Clin Auton Res (2008)
DOI 10.1007/s10286-008-0482-z

RESEARCH ARTICLE

Evaluation of autonomic malfunction in idiopathic normal pressure hydrocephalus

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Received: 19 November 2007
Accepted: 2 July 2008
Published online: 23 July 2008

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Abstract *Objective* The autonomic nervous system plays an important role in urinary disturbance which is one of the main symptoms of idiopathic normal pressure hydrocephalus (iNPH); thus, the focus of the present study was to identify the autonomic function parameters that would be useful as clinical indicators of iNPH. *Methods* The subjects consisted of 18 iNPH patients (group N) and 31 normal controls (group C). Before and after a lumbar puncture test, they were examined for CVR-R and total heart rate. A power spectral analysis of R–R interval variability of their 24-hour Holter ECGs was also done. High frequency (HF) was an indicator of parasympathetic activity, while the low to high frequency ratio (L/H) was used as an indicator of sympathetic activity. Urinary incontinence was evaluated using the overactive bladder symptom score (OABSS) questionnaire and bladder capacity. Correlations between the above indicators and clinical indicators of iNPH, such as the mini-mental state examination and the Evans index, were examined. *Results* The HF values (ms^2) were 190.3 in group C and 237.2 in group N; the difference was statistically significant. In group N, the HF value after the lumbar puncture test was lower (160.3) than the value before the lumbar puncture test, confirming that the increased parasympathetic state returned to a near normal level after CSF drainage. A significant positive correlation was noted only between the pre-lumbar puncture HF value and the OABSS. *Conclusion* iNPH is associated with increased parasympathetic activity, and the lumbar puncture test and shunt surgery may correct this autonomic imbalance to near normal levels.

Key words idiopathic normal pressure hydrocephalus · autonomic nervous dysfunction · power spectral analysis of R-R interval variability · holter electrocardiographic recordings · urinary incontinence

Introduction

Idiopathic normal pressure hydrocephalus (iNPH) presents with the triad of gait disturbance, dementia, and urinary incontinence. There is ventriculomegaly, but the cerebrospinal fluid (CSF) pressure is within normal limits, and symptomatic improvement is obtained with shunt surgery; thus, iNPH has attracted attention as a treatable cause of dementia [6, 12, 13,14, 16]. Since iNPH is an important disease that is specific to the elderly, it is predicted to become more common in the near future.

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Ahlberg et al. [3] reported that measurements of intravesical pressure in patients with iNPH often showed evidence of overactive bladder, which they ascribed to detrusor overactivity. Although symptoms of urinary disturbance, such as urinary frequency and incontinence, are the main symptoms of iNPH, few other studies have shown the importance of urinary incontinence in iNPH. However, studies have reported that, in other neurological disorders, such as cerebrovascular dementia and multiple system atrophy, central damage of the frontal lobe, Meynert's basal nucleus and brainstem (pons) causes overactive bladder as a symptom of autonomic dysfunction [20, 30, 31, 33, 34, 35].

Therefore, in the present study, we focused our attention on the fact that the autonomic nervous system plays an important role in the mechanism of urinary disturbance, and correlated the changes in autonomic function before and after lumbar puncture tests [22] with blood and CSF markers. At the same time, autonomic dysfunction in iNPH was characterized using our previously reported power spectral analysis of R-R interval variability on 24-hour Holter electrocardiographic recordings, and investigated which of the characteristic clinical indicators of iNPH were specific to this disease.

Subjects

Two groups of subjects were enrolled in this study. One group (group N) consisted of 18 patients (10 men and 8 women; mean age, 74.6 years) who had been diagnosed as having probable or definite iNPH according to the reports of Ishikawa [18], Marmarou et al. [26], and Relkin et al. [29]. All of these patients, whose iNPH symptoms improved with ventriculo-peritoneal shunting or after the lumbar puncture test, met the diagnostic criteria specified by the guidelines. We also had data relating to 8 iNPH patients whose clinical symptoms improved after repeated CSF drainage trials; however, to avoid the effect of overdrainage due to repeated CSF drainage trials, these eight patients were excluded. Only iNPH patients whose clinical symptoms improved after a single CSF drainage procedure were included in the present study.

