Asymmetric and Upper Body Parkinsonism in Patients with Idiopathic Normal-Pressure Hydrocephalus

Kyunghun Kang\textsuperscript{a,b}  
Ji-Su Jeon\textsuperscript{a}  
Taegyeong Kim\textsuperscript{c}  
Dongho Choi\textsuperscript{a}  
Pan-Woo Ko\textsuperscript{a,b}  
Sung Kyoo Hwang\textsuperscript{d}  
Ho-Won Lee\textsuperscript{a,b}  
\textsuperscript{a}Department of Neurology, Kyungpook National University School of Medicine, Daegu, Korea  
\textsuperscript{b}Brain Science & Engineering Institute, Kyungpook National University, Daegu, Korea  
\textsuperscript{c}Kyungpook National University School of Medicine, Daegu, Korea  
\textsuperscript{d}Department of Neurosurgery, Kyungpook National University School of Medicine, Daegu, Korea

Background and Purpose  Our aims were to analyze the characteristics of parkinsonian features and to characterize changes in parkinsonian motor symptoms before and after the cerebrospinal fluid tap test (CSFTT) in idiopathic normal-pressure hydrocephalus (INPH) patients.

Methods  INPH subjects were selected in consecutive order from a prospectively enrolled INPH registry. Fifty-five INPH patients (37 males) having a positive response to the CSFTT constituted the final sample for analysis. The mean age was 73.7 ± 4.7 years. The pre-tap mean Unified Parkinson’s Disease Rating Scale motor (UPDRS-III) score was 24.5 ± 10.2.

Results  There was no significant difference between the upper and lower body UPDRS-III scores (p=0.174). The parkinsonian signs were asymmetrical in 32 of 55 patients (58.2%). At baseline, the Timed Up and Go Test and 10-meter walking test scores were positively correlated with the total motor score, global bradykinesia score, global rigidity score, upper body score, lower body score, and postural instability/gait difficulties score of UPDRS-III. After the CSFTT, the total motor score, global bradykinesia score, upper body score, and lower body score of UPDRS-III significantly improved (p<0.01). There was a significant decrease in the number of patients with asymmetric parkinsonism (p<0.05).

Conclusions  In the differential diagnosis of elderly patients presenting with asymmetric and upper body parkinsonism, we need to consider a diagnosis of INPH. The association between gait function and parkinsonism severity suggests the involvement of similar circuits producing gait and parkinsonian symptoms in INPH.

Key Words  normal pressure hydrocephalus, parkinsonism, Parkinson’s disease.

INTRODUCTION

Idiopathic normal-pressure hydrocephalus (INPH) is an uncommon neurological disorder. Of 563 cases showing the neuropathology of a dementing illness at autopsy, INPH was suspected only in 9 (1.6%). Nevertheless, the diagnosis and understanding of INPH are important because INPH is regarded as a potentially treatable neurological disorder. INPH is an adult-onset syndrome of uncertain origin, with symptoms of gait disturbance, cognitive impairment, and urinary dysfunction, that involves nonobstructive enlargement of the cerebral ventricles, along with normal cerebrospinal fluid (CSF) pressure at lumbar puncture. Although patients with INPH may present with varying combinations or degrees of each of these classic clinical symptoms, the most frequent and important clinical feature of INPH is that of gait disturbance.

The CSF tap test (CSFTT) has been considered as a valuable examination for the diagnosis and prediction of shunt effectiveness in patients with INPH. Surgical treatment by placement of a ventricular shunt is indicated for patients with INPH who show a positive

©This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (http://creativecommons.org/licenses/by-nc/3.0) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.
Clinical improvement after the CSFTT is an important criterion that enhances diagnostic certainty from possible to probable, following the Japanese guideline.6 Parkinsonism is one of the most prevalent, chronic neurological syndromes facing the elderly.7 Differential diagnosis of patients with parkinsonism is important because prognosis and treatment options can differ substantially for Parkinson's disease (PD) and other parkinsonian disorders.7 A better understanding of parkinsonism in INPH is necessary, because parkinsonism is also observed in patients with INPH.8 In fact, in one report, INPH is described as shunt-responsive parkin-

sonism.8

The motor section of the Unified Parkinson's Disease Rating Scale (UPDRS-III) is well known as the gold standard for evaluating motor symptoms in PD and provides a semi-quantitative analysis of the severity of parkinsonian signs and symptoms.9 Parkinsonian motor deficits also have been assessed with the UPDRS-III in other neurodegenerative diseases, such as Alzheimer's disease.10 Clinicians and researchers have often used the UPDRS-III scale to determine the standard of response in some interventions for parkinsonian patients. And, to the authors' knowledge, their changes on the UPDRS-III following the CSFTT have not yet been reported in INPH patients.

