Cognitive and neuropsychiatric profiles of idiopathic normal pressure hydrocephalus

博士論文

Cognitive and neuropsychiatric profiles of idiopathic normal pressure hydrocephalus

（特発性正常圧水頭症における認知機能障害と精神症状・行動異常）

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1. ABSTRACT

Dementia is one of the clinical triad of idiopathic normal pressure hydrocephalus (iNPH). Although it is necessary to know detailed features of cognitive and behavioral symptoms for accurate diagnosis and appropriate treatment, systematic studies addressing these issues are very scarce. Previous investigations on cognitive dysfunction in iNPH focused on attention, executive function, and memory, and paid less attention to 'posterior cortical' functions, such as visuoperceptual and visuospatial functions. As for neuropsychiatric symptoms, no systematic investigations have been conducted so far except two observational studies. In STUDY 1, broad domains of cognitive functions were examined in patients with iNPH. In STUDY 2, neuropsychiatric symptoms in iNPH were systematically assessed by using the Neuropsychiatric Inventory (NPI). I found that patients with iNPH were impaired in broader cognitive domains and develop more diverse neuropsychiatric symptoms than previously reported. The cognitive domains affected in iNPH include not only executive function and memory but also visuoperceptual/visuospatial functions. Although negative symptoms such as apathy and decreased arousal have previously been emphasized, a high prevalence of positive symptoms such as agitation and irritability were noted. After CSF shunt surgery, a significant improvement was observed only in executive function, but not in

visuoperceptual/visuospatial functions. Among the various neuropsychiatric symptoms, only agitation and cognitive fluctuation were responsive to shunt surgery. The present studies provide useful information on detailed nature of dementia in iNPH.

2. INTRODUCTION

2-1. Diagnostic concepts of idiopathic normal pressure hydrocephalus

As the number of elderly people in Japan is increasing, the medical care of elderly people has been increasingly important. In particular, cognitive and movement disorders are serious problems because they deprive sufferers of the ability to perform independent social activities and have a profound effect on their quality of life. Idiopathic normal pressure hydrocephalus (iNPH) is a disorder causing cognitive and movement impairments in aged people, which has therefore recently elicited renewed attention.

Hakim and Adams first described normal pressure hydrocephalus (NPH) in 1965.[1, 2] NPH manifests as a triad of gait disturbance, dementia, and urinary incontinence with ventricular dilation and normal intracranial pressure.[3, 4] These symptoms can be reversed by cerebrospinal fluid (CSF) shunt surgery. NPH is classified into two types according to etiology: secondary NPH (sNPH) occurring subsequent to preceding illnesses, such as subarachnoid hemorrhage and meningitis; and iNPH of unknown etiology. Unlike sNPH, the diagnosis of iNPH is often challenging, because the specific inciting disease cannot be unidentified and the onset of symptoms is insidious and their progression gradual. Historically, this ambiguity in diagnosing iNPH produced a surge of shunt surgery in the period following Adams and Hakim's first report.[1, 2] As a result, surgical treatment was

undertaken for dementia arising from diseases other than iNPH, and failed to produce any beneficial results. After the era of enthusiasm for shunt surgery, many neurologists and neurosurgeons hesitated to give the surgical treatment to patients with suspected iNPH. However, recent developments in diagnostic imaging tools, e.g. computed tomography (CT) and magnetic resonance imaging (MRI), have enabled us to differentiate iNPH from other neurological diseases, and there is now a resurgence of interest in the diagnosis and treatment of this condition.

Until recently, there was no consensus of agreement about the diagnostic criteria for iNPH. Classically, NPH is defined simply as a condition with the triad of symptoms described above, which are improved by CSF shunt surgery. This 'classic' definition does not provide us with any tools for preoperative differentiation from other neurological diseases presenting with similar symptoms. As the first step towards the establishment of preoperative diagnostic procedures, the Japanese Society of Normal Pressure Hydrocephalus (JSNPH) recently published criteria consisting of three diagnostic levels: possible, probable, and definite iNPH.[5, 6] Possible iNPH corresponds to a condition involving the presence of one or more of the clinical triad, onset of symptoms during the sixties or older, ventricular dilation on CT and MRI, and clear CSF with normal CSF pressure. The diagnosis of probable iNPH is made when the patient's condition fulfills the

criteria for possible iNPH with improvement of symptoms after the CSF tap test or continuous CSF drainage. The diagnosis of definite iNPH is determined by the improvement of symptoms after CSF shunt surgery. Also, the international guidelines were published in 2005[7-11], and the both two guidelines are same in proposing the practical solutions to establish the preoperative diagnostic procedures, although both were different in some points. Details of the JSNPH criteria are shown in Table 1.

2-2. Clinical symptoms of iNPH

2-2-1. Gait disturbance and urinary dysfunction

Gait disturbance is an early and almost essential symptom, and shows the most notable improvement of all the triad of symptoms after CSF removal. Although gait disturbance in iNPH shares the features of short step, start hesitation, and increased instability on turning with Parkinson's disease (PD), it can be differentiated from PD by broad base and little effect of external cues. The gait disturbance of iNPH is often described as ataxic/apraxic gait.[12, 13] Improvement of gait after CSF removal is characterized by increased stride length and decreased number of steps on turning.[12]

Urinary dysfunction in iNPH is characterized by overactive bladder symptoms, e.g., nocturnal pollakisuria, urinary urgency, and urge incontinence. Although incontinence

reportedly has the lowest prevalence of the triad of symptoms and occurs after the two other symptoms, overactive bladder symptoms occur in more than 90% of iNPH patients.[14] The contribution of frontal lobe dysfunction has been demonstrated in previous neuroimaging investigations.[14-16] Sakakibara and colleagues[14] suggested that frontal lobe dysfunction is associated with both dysfunction of the lower urinary tract per se and functional incontinence arising from cognitive impairment.

2-2-2. Cognitive symptoms

Previous studies of cognitive dysfunction in iNPH (and NPH in general) have focused on attention, executive function, and memory, whereas less attention has been paid to 'posterior cortical' functions, such as visuoperceptual and visuospatial function. This imbalance presumably stems from the concept that NPH is one of a group of prototypic disorders of 'subcortical dementia'. Subcortical dementia is a cognitive-behavioral syndrome arising subsequent to disruption of the frontal-subcortical circuits, and characterized by executive dysfunction, poor attention, cognitive slowing, and memory impairment with relatively preserved recognition memory. However, pathological changes in NPH are not restricted to the frontal regions of the cerebrum, but also affect posterior brain regions.[16] In addition, these changes may be reversed to some extent as a result of

CSF shunt surgery.[17, 18] It is necessary to characterize the cognitive dysfunction of iNPH in a more comprehensive way, and to identify which symptoms is likely to response to CSF shunt treatment.

2-2-3. Neuropsychiatric symptoms

Neuropsychiatric symptoms, or behavioral and psychological symptoms of dementia (BPSD), include non-cognitive symptoms such as apathy, depression, agitation, and psychosis. Neuropsychiatric symptoms give rise to serious problems in patients' quality of life and great burden and distress in their caregivers. Although a number of studies have addressed the cognitive aspects of dementia, only a few studies have focused on the neuropsychiatric disturbances in iNPH, which have reported drowsiness and a lethargic tendency as characteristic symptoms.[19, 20] There were no studies examining systematically and quantitatively the neuropsychiatric symptoms of iNPH patients.

