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

Kyunghun Kang [a], Uicheul Yoon [b], Jong-Min Lee [c], Ho-Won Lee [a,d,*]

[a] Department of Neurology, School of Medicine, Kyungpook National University, Daegu, South Korea
[b] Department of Biomedical Engineering, College of Health and Medical Science, Catholic University of Daegu, Gyeongsan-si, South Korea
[c] Department of Biomedical Engineering, Hanyang University, Seoul, South Korea
[d] Brain Science & Engineering Institute, Kyungpook National University, Daegu, South Korea

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ABSTRACT

When considering the underlying pathophysiological mechanisms involved in idiopathic normal pressure hydrocephalus (iNPH), white matter is often the main locus of investigation. However, when an axon in the brain is damaged, degeneration of the neuron can occur proximally (dying back) and Alzheimer's disease (AD), associated with cortical thinning, is a common pathologic comorbidity with iNPH. We investigated differences in cortical thickness between CSF tap test (CSFTT) responders and non-responders in iNPH patients and compared patterns of cortical thickness in iNPH patients with that of AD patients. Thirty-two iNPH patients (16 CSFTT responders and 16 CSFTT non-responders) and 16 AD patients were imaged with MRI, including 3-dimensional volumetric images for cortical thickness analysis across the entire brain. Among the iNPH patients, CSFTT non-responders, when compared to responders, had statistically significant cortical thinning in the left superior frontal gyrus at the level of a false discovery rate (FDR) $p < 0.05$, and tended to show widespread cortical thinning in most areas of the brain. Relative to the CSFTT responders, AD patients showed statistically significant cortical thinning in superior and medial frontal gyrus, left precentral gyrus, postcentral gyrus, paracentral lobule, precuneus, and superior parietal lobule after FDR correction ($p < 0.05$). However, comparing patterns of cortical thinning between AD patients and CSFTT non-responders revealed no statistically significant differences. Differences in cortical thickness correlated with CSFTT response for iNPH patients may indicate a possibility for considering patterns of cortical thinning in patients with ventriculomegaly as potential brain imaging markers for the prediction of CSFTT responders. And, our findings suggest that comorbid AD pathology might be related to the cortical thinning patterns found in CSFTT non-responders. Larger studies, using normal controls and combinations of other biomarkers associated with AD, would be necessary to evaluate these hypotheses.

1. Introduction

Idiopathic normal-pressure hydrocephalus (iNPH) is an adult-onset syndrome of uncertain origin involving nonobstructive enlargement of the cerebral ventricles in combination with one or more symptoms of gait disturbance, urinary dysfunction, and cognitive impairment [1]. To diagnose iNPH, many neurosurgical centers recommend using the CSF tap test (CSFTT) [2]. The CSFTT also has a high positive predictive value for successful shunt surgery [2,3]. The CSFTT response has been regarded as an important mark for the prediction of shunt effectiveness in patients with iNPH and a valuable characteristic for understanding iNPH patients [2,3].

When considering the underlying pathophysiological mechanisms involved in iNPH, the cortex is usually overlooked and white matter is often the main locus of investigation [1,4–6]. Some studies suggest, however, that when an axon in the brain is damaged, degeneration of the neuron not only occurs distally (Wallerian degeneration) but also proximally (dying back) [7–9]. These mechanisms could result in thinning of cortical areas connected to damaged white matter [10]. Another consideration is that iNPH rarely exists in the absence of other neurodegenerative conditions. For example, in a report on iNPH cases, 89% were also found to have Alzheimer's disease (AD) pathology [11], and the comorbidity of AD pathology contributed to the symptomatology of iNPH and adversely affected shunt surgery outcomes [12]. And it is well-known that cortical thinning pattern is associated with AD pathology [13]. Therefore, we conjectured that degeneration in the cerebral cortex in iNPH patients might be as relevant as changes in white matter. However, to date the nature and topographical distribution of cerebral cortical changes in iNPH patients are unknown.

* Corresponding author at: Department of Neurology, School of Medicine, Brain Science & Engineering Institute, Kyungpook National University, 50 Samdeok-dong 2-ga, Jung-gu, Daegu, 700-721, South Korea. Tel.: +82 53 200 3271; fax: +82 53 200 3299.
E-mail address: neuromd@knu.ac.kr (H.-W. Lee).

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In light of the totality of these considerations, we hypothesized that there may be differences in cortical thickness in iNPH patients relative to the outcome of their CSFTT. Using automated surface-based cortical thickness analysis on iNPH patients, we investigated differences in cortical thickness between CSFTT responders and non-responders. And, to evaluate differences in cortical thinning between iNPH and AD, we compared patterns of cortical thickness in iNPH patients with that of age- and gender-matched AD patients.

2. Method

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 October 2012. Informed consent was obtained from all participants or their caregivers prior to study participation. This study was approved by the Institutional Review Boards at our institution. Among the individuals classified as iNPH according to the criteria proposed by Relkin et al [14], 39 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, 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.

Sixteen AD patients, including 8 men and 8 women, were chosen at random from our hospital, and were matched to iNPH patients based on age and gender. AD was diagnosed according to NINCDS-ADRDA criteria and DSM-IV criteria for dementia [15,16].