Our aims were to analyze the characteristics of parkinsonian features and to characterize changes in parkinsonian motor symptoms before and after the CSFTT in INPH patients who had a positive response to the CSFTT. We also explored whether a relationship exists between gait function and parkinsonism severity in these patients.

**METHODS**

**Participants**

INPH participants were prospectively recruited from patients at the Center for Neurodegenerative Diseases of Kyungpook National University Medical Center, Korea from July 2011 to November 2014. This study was approved by our local Institutional Review Board. The criteria proposed by Relkin et al.9 was used to diagnose INPH. A lumbar tap removing 30–50 mL of CSF was performed on all 72 patients with INPH. All patients were re-evaluated after the tap using the

| Table 1. Demographic data, clinical characteristics, CSF drainage volume, CSF opening pressure, and MRI findings at baseline | Baseline |
|---|---|
| Gender, male | 37 (67.3) |
| Age (year) | 73.7±4.7 |
| Duration of symptoms (year) | 2.2±1.9 |
| Education (year) | 9.3±4.6 |
| History of hypertension | 35 (63.6) |
| History of diabetes | 14 (25.5) |
| History of lipid disorder | 10 (18.2) |
| Initial symptoms | |
| Gait disturbance | 46 (83.6) |
| Cognitive impairment | 9 (16.4) |
| Full-blown symptoms | |
| Gait disturbance | 55 (100) |
| Cognitive impairment | 54 (98.2) |
| Urinary incontinence | 30 (54.5) |
| Clinical triad | 29 (52.7) |
| Drainage volume of CSF | 38±6.0 |
| CSF opening pressure (cm H2O) | 9.4±2.7 |
| Apolipoprotein E ε4+ε4- | 4/38 |
| Evan’s ratio | 0.33±0.02 |
| Hemispheric white matter lesions (Fazekas classification) | |
| Contralateral | 18±0.6 |
| Ipsilateral | 17±0.6 |
| Frontal horn diameters (mm) | |
| Contralateral | 21.5±1.7 |
| Ipsilateral | 21.3±1.5 |
| Korean-Mini Mental State Examination | 20.1±6.0 |
| Trail Making Test Part A | 163±85.3 |
| Clinical Dementia Rating Scale (0±0.5:1:2:3) | 0±29.18:5.3 |
| INPH Grading Scale | |
| Gait | 1.7±0.6 |
| Cognition | 2.6±0.6 |
| Urinary function | 1.4±1.3 |
| Total | 5.7±1.9 |
| Timed Up and Go test | 21.1±19.9 |
| 10 meter walking test | 21.8±26.0 |
| Gait Status Scale | 7.1±3.2 |

Values denote number (%) or mean±standard deviation. *No patient scored zero on the global bradykinesia score. †Fourteen patients scored zero on the global tremor score. ‡Two patients scored zero on the global rigidity score. §Of patients with asymmetric parkinsonian signs (n=32), a total of 16 patients (50%) were characterized by right-sided symptom dominance, while in 16 patients (50%) symptoms were dominant on the left side. The handedness was reported as right-sided in 55 patients (100%). CSF: cerebrospinal fluid, INPH: idiopathic normal-pressure hydrocephalus.
INPH Grading Scale (INPHGS), the Korean-Mini Mental State Examination (K-MMSE) and the Timed Up and Go Test (TUG). Gait change was evaluated repeatedly over 7 days after the tap. During the follow-up period, results with the greatest improvement were used for comparisons between baseline and follow-up measurements. Changes in cognition and urination were evaluated at one week. Response to the CSFTT was defined using these three major scales. INPH patients having a positive response to the CSFTT were enrolled to increase diagnostic certainty, and 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. The final sample for analysis was 55 INPH patients. The demographic and clinical baseline characteristics are given in Table 1.

Assessing illness severity
The patients’ general cognitive state and severity of dementia were evaluated with the K-MMSE and Clinical Dementia Rating Scale. 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. In this study, the amount of time taken to complete the TMT-A was recorded.

