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Amyloid deposits and response to shunt surgery in idiopathic normal-pressure hydrocephalus

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A B S T R A C T

Objectives: In previous studies, patients with idiopathic normal-pressure hydrocephalus (iNPH) occasionally showed Alzheimer's pathology in frontal lobe cortical biopsy during cerebrospinal fluid shunt surgery or intracranial pressure monitoring. In clinical practice, the differential diagnosis of iNPH from Alzheimer's disease (AD) can be problematic, particularly because some iNPH cases exhibit AD comorbidity. In this study, we evaluated amyloid deposition in the brains of patients with iNPH before shunt surgery, and investigated the association between brain amyloid deposits and clinical improvement following the surgery.
Materials & methods: Amyloid imaging was performed in patients with iNPH or AD and also in healthy control subjects by using positron emission tomography (PET) and a radiolabeled pharmaceutical compound, ^{11}C-BF227. Using the cerebellar hemispheres as reference regions, the standard uptake value ratio (SUVR) of the neocortex was estimated and used as an index for amyloid deposition. In patients with iNPH, clinical symptoms were assessed before shunt surgery and 3 months after surgery.
Results: Five of the 10 patients with iNPH had neocortical SUVRs that were as high as those of AD subjects, whereas the SUVRs of the 5 patients were as low as those of healthy controls. A significant inverse correlation between neocortical SUVRs and cognitive improvements after shunt surgery was observed in iNPH.
Conclusions: The amount of amyloid deposits ranges widely in the brains of patients with iNPH and is associated with the degree of cognitive improvement after shunt surgery.
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1. Introduction

Idiopathic normal-pressure hydrocephalus (iNPH) manifests as a triad of dementia, gait disturbance, and urinary incontinence, with ventriculomegaly and normal cerebrospinal fluid (CSF) pressure in addition to no preceding events, such as meningitis or subarachnoid hemorrhage. This syndrome is typically treated with CSF shunt surgery, with clinical improvement being documented following shunt placement in 47–90% of cases [1–4].

In the clinical diagnosis of iNPH, differential diagnosis from AD can be problematic, as both diseases cause dementia and ventriculomegaly. Furthermore, some iNPH cases may present comorbidity of AD, based on symptomatic or radiological features of the disease. Amyloid pathology has been found in 22.2–67.6% of cortical specimens of iNPH patients obtained during intracranial pressure monitoring or shunt surgery [5,6]. Moderate to severe AD pathology is associated with worse baseline cognitive performance and diminished postoperative improvement of symptoms [6]. Thus, knowledge about the preoperative comorbidity of AD may be useful for clinical decision-making.

Recently, in vivo imaging of AD pathology in the brain has become possible using positron emission tomography (PET). ^{11}C-BF227 is a radiopharmaceutical used for amyloid PET imaging [7]. A previous study using ^{11}C-BF227-PET demonstrated that this tracer is taken up in the cerebral cortices of patients with AD but not in those of normal subjects because of the dense amyloid deposition in patients with AD [8].

In this study, we evaluated amyloid deposition in the brains of iNPH patients before shunt surgery and investigated the association between amyloid deposition in the brain and clinical improvement following shunt surgery in patients with iNPH.

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2. Subjects and methods

2.1. Subjects

Patients who were diagnosed with iNPH and indicated for shunt surgery were enrolled in this prospective study at Tohoku University Hospital, Sendai, Japan between November 2010 and July 2013. Patients were diagnosed with iNPH by board-certified neurologists based on the diagnostic criteria of the Guidelines for Management of Idiopathic Normal Pressure Hydrocephalus from the Japanese Society of Normal Pressure Hydrocephalus [9]. The diagnostic criteria are (1) symptoms developing when the patient is aged over 60 years, (2) the presence of more than one of the triad, (3) iNPH features on MRI, i.e., ventricular dilation (Evans Index > 0.3) accompanied by narrowing of the subarachnoid CSF spaces in the high convexity areas and interhemispheric fissure, (4) normal CSF pressure and content, (5) positive results on a CSF tap test, (6) symptoms that cannot be explained by other neurological or non-neurological diseases, and (7) no obvious preceding diseases that could possibly cause ventricular dilation. Patients who fulfilled the diagnostic criteria, had no contraindications to surgery, and gave written informed consent and underwent PET imaging and ventriculoperitoneal or lumboperitoneal-shunt surgery. After surgery, the pressure settings of the programmable valves were adjusted as required on an outpatient basis.

To compare the results of PET imaging in patients with iNPH to those of healthy subjects and patients with AD, we used pooled PET data (Table 1), which were acquired between 2005 and 2009 using the same PET scanner and the same PET imaging protocol as in the current study.

The study protocol followed the clinical study guidelines of the Ethics Committee of Tohoku University Hospital and was approved by the Institutional Review Board.