Patients with stroke, other neurological, metabolic, or neoplastic disorders which might produce dementia symptoms or parkinsonism, a recent history of heavy alcohol use, or a history of hospitalization for major psychiatric disorder were excluded. No participant showed evidence of a related antecedent event, such as head trauma, intracerebral hemorrhage, meningitis, or another 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) [17,18]. The Frontal Assessment Battery (FAB) is a simple tool designed for assessing so-called frontal lobe symptoms [19]. The Trail Making Test Part A (TMT-A) is a common neuropsychological test to evaluate psychomotor speed and is often used for patients with iNPH [20]. In this study, the amount of time taken to complete TMT-A was checked. We did not use TMT-B because many patients with iNPH are unable to complete it.

The iNPH grading scale (iNPHGS) is a clinician-rated scale 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]. The score of each domain ranges from 0 to 4.

The gait assessment included measurements of time on the Timed Up and Go Test (TUG) and the 10-meter walking test [22,23]. These are valid tests of functional mobility used in many studies to evaluate walking ability [21,23–25]. They were performed four times consecutively and the mean score was measured. The features of gait disturbance related to iNPH were also estimated using the Gait Status Scale (GSS) [21]. This scale focuses on 8 factors of gait disturbance: (1) postural stability; (2) independence of walking; (3) wide base gait; (4) lateral sway; (5) petit-pas gait; (6) festinating gait; (7) freezing of gait, and (8) disturbed tandem walking. And, we assessed motor ability using the Unified Parkinson Disease Rating Scale (UPDRS). The UPDRS is the most commonly used scale for assessing parkinsonian severity [26].

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, the K-MMSE and the TUG test. Changes in gait were evaluated repeatedly over 7 days after the tap, while changes in cognition and urination were evaluated at one week [27]. Response to the CSFTT was defined by three major scales: iNPHGS, TUG and K-MMSE. The following criteria were used to identify responders: improvement of one point or more on the iNPHGS, more than 10% improvement in time on the TUG test, or more than 3 points improvement on the K-MMSE [3].

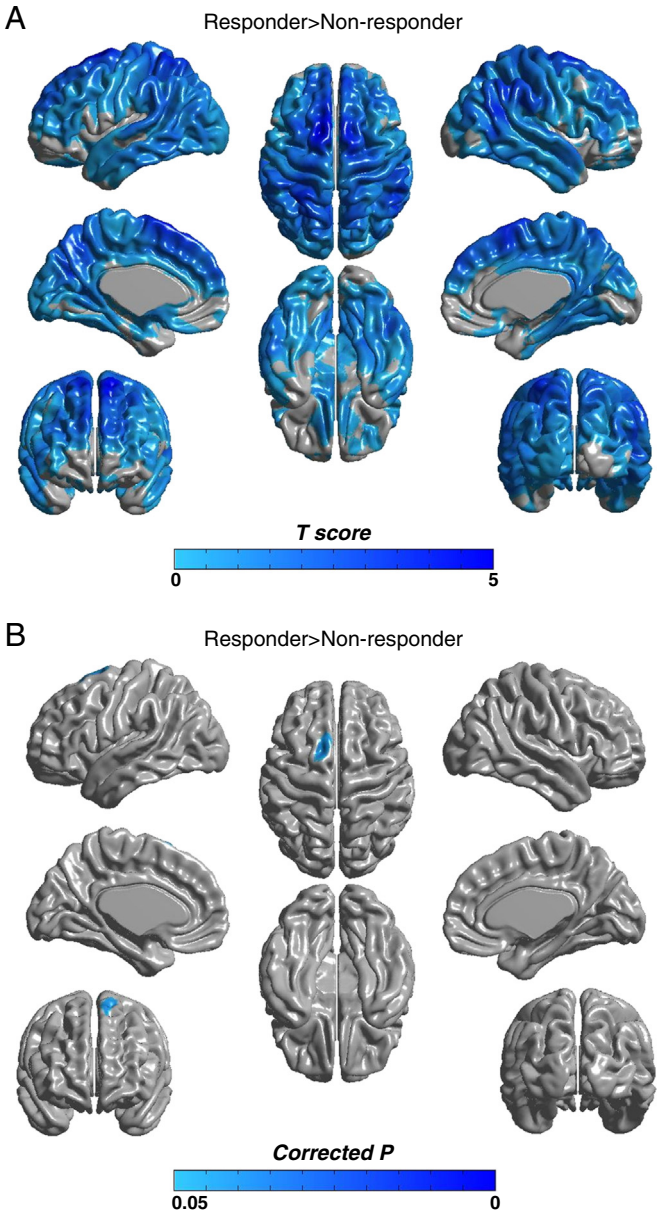

Fig. 1. Statistical maps of differences in cortical thickness between CSFTT responders and non-responders in iNPH patients. A: In statistical t-map, CSFTT non-responders, when compared to responders, tended to show wide-spread cortical thinning in most areas of the brain. B: Compared to the CSFTT non-responders, responders had statistically significant cortical thinning in the left superior frontal gyrus after false discovery rate correction ($p < 0.05$). The left-hand side of the images represents the left hemisphere of the brain.

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