The INPHGS is a clinician-rated scale to assess the severity of the fundamental symptoms of INPH (cognitive impairment, gait disturbance, and urinary disturbance) after an unstructured interview with patients and caregivers. The score of each domain ranges from 0 to 4.13,18 Grade 0 indicates normal, and grade 1 indicates subjective symptoms but no objective disturbance.13,18 Grade 2, 3, and 4 indicate mild, moderate, and severe disturbances, respectively.13,18

Gait assessment included measurements of time on the TUG and 10-meter walking test. They were performed four times consecutively and the mean score was determined. Features of gait disturbance were also estimated using the Gait Status Scale (GSS). An experienced rater, who was blinded to the patient’s diagnosis, performed UPDRS-III evaluations. We also used the following subscores based on the UPDRS-III: global bradykinesia score (items 23–26 and 31),19 global tremor score (items 20 and 21),20 global rigidity score (item 22),19 and postural instability/gait difficulties (PIGD) score (items 27–30).21 The upper body score was calculated as the sum of the mean score for right and left upper limbs on item 20, the mean score for right and left upper limbs on item 22, and the mean score for right and left upper limbs on items 23–25.19 The lower body score was calculated as the sum of the mean score for right and left lower limbs on item 20, the mean score for right and left lower limbs on item 22, and the mean score for right and left lower limbs on items 20 and 22–26.19 The right score was calculated as the sum of the scores for right upper and lower limbs on items 20 and 22–26.19 The left score was calculated as the sum of the scores for left upper and lower limbs on items 20 and 22–26. An asymmetry index was calculated as the absolute value of the right minus left scores from the UPDRS-III score.19 A UPDRS-III asymmetry index difference of at least two points was used as the threshold for defining clinical asymmetry.19 The UPDRS-III was applied again 24 hours after tap by the same rater.

Magnetic resonance imaging acquisition
MRI data were obtained using a 3.0 Tesla system (GE Discovery MR750, GE Healthcare). We performed MRI in INPH patients before the CSFTT. The evaluation of white matter lesions (WML) was provided by T2 weighted and fluid attenuated inversion recovery images. Hemispheric WML were rated using the Fazekas scale, scoring 0–3 (for deep and periventricular WML, where 0=none and 3=severe). For total hemispheric WML, we added scores in the deep and periventricular regions and obtained the average.22,23 The diameter of the each frontal horn was measured electronically at the level of the head of the caudate nucleus and the measurements were used to assess the degree of the asymmetric lateral ventricle.

Statistical analyses
The IBM SPSS Statistics for Windows version 21.0.0 was used for analyses of data. A paired t-test was used to compare the upper and lower body scores. The comparisons of the hemispheric WML and frontal horn diameters within subjects (i.e., between the contra- and ipsilateral hemispheres in accordance with the body side of the dominant motor symptoms) were also done using the paired t-test. Pearson’s or Spearman’s correlations were employed to investigate the relationship between gait function and the severity of parkinsonism at baseline in INPH. The changes in parkinsonian motor symptoms before and after the CSFTT were analyzed using the paired t-test or McNemar’s test. The paired t-test was used for comparison of the continuous variables, including the TUG, 10-meter walking test, GSS and total motor score, global bradykinesia score, global tremor score, global rigidity score, upper body score, lower body score, and PIGD score of UPDRS-III. We used McNemar’s test to compare the frequency of asymmetric parkinsonism in our INPH patients between baseline and follow-up. Statistical significance was set at p<0.05.
RESULTS

Baseline clinical characteristics and MRI findings (Table 1)
The initial mean UPDRS-III score was 24.5±10.2. There was no significant difference between the upper and lower body scores (paired t-test, p=0.174). Higher lower body scores correlated significantly with a higher upper body score (r=0.506, p<0.001). The parkinsonian signs were asymmetrical in 58.2% of the patients. No association was found between handedness and the side of symptom dominance. There were no significant differences in the hemispheric WML and frontal horn diameters between hemispheres ipsilateral and contralateral to the body side of the dominant motor symptoms (paired t-test, p=0.572 for the hemispheric WML and p=0.253 for the frontal horn diameters).

Correlations between gait function and parkinsonism severity in INPH (Table 2)
At baseline, the TUG and 10-meter walking test scores were positively correlated with the total motor score, global bradykinesia score, global rigidity score, upper body score, lower body score, and PIGD score of UPDRS-III. The GSS and INPHGS gait scores were positively correlated with the total motor score, global bradykinesia score, lower body score, and PIGD score of UPDRS-III. Not surprisingly, the TUG, 10-meter walking test, GSS, and INPHGS gait scores were more strongly correlated with the lower body score than with the upper body score.

Gait parameters and UPDRS-III measures in patients with INPH before and after the CSFTT
Differences in the gait parameters and UPDRS-III measures before and 24 hours after the CSFTT are shown in Table 3. The TUG score improved significantly (p<0.05). The 10-meter walking test and GSS results also improved significantly (p<0.01). The total motor score, global bradykinesia score, upper body score, and lower body score of UPDRS-III significantly improved (p<0.01). The PIGD score of UPDRS-III improved, but less significantly (p<0.05). Asymmetric presentation of parkinsonian features was significantly less frequent at follow-up than at baseline evaluation (p<0.05). The global tremor score of UPDRS-III marginally improved (p=0.047). The global rigidity score did not significantly improve.

