cortical region to cerebellum uptake ratio which was identical to the standardized uptake value ratios (SUVRs). For the regional FBB uptake analysis, we selected 56 cortical volumes of interest (VOIs) which consisted of the following regions: bilateral frontal, posterior cingulate, parietal, lateral temporal and occipital areas. Details of imaging processing were described in Supplementary information.

Definition of the responder to the CSF tap test

After CSF drainage of about 40–50 ml, all patients were assessed for improvement in triad symptoms using the iNPHGS and underwent the MMSE and TUG tests. Responders to the tap test were defined as patients with improvement in any of the following four criteria [30, 31]:

1. ≥ 1 level on the mRS [26].
2. Gait disturbance ≥ 1 level on the gait scale of the iNPHGS or ≥ 20% reduction in time on the best TUG test performance.
3. Cognition ≥ 1 level on the cognition scale of the iNPHGS or ≥ 4 points on the Mini-Mental State Examination.
4. Urinary disturbance ≥ 1 level on the urinary scale.

CSF analysis

Lumbar puncture was performed in all patients in the L3-4 or L4-5 intervertebral spaces to drain 40–50 cc of CSF. All CSF samples were collected into 15-ml polypropylene tubes at the time of the tap test, and then sent to Samsung Medical Center laboratory within 30 min after collection. After samples were centrifuged at 2000*g* for 10 min, aliquots (1.0 ml) prepared from these samples at room temperature were immediately stored in bar code-labeled polypropylene vials at −70 °C. In our laboratory, we run assays for CSF biomarkers once CSF samples were collected from 30 to 40 patients, using INNOTEST enzyme-linked immunosorbent assay (ELISA) kits (Fujirebio Europe N.V.). The CSF biomarkers included levels of Aβ42 (amyloid-β $(_{1–42})$), t-tau (total tau), and p-tau (181 phosphorylated tau).

Statistical analyses

Comparison of demographics and clinical characteristics between the iNPH/FBB+ and iNPH/FBB− groups was performed using the independent-sample *t* test and Fisher's exact test. Analysis of covariance was used to compare neuropsychological scores between the two groups, with age and education years as covariates. Additionally, we used receiver operating characteristic (ROC) analysis to evaluate the predictive value of each CSF biomarker for detecting amyloid positivity. To analyze the interactive effect of amyloid

positivity and the tap test on improvement in each symptom scale, we performed a linear mixed model using patients as random effects and age, the tap test, amyloid positivity and the interaction between the tap test and amyloid positivity as fixed effects. Finally, we used a backward stepwise logistic regression analysis to identify potential predictors of the positive tap test response including age and all AD biomarkers: amyloid positivity by visual assessment on FBB PET, FBB PET global SUVR, regional SUVR, CSF Aβ42, t-tau, p-tau, and p-tau/Aβ42. IBM SPSS Statistics version 20 (Armonk, NY) and STATA (version 15 StatCorp, College Station, TX) were used, and a two-tailed p value of < 0.05 was considered to be statistically significant for all analyses.

Results

Clinical characteristics of iNPH/FBB+ and iNPH/FBB− patients

Out of the 31 patients with possible iNPH, 24 (77%) patients were designated as the iNPH/FBB− group and the remaining seven patients as the iNPH/FBB+ group. Baseline demographics and clinical characteristics of the two groups are shown in Table 1. The frequency of *APOE*4 carriers was significantly higher in the iNPH/FBB+ group (85.7%) than the iNPH/FBB− group (18.8%). Other imaging parameters and patterns of clinical symptoms did not significantly differ between the two groups. iNPH/FBB− ($n = 19$) and iNPH/FBB+ ($n = 7$) groups did not differ in the neuropsychological tests either. Representative examples of patients from the two groups are shown in Fig. 1.

