

Preoperative biomarkers in patients with idiopathic normal pressure hydrocephalus showing a favorable shunt surgery outcome

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ABSTRACT

Introduction: Idiopathic normal pressure hydrocephalus (INPH) is known to be a potentially treatable neurologic condition. The neurocognitive outcomes after surgery, however, have been variable. It is important to define preoperative characteristics of patients that predicts the shunting outcome. We aimed to compare baseline differences between shunt-responsive and unresponsive patients after 1 year from surgery in order to identify preoperative predictors showing favorable clinical outcomes.

Methods: Among 69 candidates, 31 patients with probable INPH completed the study. Patients were divided into two groups, responsive group (n = 17) and unresponsive group (n = 14), according to the clinical outcomes on INPH grading scale and modified Rankin score (MRS). Preoperative cerebrospinal (CSF) A β , tau levels, MRI findings, and clinical characteristics were compared between the groups. Correlations between shunt responsiveness and preoperative characteristics were also assessed.

Results: After 1 year from shunt, gait problem was the most likely to improve. Shunt-responsive group showed lower CSF p-tau/A β , fewer lacunes, and higher incidence of disproportionately enlarged subarachnoid space (DESH) signs on MRIs compared to those in unresponsive group. Favorable outcome was related with positive DESH sign and fewer lacunes.

Conclusions: Our results suggest that biomarkers representing non-INPH related pathology including Alzheimer's disease and small vessel disease might show less favorable clinical outcomes after 1 year from surgery.

1. Introduction

Idiopathic normal pressure hydrocephalus (INPH) is known to be a potentially treatable neurologic condition. The neurocognitive outcomes after shunt surgery, however, have been variable. It is important to define preoperative characteristics of INPH patients that predict the shunting outcome. Some preoperative characteristics including shorter history of clinical symptoms, gait presentation, response to spinal tap test, younger age, less co-morbidities, and absence of severe dementia were reported to be related with favorable shunt outcomes [1–6]. Recently, baseline biomarkers suggesting Alzheimer's disease (AD) were identified as relevant predictors of poor clinical outcomes in some

studies [7–12]. However, previous studies which investigated baseline parameters for predicting shunt outcomes showed conflicting results and had some limitations: short follow-up durations, small sample size, or lack of biomarker evaluations [1–12]. Hence, prospective studies to describe the long-term outcomes of shunt surgery and clarify baseline characteristics and biomarker findings which can predict favorable shunt responsiveness are needed. Our study aimed to compare preoperative differences between shunt-responsive and unresponsive patients after 1 year from ventriculoperitoneal shunt surgery using various clinical evaluations, magnetic resonance imaging (MRI) markers, and cerebrospinal fluid (CSF) biomarkers to identify predictive factors for favorable clinical outcomes.

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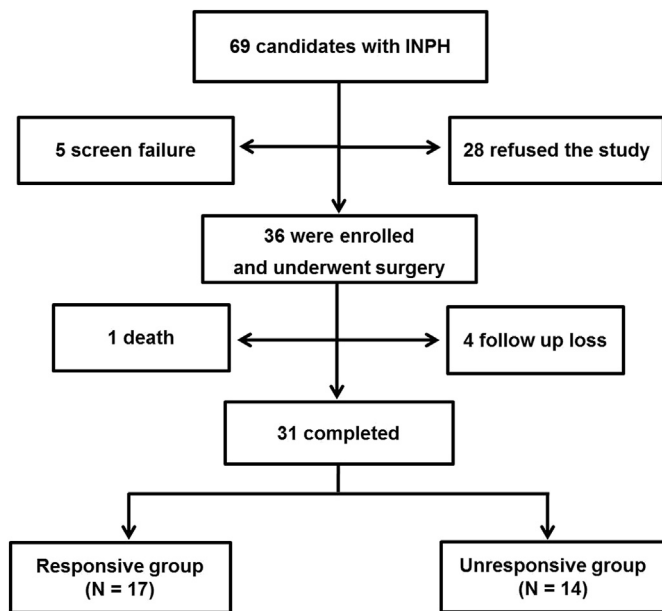


Fig. 1. Flowchart of the patients' enrollment.

2. Methods

2.1. Patients

All patients clinically diagnosed as INPH were prospectively recruited from both inpatient and outpatient clinics of neurology/neurosurgery departments at Asan Medical Center and Samsung Medical Center in South Korea. This study was conducted between December 2012 and May 2015. To be eligible for the current study, patients had to fulfill the probable INPH criteria [13]. Patients with uncontrolled, poor medical conditions according to physician's decision, severe

musculoskeletal problems, paralysis that might hinder the clinical evaluation, deep white matter hyperintensities (WMH) in diameter over 10 mm, old age over 85 years were excluded. Among 69 candidates with probable INPH, 33 were excluded due to screen failure (n = 5) or refusal of shunt surgery/study participation (n = 28). Among 36 patients who underwent shunt surgery, 5 patients dropped out due to follow-up loss (n = 4) or death during follow up (n = 1) (Fig. 1). Finally, 31 patients with INPH who completed the 1 year follow-up examinations were analyzed. Patients were divided into two groups according to the surgical outcomes at a year after using INPH grading scale and modified Rankin score (MRS): patients with improvement ≥ 3 in INPH total score or ≥ 2 in MRS for the responsive group (n = 17), and patients with progression or no change or less improvement ≤ 2 in INPH total score and ≤ 1 in MRS for the unresponsive group (n = 14). This study was approved by the Institutional Review Board of Asan Medical Center and Samsung Medical Center. Written informed consent was obtained from all participants and their caregivers.