Table 2. Correlations between gait function and other parkinsonian signs at baseline in INPH patients

| Correlation coefficients and p values | Unified Parkinson’s Disease Rating Scale motor score | Global bradykinesia score | Global rigidity score | Upper body score | Lower body score | Postural instability/gait difficulties score |
|---------------------------------------|-----------------------------------------------|---------------------------|---------------------|-----------------|-----------------|--------------------------------------------|
| Timed Up and Go test                  | 0.703 (<0.001)*                               | 0.624 (<0.001)*           | 0.422 (0.001)*      | 0.507 (<0.001)* | 0.610 (<0.001)* | 0.655 (<0.001)*                            |
| 10 meter walking test                 | 0.638 (<0.001)*                               | 0.572 (<0.001)*           | 0.354 (0.008)*      | 0.436 (0.001)* | 0.525 (<0.001)* | 0.653 (<0.001)*                            |
| Gait Status Scale                     | 0.513 (<0.001)*                               | 0.530 (<0.001)*           | 0.087 (0.529)       | 0.261 (0.055)  | 0.409 (0.002)* | 0.757 (<0.001)*                            |
| INPH Grading Scale, Gait              | 0.418 (0.001)*                                | 0.416 (0.002)*            | -0.028 (0.841)      | 0.149 (0.279)  | 0.295 (0.029)* | 0.672 (<0.001)*                            |

*Statistically significant relationships. INPH: idiopathic normal-pressure hydrocephalus.

Table 3. Gait function and other parkinsonian signs before and after CSF tap test

| Before CSF tap | 24 hours after tap | p value |
|----------------|--------------------|---------|
| Timed Up and Go test | 21.1±19.9 | 18.8±22.6 | 0.016 |
| 10 meter walking test | 21.8±26.0 | 17.1±18.9 | 0.001 |
| Gait Status Scale | 7.1±3.2 | 6.0±3.3 | <0.001 |
| Unified Parkinson’s Disease Rating Scale motor score | 24.5±10.2 | 21.7±9.0 | <0.001 |
| Global bradykinesia score | 8.9±4.6 | 7.3±4.4 | <0.001 |
| Global tremor score | 2.3±2.2 | 1.9±1.7 | 0.047 |
| Global rigidity score | 4.8±2.9 | 4.4±2.7 | 0.110 |
| Upper body score | 2.2±1.3 | 1.9±0.9 | 0.001 |
| Lower body score | 1.9±1.1 | 1.5±1.0 | <0.001 |
| Postural instability/gait difficulties score | 5.9±3.0 | 5.5±2.8 | 0.022 |
| Asymmetric parkinsonian signs | 32 (58.2) | 19 (34.5) | 0.019 |

Values denote number (%) or mean±standard deviation. CSF: cerebrospinal fluid.
DISCUSSION

One of the most important findings of this study was that there was no significant difference in the severity of parkinsonism between the upper and lower extremities in our INPH patients, as measured by the UPDRS-III. Furthermore, asymmetric parkinsonism was observed in more than half of the INPH patients.

Generally, lower body parkinsonism is characteristic in INPH. Lower body parkinsonism classically presents as a slow, wide-based gait, short shuffling steps, and difficulty in turning and tandem walking. However, the clinical presentation of INPH seems to be commonly not limited to the classical triad. In a previous study, upper extremity bradykinesia was also present in 62 percent of INPH patients. It was suggested that the features of upper limb motor disability found in INPH patients seem to resemble those encountered in PD. Our finding is consistent with the aforementioned studies. Using a strategy reported in a previous study, we found that patients with INPH suffered from a comparable degree of parkinsonism between the upper and lower extremities. As a possible explanation for this result, we can speculate as follows. The basal ganglia circuitry processes the signals that flow from the cortex, allowing the correct execution of voluntary movements. Dysfunction of basal ganglia circuitry is known to be mainly responsible for the development of the cardinal features of PD. Considering the connection between cerebral perfusion (also referred to as cerebral blood flow) and brain function, and the fact that significant reductions in mean cerebral blood flow of the basal ganglia and the thalamus were found in INPH patients compared with controls, this may explain the evident upper body parkinsonism also observed in our patients (as seen in PD).