2.2. Assessment of clinical symptoms

Clinical symptoms of patients with iNPH were assessed using the same scales and tests before shunt surgery and 3 months after surgery to evaluate clinical improvements following surgery. The triad of iNPH was assessed by the iNPH Grading Scale [10]. Based on this scale, the severity of symptoms in each domain is rated based on the clinician's observations and interviews with the patients and their caregivers. The score for each domain ranges from 0 (no symptoms) to 4 (severest symptoms). The Mini-Mental State Examination (MMSE) [11], Frontal Assessment Battery [12], Trail-Making Test-A [13], and Verbal Fluency Task [13] were used to evaluate cognitive functions. Gait was also assessed by the Timed Up and Go (TUG) test [14]. In the TUG test, the time and number of steps taken by patients when rising from a chair, walking 3 m, turning, walking back, and sitting down were recorded.

2.3. Radiosynthesis of ^{11}C-BF227 and PET procedure

The radiosynthesis of ^{11}C-BF227 and PET procedure were performed as described previously [7]. In brief, the BF227 and its *N*-desmethylated derivative (a precursor of ^{11}C-BF227) were custom synthesized by Tanabe R&D Service Co. ^{11}C-BF227 was synthesized from its precursor by *N*-methylation in dimethyl sulfoxide using ^{11}C-methyl triflate. For imaging, we used a SET-2400W PET scanner (Shimadzu Inc., Japan) at the Cyclotron and Radioisotope Center, Tohoku University. The scanner acquires 63 image slices at a center-to-center interval of 3.125 mm and has a transaxial resolution of 4.5 mm FWHM at the center of its field of view [15]. Initially, 7-min transmission data were acquired with a rotating ^{68}Ge/^{68}Ga line source for attenuation correction. Then, after intravenous injection of ^{11}C-BF227, a 60-min dynamic scan was performed in three-dimensional mode. Subjects were scanned under standard resting conditions. Standardized uptake value (SUV) images of ^{11}C-BF227-PET were obtained by normalizing tissue radioactivity concentration against the injected dose of ^{11}C-BF227 and body weight of each subject. Averaged images of the late frames (40–60 min post-injection) were used for image analysis.

Table 1
Demographic data of the subjects.

		iNPH	AD	Healthy controls
N		10	10	10
Age (years)		77.9 ± 4.1*,†	69.9 ± 5.9	70 ± 2.8
Sex (M/F)		4/6	1/9	6/4
MMSE	Baseline	20.8 ± 4.5*	20.1 ± 3.6*	30.0 ± 0.0
	3 months after surgery	23.3 ± 6.2		
Symptom duration (months)		36.5 ± 18.8		
Education (years)		12.0 ± 3.2		

iNPH, idiopathic normal-pressure hydrocephalus; AD, Alzheimer's disease.
* $p < 0.05$ vs. healthy control.
† $p < 0.05$ vs. AD.

2.4. Image analysis

For PET image analysis, axial three-dimensional MR images were taken for each patient. In patients with iNPH, spoiled gradient echo (SPGR) images were obtained with a 1.5 T MRI unit (GE Signa Horizon, Milwaukee, WI). Operating parameters were as follows: field of view, 250 mm; matrix, 256 × 256; slice thickness, 1.5 mm; repetition time, 20 msec; echo time, 4.1 msec; and flip angle, 30°. In healthy subjects and patients with AD, SPGR images were obtained using a 1.5 T MRI unit (GE Signa Hispeed, Milwaukee, WI). Operating parameters were as follows: field of view, 220 mm; matrix, 256 × 256; slice thickness, 2.0 mm; repetition time, 50 msec; echo time, 2.4 msec; flip angle, 45°.

Images were analyzed using PNEURO, a tool for brain PET/MR analysis in the dedicated PMOD software package (version 3.404; PMOD Technologies, Zurich, Switzerland).

Initially, MR images were segmented into gray matter, white matter, and cerebrospinal fluid, from which gray matter probability maps were generated. The PET images were rigidly coregistered to the MR images. Along with the coregistered PET images, the MR images were spatially normalized to the Montreal Neurological Institute T1 template. The label atlas of each region of interest (ROI) pre-installed in PNEURO was transformed to the MR space. The cortical structures were segmented with the gray matter probability map at $p > 0.7$. The ROIs were applied to the coregistered PET images for calculating the mean uptake value. Using cerebellar hemispheres as reference regions, the mean standardized uptake value ratio (SUVR) of each ROI was estimated as an index of amyloid deposition in each ROI. In accordance with previous ^{11}C-BF227-PET studies [8,16], neocortical SUVR was calculated by averaging SUVRs in the frontal, temporal, parietal, and posterior cingulate cortices.

2.5. Statistical analysis

Statistical comparisons of age and MMSE among the 3 groups were performed using the Kruskal–Wallis test followed by Dunn's multiple comparison test. Sex differences were investigated using Pearson's chi-squared test. Statistical comparison of the SUVR in each group was performed via an age- and sex-adjusted analysis of covariance (ANCOVA) with Bonferroni correction for multiple post-hoc comparisons. The *t*-test was used for comparison of demographic data except for sex, the clinical assessments at baseline, and clinical improvement following shunt surgery between the high-SUVR and low-SUVR iNPH subgroups. The chi-squared test was used for comparison of sex between the subgroups. Correlations between the neocortical SUVRs, the clinical assessments at baseline, and clinical improvement following shunt surgery were examined using partial correlation analysis with length of education and symptom duration as covariates. SPSS 17.0 software (SPSS Inc., Chicago, USA) was used for statistical analysis, and the significance level was set at $p < 0.05$.

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