A total of 28 patients were tested for CSF analysis. Patients in the iNPH/FBB+ group had lower Aβ42 (333.6 ± 73.9 vs. 638.5 ± 235.3, $p = 0.003$) and higher t-tau (324.1 ± 143.8 vs. 203.5 ± 122.5, $p = 0.040$) than the iNPH/FBB− group. CSF p-tau was not significantly different between the two groups, but p-tau/Aβ42 was significantly higher in the iNPH/FBB+ group (0.97 ± 0.31 vs. 0.37 ± 0.40 vs. $p = 0.001$) (Table 1). ROC analysis for predicting FBB PET positivity showed the CSF Aβ and p-tau/Aβ42 ratio showed high area under curve (AUC) values of 0.94 and 0.95, respectively (Supplementary Table 1, Supplementary Fig. 1).

Response to the CSF tap test according to amyloid burden on PET scans

Two of seven (28.6%) iNPH/FBB+ patients and 20 of 24 (83.3%) iNPH/FBB− patients were categorized as tap test responders (Fig. 2), the difference of which was significant. When all data representing the symptom triad (mRS, iNPHGS, TUG, and MMSE) were subjected to a linear mixed model, there was a significant group-tap test interaction with gait score on the iNPHGS ($p = 0.035$), indicating that amyloid positivity on PET scan differentially affected gait improvement after the tap test (Table 2).

When the same analysis was performed using global or regional SUVR instead of amyloid positivity on PET scan, the interaction of frontal SUVR and the tap test was also significant for gait score on the iNPHGS ($p = 0.038$), indicating that frontal SUVR differentially affected gait improvement after the tap test (Table 3).

Combination of PET positivity and CSF biomarkers as a predictor of the tap test response

When AD biomarkers were compared between the tap test responders and non-responders, the ratio of amyloid positivity on FBB PET scan by visual assessment was significantly different between the responders and non-responders (9.1 vs. 55.6%, $p = 0.005$), while quantitative amyloid burden represented by global SUVR (1.36 ± 0.34 vs. 1.55 ± 0.33, $p = 0.175$),frontal SUVR (1.32 ± 0.35 vs. 1.58 ± 0.38, $p = 0.092$), temporal SUVR (1.37 ± 0.34 vs. 1.55 ± 0.34, $p = 0.209$), parietal SUVR (1.37 ± 0.39 vs. 1.59 ± 0.39, $p = 0.181$), or occipital SUVR (1.40 ± 0.28 vs. 1.48 ± 0.27, $p = 0.466$) were not statistically different between the two groups. However, frontal SUVR had a statistical tendency to be higher in responders than in non-responders. When we compared CSF profiles between the two groups, responders showed lower CSF p-tau (36.3 ± 12.0 vs. 53.7 ± 20.8, $p = 0.013$), t-tau (179.5 ± 68.4 vs. 347.9 ± 174.4, $p = 0.020$), and p-tau/Aβ42 (0.34 ± 0.21 vs. 0.90 ± 0.60, $p = 0.023$) compared to non-responders, while CSF Aβ42 levels (607.0 ± 254.4 vs. 467.9 ± 207.7, $p = 0.166$) were not significantly different (Table 4). A backward stepwise logistic regression showed that amyloid positivity on FBB PET scans by visual assessment [OR 0.03, 95% CI (0.001, 0.70) $p = 0.029$] and CSF p-tau [OR 0.87, 95% CI (0.76, 0.99) $p = 0.044$] were independently associated with the positive tap test response (Table 5).

Ventriculoperitoneal shunt surgery

We did not perform shunt surgeries in the tap test non-responders regardless of amyloid positivity. We also did not recommend surgery in any of the iNPH/FBB+ patients even if they responded to the tap test, since recent studies demonstrated unsatisfactory outcomes of shunt surgery in patients with amyloid deposits [8–10, 32]. In contrast, shunt surgery was recommended for all tap test responders in the iNPH/FBB− group. Six out of the 20 total patients refused surgery. Among the 14 patients who received the surgery, only two patients failed to show objective improvement, while the remaining 12 (85.7%) patients benefited from the