In general, asymmetry with regard to parkinsonian features is considered as strong evidence toward a PD diagnosis. In addition, it was reported that of the 4,057 right-handed patients who experienced asymmetrical onset of PD motor symptoms, 2,413 (59.5%) had right-dominant and 1,644 (40.5%) had left-dominant PD symptoms. A careful clinical evaluation revealing asymmetry of symptoms and signs has been known as the one of the best methods for differentiating PD from other parkinsonian diseases, such as INPH. However, in INPH, information about motor asymmetry has been unclear. Interestingly, the frequency of asymmetric parkinsonism in our INPH patients was comparable with previous reports, showing between 50% and 60% of PD patients with asymmetric disease, although inconsistent classification criteria limit comparisons across studies. In our study, similar right or left distribution of sidedness among patients was observed. One potential explanation of the asymmetry is that some neurodegenerative diseases are believed to progress asymmetrically. For example, brain atrophy in Alzheimer’s disease is asymmetric but not lateralized (i.e., asymmetric directed toward one hemisphere). And this asymmetry seemed to account for the overt asymmetric symptoms. Additionally, in a report on INPH cases, most of them were also known to have Alzheimer’s disease pathology, and the comorbidity of such pathology has been shown to greatly influence the symptomatology of INPH. Further studies comparing the frequency and degree of motor asymmetry in INPH and those in PD would be needed to confirm our findings.

Unexpectedly, tremor was a common symptom in our INPH patients. Pathophysiologically, tremor is linked to altered activity in not one, but two distinct circuits: the basal ganglia and cerebellum. Furthermore, tremor seems to be more directly produced by the cerebellar pathways. Considering the fact that a significant reduction in mean cerebral blood flow of the cerebellum was found for INPH patients compared with controls, our finding is not surprising. In fact, one previous study reported that tremor was observed in 28 of 65 patients with INPH (43%). The possible association of tremor with hydrocephalus needs further clarification.

Our data showed that all gait measures were correlated with the total motor score, global bradykinesia score, lower body score, and PIGD score of UPDRS-III. The TUG and 10-meter walking test scores were also correlated with the upper body score of UPDRS-III. The TUG, 10-meter walking test, GSS, and INPHGS gait scores have been commonly used as a clinical measure of gait in INPH patients. The origin of the gait disturbance in INPH is not fully understood. The typical gait disturbances observed in INPH patients had characteristics of basal ganglia gait disorder. And a previous PET study reported that [11C]raclopride binding in the dorsal
putamen significantly correlated with gait performance in INPH patients. Considering the aforementioned information about the basal ganglia circuitry and parkinsonian signs, we can hypothesize that some degree of association may exist between gait function and parkinsonism severity in INPH. And these results may suggest potentially co-affected basal ganglia circuits simultaneously producing gait and parkinsonian symptoms in INPH patients.

The CSFTT is considered to represent an acute treatment of INPH. And, the clinical parameters improving during the CSFTT might be very specific to the condition of INPH. Furthermore, not only gait patterns can improve after CSF removal, but other areas as well such as finger motor performance. Interestingly, our INPH patients showed significant improvements in the various subscores of UPDRS-III (especially in the global bradykinesia score, upper body score, lower body score, and PIGD score). At the same time, according to the criteria defined in a previous study, there was a significant decrease in the number of patients with asymmetric parkinsonism in our study after CSF removal. Although these improvements in our patients further imply that distinct asymmetric and upper body Parkinsonism might be caused by INPH, no previous study has analyzed changes in UPDRS motor score after CSF removal.

The basal ganglia is known to interact closely with the cortex. It is possible that a complex network of the basal ganglia may exist. A functional magnetic resonance imaging study reported that reduced brain activity occurred in the basal ganglia and cortex of patients with non-tremor-dominant PD compared with patients with tremor-dominant PD. Considering the fact that in a previous study, brain function and local connectivity were linked, it seems that several parkinsonian symptoms are not generated by identical neuronal circuits. Furthermore, tremor, rigidity, bradykinesia, and gait dysfunction in PD may respond differently to levodopa treatment or surgical procedures, presumably because motor control of these functions is mediated by somewhat different anatomical-functional pathways. It was suggested that motor function recovery in INPH patients after CSF removal was related to a reversible suppression of frontal periventricular cortico-basal ganglia-thalamocortical circuits. In our study, the global tremor score of UPDRS-III only marginally improved and the global rigidity score did not significantly improve. The question remains why several parkinsonian symptoms in INPH may respond differently to the CSFTT. Further studies of the complex network of the basal ganglia and their related neuronal structures in INPH will shed more light on their role in INPH.

