



## Predictors of the disappearance of triad symptoms in patients with idiopathic normal pressure hydrocephalus after shunt surgery<sup>☆</sup>

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### ABSTRACT

We identified factors that predict the disappearance of the triad of symptoms (gait disturbance, cognitive impairment and urinary incontinence) of idiopathic normal pressure hydrocephalus (iNPH) following shunt surgery in this study. We classified 71 patients with iNPH into those whose objective symptoms disappeared (disappearance group) or remained (residual group), for each of the triad symptoms 12 months after shunt surgery. Logistic regression analyses were used to identify the predictors of the disappearance of symptoms among 10 variables before shunt surgery (e.g., age, sex, severity of symptoms, Evans index, cerebrospinal fluid (CSF) pressure, CSF stasis on computerized tomographic cisternography, regional cerebral blood flow on single photon emission computed tomography, three kinds of prior diseases). For each of the triad symptoms, mild symptoms before shunt surgery were predictors of the disappearance of the symptom. Young age was also a predictor of the disappearance of gait disturbance. When the analysis was conducted using subscores of the Mini Mental State Examination, a successful visuoconstruction subtest and an absence of hypertension were predictors of the disappearance of cognitive impairment. None of the neuroimaging examinations predicted the disappearance of symptoms after shunt surgery in this study.

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### 1. Introduction

Normal pressure hydrocephalus (NPH) is well known as a syndrome of the classical triad of gait disturbance, cognitive impairment, and urinary incontinence with enlarged ventricles and absence of raised intracranial pressure [1]. Idiopathic NPH (iNPH), which develops with no identifiable causative antecedent disease, has a prevalence in community-dwelling elderly people of approximately 1% [2,3].

Predictors for improvement after shunt surgery have been evaluated, because shunt surgery is not always useful for patients with iNPH. The predictors include severity of symptoms [4,5] and a dominant symptom

[6] before shunt surgery, high cerebrospinal fluid (CSF) pressure [7,8], a noticeable morphological change of brain [9,10], reduced regional cerebral blood flow in the frontal area [11], and ventricular stasis on computerized tomographic cisternography (CTC) [12]. Hypertension [13–15], diabetes mellitus [14,16], and dyslipidemia [14], which are well known risk factors for cerebrovascular disease, were also reported to be risk factors for iNPH, although the association between iNPH and cerebrovascular disease is unknown. These risk factors for iNPH could also influence the results of shunt surgery. Refinements in the patient selection criteria and in the shunt surgical technique have increased the efficacy of shunt surgery, resulting in 75% [9] and 80% [10] of the patients showing remarkable improvement. However, the symptoms in iNPH patients do not always disappear completely, even in patients where remarkable improvements are observed. Partial improvements of symptoms generally do not reduce the constraints on everyday life experienced by caregivers of iNPH [17]. Thus, for iNPH patients, disappearance of symptoms, not just improvement of symptoms, is

<sup>☆</sup> Location of work: SINPHONI was a project of the Japanese Society of Normal Pressure Hydrocephalus and involved 26 centers in Japan.

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important. However, predictors of the disappearance of triad symptoms after shunt surgery have not been clarified.

A multicenter prospective cohort study, called the study of idiopathic normal pressure hydrocephalus on neurological improvement (SINPHONI), was conducted in Japan between 2004 and 2006 to examine the therapeutic outcome of installing a shunt with a programmable valve in iNPH patients [10]. In this paper, we analyzed the SINPHONI data to identify factors that predict the disappearance of each of the triad symptoms in patients with iNPH after shunt surgery.

## 2. Materials and methods

### 2.1. SINPHONI

SINPHONI was conducted in compliance with the Guidelines for Good Clinical Practice and the Declaration of Helsinki (2002) of the World Medical Association and is registered with the U.S. National Institutes of Health (<http://www.clinicaltrials.gov/ct2/show/NCT00221091?term=NCT00221091&rank=1>). The study protocol was approved by the institutional review boards of each of the 26 centers involved in the study. In SINPHONI, 100 patients with iNPH were recruited according to the criteria described below, and all received a ventriculoperitoneal (VP) shunt surgery with programmable shunt valve by experienced neurosurgeons.

The methods and main results of SINPHONI were reported elsewhere [10]. The primary endpoint was improvement of  $\geq 1$  level in the modified Rankin Scale (mRS) [18] at one year after the surgery (favorable outcome). In summary, the improvement rate, defined as the percent of patients that showed a favorable outcome, was 69.0%, and the response rate, defined as the percent of patients that showed more than one-point improvement on mRS at any of the three evaluation points (3, 6 and 12 months after the shunt surgery), was 80.0%. Fifteen patients experienced serious adverse events (SAEs) that were directly related to surgery or VP shunt.