2-3. Objectives

In STUDY 1, to delineate the profile of neuropsychological deficits in iNPH, various cognitive domains were evaluated in preoperative patients with iNPH comparing with those with Alzheimer's disease (AD), and repeated after CSF shunt treatment. In STUDY

2, to elucidate the features of BPSD in iNPH, neuropsychiatric symptoms in iNPH were assessed by using the Neuropsychiatric Inventory (NPI), an established and widely used tool for the assessment of BPSD, comparing with AD, and delineate the changes in the neuropsychiatric profile after CSF shunt surgery.

3. STUDY 1. Cognitive profile of iNPH

3-1. Methods

3-1-1. Subjects

All procedures in this study followed the clinical study guidelines of Tohoku University Hospital and Akita Prefectural Center of Rehabilitation and Psychiatric Medicine, and were approved by the Tohoku University Graduate School Medicine Ethical Committee. Written informed consent was obtained from all participants after they were fully explained the study procedure.

Patients with iNPH were consecutively recruited from patients who were admitted to the Department of Behavioral Neurology and Cognitive Neuroscience at Tohoku University Hospital and the Department of Rehabilitation Medicine at Akita Prefectural Center of Rehabilitation and Psychiatric Medicine from May 2006 to April 2009. All patients underwent comprehensive neurological and behavioral examination by neurologists, laboratory investigations, and MRI, single photon emission computed tomography (SPECT), and lumbar CSF tap test. Patients who fulfilled the JSNPH criteria for possible iNPH (see Table 1)[6] and had narrowing of the high convexity/midline subarachnoid spaces on MRI underwent shunt surgery regardless of the result of CSF tap test. The subjects of the present study were those with definite iNPH according to the

criteria of JSNPH, i.e., those who showed 'significant' improvement of clinical symptoms following shunt surgery were documented at any point during the postoperative period (2 weeks to 1 year) (see Table 1).[6] Clinical symptoms were rated by using a validated scale developed specifically for iNPH, the iNPH Grading Scale (iNPHGS),[21] in which each of the triad of symptoms is rated on a 4-point scale [from 0 (normal) to 12 (severe)]. 'Significant' improvement was defined as improvement of 1 point or more postoperatively by relative to baseline on the total iNPHGS score.[21] Patients who could not complete the neuropsychological tests for clinical reasons such as refusal of examination, delirium, and severe apathy were excluded.

Thirty-four of the patients (16 women, 18 men) were included the STUDY 1 baseline part. Their mean (SD) age was 76.2 (4.6) years (range 65–84), and their mean duration of education was 10.2 (3.5) years. The mean (SD) iNPHGS scores before and after CSF shunt surgery were 2.5 (0.7) and 2.1 (0.8) (Wilcoxon test; $Z = -3.260$, $p = 0.001$) for cognitive, 2.4 (0.7) and 1.7 (0.9) ($Z = -4.070$, $p < 0.001$) for gait, 2.0 (1.0) and 0.9 (1.0) ($Z = -4.185$, $p < 0.001$) for urinary score, and 6.9 (1.7) and 4.7 (1.8) ($Z = -5.149$, $p < 0.001$) for total score, respectively. Twenty-three patients received ventriculo-peritoneal (VP) shunt surgery and 11 patients received lumbo-peritoneal (LP) shunt surgery. The mean (SD) interval between the neuropsychological tests and shunt surgery was 71.4 (43.4) days.

As disease controls, 34 patients with AD (20 women, 14 men) matched for age, sex, duration of education, and degree of cognitive dysfunction as assessed by the Mini-Mental State Examination (MMSE) were selected from the same pools of patients described above. Diagnosis was made according to the National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer's Disease and Related Disorders Association (NINCDS/ADRDA) criteria for probable AD.[22] The means (SD) of age and years of education were 76.7 (4.9) years (range 64–87) and 9.5 (2.3) years, respectively.

Thirty healthy elderly volunteers recruited from the community based on their age, sex, and duration of education [mean (SD) age 76.8 (5.8) years (range 70–91); 15 women, 15 men; mean (SD) duration of education 10.5 (2.8) years] were included as normal controls (NC). There were no significant differences among the iNPH, AD, and NC groups in terms of age (F (2, 95) = 0.137, p = 0.870), sex (Pearson's χ^2 test, χ =1.015, p = 0.602), and duration of education (F (2, 95) =0.885, p = 0.416) (Table 2).

Of the 34 patients, 23 were the subjects of the STUDY 1 longitudinal part. Mean (SD) duration of follow-up was 12.4 (1.0) months (range 12-15 months). The mean (SD) age of the patients was 75.4 (4.5) years (range 67–84), and mean duration of education was 10.0 (3.2) years.

3-1-2. Neuropsychological assessments

The following neuropsychological tests were carried out to evaluate various aspects of cognitive domains.

(1) MMSE [23, 24] for general cognitive function.

(2) Digit Span and Spatial Span tests of the Wechsler Memory Scale-Revised (WMS-R) [25, 26] for attention.

Summed scores of forward and backward spans were used for the analyses.

(3) Word Fluency,[27, 28] Trail Making Test-A (TMT-A),[27, 29] and Frontal Assessment Battery (FAB) [30] for executive function.

In the Word Fluency, 1-minute free recall of words with “Fu” “A” “Ni” for phoneme and of animal names for category were tested. In TMT-A, the number of seconds required to complete the task was measured.

(4) Object Naming subtest of the Western Aphasia Battery (WAB)[31, 32] for language.

(5) Word Recall and Word Recognition subtests of the Alzheimer’s Disease Assessment Scale (ADAS)[33, 34] for episodic memory.

Episodic memory involves two distinct processes, recall and recognition. Recall is defined as the ability to retrieve memory contents without the use of external cue, and recognition is the ability to judge whether given information has been experienced before

or not. In the present study, Word Recall subtest of the ADAS measured the free recall ability, and Word Recognition subtest measured of the recognition memory. In addition, I used *d'* for measures of general performance of recognition (true recognition and false recognition), which was calculated according to the formula:

$d' = z(\text{true recognition rate}) - z(\text{false recognition rate})$.[35]

(6) Visual Discrimination (Length, Size, Direction, and Complex Form), Overlapping Figures, and Visual Counting tasks[36-38] for visuoperceptual and visuospatial functions.

Length and Size Discrimination. The stimuli consisted of 6 sets of lines, 3 sets of circles, and 3 sets of rectangles printed on separate sheets of A4-sized paper (total 12 sheets). Subjects were asked to point out the longest and shortest, the largest and smallest. The total score ranged from 0 to 20.

Direction Discrimination. An examiner presented 15 pairs of lines printed on separate sheets of paper one by one. Five pairs were parallel to each other and 10 pairs were inclined at angles from 4 to 7 degrees. Subjects were asked to determine whether pairs of lines were parallel or not. Total score ranged from 0 to 15.