INPH subjects were selected in consecutive order from our prospectively enrolled INPH registry. In a relatively large sample of INPH patients, we tried to reduce potential bias related to clinical evaluation before and after the CSFTT through using various objective grading scales. One limitation of this study is that we did not include INPH patients who had a negative response to the CSFTT. However, we were motivated to enhance diagnostic certainty of INPH by restricting our study to CSFTT responders. Additionally, INPH patients with a negative response to the CSFTT were more likely to have other cerebral comorbidities. Moreover, from a clinical perspective, it seemed that information about parkinsonian signs in INPH patients with a positive response to the CSFTT was especially important in the differential diagnosis between INPH and other neurological disorders. Additional studies with CSFTT non-responders are also necessary to achieve a further understanding of parkinsonism in INPH. A second limitation was that we did not utilize the quantitative human motion analysis using motion sensor systems in our INPH patients. Although the clinical rating scales we used may not be as precise as kinematic analysis, these clinical measures are considered to be sufficiently validated and easy to administer. And raters were blinded to the outcome of CSFTT. Third, dopaminergic system imaging was not performed in our INPH patients. The dopamine transporter imaging is an effective tool in the identification of diseases involving presynaptic dopaminergic system neurodegeneration. It is possible that INPH and PD may coexist in this age group. However, we observed an apparent improvement in upper body parkinsonism and a significant decrease in the number of patients with asymmetric parkinsonism following CSF removal.

In the differential diagnosis of elderly patients presenting with asymmetric and upper body parkinsonism, we also need to consider a diagnosis of INPH. Association between gait function and parkinsonism severity suggests the involvement of similar circuits producing gait and parkinsonian symptoms in INPH.

Conflicts of Interest
The authors have no financial conflicts of interest.

Acknowledgements
The authors would like to thank Wade Martin of Medical Research International for his critical English revision. This research was supported by a grant of the Korea Health Technology R&D Project through the Korea Health Industry Development Institute (KHIDI), funded by the Ministry of Health & Welfare, Republic of Korea (HI14C3331).

REFERENCES
1. Cabral D, Beach TG, Vedders L, Sue LI, Jacobson S, Myers K, et al. Frequency of Alzheimer's disease pathology at autopsy in patients with clinical normal pressure hydrocephalus. Alzheimers Dement 2011;7:509-513.
2. Kim MJ, Seo SW, Lee KM, Kim ST, Lee JJ, Nam DH, et al. Differen-
tional diagnosis of idiopathic normal pressure hydrocephalus from other dementias using diffusion tensor imaging. AJNR Am J Neuroradiol 2011;32:1496-1503.

3. Adams RD, Fisher CM, Hakim S, Ojemann RG, Sweet WH. Symptomatic occult hydrocephalus with “normal” cerebral spinal-fluid pressure: a treatable syndrome. N Engl J Med 1965;273:117-126.

4. Olver BK, Monjjan S, Czosnyka Z, Czosnyka M, Péna A, Harris NG, et al. Normal pressure hydrocephalus and cerebral blood flow: a PET study of baseline values. J Cereb Blood Flow Metab 2004;24:17-23.

5. Ishikawa M, Hashimoto M, Kuwana N, Mori E, Miiyake H, Wachi A, et al. Guidelines for management of idiopathic normal pressure hydrocephalus. Neurol Med Chir (Tokyo) 2008;48 Suppl:S1-S23.

6. Barbosa MT, Caramelli P, Maia DP, Cunningham MC, Guerra HL, Lima-Costa MF, et al. Parkinsonism and Parkinson's disease in the elderly: a community-based survey in Brazil (the Bambui study). Mov Disord 2006;21:800-808.

7. Eckert T, Barnes A, Dhawan V, Frucht S, Gordon MF, Feigin AS, et al. FDG PET in the differential diagnosis of parkinsonian disorders. Neuroimage 2005;26:912-921.

8. Akiguchi I, Ishii M, Watanabe Y, Watanabe T, Kawasaki T, Yagi H, et al. Shunt-responsive parkinsonism and reversible white matter lesions in patients with idiopathic NPH. J Neurol 2008;255:1392-1399.

9. Granahalming KK, Byrne EI, Thornton A, Sambrook MA, Bannister P. Motor and cognitive function in Lewy body dementia: comparison with Alzheimer's and Parkinson's diseases. J Neurol Neurosurg Psychiatry 1997;62:243-252.

10. Relkin N, Marinaro A, Klingen P, Bergsneider M, Black PM. Diagnosing idiopathic normotensive pressure hydrocephalus. Neurosurgery 2005; 57(Suppl):S4-S16; discussion ii-v.

11. Kang K, Hwang SK, Lee HW. Shunt-responsive idiopathic normotensive pressure hydrocephalus patient with delayed improvement after tap test. J Korean Neurosurg Soc 2013;54:437-440.

12. Baghaloo P, Ales V, Miguel R. Gait dysfunction in Parkinson's disease and normal pressure hydrocephalus: a comparative study. J Neurol Neurosurg Psychiatry 2013;84:1201-1207.

13. Ishikawa M, Hashimoto M, Mori E, Kuwana N, Kazui H. The value of the cerebrospinal fluid tap test for predicting shunt effectiveness in idiopathic normotensive pressure hydrocephalus. Fluids Barriers CNS 2012;9:1.