Table 1 Comparison of baseline characteristics between the iNPH/FBB− and iNPH/FBB+ groups

	iNPH/FBB− ($n = 24$)	iNPH/FBB+ ($n = 7$)	$p^{\dagger}$
Age	73.3 ± 7.0	74.1 ± 5.3	0.769
Female gender	5 (20.8)	3 (42.9)	0.335
Education years	11.0 ± 5.3	14.4 ± 3.0	0.043*
APOE4 carriers/number of patients tested	3/16 (18.8)	6/7 (85.7)	0.005*
Neuropsychological test results	($n = 19$)	($n = 7$)	
MMSE	21.8 ± 6.4	21.4 ± 7.0	0.850
Digit span forward	5.7 ± 1.8	6.1 ± 0.9	0.959
Digit span backward	3.1 ± 1.2	3.6 ± 1.3	0.469
K-BNT	40.8 ± 11.7	37.4 ± 12.9	0.286
RCFT copy	24.4 ± 9.8	26.1 ± 10.4	0.942
SVLT immediate recall	13.4 ± 5.0	12.9 ± 3.8	0.850
SVLT delayed recall	1.6 ± 2.3	2.3 ± 2.6	0.249
SVLT recognition score	17.7 ± 2.9	17.7 ± 3.4	0.794
RCFT immediate recall	5.5 ± 4.2	5.4 ± 5.2	0.964
RCFT delayed recall	5.8 ± 6.1	5.8 ± 5.3	0.914
RCFT recognition score	18.1 ± 3.4	16.0 ± 3.1	0.404
COWAT_animal	9.2 ± 3.5 ($n = 18$)	10.8 ± 4.8 ($n = 6$)	0.329
COWAT_supermarket	8.8 ± 5.0 ($n = 15$)	5.4 ± 4.2 ($n = 5$)	0.312
COWAT_phonemic	14.9 ± 9.9 ($n = 14$)	12.6 ± 8.9 ($n = 5$)	0.762
MRI imaging parameters			
Evans' index	0.35 ± 0.03	0.35 ± 0.02	0.630
Presence of DESH sign	8 (33.3)	4 (57.1)	0.384
Fazekas PVH	2.2 ± 0.6	2.0 ± 0.8	0.540
Fazekas DWMH	1.1 ± 0.3	1.1 ± 0.4	0.653
First clinical manifestation			0.736
Cognition	9 (37.5)	5 (71.4)	
Cognition and gait	5 (20.8)	1 (14.3)	
Cognition and urinary	3 (12.5)	1 (14.3)	
Cognition, gait, and urinary	1 (4.2)	0 (0)	
Gait and urinary	2 (8.3)	0 (0)	
Gait	2 (8.3)	0 (0)	
Urinary	2 (8.3)	0 (0)	
Symptoms at admission			
Cognitive impairment	23 (95.8)	7 (100)	1.000
Gait disturbance	24 (100)	7 (100)	1.000
Urinary disturbance	21 (87.5)	6 (85.7)	1.000
mRS	2.8 ± 1.0	2.7 ± 0.8	0.706
CSF analysis profile			
Aβ42	638.5 ± 235.3	333.6 ± 73.9	0.003*
t-tau	203.5 ± 122.5	324.1 ± 143.8	0.040*
p-tau	39.3 ± 13.6	48.3 ± 24.5	0.227
p-tau/Aβ42	0.37 ± 0.40	0.97 ± 0.31	0.001*

Values are presented as mean ± SD or number of cases (percentage)

iNPH idiopathic normal pressure hydrocephalus, *iNPH/FBB−* iNPH patients with florbetaben PET negative, *iNPH/FBB+* iNPH patients with florbetaben PET positive, *MMSE* Mini-Mental State Examination, *MRI* magnetic resonance imaging, *K-BNT* Korean version of Boston Naming Test, *RCFT* Rey–Osterrieth Complex Figure Test, *SVLT* Seoul Verbal Learning Test, *COWAT* Controlled Oral Word Association Test, *DESH* disproportionately enlarged subarachnoid space hydrocephalus, *PVH* periventricular hyperintensity, *DWMH* deep white matter hyperintensity, *mRS* Modified Rankin Scale, *CSF* cerebrospinal fluid, *Aβ* amyloid β, *t-tau* total tau, *p-tau* phosphorylated tau