Complex Form Discrimination. Four line-drawn geometric figures were placed in a 2 x 2 array on each of 20 sheets of paper. Of each set of 4 figures, 3 were the same and 1 was slightly different, rotated or flipped. The subjects were instructed to point to the odd figure.

The maximum possible score was 20.

Overlapping Figures. There were 3 sets of overlapping line drawings. Each set contained 3 simple geometric figures, 4 man-made objects, and 5 fruits (a total of 12 objects). The subjects were asked to identify all individual figures, by naming, describing, tracing by finger, or matching them with non-overlapping drawings. The maximum possible score was 12.

Visual Counting. The task consisted of 28 sheets of A4-sized paper, on each of which there were 4 to 12 simple figures (circles and triangles) of 1 or 2 colors (red and blue). Subjects were asked to count the number of figures with a specified color (red or blue) and form (circle or triangle), and the total number of figures. The maximum possible score was 56. Details of the visuoperceptual and visuospatial tasks have been described elsewhere.[36-38]

3-1-3. Statistical analyses

Group comparisons at baseline were made by using Kruskal-Wallis test (p = 0.05). Post-hoc pairwise comparisons between the iNPH and NC and between the iNPH and AD groups were tested using Mann-Whitney U test with Bonferroni correction (p = 0.025) Comparisons between baseline and post-shunt surgery were made by using Wilcoxon's

signed rank test (p = 0.05). All statistical analyses were performed with R 2.9.0 (R Development Core Team 2008).

3-2. Results

3-2-1. Group comparisons of neuropsychological test performances at baseline

The results are summarized in Table 3. There were significant differences among the three groups for all test scores ($p < 0.05$) except for the WAB Object Naming (p = 0.055), ADAS False Recall (p = 0.196), and Length and Size Discrimination (p = 1.000). Below are described in detail the results of pairwise comparisons on the tests, in which significant group-level differences were found.

Although the iNPH group performed significantly worse than the NC group on the MMSE, there was no significant difference between the iNPH and AD groups. Compared to the NC group, the iNPH group performed significantly worse on the Digit Span and Category Fluency. There were no significant differences between the iNPH and AD groups on these tests. On the Spatial Span, Phoneme Fluency, TMT-A and FAB, the performance of the iNPH group was worse than the performances of the other two groups.

Compared to the NC group, the iNPH group was impaired on True Recall, True Recognition, and *d*' of the ADAS, whereas the iNPH and AD groups were comparable on

these measures. The iNPH patients made fewer false recognition responses than the AD patients. No significant differences were found between the iNPH and NC groups in terms of the number of false recognition responses.

Although the performance of the iNPH group was significantly worse than that of the NC group on the Direction Discrimination and Overlapping Figure, there was no significant difference between the iNPH and AD groups. On the Complex Form Discrimination and Visual Counting, the performance of the iNPH group was significantly worse than those of the other two groups.

3-2-2. Changes in neuropsychological test performances after shunt surgery

The results are shown in Table 4. One year after CSF shunt surgery, performances of the TMT-A and FAB were significantly improved ($p < 0.05$). The other test performances were not significantly different before and after shunt surgery ($p > 0.05$).

3-3. Discussion

In line with previous studies,[39-41] STUDY 1 demonstrated that iNPH patients were impaired in measures of executive functions. This finding is consistent with the characterization of the cognitive and behavioral disturbances of iNPH as 'subcortical

dementia', whose neuropsychological deficits involve executive or 'frontal lobe' dysfunction.[42-44] Previous neuroimaging studies support the view that 'frontal lobe' dysfunction originates not from damage to the frontal cortex itself, but remote effects of subcortical lesions in iNPH; SPECT studies[45-47] have demonstrated regional cerebral blood flow (rCBF) decrease in the lateral and medial frontal cortices, whereas there was no significant gray matter loss in these regions in a voxel-based morphometric (VBM) study.[48]

It has been repeatedly claimed that the pattern of memory deficit in iNPH is of 'frontal lobe' type, in which recall is disproportionately affected relative to recognition memory.[49-51] However, no previous studies have provided empirical evidence of relative preservation of recognition memory in iNPH. In this study, these two different aspects of memory were directly evaluated in iNPH and AD, and were affected comparably in the two disorders. The present results suggest that memory impairment in iNPH is not exclusively ascribable to frontal lobe dysfunction. Episodic memory is a function subserved by a network consisting of several neuroanatomical regions, including the medial temporal lobe, thalamus, retrosplenial cortex, and white-matter structures containing fibers interconnecting these brain regions. A recent neuroimaging study demonstrated medial temporal volume reduction in iNPH.[48] Damage to the hippocampus

and the adjacent medial temporal structures are major candidates for the memory deficit in iNPH. Increased false recognitions have been reported to be one of the characteristic features of recognition memory in AD.[52] Some investigators have stressed the contribution of executive dysfunction to the emergence of false recognitions.[53] However, a lower rate of false recognitions in iNPH cannot be explained by this hypothesis, because executive function was more defective in iNPH than in AD. Previous studies showed that patients with depressive pseudo-dementia[54] and with progressive supranuclear palsy[55] made fewer false recognition errors than those with AD. Severer apathy or less productivity in iNPH and other subcortical dementias[20] than in AD might explain conservative response bias and a lower rate of false recognitions.

Visuoperceptual and visuospatial functions have not been addressed in previous studies of iNPH. The present investigation demonstrated significant impairment of these functions in this disorder. Defective performance on the visual discrimination tasks suggests that patients with iNPH are impaired in visual form perception or constructive function.[36-38] This result is consistent with those of a previous study showing impaired performance of iNPH patients on the Block Design task.[40] The patients with iNPH are impaired also on the Visual Counting task.[36-38, 56] Although this task requires working memory, the primary contribution of the parietal cortex is suggested by the previous observation,[57] in which

patients with frontal lobe damage performed normally on this task. We should consider the roles of the extensive subcortical white matter lesions in parietal lobe dysfunction.[46]

The longitudinal part of STUDY 1 revealed that CSF shunt surgery improved executive function that was impaired at baseline. Previous studies demonstrated that the FAB had good a good test-retest reliability in patients with dementia[73, 74], and that the TMT-A had no practice effect in patients with NPH[75]. Therefore, a practice effect is unlikely, and the improvement demonstrated on these tests are attributable not to practice but to the shunt effect. These results are consistent with those of previous neuroimaging studies that showed improvement of the frontal and parietal CBF after shunt surgery.[17, 18] Improvement of visuoperceptual and visuospatial functions did not reach statistical significance in this study. The negative result may come from the small sample size in the present study.

