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Association between high biomarker probability of Alzheimer's disease and improvement of clinical outcomes after shunt surgery in patients with idiopathic normal pressure hydrocephalus

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ABSTRACT

We examined the effect of the pathology of Alzheimer's disease (AD) on improvement of clinical symptoms after shunt surgery in patients with idiopathic normal pressure hydrocephalus (iNPH). Forty-four iNPH patients were classified into 18 patients with (iNPH/AD+) and 26 patients without (iNPH/AD−) combination with low amyloid β42 and high total tau in cerebrospinal fluid (CSF). We compared improvements after lumbo-peritoneal shunt surgery (LPS) between the two groups in Timed Up & Go Test, 10-m reciprocating walking test, Digit Symbol Substitution Test, attention test, delayed recall test, Mini-Mental State Examination, iNPH grading scale, Neuropsychiatric Inventory, Zarit Burden Interview, and other evaluations. Three months after LPS, gait, urination, overall cognition, psychomotor speed, attention, and neuropsychiatric symptoms significantly improved in both groups, but the improvement in delayed recall and reduction of caregiver burden were significantly greater in iNPH/AD− than iNPH/AD+. In addition, improvement in delayed recall score after LPS was significantly and negatively correlated with the probability of AD as judged by amyloid β42 and total tau levels in CSF. Three months after LPS, almost all of the triad symptoms decreased in iNPH patients with and without AD pathology but memory improved only in iNPH patients without AD pathology.

1. Introduction

Normal pressure hydrocephalus (NPH) was first described in 1965 by Hakim and Adams [1] as ventricular dilation accompanied by a progressive syndrome of the triad symptoms of gait disturbance, cognitive impairment and urinary disturbance. Idiopathic NPH (iNPH), for which there is no antecedent cause, is a common disease with a prevalence of 2.8% in Japanese [2] and 2.1% in Swedish [3] elderly community residents. iNPH is increasingly gaining clinical importance in the elderly, because of its high prevalence and treatable nature.

The Japanese clinical guidelines for iNPH consider three types of iNPH: possible iNPH, probable iNPH and definite iNPH [4]. Possible iNPH is diagnosed based on clinical symptoms and the results of neuroimaging examinations. Probable iNPH is diagnosed when at least one of the triad symptoms is improved by removing transiently excess cerebrospinal fluid (CSF) (CSF tap test). Definite iNPH is diagnosed when at least one of the triad symptoms is confirmed to have improved after shunt surgery. In definite iNPH patients, the kinds of symptoms that improve and the extent of their improvement varies with the patient [5,6]. A potential contributor to shunt unresponsiveness is the presence of comorbidity of iNPH and other diseases. The effect of Alzheimer's disease (AD) on the success of shunt surgery has received

Abbreviations: NPH, normal pressure hydrocephalus; iNPH, idiopathic NPH; AD, Alzheimer's disease; iNPH/AD+, iNPH patients with high biomarker probability of AD; iNPH/AD−, iNPH patients without high biomarker probability of AD; CSF, cerebrospinal fluid; Aβ, amyloid β; Aβ42, Aβ1-42; t-tau, total tau; p-tau, hyperphosphorylated tau; VPS, ventriculo-peritoneal shunt surgery; LPS, lumboperitoneal shunt surgery; iNPHGS, iNPH grading scale; MRI, magnetic resonance image; TUG, Timed Up & Go Test; WT, 10-m reciprocating walking test; GSSR, Gait Status Scale-Revised; DSST, Digit Symbol Substitution Test; RBMT, Rivermead Behavioral Memory test; A/C, attention/concentration; WMS-R, Wechsler Memory Scale-Revised; MMSE, Mini-Mental State Examination; FAB, Frontal Assessment Battery; ICIQSF, International Consultation on Incontinence Questionnaire-Short Form; QOL, quality of life; NPI, Neuropsychiatric Inventory; ZBI, Zarit Burden Interview; PVH, periventricular hyperintensity; DWMH, deep white matter hyperintensity; NIA/AA, National Institute on Aging-Alzheimer's Association; ANOVA, analysis of variance.

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much attention. Moderate to severe AD pathology, which includes neurofibrillary tangles and amyloid β (Aβ) plaques in the brain, was found to reduce postoperative improvement of NPH symptoms in possible iNPH patients [7]. In the CSF of patients with AD, the concentration of Aβ1-42 (Aβ42) is low, whereas the concentrations of total tau (t-tau) and hyperphosphorylated tau (p-tau) are high [8]. These three AD biomarkers have sensitivities and specificities in the range 85% to 90% [8]. There is also evidence that these biomarkers can predict the presence of AD pathology in the brain of possible iNPH patients [9]. A combination of low Aβ42 and high t-tau levels in CSF predicted poor improvement after shunt surgery with a sensitivity of 80% and specificity of 82.4% in possible iNPH [10]. These studies were conducted with the aim of excluding possible iNPH patients with AD-related pathology as candidates for shunt surgery.

However, recent studies revealed that AD-related pathology is highly prevalent in possible iNPH patients. Twenty-five (67.6%) of 37 iNPH patients [7], and 52 (47%) of 111 possible iNPH patients [9] displayed AD-related pathology in cortical biopsies. Eight (32%) of 25 possible iNPH patients showed low Aβ42 in CSF [11] and 5 (50%) of 10 possible iNPH patients had amounts of neocortical amyloid deposits similar to those of AD subjects in amyloid imaging [12]. In a median follow-up time of 4.4 years, 94 (22%) of 433 patients with possible iNPH developed clinical AD [13]. Because many iNPH patients have AD-related pathology, it is necessary to know how AD-related pathology affects the improvement of clinical symptoms in iNPH patients after shunt surgery.