The secondary outcome measures of SINPHONI included the iNPH grading scale (iNPHGS) [19], timed 3 m up-and-go test (TUG) [20], and the Mini Mental State Examination (MMSE) [21]. The iNPHGS is a clinician-rated scale to separately rate the severity of each of the triad symptoms of iNPH. The score of each domain ranges from 0 to 4. Zero indicates normal and higher scores indicate worse symptoms. iNPHGS score of below 2 indicates no objective symptom and that of 2 or more indicates the presence of an objective symptom in each domain. The TUG is a test of functional mobility that measures the time it takes a subject sitting in an armchair to stand up, walk forward 3 m, and return to the seated position. These measures were repeated before and at 3, 6 and 12 months after the shunt surgery.

CTC with iohexol (Omnipaque®: 180 mg/ml) at 30 mg/kg injected into the lumbar subarachnoid space was carried out in all patients before shunt surgery. The detailed methods and results of the CTC study were described in our previous paper [22]. CT scan was performed before injection of the contrast medium and at 6, 24, and 48 h after the injection. The degree of disturbance in CSF circulation was scored according to the change in density of the contrast medium at the lateral ventricles, Sylvian fissure, and parietal sulci compared with the baseline scan. The CTC scores were assigned as follows: Score = 0, no stasis of contrast medium at observed points, that is, the density in the CSF space is the same as that in the baseline CT scan; Score = 1, the density is between 0 and 2; Score = 2, the density is the same as that of the brain parenchyma in the baseline CT scan; Score = 3, the density is higher than that of the brain parenchyma in the baseline CT scan. In this study, the CTC scores in the lateral ventricles, Sylvian fissure, and parietal sulci at 24 and 48 h after injection were used as the degree of disturbance in CSF circulation.

Eighty-four of the 100 patients underwent single photon emission computed tomography (SPECT) examination using N-isopropyl-p-

[123 I] iodoamphetamine to evaluate cerebral blood flow (CBF) before shunt surgery. The detailed methods of the SPECT examination were described elsewhere [23]. The perfusion patterns on SPECT were classified: anterior-dominant CBF reduction type (A type), posterior-dominant CBF reduction type (P type), and mixed or diffuse CBF reduction type (M type).

### 2.2. Subjects

Written informed consent was obtained from all subjects, or from their representatives when applicable. The consenting patients were pre-registered and received lumbar puncture. The inclusion criteria of SINPHONI were (1) age between 60 and 85 years, (2) presence of symptom(s) of the iNPH triad which are measurable on the iNPHGS, (3) presence of Magnetic Resonance (MR) imaging features of iNPH, i.e., both ventriculomegaly of Evans index  $> 0.3$  and tight high-convexity and medial subarachnoid spaces on coronal T1-weighted MR images [24], (4) absence of known disorders causing ventriculomegaly, and (5) normal CSF content (protein  $\leq 50$  mg/dl and cell count  $\leq 3$  cu  $\mu\text{m}$ ) and pressure ( $\leq 20$  cm  $\text{H}_2\text{O}$ ). In this study, the criterion of (6) available data of both CTC and SPECT was added. Exclusion criteria of SINPHONI were (1) presence of musculoskeletal, cardiopulmonary, renal, hepatic, or mental disorders that would make it difficult to evaluate changes of symptoms, (2) obstacles to one-year follow-up, and (3) hemorrhagic diathesis or anticoagulant medication.

### 2.3. Statistical analyses

We classified the patients into a disappearance group (patients with scores of 0 or 1 on the iNPHGS) and a residual group (scores of 2–4) for each of the triad symptoms 12 months after shunt surgery. The analyses were separately performed for each of the triad symptoms.

We first conducted a univariate logistic regression analysis to examine the association between disappearance of gait disturbance after shunt surgery and 11 explanatory variables. The response variable was whether the patients were classified into disappearance group or residual group. The explanatory variables were age, sex, Evans index, CSF pressure, six kinds of CTC scores, patterns of hypoperfusion on SPECT, and the presence of hypertension, hyperlipidemia and diabetes mellitus, the iNPHGS gait score, and TUG score before shunt surgery. We next conducted a multivariate logistic regression analysis to identify the predictors of the disappearance of gait disturbance after shunt surgery among the explanatory variables before shunt surgery. The iNPHGS gait score and TUG score were used separately because of potential issues with multicollinearity. Of the six CTC scores, we selected the one with the lowest p value in the univariate logistic regression analysis of gait disturbance. Then, the 10 variables were entered into the forward stepwise multivariate logistic regression model. The odds ratios (ORs) with 95% confidence intervals (CIs) were calculated for all explanatory variables.

Urinary incontinence and cognitive impairment were analyzed by the same method used to analyze gait disturbance. In the analysis of urinary incontinence, the iNPHGS urinary score was used instead of iNPHGS gait score. In the analysis of cognitive impairment, the iNPHGS cognitive score, the MMSE total score, or the MMSE subtests scores were used instead of the iNPHGS gait score. MMSE subtests were classified into 4 categories; attention (immediate recall of three words and Serial 7; total score was 8), memory (orientation and delayed recall of the three words; total score was 13), language (confrontation naming of two words, comprehension of three step commands, repetition, reading and writing; total score was 8), and visuoconstruction (copy of double pentagon; total score was 1).

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