4. STUDY 2. Neuropsychiatric profile of iNPH

4-1. Methods

4-1-1. Subjects

Inclusion criteria for the patients were the same as those of STUDY 1. Written informed consent was obtained from all the participants. Forty-five patients (20 women, 25 men) with definite iNPH on the JSNPH criteria[6] (Table 1) were recruited from consecutive iNPH patients who underwent detailed evaluation in the two hospitals described above from January 2005 to February 2009. The definition of significant clinical improvement was same as in STUDY 1. The subjects' mean (SD) age, duration of education, and MMSE scores were 76.2 (4.2) years (range 65-84), 10.2 (3.5) years, and 20.9 (4.7), respectively. The mean (SD) iNPHGS scores before and after CSF shunt operation were 2.5 (0.7) and 2.0 (1.0) (Wilcoxon test; Z = -3.213, p = 0.001) for cognitive, 2.3 (0.6) and 1.5 (0.9) (Z = -4.021, $p < 0.001$) for gait, 1.8 (1.0) and 0.9 (1.1) (Z = -3.531, $p < 0.001$) for urinary, and 6.7 (1.8) and 4.3 (2.3) (Z = -4.400, $p < 0.001$) for total score, respectively. Thirty-two patients received VP shunt surgery and 13 patients received LP shunt surgery. The mean (SD) interval between interview and surgery was 69.4 (41.2) days. For longitudinal part of STUDY 2, patients who could not follow up for clinical reasons such as death, institutionalization, and complications after surgery were excluded, and thus

postoperative evaluation was carried out in 29 patients approximately one year after shunt surgery. The mean (SD) duration of the follow-up was 12.6 (1.1) months (range 11-15 months). The mean (SD) age of the patients was 75.6 (4.0) years (range 67–84 years), and their mean duration of education was 10.0 (3.2) years. The neuro-psychopharmacological treatment was unchanged in most of the patients from baseline to 1-year after surgery except for 4 patients: trazodone 25mg/day was substituted by paroxetine 40 mg/day (n = 1) or by donepezil 5mg/day (n = 1); amantadine 50mg/day and paroxetine 20 mg/day were discontinued (n = 1); risperidone 0.3mg/day were started (n =1).

As a disease control group, 45 patients with AD (26 women, 19 men) matched for age, sex, duration of education, and degree of cognitive dysfunction represented by the MMSE were selected from the same pools of patients described above. The means (SD) of age, duration of education, and MMSE score were 76.0 (4.5) years (range 64–87 years), 10.3 (2.6) years, and 21.9 (3.8), respectively. I found no significant differences between the iNPH and AD groups in terms of age (t = 0.289, p = 0.773), sex (Pearson's χ^2 test, χ = 1.601, p = 0.206), duration of education (t = -0.205, p = 0.838), and MMSE score (t = -1.090, p = 0.279) (Table 5).

4-1-2. Clinical and neuropsychiatric assessments

A modified version of NPI[58] was used for the assessment of neuropsychiatric symptoms. The NPI is a caregiver-based behavioral rating system validated for the assessment of mental state and behavioral abnormalities in dementia. In the original NPI,[59] the 10 neuropsychiatric symptoms (delusions, hallucinations, agitation/aggression, depression/dysphoria, anxiety, euphoria, apathy, disinhibition, irritability/lability, and aberrant motor behavior) of dementia were rated in terms of frequency (range 1-4) and severity (1-3) on the basis of the patient's condition in the month preceding the interview. A frequency rating multiplied by a severity rating produces a subscale score for each behavior, and the summation of subscale scores produces the total NPI score.[60] In this study, the modifications included a distinction of 'delusion' between two different categories – persecution delusion and delusional misidentification – and an addition of a domain for fluctuation of cognition.[58, 61] Therefore, the modified NPI consisted of 12 domains, and the maximum total score was different from that of the original version (120 in the original and 144 in our modified version).

Locomotor function was assessed only in iNPH patients using the 3-Meter Timed Up & Go (TUG) test.[62] TUG is a valid test of functional mobility used in many studies to evaluate locomotor function. The TUG measures the time to take to stand up from sitting in an armchair, walk forward 3 meters, and return to the seated position. No physical

assistance is given. In the present study, if a patient was at risk of falling, the examiner followed a half-step behind the patient as a precaution in case of falling, but without affecting the patient's walking pace.

4-1-3. Statistical analyses

Group comparisons of NPI at baseline were made using the χ^2 test for analysis of prevalence, and the Mann-Whitney U test for analysis of scoring data (p = 0.05). Correlation analysis was made with Spearman's correlation coefficients (p = 0.05). Comparisons between baseline and post-shunt surgery were made by using McNemar test (for prevalence) and Wilcoxon's Signed Rank test (for scoring data) (p = 0.05). All statistical analyses were performed with the R 2.9.0 (R Development Core Team 2008).

4-2. Results

4-2-1. Group comparisons of neuropsychiatric profiles at baseline

The results of NPI at baseline are summarized in Table 6. In the iNPH group, apathy was the most frequently occurring symptom (80.0%), followed by agitation (48.9%) and irritability (42.2%). I found that apathy and irritability were significantly more common in the iNPH group than in the AD group ($p < 0.05$) (Table 6). Prevalence of the other

symptoms was not significantly different between the two groups. The iNPH group had significantly higher scores than the AD group for agitation/aggression, apathy, irritability/lability, and fluctuation of cognition (Table 6). Scores of the remaining domains were not significantly different between the two groups.

4-2-2. Correlations between neuropsychiatric symptoms and motor or cognitive abilities in the iNPH group

Four patients could not complete TUG within 60 sec. The mean (SD) time required for completing TUG by patients in the iNPH group was 18.2 (9.3) sec. The results of correlation analyses between the neuropsychiatric symptoms and cognitive or locomotor dysfunctions in iNPH are shown in Table 7. There were no significant correlations between the scores for neuropsychiatric symptoms and the TUG. I found significant negative correlation between apathy and MMSE score (Spearman's r.s. = -0.303, p = 0.043), and trends of correlation between agitation score and MMSE score (Spearman's r.s. = 0.267, p = 0.076), aberrant motor behavior score and MMSE score (Spearman's r.s. = -0.273, p = 0.069), and fluctuation of cognition and MMSE score (Spearman's r.s. = -0.246, p = 0.080). There was no significant correlation between irritability and MMSE score (Spearman's r.s. = 0.005, p = 0.973). There were highly significant correlations

between hallucination score and aberrant motor behavior score (Spearman's r.s. = 0.699, $p < 0.001$), agitation score and irritability score (Spearman's r.s. = 0.411, $p = 0.005$), anxiety score and irritability score (Spearman's r.s. = 0.421, $p = 0.004$), and dysphoria score and anxiety score (Spearman's r.s. = 0.626, $p < 0.001$).

4-2-3. Changes in neuropsychiatric profiles after shunt surgery

The mean (SD) MMSE score was significantly improved 1 year after CSF shunt surgery (from 22.1 (4.3) to 23.4 (4.5); Wilcoxon test; $Z = -3.260$, $p < 0.05$). The changes in scores on the modified NPI 1 year after CSF shunt surgery are shown in Table 7. The prevalence of agitation/aggression was significantly reduced compared to baseline ($p < 0.05$) (Table 8). The prevalence of the other symptoms was not significantly different before and after surgery ($p > 0.05$). The scores of agitation/aggression and fluctuation of cognition were significantly reduced after surgery. Scores of the remaining domains were not significantly different before and after surgery ($p > 0.05$).