The other group (group C) consisted of 31 normal subjects (17 men and 14 women; mean age, 72.9 years) who had undergone voluntary health examinations and subsequently had no evidence of supratentorial lesions on the MRI of the head. Since the subjects were to undergo analysis of R-R interval variability on Holter ECG recordings, patients with the following conditions were excluded: definite heart failure with irregular R-R intervals or arrhythmias such as atrial fibrillation and extrasystoles; diabetes mellitus; hypertension controlled by β-blocker therapy; and urological diseases such as prostate hyperplasia. In addition, iNPH patients who were already taking anticholinergic agents, such as antidepressants and antipsychotic drugs, were excluded from this study.

This study was approved by the ethics committee of our university and conducted in accordance with the Declaration of Helsinki.

Methods

Imaging studies

Axial and coronal MRI scans of the head were performed using a 1.5-T MRI system (Gyroscan Intera, Philips Medical Systems, Best, The Netherlands) in all iNPH patients and control subjects to evaluate ventriculomegaly; the Evans index (frontal horn ratio), which is defined as the maximal frontal horn ventricular width divided by the transverse inner diameter of the skull, and signifies ventriculomegaly if it is 0.3 or greater [15], was calculated for all subjects. These images were evaluated by the authors (T.T., N.K., and K.Y.), two of whom are board-certified neurologists, and one who is a board-certified radiologist. All of the evaluators were blinded to the patient data.

Correlations between the data from the power spectral analysis of the R-R intervals on Holter ECG recordings and the characteristic clinical indicators of iNPH

All iNPH patients and normal subjects underwent 24-hour ambulatory ECG recording (using an ECG recorder, DMC-4502, Nikon Kohden, Japan). All subjects were admitted to the hospital during the recording. The recording was performed under conditions of minimal indoor motion with the cooperation of all of the subjects. The data obtained from all patients, including their R-R intervals and R wave peaks, were recorded on 24-hour magnetic tapes, and these signals were then converted to digital signals. The components of the power spectrum that quantitatively reflected both sympathetic and parasympathetic cardiovascular regulatory functions were determined from the patients' ECGs which were recorded before and then one and two days after the lumbar puncture test. Since the drainage of 30 ml of CSF sometimes causes headache and has a risk of infection as well as continuous CSF leakage, the lumbar puncture test was not done in the normal control subjects due to ethical considerations.

Power spectrum analyses were then performed to evaluate patients' autonomic function. The power

Table 1 Overactive bladder symptom score (OABSS) (from Homma Y et al. Urology 68:318–323, 2006

Please circle the score that applies to your urinary condition during the last week		
Question	Score	Frequency
How many times do you typically urinate from waking in the morning until sleeping at night?	0	≤ 7
	1	8–14
	2	≥15
How many times do you typically wake up to urinate from sleeping at night until waking in the morning?	0	0
	1	1
	2	2
	3	≥ 3
How often do you have a sudden desire to urinate which is difficult to defer?	0	Not at all
	1	Less than once a week
	2	Once a week or more
	3	About once a day
	4	2–4 times a day
	5	5 times a day or more
How often do you leak urine because you cannot defer the sudden desire to urinate?	0	Not at all
	1	Less than once a week
	2	Once a week or more
	3	About once a day
	4	2–4 times a day
	5	5 times a day or more
Sum of scores		