The results of previous studies were inconsistent. One study reported that possible iNPH patients with high p-tau/Aβ42 ratio values in CSF showed less improvement in gait, memory, psychomotor speed and visuospatial function after ventriculo-peritoneal shunt surgery (VPS) [14]. On the other hand, another study found no significant differences between possible iNPH patients with and without AD pathology in the magnitude of gait and psychometric change or in the proportion of cases that exhibited improved urinary control after VPS [15]. In these studies, outcome measures were limited, and VPS was used, which can produce puncture-induced damage to the brain and, therefore, could cause residual symptoms after shunt surgery. To evaluate the effect of AD-related pathology on clinical outcomes in iNPH, lumboperitoneal shunt surgery (LPS) is a more suitable shunt configuration, that has been recently confirmed to be effective for iNPH [16].

Here, to clarify the effect of AD on shunt surgery outcome, we compared the performance on various clinical outcome measures 3 months after LPS between iNPH patients with and without the combination of low Aβ42 and high t-tau in CSF.

2. Materials and methods

2.1. Subjects

This study followed the clinical study guidelines of the Ethics Committee of Osaka University Hospital and was approved by the Internal Review Board. Written informed consent was obtained from the patients or their families.

This study was conducted on patients who were admitted to the neuropsychological clinic of the Department of Psychiatry of Osaka University Medical Hospital from November 2007 to August 2015. In the clinic, possible iNPH patients were examined by geriatric psychiatry and neurology specialists. The patients were given standard neuropsychological and gait examinations, routine laboratory tests, and neuroimaging examinations. The triad symptoms of iNPH were evaluated with the iNPH grading scale (iNPHGS), which is a clinician-rated scale to separately rate the severity of each of the triad symptoms from 0 to 4 [17]. The possible iNPH patients were also given a CSF tap test, in which we removed 30 ml of CSF via lumbar tap. If the symptoms improved after the transient CSF removal, shunt surgery was considered.

Inclusion criteria for iNPH in this study were as follows: (1) age > 60 years, (2) presence of one or more triad symptoms (gait disturbance, cognitive impairment, or urinary disturbance), (3) presence of ventricular dilatation (Evans index >0.3), (4) tight high-convexity/medial subarachnoid spaces, as shown on magnetic resonance images (MRIs) [18], (5) absence of diseases or conditions that could cause the clinical symptoms or radiological findings, (6) no history or evidence of conditions that might cause secondary NPH, (7) normal CSF contents and pressure and normal results of the Queckenstedt's test, (8) signed agreement to measure Aβ42 and t-tau in CSF, and (9) no adverse event before the evaluation at 3 months after LPS.

2.2. Clinical assessments

Gait speed was assessed with the Timed Up & Go Test (TUG) [19] and 10-m reciprocating walking test (WT). The quality of gait was assessed with Gait Status Scale-Revised (GSSR) [17], which examines the following 10 factors of gait disturbances: (1) postural stability (range, 0–4); (2) independence of walking (0–2); (3) wide base gait (0–1); (4) lateral sway (0–2); (5) petit pas gait (0–2); (6) festinating gait (0–2); (7) freezing of gait (0–2); (8) disturbed tandem walking (0–1); (9) shuffle (0–1); and (10) bow-leggedness (0–1). We used the total score of the 10 items of the GSSR to obtain scores that ranged from 0 to 18.

Cognition was assessed with the following tests: Digit Symbol Substitution Test (DSST) of the Wechsler Adult Intelligence Scale-III, subtest of delayed recall of a short story of the Rivermead Behavioral Memory test (RBMT) [20], attention/concentration (A/C) of the Wechsler Memory Scale-Revised (WMS-R), Mini-Mental State Examination (MMSE), and Frontal Assessment Battery (FAB) [21].

Urination was assessed with International Consultation on Incontinence Questionnaire-Short Form (ICIQSF), which is a questionnaire that evaluates the patient's quality of life (QOL) relevant to urinary incontinence [22].

Neuropsychiatric symptoms were assessed with the Neuropsychiatric Inventory (NPI) [23], and caregiver burden was with the Zarit Burden Interview (ZBI) [24].

Higher scores indicated better performance in DSST, RBMT, A/C, MMSE, and FAB and worse performance in iNPHGS, TUG, WT, GSSR ICIQ-SF, NPI and ZBI. These evaluations were conducted by geriatric psychiatrists and neuropsychologists, who remained blind to the CSF patients' results.

The degree of improvement after shunt surgery in iNPH is reported to decrease with duration after shunt surgery [25] and the postoperative clinical assessment was conducted at approximately 4 months after shunt surgery in a previous study, in which the improvement of clinical symptoms after shunt surgery was compared between iNPH with and without AD pathology [7]. Therefore, the examinations were conducted before and 3 months after shunt surgery in this study.

We rated the extent of periventricular hyperintensity (PVH) and deep white matter hyperintensity (DWMH) in patients' T2-weighted fluid-attenuated inversion recovery MRI before shunt surgery according to the Fazekas scale [26]. H. Kazui, who was blind to the patients' clinical data independently scored these scales. We evaluated whether the iNPH patients of this study met the criteria for probable AD dementia according to the updated recommendations from the National Institute on Aging-Alzheimer's Association (NIA/AA) workgroups [27].

2.3. CSF analysis

CSF samples were collected with lumbar puncture before shunt surgery, placed in 15-ml polypropylene tubes and centrifuged at 1500 rpm. If the supernatant was bloody, the patient was excluded from the study. One ml aliquots of the supernatant were placed in 1.5 ml polypropylene tubes and stored at −80 °C. After we had accumulated CSF samples from 20 to 30 patients, the Aβ40, Aβ42 and t-tau levels were measured in one batch using 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),