4-2-4. Subgroup analysis for changes in MMSE and NPI-agitation scores after shunt surgery

A subgroup analysis was carried out to further explore the relationship between the

changes of MMSE and NPI-agitation scores. The iNPH patients were divided into two subgroups according to severity of cognitive impairment, group of patients with minimal cognitive impairment (MMSE≧23; 5 women, 9 men; mean (SD) age: 75.4 (4.8) years; mean (SD) years of education: 11.6 (3.1) years), and group of patients with more severe cognitive impairment (MMSE<23; 7 women, 8 men; mean (SD) age: 75.7 (3.5) years; mean (SD) years of education: 8.9 (3.0) years). The minimally impaired group did not improve for MMSE score (from 25.1 (2.2) to 25.4 (3.5); Wilcoxon test; Z = -0.158, p = 0.875), but for NPI-agitation score (from 2.0 (2.3) to 0.3 (1.1); Z = -2.442, p = 0.015) (Figure 1). In the severely impaired group, the mean MMSE score was improved (from 19.2 (3.8) to 21.6 (4.7); Z = -2.215, p = 0.027), although NPI-agitation score was not significantly changed (from 0.9 (1.4) to 0.5 (1.0); Z = -0.816, p = 0.414) (Figure 1).

4-3. Discussion

In STUDY 2, the features of neuropsychiatric symptom in iNPH were elucidated. The results can be summarized as follows; (i) Apathy, agitation, and irritability were common neuropsychiatric symptoms; (ii) In a comparison with AD, iNPH was characterized by higher prevalence and greater severity of apathy, and greater severity of agitation, irritability, and fluctuation of cognition; (iii) These neuropsychiatric symptoms were

linked to cognitive dysfunction but not to motor impairment; severity of apathy paralleled that of cognitive dysfunction, whereas agitation tends to dominate in patients with relatively mild cognitive dysfunction: and (iv) Shunt surgery improved agitation and fluctuation of cognition but not apathy.

Apathy is defined as loss of drive/motivation, or lack of feeling/emotion. This symptom is commonly observed in various cerebral diseases. For example, apathy has been reported to be one of the most common behavioral symptoms in AD, frontotemporal lobar degeneration, dementia in Parkinson's disease, and vascular dementia. Compared to previous reports of these disorders, however, the prevalence of apathy is exceptionally high in iNPH. As was found in the present study, previous studies have reported the presence of apathy in more than 80% of patients with iNPH.[19, 20] There is a possibility that concomitant motor deficits lead to an overestimation of the incidence of apathy. However, the significant correlation of apathy with cognitive dysfunction but not with gait disturbance negates this possibility. Previous neuroimaging studies of AD, cerebral infarction, and iNPH suggest that apathy is associated with dysfunction of the anterior cingulate cortex.[63-66] A SPECT study has indicated that rCBF in the anterior cingulate cortex is more severely decreased in iNPH than in AD,[16] a finding that may be explained by the higher prevalence and greater severity of this symptom in iNPH.

The scores of agitation and irritability were highly correlated with each other, suggesting that these symptoms share underlying mechanisms in iNPH. The close relationship between agitation and irritability was also demonstrated in AD and vascular dementia.[67] Irritability and agitation are often described in relation to frontal lobe damage. In particular, these behavioral symptoms emerge as a manifestation of disinhibition and antisocial behaviors in those with orbitofrontal injury.[68] In AD and traumatic brain injury, agitation is reportedly prevalent and severe in patients with frontotemporal involvement.[69, 70] In contrast, a VBM study[71] failed to find any neural correlates of agitation and irritability in frontotemporal lobar degeneration. The lack of consistency of neuronal correlates across the diseases suggests that mechanisms underlying agitation and irritability are multifaceted. However, a trend of negative correlation between cognitive dysfunction and agitation suggests that relative preservation of cognition is a contributing factor to the development of this symptom. Although disruption of the frontal-subcortical circuits due to white matter pathology may be associated with the development of agitation and irritability, additional factors should be considered to explain the high prevalence of these symptoms in iNPH.

There are many common symptomatic features between iNPH and confusional state/delirium: poor attention, psychomotor retardation, fluctuation of symptoms, loss of

spontaneity, and agitation/irritability. Some investigators pointed out impaired arousal and wakefulness in iNPH and their similarity to consciousness disturbance.[20] Arousal is a function of ascending activating projections to the cerebral cortex that arise from the upper brainstem, thalamus, and basal forebrain.[68, 72] In NPH, compression or congestion in the white matter structures due to excessive retention of CSF in the cranial cavity may be associated with confusion/delirium-like behavioral changes such as agitation, apathy, and fluctuation of cognition. This view predicts global improvement of brain function as a result of CSF shunt surgery. This prediction is in line with previous neuroimaging studies showing extensive increase of rCBF in the frontal, parietal, and subcortical regions after shunt surgery.[17, 18]

Improvement of agitation and cognitive fluctuation after CSF shunt treatment are also reminiscent of the processes of recovery from delirium/confusional state. However, the lack of improvement in apathy in the present study is incompatible with such a 'global hypothesis'. Lindqvist and colleagues[20] found that shunt surgery improves arousal deficit only in patients with somnolence-sopor-coma disorder, the most severe forms of consciousness disturbance in iNPH. Mild to moderate disturbance of arousal and spontaneity, which is observed in the majority of the present patient population, may be less responsive to shunt treatment.[19, 20]

MMSE score and severity of agitation were positively correlated with each other at baseline. Both the MMSE score was increased and agitation was improved after CSF shunt surgery. A Subgroup analysis revealed that the group of minimal cognitive impairment did not improve for the MMSE but for agitation score. In contrast, the group of severe cognitive impairment improved for the MMSE score, but not for agitation score. These results suggest that the improvement of neuropsychiatric symptom is not in parallel with cognitive improvement. Applying a shunt surgery to a patient with relatively mild cognitive impairment benefits neuropsychiatric symptoms rather than cognitive impairment.

5. GENERAL DISCUSSION

The cognitive and behavioral/neuropsychiatric characteristics of iNPH have been classified into a category of 'subcortical dementia' as like vascular dementia, progressive supranuclear palsy, Parkinson's disease with dementia, and so on. Although such a labeling adequately captures some aspects of the clinical features of these disorders, it does not provide enough of the information that is required in clinical settings. Deeper understanding of the symptoms is necessary for establishment of accurate diagnosis and appropriate therapeutic indication. For example, recent progress in understanding the cognitive and behavioral symptoms of Parkinson's disease, which has classically been considered to be a pure motor disease, has provided the foundation for new therapeutic strategies such as cholinesterase inhibitors. In contrast, there have been few systematic investigations of the clinical features of iNPH to date, which is why I conducted the two investigations described here.

The present studies delineate the core and diverse cognitive and behavioral features of iNPH. STUDY 1 demonstrated that patients with iNPH were impaired in broader cognitive domains than previously believed. Their deficits extend beyond executive function and memory into visuoperceptual/visuospatial functions. STUDY 2 revealed that patients with iNPH present with various neuropsychiatric symptoms. Although negative symptoms such

as apathy and decreased arousal have previously been emphasized as neuropsychiatric features of iNPH, a high prevalence of positive symptoms, such as agitation and irritability, was noted.

