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Cerebrospinal fluid biomarkers for prognosis of long-term cognitive treatment outcomes in patients with idiopathic normal pressure hydrocephalus

Madoka Nakajima *, Masakazu Miyajima, Ikuko Ogino, Chihiro Akiba, Hidenori Sugano, Takeshi Hara, Keiko Fusegi, Kostadin Karagiozov, Hajime Arai

Department of Neurosurgery, Juntendo University School of Medicine, 2-1-1, Hongo, Bunkyo-ku, Tokyo 113-8342, Japan

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ABSTRACT

The prognosis of cognitive improvement after cerebrospinal fluid (CSF) shunting in idiopathic normal pressure hydrocephalus (iNPH) remains uncertain, with no reports on CSF biomarkers related to long-term cognitive prognosis. We performed a preliminary study of CSF biomarker protein levels for cognitive outcome prognostication of two-year outcomes after shunt treated iNPH in 36 patients (13 women) with a median age of 75 years (IQR 69–78). CSF biomarkers included soluble amyloid precursor proteins (sAPP, sAPPα, sAPPβ), amyloid β ($A\beta)_{1-38}$, $A\beta_{1-42}$ and phosphorylated tau (*p*-tau), lipocalin-type prostaglandin D synthase (L-PGDS)/β-trace, and cystatin C. The results clearly showed that *p*-tau levels (sensitivity of 71.4%, specificity of 77.8%, cut-off value of 22.0 pg/mL), $A\beta_{1-38}/A\beta_{1-42}$ ratio (77.8%, 81%, 3.58), and the $A\beta_{1-42}$/*p*-tau ratio (76%, 72.7%, 14.6) in preoperative CSF have the potential to determine postoperative prognosis. Improved cognition may be associated with the improvement in CSF circulation after LPS, which likely induces cystatin C and L-PGDS and switches synthesis from $A\beta_{1-42}$ to $A\beta_{1-38}$.

1. Introduction

Idiopathic normal pressure hydrocephalus (iNPH) is increasingly being regarded as important because of its disease specificity, leading to cognitive disorder, gait impairment, dysuria, falls, and bedridden status in the elderly [5]. Diagnosis of iNPH has progressed with the release of new guidelines [15,20] and introduction of a cerebrospinal fluid (CSF) shunting procedure. However, the mechanism by which shunt surgery improves the symptoms of iNPH is unclear. In the healthy brain, a balance is maintained between the production and absorption of the CSF, with four or five CSF turnovers occurring each day. With increasing age, however, people show increased resistance to CSF absorption. In patients with iNPH, the turnover of CSF appears to have declined more than average due to a reduced ability to absorb CSF [8]. A conspicuous decline in CSF circulation appears to affect the metabolism of a variety of proteins that are produced intracerebrally. In the shunting procedure, the CSF is drained into the abdominal cavity through the shunt system, compensating for the loss of CSF absorption capabilities caused by iNPH. It appears that CSF shunting not only corrects intracranial pressure but also effectively promotes CSF turnover [33].

The prognosis after CSF shunting in iNPH remains uncertain even after the establishment of the latest diagnostic criteria, and only a few reports exist on biomarkers related to prognosis [30]. Most reports on the clinical outcomes of CSF shunting for iNPH are the result of short-term follow-up studies (about 1 year) [7,11], with no reports on CSF biomarkers that predict long-term prognosis.

In this study, we explored the levels of CSF biomarkers for their association with prognosis of cognitive functional outcome in shunt-treated iNPH. We examined and compared patients whose activities of daily living (ADL) improved after CSF shunting and those whose degree of improvement was poor. We analyzed the changes in various biomarkers, focusing on amyloid-related proteins in the CSF, and explored those that may predict the cognitive functional prognosis of

Abbreviations: Aβ, amyloid-beta; iNPH, idiopathic normal pressure hydrocephalus; LPS, lumboperitoneal shunting; iNPHGS, iNPH Grading Scale; MMSE, Mini Mental State Examination; FAB, frontal assessment battery; TMT-A, trail making test part A; mRS, modified Rankin Scale; NC, normal control; LP, lumbar puncture; sAPP, soluble amyloid precursor protein; sAPPα, sAPP alpha; sAPPβ, sAPP beta; APP, amyloid precursor protein; AUC, area under the curve; ROC, receiver operating characteristic; IQR, interquartile range; L-PGDS, lipocalin-type prostaglandin D synthase.

* Corresponding author.
E-mail addresses: madoka66@juntendo.ac.jp (M. Nakajima), mmasaka@juntendo.ac.jp (M. Miyajima), i-ogino@juntendo.ac.jp (I. Ogino), chihi-rocket@hotmail.co.jp (C. Akiba), debo@juntendo.ac.jp (H. Sugano), thara79nouge@gmail.com (T. Hara), keiko-fusegi@nifty.com (K. Fusegi), kostadinkaragiozov@yahoo.com (K. Karagiozov), harai@juntendo.ac.jp (H. Arai).

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patients with iNPH. The biomarkers chosen comprised those belonging to or associated with Aβ pathways [6,22].

