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Clinical Study

Idiopathic normal-pressure hydrocephalus, cerebrospinal fluid biomarkers, and the cerebrospinal fluid tap test

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ABSTRACT

Cerebrospinal fluid (CSF) biomarkers, including soluble amyloid β-42 (Aβ-42) and phosphorylated-tau (P-tau), reflect core pathophysiological features of Alzheimer's disease (AD). AD is frequently a concomitant pathology in older patients with idiopathic normal-pressure hydrocephalus (iNPH), and somewhat similar altered CSF dynamics exist in both AD and iNPH. We therefore investigated relationships between lumbar CSF biomarkers Aβ-42 and P-tau and clinical parameters in iNPH patients, along with differences in these biomarkers between CSF tap test (CSFTT) responders and non-responders. Thirty-one iNPH patients (14 CSFTT responders and 17 CSFTT non-responders) were included in the final analysis. We found lower CSF Aβ-42 correlated with poor cognitive performance ($r = 0.687$, $p < 0.001$ for Korean Mini Mental State Examination; $r = 0.568$, $p = 0.001$ for Frontal Assessment Battery; $r = -0.439$, $p = 0.014$ for iNPH grading scale [iNPHGS] cognitive score; $r = -0.588$, $p = 0.001$ for Clinical Dementia Rating Scale), and lower CSF P-tau correlated with gait dysfunction ($r = -0.624$, $p < 0.001$ for Timed Up and Go Test; $r = -0.652$, $p < 0.001$ for 10 meter walking test; $r = -0.578$, $p = 0.001$ for Gait Status Scale; $r = -0.543$, $p = 0.002$ for iNPHGS gait score). In subgroup analysis, CSF P-tau/Aβ-42 ratios were significantly higher in CSFTT non-responders compared to responders ($p = 0.027$). Two conjectures are suggested. One, CSF biomarkers may play different and characteristic roles in relation to different iNPH symptoms such as cognition and gait. Two, comorbid AD pathology in iNPH patients may affect the response to the CSFTT. Larger studies using combinations of other biomarkers associated with AD would be necessary to evaluate these hypotheses.

1. Introduction

Idiopathic normal-pressure hydrocephalus (iNPH) is regarded as a potentially treatable dementia. It is an adult-onset syndrome of uncertain origin, with symptoms of gait disturbance, cognitive deterioration and urinary incontinence, and involves non-obstructive enlargement of the cerebral ventricles along with normal cerebrospinal fluid (CSF) pressure [1].

Alzheimer's disease (AD) is frequently concomitant with iNPH, with one study finding that 89% of iNPH patients exhibited AD pathology [2]. Moreover, both AD and iNPH are reported to exhibit somewhat similar altered CSF dynamics, and some reports suggest there may be an overlapping pathology [3]. And although the role of AD in patients with iNPH is debated, one study suggested AD pathology contributed to the symptomatology of iNPH and had an adverse effect on shunt surgery outcomes [4].

CSF biomarkers measured with enzyme-linked immunosorbent assay (ELISA), including soluble amyloid β-42 (Aβ-42) and phosphorylated-tau (P-tau), have been well-established and internationally validated in diagnosing AD [5], and the specific combination of low CSF Aβ-42 and elevated CSF P-tau is regarded as a biomarker signature of AD [6]. Aβ-42 and P-tau are believed to reflect core pathophysiological features of the disease [7], and this view has been validated in *post mortem* studies [8,9].

Similarly, CSF biomarker studies on iNPH patients have been carried out in several laboratories, but with only moderate agreement in the results. Most studies on iNPH patients report decreased CSF Aβ-42 levels [10–14], although one reported no change [15]. Studies on iNPH patients have tended to report decreased CSF P-tau levels [10,11,15], although one reported increased levels [13], and one reported no change [14].

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There has been little investigation into specific relationships in iNPH patients between CSF biomarkers and clinical characteristics. One study investigated the relationship between cognitive deficits and CSF Aβ-42 and total tau levels in iNPH patients [12]. Another study analyzed the correlation of P-tau with Mini Mental State Examination score [13]. In both studies, no statistically significant relationships were found, and there have been no iNPH studies correlating CSF biomarkers and gait to our knowledge.

Finally, the CSF tap test (CSFTT) response is regarded as an important marker for the prediction of shunt effectiveness in patients with iNPH and a valuable characteristic for understanding iNPH patients [16]. There may be unknown relevant relationships between CSF biomarkers and CSFTT response. One hypothesis is that AD pathology may affect CSFTT response. Analyzing the Aβ-42/P-tau ratio between CSFTT responders and non-responders might shed light on this issue.

We investigated relationships between CSF biomarkers, including Aβ-42 and P-tau, and clinical parameters in iNPH patients. We also evaluated differences in these CSF biomarkers in iNPH patients relative to the outcome of their CSFTT. We hypothesized that there may be specific relationships between CSF biomarkers and clinical characteristics, and that the biomarker signature of AD, the Aβ-42/P-tau ratio, may be different according to CSFTT response.