Another important issue addressed in the present studies was which symptoms can be relieved by CSF shunt surgery. Although the beneficial effects of CSF shunt surgery on gait ability have been well documented, it remains unclear which aspects of cognitive and behavioral symptoms are likely to respond to CSF shunt surgery. As for cognitive symptoms, significant improvement was observed only in executive function, not in visuoperceptual/visuospatial functions. Among the various neuropsychiatric symptoms, only agitation and cognitive fluctuation were responsive to CSF shunt surgery.

The MMSE was not significantly improved after shunt surgery in STUDY 1, but was improved in STUDY 2. This disagreement would be attributed to the small sample size and hence lower statistical power. The number of patients included in STUDY 1 longitudinal part (n = 23) was smaller than that in STUDY 2 (n = 29), because the patients who could not complete a full of neuropsychological examinations were excluded. Although a selection bias might characterize the subjects, little difference exists between the two studies on the mean (SD) MMSE score before (STUDY 1: 22.0 (4.7); STUDY 2: 22.1 (4.3)) and after shunt surgery (STUDY 1: 23.1 (4.7); STUDY 2: 23.4 (4.5)).

While iNPH is one of a group of prototypic disorders of 'subcortical dementia', AD patients were selected as a disease control group because AD is the most common and important cause of dementia. In terms of clinical implications, it is important to clarify the differences from AD patients for cognitive dysfunction and neuropsychiatric symptoms. For example, the cognitive dysfunction in AD patients, which is characterized as amnesia and posterior cortical dysfunctions, are now widely known, whereas they were not fully investigated in iNPH. The fact that posterior cortical dysfunction in iNPH was more severe than in AD suggests that it could be useful index in the differential diagnosis in clinical situations. However, it is also necessary to differentiate other subcortical dementias, such as progressive supranuclear palsy or subcortical ischemic vascular dementia, where both similar parkinsonian gait disturbance and frontal-type cognitive dysfunction emerge. Although it would be more difficult to distinguish from these disorders, distinctive features should be delineated in future studies.

On the basis of the present findings, two issues are to be pursued in future study. The first issue concerns the relationship between cognitive and neuropsychiatric symptoms and patients' quality of life as well as the burden placed on their caregivers. Previous studies of dementia have indicated that positive symptoms such as agitation are the main cause of distress for caregivers and that euphoria is less of a problem.[76] The effect of CSF shunt

surgery on quality of life and on the burden for caregivers should be clarified. The next issue is related to the neural (lesional) correlates of symptoms. Brain-behavior correlation analyses using quantitative neuroimaging techniques such as VBM and diffusion tensor imaging will be useful. I believe that these investigations will provide fundamental evidence of the pathophysiology of iNPH.

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8. FIGURE

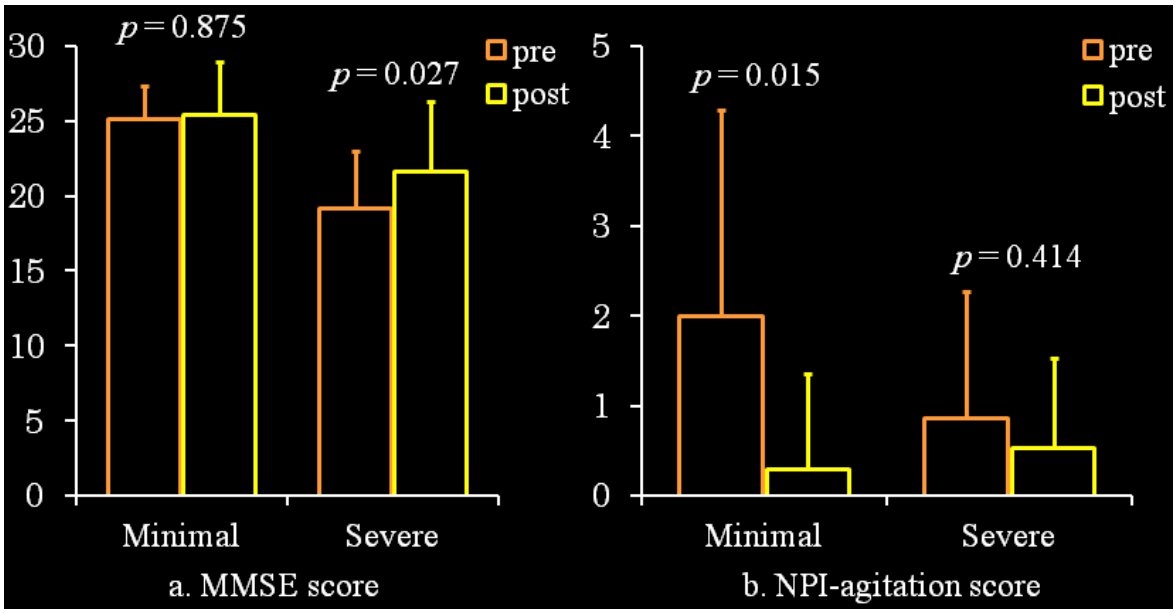

Figure 1. The mean scores of the MMSE and NPI-Agitation before and after surgery for the subgroups of mild and moderate cognitive impairments at baseline.

p values are based on Wilcoxon test.

MMSE: Mini Mental State Examination, NPI: Neuropsychiatric Inventory.

9. TABLES

Table 1. Diagnostic criteria of iNPH[6]

Diagnostic criteria	Supplementary notes
Possible iNPH	
1. Individuals who develop symptoms in their 60s or older.	1. Small stride, shuffle, instability in walking and increase of instability on turning.
2. More than one of the clinical triad: gait disturbance, cognitive impairment, and urinary incontinence.	2. Symptoms are slowly progressive; however, sometimes an undulating course, including temporal discontinuation of development and exacerbation, is observed.
3. Ventricular dilation (Evans Index > 0.3)*.	3. Other neurological diseases, including Parkinson's disease, Alzheimer's disease, and cerebrovascular diseases, may coexist; however, all such diseases should be mild.

4. CSF pressure of 200 mmH_2O or less and normal CSF content.	4. Narrowing of sulci and subarachnoid spaces over the high convexity and midline surface, and dilation of the sylvian fissure and basal cistern are often observed.
5. The above-mentioned clinical symptoms cannot be completely explained by other neurological or non-neurological diseases.	5. Periventricular lucency or periventricular hyperintensity is not essential.
6. Preceding diseases possibly causing ventricular dilation are not obvious, including subarachnoid hemorrhage, meningitis, head injury, congenital hydrocephalus, and aqueductal stenosis.	6. Measurement of CBF is useful for differentiation from other dementias.
Probable iNPH	
1. Meet requirements for possible iNPH.	
2. Meet one of the following;	

a) Improvement of symptoms after CSF tap test.

b) Improvement of symptoms after CSF drainage test.

c) Abnormality in Ro measurement and ICP monitoring.

Definite iNPH

1. Improvement of symptoms after shunt surgery.

*Evans Index: the ratio of the maximum width of the frontal horns to the maximum width of the inner table of the cranium. CBF: cerebral blood flow, ICP intracranial pressure, Ro: cerebrospinal fluid outflow resistance.