2. Material & methods

2.1. Patients

Sixty patients (15 women), mean age of 75 years [25% and 75% interquartile range: interquartile range (IQR) 69–78] with iNPH diagnosis at the Department of Neurosurgery [16], Juntendo University in Tokyo, Japan, based on existing guidelines [20], underwent lumboperitoneal shunting (LPS) [23] between September 2008 and May 2012. Inclusion criteria were symptoms and signs, and magnetic resonance imaging (MRI) findings compatible with iNPH [26]. Of these, 13 patients did not have CSF collected. Eleven patients were not followed up, including 4 deaths. Thirty-six patients (13 women) were re-examined 2 years after LPS, prior to this study (Fig. 1). Postoperative course was analyzed using the modified Rankin Scale (mRS) [37], Japanese iNPH grading scale (JNPHGS) [21], the Mini-Mental State Examination (MMSE) [4], Frontal Assessment Battery (FAB) [3], and Trail Making Test A (TMT-A) [27,28]. Performance was compared before and 2 years after LPS.

In the first classification method, we compared two groups: the "*Improved Cognitive group*", who either maintained a favorable cognitive function of 25 points or higher in MMSE score or improved by 3 points in 2 years after LPS surgery; and the "*Poor Cognitive group*", whose MMSE scores were less than 24 points without improvement of at least 3 points after LPS surgery. CSF biomarkers were compared between groups.

In the second classification method, we divided the subjects according to age at surgery (60s, 70s, or 80s) and studied the degree of symptom improvement.

2.2. CSF analysis

The study was approved by the Ethics Committee of Juntendo University. All patients included in the study, or their relatives, gave informed consent to their participation. Written informed consent was also obtained from patients and families prior to LPS placement for all patients who were positive for the tap test. LPS was performed using adjustable valves in all patients, a non-siphon control (NSC) valve with a small lumen catheter (Medtronic Neurosurgery, Goleta, CA) [23].

Lumbar puncture (LP) was performed in the L3–L4 or L4–L5 interspace before LPS. The CSF before LPS was sampled through an 18G spinal needle. Two years after LPS, CSF was sampled again through a puncture of the reservoir using a 27-gauge needle to confirm that the shunt system was operating effectively. No infections were reported following the tap test or shunt valve puncture. We obtained lumbar CSF before and after LPS. All CSF samples were centrifuged to remove cells and debris, aliquoted, and stored in polypropylene tubes at −80 °C until biochemical analysis [18].

Shunt reservoir and lumbar CSF biomarkers were also compared. CSF biomarkers included total soluble amyloid precursor proteins (sAPP) α and β, amyloid β ($Aβ_{1-38}$, $Aβ_{1-42}$ [32], and phosphorylated tau (*p*-tau) [29]. We also measured lipocalin-type prostaglandin D synthase (L-PGDS)/β-trace and cystatin C, a known chaperone of Aβ protein. The bicinchoninic acid (BCA) method was used for total

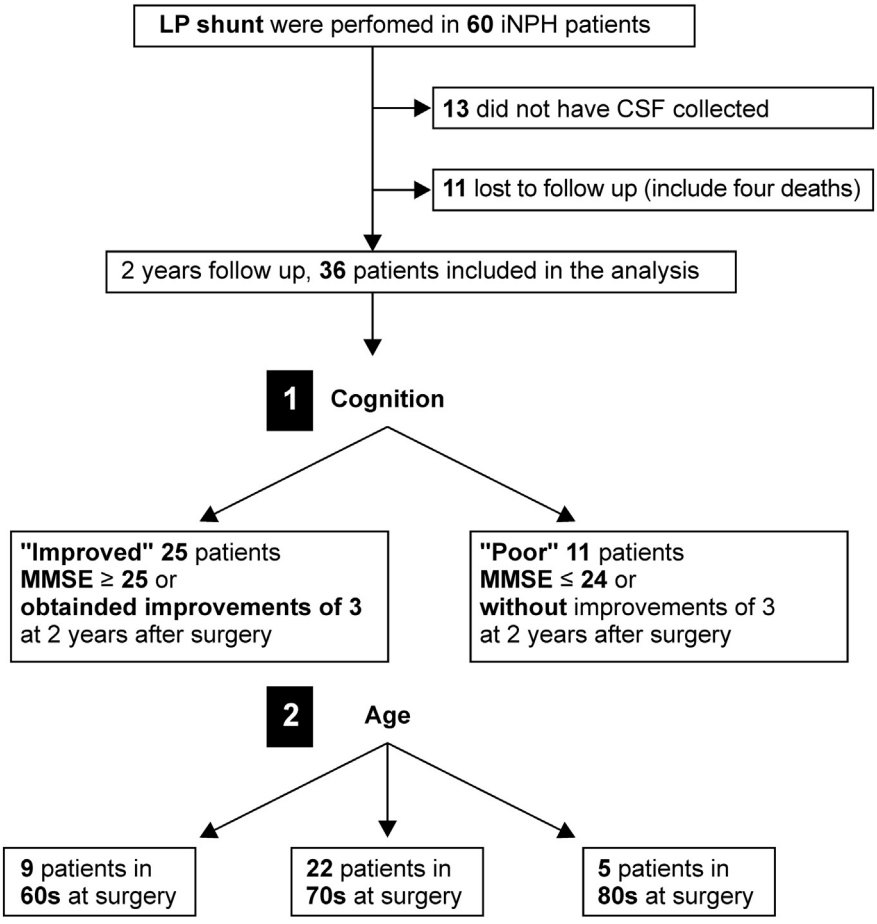

Fig. 1. Overview of patient selection. Four deaths: Four patients died during the course due to myocardial infarction, malignant lymphoma, suffocation due to foreign body aspiration, and complications of liver cancer.

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