*$p < 0.05$

†Independent sample *t* test, Fisher's exact test, or analysis of covariance as appropriate

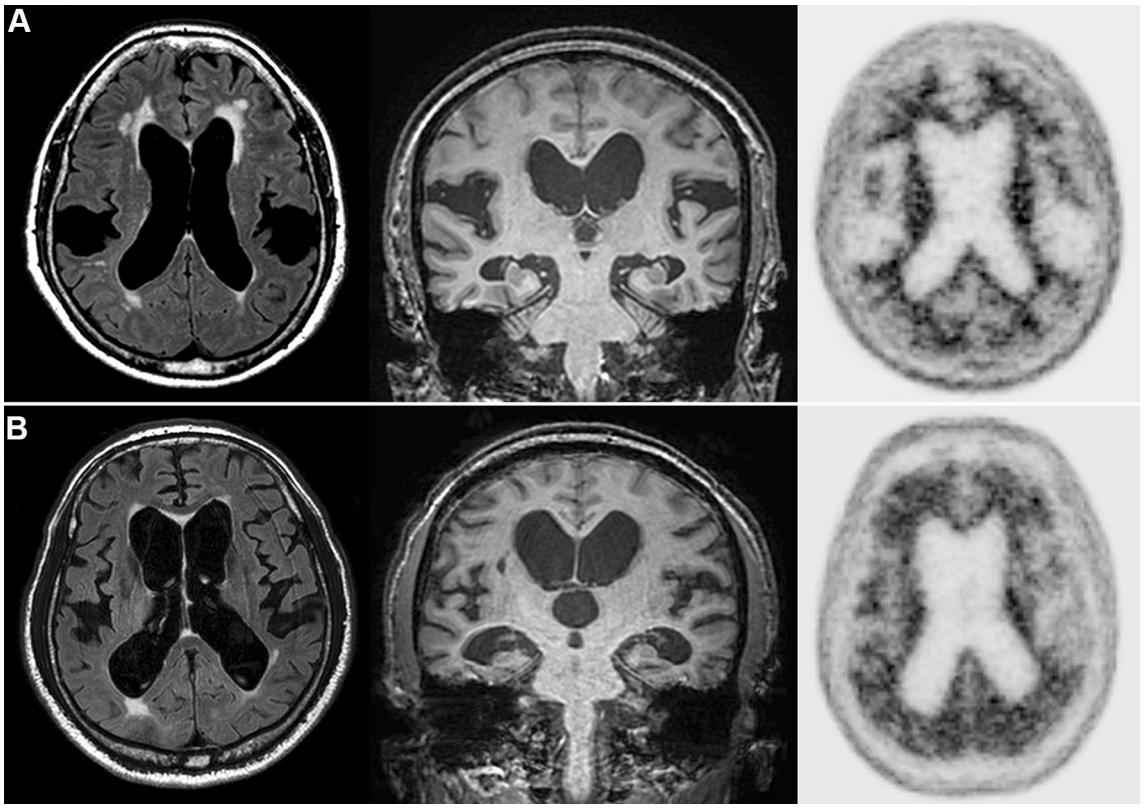

Fig. 1 Amyloid negative and positive normal pressure hydrocephalus (NPH) patients. Representative examples of patients with amyloid negative (**a**) and positive (**b**) PET scans

surgery. Of these patients with favorable outcomes, 11 were followed up for more than 3 months; four of these patients showed sustained symptom improvement up to 12 months, four showed improvement up to 6 months, and two patients showed only transient improvement that deteriorated after 3 months post-surgery. One patient was at 3 months' follow-up as of the time of this writing.