2.2. Preoperative brain MR imaging

Using the same 3.0 Tesla MRI scanner in the 2 centers (Philips 3.0 T 164 Achieva, Eindhoven, the Netherlands), MRIs were acquired from all participants preoperatively at Asan Medical Center and Samsung Medical Center. Axial fluid-attenuated inversion recovery (FLAIR), T2-weighted image, T1-weighted image, and coronal T1-weighted images were included routinely.

2.3. Neuropsychological tests

All patients underwent a standardized neuropsychological tests battery named the Seoul Neuropsychological Screening Battery [14] at baseline to assess cognitive function. It contains tests evaluating attention, language, praxis, visuospatial function, verbal and visual memory, and executive function as well as the Korean version of the Mini-Mental State Examination (K-MMSE) [15]. Scores below the 16th percentile (1 SD) compared with age, and education- specific norms

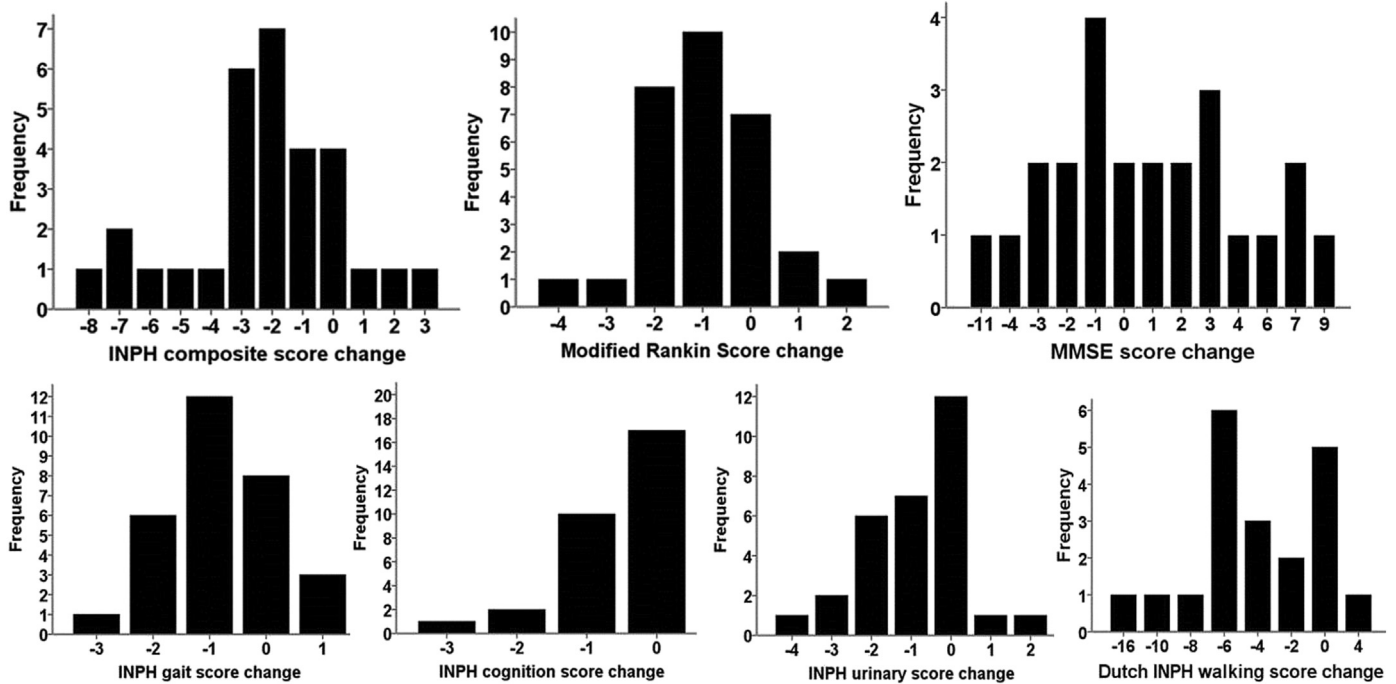


Fig. 2. Outcomes in all patients after 1 year from shunt surgery. INPH, idiopathic normal pressure hydrocephalus; MMSE, mini-mental state examination. Negative numbers represent clinical improvements in INPH composite scores and modified Rankin scores. Positive numbers represent cognitive improvements in MMSE scores.

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