spectral analysis of the 24-hour ECG-recorded R-R interval variability was carried out using the MemCalc/CHIRAM program (GMS Co., Ltd., Japan), as previously described [4, 7, 8, 23, 24, 25, 28]. Power spectral densities of rhythmic oscillations over a frequency range of 0.4 Hz and less were obtained from the patients' 24-hour ECGs to analyze their total power (<0.4 Hz), high-frequency power (HF, 0.15–0.40 Hz) as an indicator of parasympathetic activity, and the ratio of low-frequency power (LF, 0.04–0.15 Hz) to HF as an indicator of sympathetic activity. Next, the correlations between the L/H ratio and the HF value thus obtained, the following variables were examined: mini-mental state examination (MMS-E) before and after the lumbar puncture test, the Evans index, age, CSF pressure, up-and-go time (in a 3-m gait test of going to and fro a place) before the lumbar puncture test, up-and-go time after the lumbar puncture test, and the percent of time and step improvement on the gait test.

In the surgically treated patients, 24-hour Holter ECGs were recorded again 1 month after surgery, and their agreement to undergo Holter ECG monitoring after the lumbar puncture test was confirmed.

Cystometric (urodynamic) evaluation

Screening for urinary incontinence and hyperactive bladder was performed using the overactive bladder symptom score (OABSS) questionnaire within the guidelines for the treatment of overactive bladder, according to the report of Homma et al. (Table 1) [17]. The correlation between the OABSS and catecholamine levels was examined. Based on previous reports, patients with an OABSS of 12 or higher were suspected of having overactive bladder, and as previously reported, their residual urine volume and intravesical pressure were measured by water instillation with a 10-Fr double-lumen catheter. They were observed for the bladder contraction reflex in the urology outpatient clinic [23].

A urological history was obtained from all patients, with special emphasis on the onset and progression of urological symptoms in group N. The patients underwent urodynamic evaluation by board-certified urologists in our hospital. A 10-Fr double-lumen urodynamic catheter was inserted transurethrally into the bladder. Distilled water at room temperature was instilled through one lumen at a constant rate, and the intravesical pressure was measured from the other lumen. These pressures were transduced for display on a chart recorder, with the patients in the supine position. The bladder capacity, detrusor pressure at which involuntary contractions occurred and residual urine volume were measured by catheterization at appropriate intervals. Cystometric evaluation was not performed in the normal control subjects due to ethical considerations.

Statistical analysis

Statistical analyses were performed using Statview software version 5.0. The results of the two groups were compared using the Wilcoxon signed-ranks test.

Table 2 Comparison of group C and group N subjects

n	Group C 31	Group N 18
Age (years)	72.9 ± 4.1	74.6 ± 4.5
Sex (male/female)	17/14	10/8
Evens index	0.22 ± 0.09	0.35 ± 0.13**
MMSE (score)	28.4 ± 2.5	22.9 ± 3.6**
Up-and-go test (sec)	12.4 ± 4.5	27.2 ± 10.8**
OABSS (score)	3.4 ± 2.5	9.7 ± 4.3**

The MMS-E, Evans index, up-and-go time and OABSS before the lumbar puncture test were significantly different between the two groups; results in group N were in accordance with the criteria of the iNPH guideline (**$P < 0.01$)

P values less than 0.05 were considered significant. The correlations between various clinical indicators of iNPH and power spectral components were examined by regression analysis. $P < 0.05$ were considered significant.

Results

Comparison of the two groups

The MMS-E, the Evans index, up-and-go time, and the OABSS before the lumbar puncture test were significantly different between the two groups (*$P < 0.05$) (Table 2), with the values in group N fulfilling the iNPH guideline criteria.

In group N, there were no correlations between the change in the L/H ratio and the important diagnostic variables included in the iNPH diagnostic guidelines, such as the MMS-E, the Evans index, age, CSF opening pressure, up-and-go time before the lumbar puncture test, up-and-go time after the lumbar puncture test, and the percent of time and step improvement on the gait test. There were also no correlation between the HF value changes after the lumbar puncture tests and the important diagnostic variables in group N.

Comparison of 24-hour Holter ECG-related indicators between the two groups

Most changes could be observed on the recording of the second day; there were no significant differences in the recordings between the first and second days (data not shown). Thus, in the present study, clinical improvement and autonomic nervous system activity were assessed two days after the lumbar puncture.