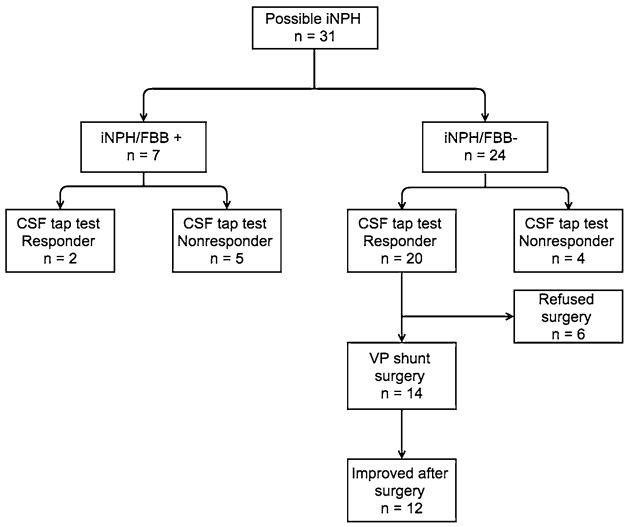

Fig. 2 Flow diagram of subjects included in the study. *iNPH* idiopathic normal pressure hydrocephalus, *iNPH/FBB+* iNPH patients with florbetaben PET positive, *iNPH/FBB−* iNPH patients with florbetaben PET negative, *PET* positron emission tomography, *CSF* cerebrospinal fluid, *VP* ventriculoperitoneal

Discussion

The major findings of our study are as follows. First, we found that the rate of amyloid positivity in iNPH patients was about 23%. Second, when the two groups were compared, the iNPH/FBB+ group had more *APOE*4 carriers, significantly lower CSF Aβ42 levels, and higher t-tau levels than the iNPH/FBB− group. Third, there was a higher frequency of tap test responders in the iNPH/FBB− group compared to the iNPH/FBB+ group and amyloid positivity was associated with differential improvement especially in gait disturbance after the tap test. Finally, the combination of amyloid positivity on the PET scan and CSF p-tau independently predicted the positive tap test response. Overall, patients with positive AD biomarkers are expected to be less likely responsive to shunt surgery.

The first major finding of our study was that about 23% of clinically suspected iNPH patients had positive amyloid scans. This number is slightly lower than previous reported

Table 2 Comparison of tap test response rates and linear mixed effects model for the interactive effects of amyloid positivity and the tap test

	iNPH/FBB+ ($n = 7$)		iNPH/FBB− ($n = 24$)		p†		
Tap test responders	20 (83.3)		2 (28.6)		0.012*		
	Pre	Post	Pre	Post	Group effect	Tap effect	Group* tap test interaction
	Mean ± SD		Mean ± SD		p§		
mRS	2.8 ± 1.0	2.6 ± 0.8	2.7 ± 0.8	2.7 ± 0.8	0.780	0.229	0.229
Gait							
iNPHGS_gait	2.0 ± 0.9	1.6 ± 0.8	1.7 ± 1.0	1.7 ± 1.0	0.673	0.035*	0.035*
Timed up and go, s	13.9 ± 7.1[a]	11.1 ± 4.2[a]	10.1 ± 5.5	9.1 ± 4.0	0.228	0.015*	0.219
Cognition							
iNPHGS_cognition	2.2 ± 0.8	2.0 ± 0.8	2.4 ± 0.5	2.4 ± 0.5	0.371	0.262	0.262
MMSE	21.8 ± 6.4	22.8 ± 6.5	21.4 ± 7.0	21.9 ± 6.1	0.914	0.088	0.452
Urinary							
iNPHGS_urinary	1.8 ± 1.0	1.4 ± 0.9	1.3 ± 0.8	1.3 ± 0.8	0.424	0.099	0.099

Values are presented as number of cases (percentage) or mean ± SD

iNPH idiopathic normal pressure hydrocephalus, *iNPH/FBB−* iNPH patients with florbetaben PET negative, *iNPH/FBB+* iNPH patients with florbetaben PET positive, *CSF* cerebrospinal fluid, *mRS* Modified Rankin Scale, *iNPHGS* iNPH grading scale, *MMSE* Mini-Mental State Examination

*$p < 0.05$

†Fisher's exact test, §Linear mixed model

[a]In iNPH/FBB− group, three patients at baseline and two patients after the tap test were not included in the analysis because they could not walk independently