14. Kang K, Yoon U, Lee JM, Lee HW. Idiopathic normotensive pressure hydrocephalus, cortical thinning, and the cerebrospinal fluid tap test. J Neurol Sci 2013;334:55-62.

15. Choi SH, Na DL, Lee BH, Hahn DS, Jeong JH, Yoon SJ, et al. Estimating the validity of the Korean version of Expanded Clinical Dementia Rating (CDB) scale. J Korean Neurol Assoc 2001;19:589-591.

16. Kang Y, Na DL, Hahn S. A validity study on the Korean Mini-Mental State Examination (K-MMSE) in dementia patients. J Korean Neurol Assoc 1997;15:300-308.

17. Mataro M, Matarín M, Poca MA, Pueyo R, Sahuquillo J, Barrios M, et al. Functional and magnetic resonance imaging correlates of corpus callosum in normal pressure hydrocephalus before and after shunting. J Neurol Neurosurg Psychiatry 2007;78:395-398.

18. Kubo Y, Kazui H, Yoshida T, Kito Y, Kimura N, Tokunaga H, et al. Validation of grading scale for evaluating symptoms of idiopathic normal-pressure hydrocephalus. Dement Geriatr Cogn Disord 2008;25:37-45.

19. Hassin-Baer S, Sirota P, Korczyn AD, Tissue PA, Epstein B, Shbatai H, et al. Clinical characteristics of neuroleptic-induced parkinsonism. J Neurol Neurosurg Psychiatry (Vienna) 2001;108:1299-1308.

20. Oosterveeld JP, Allen JC Jr, Reinoso G, Sead SH, Tay KY, Au WL, et al. Prognostic factors for early mortality in Parkinson's disease. Parkinsonism Relat Disord 2015;21:226-230.

21. Nocera J, Hass C. Should gait speed be included in the clinical evaluation of Parkinson's disease? Adv Parkinson Dis 2012;1:1-4.

22. Fazekas F, Chawluk JB, Alavi A, Hurtig HI, Zimmerman RA. MR signal abnormalities at 1.5 T in Alzheimer's dementia and normal aging. AJR Am J Roentgenol 1987;149:351-356.

23. Potter GM, Doulah FN, Jackson CA, Sudlow CL, Dennis MS, Wardlaw JM. Lack of association of white matter lesions with ipsilateral carotid artery stenosis. Cerebrovasc Dis 2012;33:378-384.

24. Kiroglu V, Karabulut N, Oncel C, Yagi B, Sabir N, Ozdemir B. Cerebral lateral ventricular asymmetry on CT: how much asymmetry is representing pathology? Surg Radiol Anat 2008;30:249-255.

25. Espay AJ, Narayan RK, Duker AP, Barrett ET Jr, de Courten-Myers G. Lower-body parkinsonism: reconsidering the threshold for external lumbar drainage. Nat Clin Pract Neurol 2008;4:50-55.

26. Gallin GL, Rigamonti D, Williams MA. The diagnosis and treatment of idiopathic normal pressure hydrocephalus. Nat Clin Pract Neurol 2006;2:375-381.

27. Nowak DA, Topka HR. Broadening a classic clinical triad: the hypokinetic motor disorder of normal pressure hydrocephalus also affects the hand. Exp Neurol 2006;198:81-87.

28. Krauss JK, Regel JP, Droste DW, Orszagh M, Borremans JJ, Vach W. Movement disorders in adult hydrocephalus. Mov Disord 1997;12:53-60.

29. Blandini F, Nappi G, Tassorelli C, Martignoni E. Functional changes of the basal ganglia circuitry in Parkinson's disease. Prog Neurobiol 2000;62:63-88.

30. Obejo JA, Marin C, Rodriguez-Oroz C, Blesa J, Benitez-Temio B, Mena-Segovia J, et al. The basal ganglia in Parkinson's disease: current concepts and unexplained observations. Ann Neurol 2008;64 Suppl 2:530-S46.

31. Wu T, Wang J, Wang C, Hallett M, Zang Y, Wu X, et al. Basal ganglia circuits changes in Parkinson's disease patients. Neurosci Lett 2012;524:55-59.

32. Tohgi H, Yonezawa H, Takahashi S, Sato N, Kato E, Kudo M, et al. Cerebral blood flow and oxygen metabolism in senile dementia of Alzheimer's type and vascular dementia with deep white matter changes. Neuroendocrinology 1998;60:131-137.

33. van der Hoorn A, Burger H, Leenders KL, de Jong BM. Handedness correlates with the dominant Parkinson side: a systematic review and meta-analysis. Mov Disord 2012;27:206-210.