Table 2. Demographic and clinical profiles of the iNPH, AD, and NC groups in STUDY 1.

	iNPH	AD	NC	*p* value
n (female/male)	34 (16/18)	34 (20/14)	30 (15/15)	0.602#
Age (SD) in years	76.2 (4.6)	76.7 (4.9)	76.8 (5.7)	0.872*
Years of education (SD)	10.2 (3.5)	9.5 (2.3)	10.5 (2.8)	0.416*
CSF shunt operation (VP/LP)	23/11	-	-	

p values are based on χ^2 test# and one-way ANOVA*.

SD: standard deviation, CSF: cerebrospinal fluid, VP: ventriculo-peritoneal, LP: lumbo-peritoneal.

Table 3. The mean (SD) neuropsychological test scores of the iNPH, AD, and NC groups.

Test/subtest		iNPH (/34)	AD (/34)	NC (/30)	$\chi^2(2)$	*p* value	Pairwise comparisons
MMSE	/30	21.6 (4.5)	21.0 (3.3)	28.7 (1.3)	55.585	< 0.001	NC > iNPH†
Digit Span		7.7 (1.8)	8.4 (1.4)	9.4 (1.6)	14.309	0.001	NC > iNPH†
Spatial Span		7.6 (1.9)	8.6 (1.4)	10.6 (1.8)	33.294	< 0.001	NC, AD > iNPH
Word Fluency							
Phoneme		11.5 (6.2)	16.3 (7.5)	22.1 (7.8)	27.277	< 0.001	NC, AD > iNPH
Category		7.4 (4.2)	8.0 (3.0)	15.1 (5.3)	39.229	< 0.001	NC > iNPH†
TMT-A	Sec	158.6 (109.1)	97.6 (62.8)	52.3 (19.5)	33.652	< 0.001	iNPH > NC, AD
FAB	/18	9.9 (2.9)	11.9 (2.5)	15.7 (1.7)	50.342	< 0.001	NC, AD > iNPH
WAB Object Naming	/60	57.9 (3.2)	57.0 (3.5)	58.7 (1.6)	5.783	0.055	
ADAS							
True Recall	/30	13.1 (4.3)	13.9 (3.9)	21.5 (2.8)	48.848	< 0.001	NC > iNPH†

False Recall		0.6 (0.9)	0.9 (1.6)	0.3 (0.5)	3.263	0.196	
True Recognition	/36	24.1 (9.4)	25.4 (10.5)	31.3 (3.9)	11.701	0.003	NC > iNPH†
False Recognition	/36	0.7 (2.3)	4.0 (6.3)	0.1 (0.3)	29.394	< 0.001	AD > iNPH†
d'		2.60 (0.96)	2.17 (0.95)	3.37 (0.52)	27.211	< 0.001	NC > iNPH†
Visual Discrimination							
Length and Size	/20	20.0 (0.0)	20.0 (0.0)	20.0 (0.0)	0.000	1.000	
Direction	/15	13.9 (2.2)	13.6 (1.7)	15.8 (0.5)	14.564	0.001	NC > iNPH†
Complex Form	/20	18.3 (2.4)	19.6 (0.7)	19.7 (0.6)	14.856	0.001	NC, AD > iNPH
Overlapping Figures	/12	11.9 (2.1)	11.7 (0.6)	12.0 (0.2)	7.055	0.029	NC > iNPH†
Visual Counting	/56	50.0 (5.2)	53.8 (2.7)	55.2 (1.0)	33.237	< 0.001	NC, AD > iNPH

Values are means (SD) with *p* values based on the Kruskal-Wallis and the post hoc Mann-Whitney test with Bonferroni correction.

SD: standard deviation, MMSE: the Mini-Mental State Examination, TMT-A: Trail Making Test-A, FAB: the Frontal Assessment Battery, WAB: the Western Aphasia Battery, ADAS: the Alzheimer's Disease Assessment Scale.

†Other comparisons were not significant.

Table 4. The mean (SD) neuropsychological test scores before and after shunt surgery.

Test/subtest		Pre (n=23)	Post (n=23)	*Z* value	*p* value
MMSE	/30	22.0 (4.7)	23.1 (4.7)	-1.621	0.105
Digit Span		7.7 (2.0)	7.8 (1.7)	-0.681	0.496
Spatial Span		7.7 (2.0)	7.8 (1.6)	-0.209	0.834
Word Fluency					
Phoneme		11.6 (5.7)	11.9 (6.4)	-0.718	0.473
Category		7.6 (3.1)	7.6 (4.0)	-0.131	0.895
TMT-A	Sec	173.4 (123.0)	129.4 (86.3)	-2.403	0.016
FAB	/18	10.1 (3.0)	11.4 (3.6)	-2.401	0.016
WAB Object Naming	/60	58.3 (3.3)	58.9 (2.5)	-1.318	0.187
ADAS					
True Recall	/30	13.4 (4.2)	13.7 (5.3)	-0.458	0.647
False Recall		0.5 (0.9)	0.4 (0.8)	-0.318	0.751
True Recognition	/36	23.5 (8.5)	22.6 (10.0)	-0.455	0.649
False Recognition	/36	0.8 (2.7)	0.1 (0.5)	-1.289	0.197
d'		2.51 (0.84)	2.50 (0.97)	0.000	1.000
Visual Discrimination					
Length and Size	/20	20.0 (0.0)	20.0 (0.0)	0.000	1.000
Direction	/15	13.5 (1.5)	13.3 (1.7)	-0.676	0.499
Complex Form	/20	18.1 (2.3)	18.7 (1.5)	-1.377	0.169
Overlapping Figures	/12	11.5 (0.8)	11.6 (0.9)	-0.776	0.438
Visual Counting	/56	50.3 (5.6)	52.2 (3.9)	-1.637	0.102

SD: standard deviation, MMSE: the Mini-Mental State Examination, TMT-A: Trail

Making Test-A, FAB: the Frontal Assessment Battery, WAB: the Western Aphasia Battery, ADAS: the Alzheimer's Disease Assessment Scale.

Table 5. Demographic and clinical profiles of the iNPH and AD groups in STUDY 2.

	iNPH	AD	*p* value
n (female/male)	45 (20/25)	45 (26/19)	0.206#
Age (SD) in years	76.2 (4.2)	76.0 (4.5)	0.773*
Years of education (SD)	10.2 (3.5)	10.3 (2.6)	0.838*
MMSE	20.9 (4.7)	21.9 (3.8)	0.279*
CSF shunt operation (VP/LP)	32/13	-	

p values are based on the χ^2 test# and *t* test*.
SD: standard deviation, CSF: cerebrospinal fluid, VP: ventriculo-peritoneal, LP: lumbo-peritoneal.

Table 6. The prevalence and mean scores of NPI symptoms in the iNPH and AD groups.