Table 3 Linear mixed effects model for the interactive effects of amyloid deposition and the tap test

	Model 1			Model 2		
	Global SUVR effect	Tap test effect	Global SUVR *tap test effect	Frontal SUVR effect	Tap test effect	Frontal SUVR* tap test effect
	Coefficient (SE)		p for interaction	Coefficient (SE)		p for interaction
mRS	0.1 (0.4)	− 0.4 (0.4)	0.584	− 0.05 (0.4)	− 0.4 (0.4)	0.507
Gait						
iNPHGS_gait	− 0.3 (0.4)	− 1.2 (0.4)*	0.073	− 0.3 (0.4)	− 1.2 (0.4)*	0.038*
Timed up and go, s	− 0.2 (4.2)	− 3.2 (3.9)	0.874	− 0.7 (3.6)	− 3.6 (3.4)	0.755
Cognition						
iNPHGS_cognition	0.5 (0.4)	− 0.3 (0.2)	0.407	0.4 (0.3)	− 0.3 (0.2)	0.293
MMSE	− 4.8 (3.1)	0.1 (1.6)	0.679	− 4.0 (2.9)	0.5 (1.4)	0.879
Urinary						
iNPHGS_urinary	− 0.5 (0.5)	− 0.8 (0.3)	0.095	− 0.5 (0.5)	− 0.8 (0.3)*	0.056

Model 1: Fixed effects: age, Global PET SUVR, follow-up (pre–post tap test), Global PET SUVR*follow-up. Random effects: patients

Model 2: Fixed effects: age, Frontal PET SUVR, follow-up (pre–post tap test), Frontal PET SUVR*follow-up. Random effects: patients

SUVR standardized uptake value ratio, *SE* standard error, *iNPHGS* idiopathic normal pressure hydrocephalus grading scale, *MMSE* Mini-Mental State Examination

*$p < 0.05$

rates, which ranged from 30 to 45% based on neuropathologic studies using cortical samples at shunt implantation [3, 4, 33]. Previous studies have shown that up to 10–20% of normal elderly in their 60s and 70s show amyloid positivity on FBB PET scans [19, 34]. Therefore, we cannot completely exclude the possibility that our finding of 23%

Table 4 Comparison of AD biomarkers between the tap test responders and non-responders

	Responders	Non-responders	$p^{\dagger}$
FBB PET finding			
Global SUVR	1.36 ± 0.34	1.55 ± 0.33	0.175
Frontal SUVR	1.32 ± 0.35	1.58 ± 0.38	0.092
Temporal SUVR	1.37 ± 0.34	1.55 ± 0.34	0.209
Parietal SUVR	1.37 ± 0.39	1.59 ± 0.39	0.181
Occipital SUVR	1.40 ± 0.28	1.48 ± 0.27	0.466
Amyloid positivity (visual assessment)	2/22 (9.1%)	5/9 (55.6%)	0.005*
CSF analysis			
Aβ42	607.0 ± 254.4	467.9 ± 207.7	0.166
t-tau	179.5 ± 68.4	347.9 ± 174.4	0.020*
p-tau	36.3 ± 12.0	53.7 ± 20.8	0.013*
p-tau/Aβ42	0.34 ± 0.21	0.90 ± 0.60	0.023*

Values are presented as mean ± SD

AD Alzheimer's disease, *FBB PET* [18F]Florbetaben positron emission tomography, *SUVR* standardized uptake value ratio, *CSF* cerebrospinal fluid, *Aβ* amyloid β, *t-tau* total tau, *p-tau* phosphorylated tau

†Independent sample *t* test or Chi-square test as appropriate

$^{*}p < 0.05$

Table 5 Multivariable logistic regression analysis for the association of potential predictors with the positive tap test response

Predictor variables	Positive tap test response as main outcome		
	OR	95% CI	*p* value
Age	1.20	1.01,1.46	0.051
Amyloid positivity (visual assessment)	0.03	0.001,0.70	0.029*
p-tau	0.87	0.76, 0.99	0.044*

OR odds ratio, *CI* confidence interval, *p-tau* phosphorylated tau

$^{*}p < 0.05$

amyloid positivity may be an incidental finding given that patients were in their 70s and majority of iNPH/FBB+ patients were *APOE*4 carriers.