34. Malm J, Grafit-Radford NR, Ishikawa M, Kristensen B, Leinonen V, Mori E, et al. Influence of comorbidities in idiopathic normal pressure hydrocephalus - research and clinical care. A report of the ISHCSE task force on comorbidities in INPH. Fluids Barriers CNS 2013;10:22.

35. Yamamouchi H, Nagura H. Neurological signs and frontal white matter lesions in vascular parkinsonism. A clinicopathologic study. Stroke 1997;28:965-969.

36. Elbaz A, Bowler H, Peterson BJ, Maraganore DM, McDonnell SK, Ahlskog JE, et al. Survival study of Parkinson disease in Olmsted County, Minnesota. Arch Neurol 2003;60:91-96.

37. Derflinger S, Sorg C, Gaser C, Myers N, Arsic M, Kurz A, et al. Grey matter atrophy in Alzheimer's disease is asymmetric but not lateralized. J Alzheimers Dis 2011;25:347-357.

38. Hamilton R, Patel S, Lee EB, Jackson EM, Lopinto J, Arnold SE, et al. Lack of shunt response in suspected idiopathic normal pressure hydrocephalus with Alzheimer disease pathology. Ann Neurol 2010; 68:535-540.

39. Herman T, Rosenberg-Katz K, Jacob Y, Aurél T, Gurevich T, Gilad N, et al. White matter hyperintensities in Parkinson's disease: do they explain the disparity between the postural instability gait difficulty and tremor dominant subtypes? PLoS One 2013;8:e55193.

40. Palm WM, Walchenbach B, Bruinsma B, Admiral-Abehlof F, Middelkoop HA, Launer LJ, et al. Intracranial compartment volumes in normal pressure hydrocephalus: volumetric assessment versus outcome. AJNR Am J Neuroradiol 2006;27:76-79.

41. Helmich RC, Hallett M, Deuschl G, Tonii I, Bloem BR. Cerebral causes and consequences of parkinsonian resting tremor: a tale of two circuits? Brain 2012;135(Parl 11):3206-3226.

42. Hallett M. Parkinson's disease tremor: pathophysiology. Parkinsonism Relat Disord 2012;18 Suppl 1:858-886.
cephalus: a clinical study. Parkinsonism Relat Disord 2007;13:434-437.
44. Ouchi Y, Nakayama T, Kanno T, Yoshikawa E, Shinke T, Torizuka T. In vivo presynaptic and postsynaptic striatal dopamine functions in idiopathic normal pressure hydrocephalus. J Cereb Blood Flow Metab 2007;27:803-810.
45. Stolze H, Kohtz-Buschbeck JP, Drücke H, Jöhnk K, Diercks C, Palmiš S, et al. Gait analysis in idiopathic normal pressure hydrocephalus--which parameters respond to the CSF tap test? Clin Neurophysiol 2000;111:1678-1686.
46. Lenfeldt N, Larsson A, Nyberg L, Andersson M, Birgander R, Eklund A, et al. Idiopathic normal pressure hydrocephalus: increased supplementary motor activity accounts for improvement after CSF drainage. Brain 2008;131(Pt 11):2904-2912.
47. Haber S, McFarland NR. The place of the thalamus in frontal cortical-basal ganglia circuits. Neuroscientist 2001;7:315-324.
48. Rosin B, Nevet A, Elias S, Rivlin-Etzion M, Israel Z, Bergman H. Physiology and pathophysiology of the basal ganglia-thalamo-cortical networks. Parkinsonism Relat Disord 2007;13 Suppl 3:S437-S439.
49. Prodoehl J, Planetta PJ, Kurita AS, Comella CL, Corcos DM, Vaillancourt DE. Differences in brain activation between tremor- and non-tremor-dominant Parkinson disease. JAMA Neurol 2013;70:100-106.
50. Várkuti B, Cavusoglu M, Kullik A, Schuiller B, Veit R, Yilmaz O, et al. Quantifying the link between anatomical connectivity, gray matter volume and regional cerebral blood flow: an integrative MRI study. PLoS One 2011;6:e14801.
51. Obeso JA, Rodriguez-Oroz MC, Rodriguez M, DeLong MR, Olanow CW. Pathophysiology of levodopa-induced dyskinesias in Parkinson’s disease: problems with the current model. Ann Neurol 2000;47(4 Suppl 1):S22-S32; discussion S32-S34.
52. Fasano A, Aquino CC, Krauss JK, Honey CR, Bloem BR. Axial disability and deep brain stimulation in patients with Parkinson disease. Nat Rev Neurol 2015;11:98-110.
53. Kang K, Ko PW, Jin M, Suk K, Lee HW. Idiopathic normal-pressure hydrocephalus, cerebrospinal fluid biomarkers, and the cerebrospinal fluid tap test. J Clin Neurosci 2014;21:1398-1403.