There were no significant differences between the groups in the CVR-R, total heart rate, and L/H ratio. In contrast, the HF value (an indicator of parasympathetic activity) was significantly higher ($P = 0.031$) in group N (237.2 ± 76.2 ms^2) than in group C (190.3 ± 68.4 ms^2)(Figure 1).

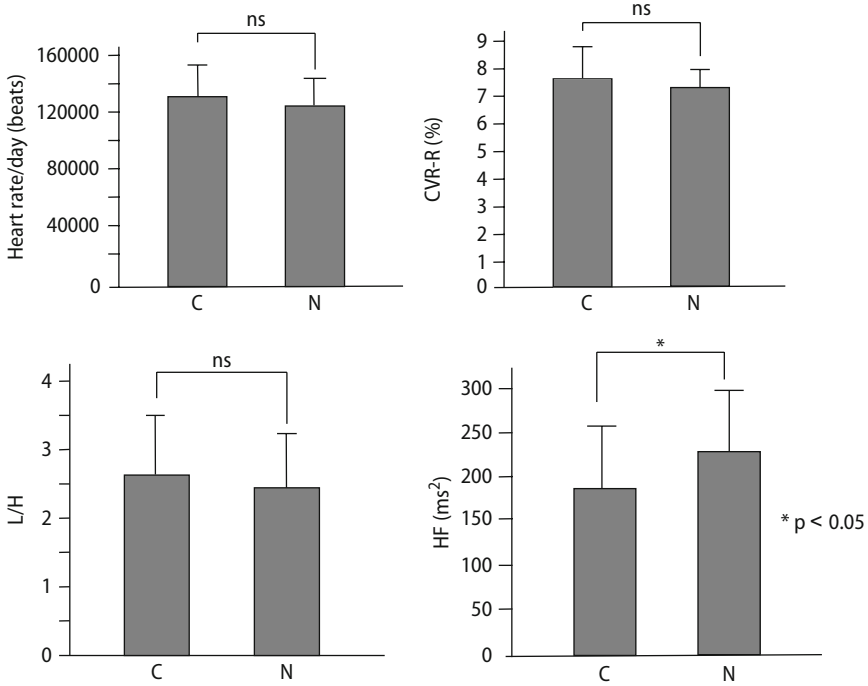

Fig. 1 Holter ECG parameters in iNPH patients (N) and control subjects (C). The HF value (ms^2) was significantly higher in group N (237.2 ± 76.2) than in group C (190.3 ± 68.4; $P < 0.05$). The heart rate, L/H ratio, and HF were taken from the Holter ECG recording and compared between the two groups. Data are given as means ± SD. ns indicates "not significant" and *indicates a significant intergroup difference. HF value (ms^2) of group N was increased. *$P < 0.05$ vs. controls (C)