The role of amyloid in this mixed condition (AD and NPH) is intriguing. AD and NPH are known to be closely related [35, 36]. Decreased CSF turnover and failure of the CSF to clear potentially toxic metabolites can lead to accumulation of amyloid-β peptide (Aβ) in the brain [36]. In reverse, high concentrations of amyloid in cerebral interstitial fluid lead to amyloid deposition in the brain including the choroidal plexus [37] which subsequently prevents CSF absorption and hydrocephalus. Based on this speculation, we assumed that both diseases could affect each other by sharing a common physiological dysfunction in CSF circulation [35]. Our results showed that there was a higher frequency of *APOE*4 carriers in the iNPH/FBB+ group than the iNPH/FBB− group. This finding is compatible with the important role of *APOE*4 in the development of AD pathology in iNPH and vice versa, despite the uncertainty in the cause and effect relationship between AD and NPH. Further research is needed to delineate the mechanism of their co-existence.

The second major finding of our study was that the iNPH/FBB+ group had significantly lower CSF Aβ42 and higher t-tau levels than the iNPH/FBB− group. This may have a practical implication since the measurement of Aβ42 and t-tau in CSF could be used as a substitute for an amyloid PET scan in clinically suspected iNPH patients whose CSF are already obtained from the tap test. A recent study showed that CSF Aβ42 levels can be decreased in pure NPH, thus leading to misdiagnosis of combined AD [17]. Therefore, this study might be helpful to determine the cut-off values for CSF biomarkers to distinguish pure NPH from comorbid AD and NPH. CSF p-tau levels, which were assumed to be associated with neurofibrillary tangles [38], did not differ between the two groups, although the CSF p-tau/Aβ42 ratio was significantly different between the two groups. This ratio showed high sensitivity and specificity for predicting amyloid PET positivity. Therefore, the combination of p-tau and Aβ42 levels might be more useful in the prediction of concomitant AD pathology in iNPH.

Another interesting finding of this study was the lack of significant differences in imaging parameters between the iNPH/FBB+ and iNPH/FBB− groups. Especially, the frequency of the DESH sign was not significantly different, even though this sign is known to be one of the most useful imaging characteristics for diagnosing iNPH and predicting shunt response [30, 31]. Our study showed that the DESH sign was still found in iNPH/FBB+ patients, which indicated that this sign was not exclusive to pure iNPH. However, all two of the responders with FBB+ had the DESH sign which suggested that it might still be useful for predicting the tap test response. This requires further study with a larger sample size.

The third major finding of our study was that the frequency of tap test responders was significantly higher in the iNPH/FBB+ group compared to the iNPH/FBB− group. When we analyzed changes in each symptom after the tap test using a linear mixed model, gait (on the iNPHGS and TUG tests) was the only parameter which significantly changed after the tap test in both groups. Especially, the gait score on the iNPHGS improved only in the iNPH/FBB− group after the tap test. As an improvement by 1 point on the iNPHGS indicates a notable gait change, we could assume that amyloid positivity affected the level of improvement in gait after the tap test. Furthermore, among

the three patients from the iNPH/FBB− group who were so severely impaired in gait that they could not walk independently at baseline, only one patient could walk after the tap test. This also indicated that dramatic gait improvement was observed only in the iNPH/FBB− group. The effect of FBB uptake on the tap test response was also analyzed using quantitative amyloid burden represented by SUVR instead of dichotomous approach on FBB PET scan. The results from the dichotomous approach were replicated, showing that frontal SUVR had a differential effect on the tap test response in iNPH patients. The reason why frontal, rather than global, SUVR had an impact on the tap test response remains to be elucidated. However, the frontal lobe is one of the brain regions having greatest amyloid accumulation in AD [39], which might explain this finding. Alternatively, amyloid deposition in AD patients combined with NPH might be most prominent in frontal region, which is possibly the most vulnerable to mechanical and ischemic factors in NPH.