	Prevalence				Mean (SD) score			
Question items	iNPH (/45)	AD (/45)	χ^2	*p* value	iNPH (/45)	AD (/45)	*Z* value	*p* value
Persecution delusion	20.0%	28.9%	0.963	0.327	0.56 (1.91)	1.18 (2.52)	-1.210	0.226
Delusional misidentification	6.7%	4.4%	0.212	0.645	0.07 (0.25)	0.04 (0.21)	-0.458	0.647
Hallucination	6.7%	2.2%	1.047	0.306	0.16 (0.64)	0.02 (0.15)	-1.040	0.299
Agitation/aggression	48.9%	28.9%	3.787	0.052	1.53 (2.40)	0.42 (0.81)	-2.504	0.012
Dysphoria/depression	31.1%	35.6%	0.200	0.655	0.62 (1.11)	0.64 (1.11)	-0.329	0.742
Anxiety	26.7%	33.3%	0.476	0.490	0.67 (1.33)	0.71 (1.25)	-0.559	0.576
Euphoria	0.0%	4.4%	2.045	0.153	0.00 (0.00)	0.18 (0.94)	-1.422	0.155
Apathy	80.0%	48.9%	9.504	0.002	4.00 (3.20)	1.93 (2.44)	-3.301	0.001
Disinhibition	11.1%	13.3%	0.104	0.748	0.22 (0.93)	0.40 (1.32)	-0.376	0.707
Irritability/lability	42.2%	17.8%	6.402	0.011	1.04 (1.69)	0.87 (2.44)	-2.153	0.031
Aberrant motor behavior	13.3%	15.6%	0.090	0.764	0.64 (1.90)	0.53 (1.50)	-0.178	0.859

Fluctuation of cognition	37.8%	20.0%	3.462	0.063	1.00 (1.57)	0.42 (0.97)	-1.974	0.048
Total	91.1%	88.9%	0.123	0.725	10.51 (7.99)	7.31 (6.65)	-2.005	0.045

Values are means (SD) with *p* values based on the χ^2 test or *t* test.

SD: standard deviation.

Table 7. Correlations between neuropsychiatric symptoms and motor or cognitive abilities in iNPH.

		TUG	MMSE	Persecution	Misidentification	Hallucination	Agitation	Dysphoria	Anxiety	Euphoria	Apathy	Disinhibition	Irritability	Aberrant motor	Fluctuation of cognition
TUG	Correlation coefficient	1.000													
	p value (2-tailed)	-													
MMSE	Correlation coefficient	-0.324	1.000												
	p value (2-tailed)	0.030	-												
Persecution delusion	Correlation coefficient	-0.061	-0.188	1.000											
	p value (2-tailed)	0.692	0.217	-											
Delusional misidentification	Correlation coefficient	0.124	-0.230	0.074	1.000										
	p value (2-tailed)	0.419	0.128	0.630	-										
Hallucination	Correlation coefficient	0.144	-0.232	0.114	0.293	1.000									
	p value (2-tailed)	0.347	0.126	0.458	0.050	-									
Agitation/aggression	Correlation coefficient	-0.014	0.267	-0.260	0.041	-0.066	1.000								
	p value (2-tailed)	0.926	0.076	0.084	0.791	0.665	-								
Dysphoria/depression	Correlation coefficient	0.079	-0.101	0.057	0.201	0.047	0.330	1.000							
	p value (2-tailed)	0.604	0.509	0.708	0.185	0.760	0.027	-							
Anxiety	Correlation coefficient	0.165	0.005	0.048	0.071	0.013	0.326	0.626	1.000						
	p value (2-tailed)	0.278	0.975	0.756	0.645	0.935	0.029	<0.001	-						
Euphoria	Correlation coefficient	-	-	-	-	-	-	-	-	-					
	p value (2-tailed)	-	-	-	-	-	-	-	-	-					
Apathy	Correlation coefficient	-0.028	-0.303	0.060	0.046	-0.027	0.182	0.223	0.199	-	1.000				
	p value (2-tailed)	0.853	0.043	0.694	0.763	0.861	0.231	0.140	0.190	-	-				
Disinhibition	Correlation coefficient	-0.080	-0.039	0.210	-0.094	-0.094	0.267	0.183	0.228	-	-0.097	1.000			
	p value (2-tailed)	0.600	0.801	0.167	0.537	0.538	0.076	0.228	0.132	-	0.527	-			
Irritability/lability	Correlation coefficient	-0.110	0.005	0.183	-0.046	-0.042	0.411	0.153	0.421	-	0.228	0.240	1.000		
	p value (2-tailed)	0.472	0.973	0.228	0.764	0.783	0.005	0.316	0.004	-	0.132	0.113	-		
Aberrant motor behavior	Correlation coefficient	0.026	-0.273	0.364	0.180	0.699	-0.034	0.072	0.046	-	0.076	0.082	0.210	1.000	

	p value (2-tailed)	0.867	0.069	0.014	0.237	<0.001	0.827	0.638	0.762	-	0.618	0.590	0.166	-	
Fluctuation of cognition	Correlation coefficient	0.135	-0.264	-0.083	-0.071	0.056	-0.029	0.067	0.107	-	0.237	0.077	-0.064	0.052	1.000
	p value (2-tailed)	0.378	0.080	0.587	0.643	0.714	0.851	0.661	0.486	-	0.117	0.617	0.676	0.734	-

TUG: the 3-Meter Timed Up & Go test, MMSE: the Mini-Mental State Examination.

Table 8. The prevalence and mean scores of NPI symptoms pre and post shunt surgery.

Question items	Pre (/29)	Post (/29)	*p* value	Pre (/29)	Post (/29)	*Z* value	*p* value
Persecution delusion	13.8%	6.9%	0.625	0.52 (2.23)	0.31 (1.49)	-1.414	0.157
Delusional misidentification	0.0%	3.4%	-	0.00 (0.00)	0.03 (0.19)	-1.000	0.317
Hallucination	3.4%	0.0%	-	0.03 (0.19)	0.00 (0.00)	-1.000	0.317
Agitation/aggression	51.7%	17.2%	0.006	1.41 (1.94)	0.41 (1.02)	-2.405	0.016
Dysphoria/depression	31.0%	17.2%	0.289	0.52 (0.99)	0.28 (0.65)	-1.165	0.244
Anxiety	20.7%	17.2%	1.000	0.55 (1.27)	0.48 (1.18)	-0.318	0.750
Euphoria	0.0%	0.0%	-	0.00 (0.00)	0.00 (0.00)	0.000	1.000
Apathy	75.9%	65.5%	0.508	3.48 (2.65)	3.31 (3.48)	-0.352	0.725
Disinhibition	10.3%	13.8%	1.000	0.27 (1.13)	0.17 (0.47)	-0.378	0.705
Irritability/lability	37.9%	27.6%	0.453	0.72 (1.16)	0.41 (0.87)	-1.196	0.232
Aberrant motor behavior	6.9%	6.9%	1.000	0.17 (0.76)	0.07 (0.26)	-0.378	0.705
Fluctuation of cognition	31.0%	10.3%	0.109	0.90 (1.61)	0.17 (0.60)	-2.509	0.012
Total	86.2%	75.9%	0.250	8.66 (6.83)	5.72 (5.64)	-2.559	0.010