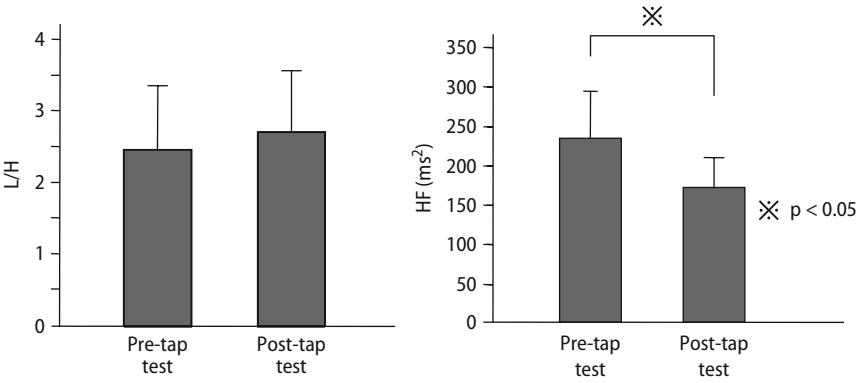

Fig. 2 Comparison of Holter ECG parameters before and after the lumbar puncture test (tap test) in the iNPH (N) group. The L/H ratio after the lumbar puncture test (tap test) was somewhat higher, but not significantly, than that before the tap test. In group N, the HF value 3 days after the lumbar puncture test was significantly lower (160.3 ± 38.1 ms^2), than that before the lumbar puncture test (paired t test, $^*P < 0.05$), confirming recovery of the parasympathetic rhythm to near normal levels. Data are given as means ± SD

Comparison of Holter ECG-related indicators before and after the lumbar puncture test in group N showed that the L/H ratio tended to be higher after the test (2.7 ± 0.9) than it was before the test (2.4 ± 1.1), although the difference was not significant. In contrast, in group N, the HF value (an indicator of parasympathetic activity) 2 days after the lumbar puncture test was significantly lower (160.3 ± 38.1 ms^2) than it was before the test (237.2 ± 76.2 ms^2; $P < 0.05$), confirming that the increased parasympathetic state before the test returned to near normal levels after CSF drainage (Figure 2). No remarkable changes in heart rate occurred during the observation period.

Correlation between 24-hour Holter ECG-related indicators (L/H ratio and HF value) and clinical diagnostic variables in group N

No correlations were observed between the L/H ratio and the important diagnostic variables include in the iNPH diagnostic guidelines, such as MMS-E, Evans index, age, CSF pressure, up-and-go time before the lumbar puncture test, up-and-go time after the lumbar puncture test, and the percent of time and step improvement on the gait test. Similarly, no correlations were found between the L/H ratio changes after the lumbar puncture test and the above diagnostic variables. Additionally, in group N, no correlations were observed between the HF value changes after the lumbar puncture test and the important diagnostic variables (data not shown).

Correlation of OABSS and cystometric evaluation with Holter ECG-related indicators in group N

A significant positive correlation was observed between the pre-lumbar puncture test HF value (a parasympathetic activity indicator) and the OABSS ($P < 0.05$, Figure 3). No significant correlation was found between the L/H ratio and the OABSS. No data on bladder capacity or detrusor pressure were obtained in group C due to ethical considerations; thus, no comparisons between the two groups could be made.

Eleven group N patients had an OABSS of 12 or higher; they were suspected of having overactive bladder, as reported previously, and underwent cystometric evaluation. No statistically significant correlation was observed between the HF value and bladder capacity (mean, 214 ml) or detrusor pressure (mean, 79 cmH_2O). However, patients with a higher HF value tended to have a lower bladder capacity. The correlation between bladder capacity or detrusor pressure and the HF value was also examined. Detrusor pressure showed a linear correlation ($P = 0.042$), while bladder capacity showed a mild tendency, similar to that of detrusor pressure, though it was not statistically significant (data not shown). On urological evaluation, 9 of these 11 patients were diagnosed as having overactive bladder with uninhibited detrusor contraction; oral anticholinergic medication resulted in symptomatic improvement.

The six patients who received shunts underwent 24-hour Holter ECG monitoring 1 month after shunt surgery, and the concordance of the ECG data immediately after the lumbar puncture test and after shunt surgery was examined. In 3 of the 6 patients, the post-shunt HF value was nearly concordant with the post-lumbar puncture test HF value. No postoperative Holter ECG monitoring was performed in the remaining three patients due to a lack of informed consent.