The fourth major finding of our study was that amyloid positivity on PET scans and CSF p-tau were significantly predictive of the positive tap test. A univariate comparison of FBB−PET biomarkers between responder and nonresponder group showed that the ratio of amyloid positivity by visual assessment was significantly different. We also observed a statistical tendency for the difference in frontal SUVR between groups ($p = 0.092$). As for the CSF biomarkers, responders had significantly lower t-tau, p-tau and p-tau/Aβ42 ratio levels, which suggested that tau, as a marker of neuronal injury, was more useful than Aβ42 alone to infer responses to the tap test. On the other hand, a multivariable regression model suggests that amyloid positivity on PET scan is an independent predictor of the positive tap test regardless of CSF p-tau levels, and a combined use of FBB positivity and CSF p-tau level help to better predict the positive tap test response. Especially, in a clinical setting, the use of amyloid positivity on PET scan by visual assessment is easier and more useful compared with FBB PET SUVR which requires preprocessing steps.

Our study tried to investigate whether patients responded differently to shunt surgery according to amyloid positivity. For all patients, initial clinical diagnosis was most likely NPH because even iNPH/FBB+ patients had developed gait disturbance in relatively early stage of disease. Besides, detailed cognitive tests failed to show any difference between iNPH/FBB− and iNPH/FBB+ group, which led us to consider that all patients might benefit from shunt surgery. However, as has been already mentioned, we did not recommend shunt surgeries for tap responders in the iNPH/FBB+ group because recent evidence suggested that shunt surgeries could not improve cognition in comorbid NPH and AD patients [8, 9, 32]. Among pure iNPH (iNPH/FBB−) patients who underwent the surgery, about 86 percent improved. This is a relatively higher rate compared to outcomes presented in previous studies which demonstrated that shunt response in NPH patients varied from 30 to 80% [40–42], with rates as high as 90% in a few studies [41, 43]. This suggested that diagnosing comorbid AD using amyloid PET may be helpful to predict shunt outcome in iNPH patients.

This study has several limitations. First, we defined "responders" as patients who responded to the tap test rather than to shunt surgery. Low sensitivity of the tap test for detecting shunt responders might have caused a bias in our selection of candidates for surgery. Second, we did not recommend shunt surgery for patients with iNPH/FBB+, in whom Alzheimer's pathology might be partially or fully responsible for profound cognitive impairment. In these patients, there is a paucity of data that ensures improvement in symptoms including cognition after surgery. Third, we used MMSE as a repetitive cognitive measure, which might not be ideal to evaluate frontal dysfunction observed in NPH or memory impairment characteristics of AD. Finally, the sample size was small especially in iNPH/FBB+ group, which may limit generalization of our results.

Conclusion

The iNPH patients with or without AD pathology had different clinical and biomarker characteristics. In particular, our study showed that the iNPH/FBB− group had a higher percentage of tap responders and showed a greater improvement in gait scores after the tap test than the iNPH/FBB+ group. In addition, approximately 86% of the tap test responders in the iNPH/FBB− group benefited from surgery. Finally, amyloid positivity and CSF p-tau levels were independently associated with the positive tap test response. This might suggest that amyloid PET scans can help determine patients who will benefit from shunt surgery.

Author Contributions HJ: design of the study, acquisition and analysis of the data, and drafting the manuscript. YK, KWK, YJK, CWY: acquisition and interpretation of the data. STK, KHL: acquisition of the data. SWS, HJK: design of the study and interpretation of the data. DLN: design of the study, acquisition and analysis of the data, interpretation of the data, revising the manuscript, and study supervision. SBP, YSC: imaging data analysis

Compliance with ethical standards

Conflicts of interest The authors declare that they have no competing interests.

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Ethical standards The study was approved by the Institutional Review Board of Samsung Medical Center. Written informed consent was obtained from all patients.

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