2. Methods

2.1. Participants

Participants were recruited from patients who visited the Center for Neurodegenerative Diseases of Kyungpook National University Hospital, South Korea from July 2011 to February 2013. Informed consent was obtained from all participants or their caregivers prior to study participation. This study was approved by the Institutional Review Board at our institution. From the individuals classified as iNPH according to the criteria proposed by Relkin et al. [17], 35 patients agreed to enroll in this study. Patients had to be older than 40 years of age with an insidious progression of symptoms (gait disturbance, plus at least one other area of impairment in either cognition or urinary symptoms, or both) for at least 6 months and have normal CSF opening pressure. Brain MRI of all iNPH patients showed widening of the ventricles (Evan's ratio >0.3) and no obstruction of CSF flow.

Patients with stroke, neurological, metabolic, or neoplastic disorders that might produce dementia symptoms or parkinsonism, a recent history of heavy alcohol use, or a history of hospitalization for a major psychiatric disorder, were excluded. No participant had a related antecedent event, such as head trauma, intracerebral hemorrhage, meningitis, or any other known cause of secondary hydrocephalus.

2.2. Assessing illness severity

The patients' general cognitive state and severity of dementia were evaluated by means of the Korean Mini Mental State Examination (K-MMSE) and Clinical Dementia Rating Scale (CDR) [18,19]. The Frontal Assessment Battery (FAB), a simple tool designed for assessing frontal lobe symptoms, was used [20]. The length of time taken to complete the Trail Making Test Part A (TMT-A), a common neuropsychological test to evaluate psychomotor speed, often used for patients with iNPH, was recorded [21].

We also utilized the iNPH grading scale (iNPHGS), a clinician-rated scale used to assess the severity of each fundamental symptom of iNPH (cognitive impairment, gait disturbance and urinary disturbance) after an unstructured interview with patients and caregivers [21].

Gait assessment included measurements on the Timed Up and Go test (TUG) and the 10 meter walking test [21,22]. They were performed four times consecutively and the mean score was used. The features of gait disturbance related to iNPH were also estimated using the Gait Status Scale (GSS) [21].

2.3. CSFTT

A lumbar tap removing 30–50 ml of CSF was performed in all iNPH patients. CSF pressure was measured at the site of puncture. After the tap, all patients were re-evaluated using the iNPHGS, K-MMSE and TUG test. Changes in gait were repeatedly evaluated over 7 days after the tap, while changes in cognition and urination were evaluated at 1 week [23]. Response to the CSFTT was defined using the iNPHGS, TUG and K-MMSE. Responders were defined as showing improvement of one point or more on the iNPHGS, more than 10% improvement in time on the TUG test, or more than three points improvement on the K-MMSE [16].

2.4. Laboratory CSF analysis

CSF samples were collected in the morning through a lumbar puncture with the patient in a recumbent position. Bloody or cloudy samples were rejected. All CSF samples were collected in polypropylene tubes, centrifuged, aliquoted, and frozen at −80 °C until analyzed.

The levels of Aβ-42 and P-tau in the CSF were measured by commercially available single-parameter ELISA kits (Innotest β-Amyloid(1–42), Innotest Phosphotau(181P); Innogenetics, Ghent, Belgium). In each assay, CSF samples and the appropriate controls were tested following the instructions provided by the manufacturer. All measurements were gathered from duplicated assays. The reference concentration ranges of the test kits were Aβ-42 = 125–2000 pg/ml, and P-tau = 15.6–500 pg/ml.

2.5. Statistical analyses

The Statistical Package for the Social Sciences version 21.0.0 (SPSS, Chicago, IL, USA) was used for analysis of data. Spearman's correlations were employed to investigate the relationship between CSF biomarkers, clinical measures, and MRI features in iNPH. The demographic data, clinical characteristics, CSF drainage volume and CSF opening pressure during the tap test and MRI features were compared in iNPH patients between CSFTT responders and non-responders. Fisher's exact and chi-squared tests were used to compare categorical variables, while the Mann–Whitney U test was used to compare continuous variables. We also compared CSF biomarkers, including Aβ-42, P-tau, and P-tau/Aβ-42 ratios, between CSFTT responders and non-responders using Student's *t*-test. The statistical significance level was set at $p < 0.05$. Data are presented as mean ± standard deviation.

3. Results

3.1. Baseline clinical characteristics, neuropsychological testing, and CSF biochemical profile

Four participants who completed the CSFTT were excluded due to bloody or cloudy CSF samples. The remaining 31 iNPH patients constituted the final sample for analysis. The study participants included 18 men and 13 women; the mean age was 73.5 ± 5.2 years. In 26 (83.9%) patients, gait disturbance was the initial presenting symptom. All 31 patients had gait disturbance, 30 (96.8%) had cognitive disturbance, and 16 (51.6%) had urinary

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