Discussion

Idiopathic normal pressure hydrocephalus, a syndrome that occurs in the elderly, was proposed in 1965 by Adams et al. [2]. It presents with gait dis-

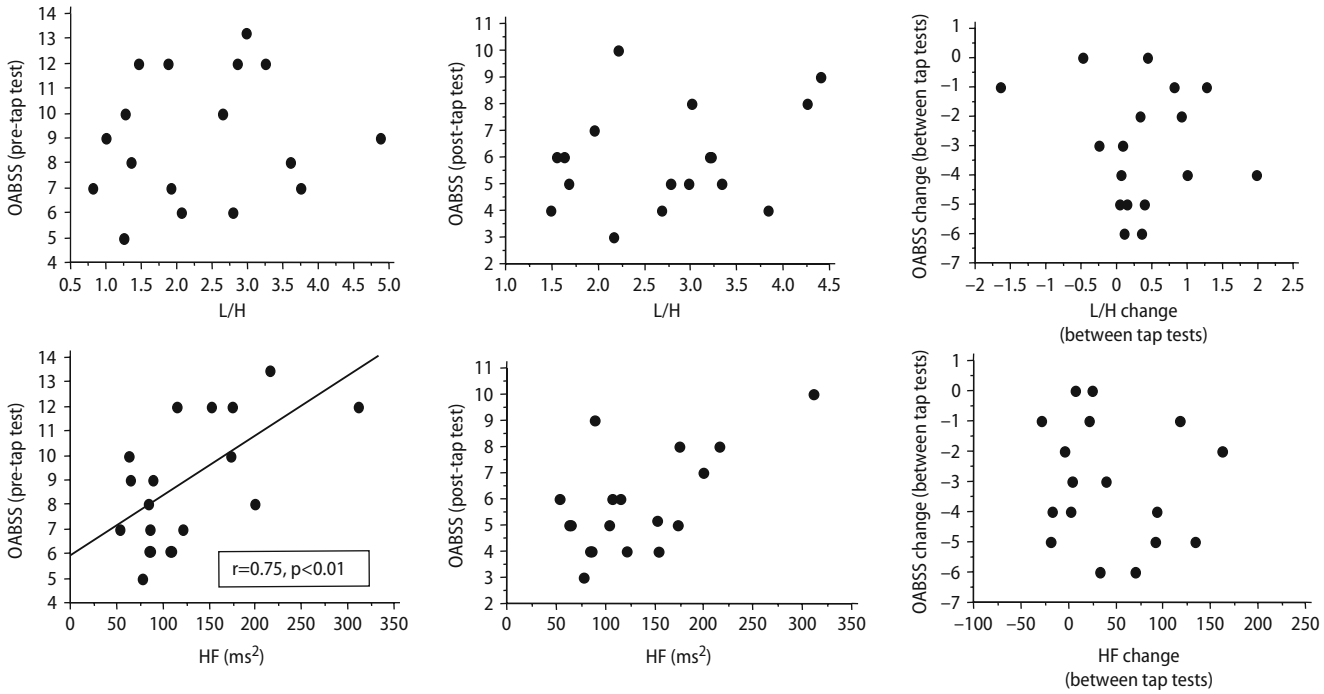

Fig. 3 Correlation between the overactive bladder symptom score (OABSS) and the Holter ECG parameters (L/H, HF) in group N. A significant positive correlation was observed between the OABSS and the pre-lumbar puncture (tap test) HF value (parasympathetic indicator) ($P < 0.01$)

turbance, dementia, urinary incontinence, and a normal CSF pressure in the presence of ventriculomegaly. However, since these symptoms are not specific to the elderly, the condition has tended to be overlooked. More than 40 years have been passed since iNPH was first reported, but iNPH is still preceded by the term idiopathic; there have been few epidemiological studies, and a firm elucidation of the pathogenesis of iNPH is still lacking. Although iNPH patients account for fewer dementia patients than those with Alzheimer's disease or cerebrovascular dementia, the prevalence of iNPH among dementia patients has been reported to be several percent, including those with these complications [10, 11]. The several-percent incidence is similar to that of important neurological diseases such as progressive supranuclear palsy and corticobasal degeneration; thus, iNPH occupies an important place among the dementias. However, since appropriate treatment, including shunt surgery, may cure iNPH, the condition deserves more attention than other, relatively rare, neurodegenerative diseases. It is also a socially important issue for rapidly aging countries to have a clear understanding of the pathogenesis of iNPH [1].

As with many other diseases, such as spinal cord diseases and multiple system atrophy, iNPH has attracted attention because of the presence of urinary disturbance, for which these patients have conventionally been treated [1, 27]. It is generally well known that autonomic dysfunction is involved in the development of urinary incontinence. However, in the absence of detailed studies limited to iNPH patients, neurogenic bladder associated with iNPH has not been well characterized, except that it has reportedly been observed in 77% of iNPH patients [21]. Ahlberg et al. [3] have reported that iNPH patients often present clinically with overactive bladder on intravesical pressure measurement, and this was ascribed to detrusor overactivity. However, to date, few studies have used simple, objective tests of urinary disturbance associated with iNPH, and the tests used in a few studies of iNPH patients have not been adequately validated; therefore, at this time, the presence or absence of subjective symptoms, such as urinary frequency and incontinence, inevitably remains the mainstay of screening for iNPH.

Therefore, the present study included, in addition to conventional residual urine volume measurement, the OABSS questionnaire which the patients completed themselves. This questionnaire was useful as a simple method of evaluation and to examine how it reflected the pathogenesis. The relationship between autonomic function assessment using Holter electrocardiography and the effects of an oral anticholinergic drug on the neurogenic bladder of iNPH were also examined.

In contrast to the normal subjects, the iNPH patients in the present study showed evidence of an autonomic imbalance with high HF values, implying potentially increased parasympathetic activity. It was also found that the HF values were correlated with the OABSS, which is used as a screening test for overactive bladder; this confirms the usefulness of the OABSS in screening for iNPH. Moreover, interestingly, the increased parasympathetic state in iNPH tended to return to near normal levels after the lumbar puncture test or shunt surgery. On urological examination, nine patients with urinary incontinence who required treatment showed an overactive bladder pattern with uninhibited detrusor contraction. The administration of an anticholinergic drug (oxybutynin or propiverine) (acting on the parasympathetic nerves) to these patients resulted in symptomatic improvement, suggesting that these patients had functional damage to the cholinergic nervous system.

The basal ganglia and the cingulate gyrus (frontal urination center) on the medial surface of the frontal lobe have been reported to be urination centers and control urination, primarily tonically [5, 32]. These reports suggest that supranuclear damage to the pelvic plexus (parasympathetic nerve plexus) innervating the detrusor muscles of the bladder and damage to the medial frontal lobe (the anterior part of the cingulate gyrus and the upper part of the superior frontal gyrus) or its descending tract may play important roles in the pathogenesis of iNPH. In the present study, cerebral blood flow scintigraphy showing decreased frontal lobe function and higher brain function tests (word fluency test and trail making test) were not directly correlated with autonomic dysfunction-related urinary disturbance (data not shown). Further detailed studies, for example, on brain function-metabolism on PET, may effectively locate the main pathology of the autonomic disturbance in iNPH. In addition, pathological studies have reported neuronal loss and gliosis in the regions considered to be the higher centers for the lower urinary tract, that is, in the cortex, including the frontal lobe and around the lateral ventricles [9, 19]; therefore, further detailed studies of these brain functions require such pathological examinations.

It is noteworthy that the iNPH patients in the present study had high HF values, which may reflect parasympathetic dysfunction. Therefore, when iNPH patients are treated with various drugs acting on the autonomic nervous system, including β-blockers as antihypertensive drugs and anticholinergics, such as antidepressants and antipsychotic drugs, the potential for worsening of the iNPH-related autonomic disturbance and primary disease-related symptoms must be considered.

In summary, iNPH patients were shown to have increased parasympathetic activity that may be corrected by the lumbar puncture test and shunt surgery. Further detailed studies, such as pharmacological stress tests or [^{123}I]meta-iodobenzylguanidine scintigraphy, are needed to determine the possible usefulness of these changes in the diagnosis of iNPH.

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