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Cerebral perfusion pattern of idiopathic normal pressure hydrocephalus studied by SPECT and statistical brain mapping

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Objectives: To investigate the specific pattern of cerebral blood flow (CBF) in subjects with idiopathic normal pressure hydrocephalus (iNPH) using voxel-based analysis. ***Methods:*** *N*-isopropyl-*p*-[^{123}I]iodoamphetamine (IMP) single photon emission computed tomography (SPECT) images were performed in 30 iNPH patients, who met probable iNPH criteria, 30 Alzheimer disease (AD) patients and 15 normal control (NC) subjects. Inter-group comparisons between iNPH patients and NC subjects and between AD patients and NC subjects were performed using three-dimensional stereotactic surface projection (3D-SSP) analysis. Individual 3D-SSP images of the iNPH patients were assessed by visual inspection. ***Results:*** On the Z-score maps, areas of relative hypoperfusion were recognized around the corpus callosum in all 30 iNPH patients, as well as in the Sylvian fissure regions in 19 of 30 iNPH patients which included artifacts by dilated ventricles and the Sylvian fissures. Ten frontal dominant, eight parietotemporal dominant, and 12 diffuse hypoperfusion types were demonstrated. Inter-group comparison between iNPH and NC subjects showed relative hypoperfusion in the frontal and parietotemporal areas and severe hypoperfusion around the corpus callosum and Sylvian fissure regions, while parietotemporal and posterior cingulate CBF reduction was demonstrated between the AD and NC groups. ***Conclusion:*** Voxel-based analysis showed a characteristic pattern of regional CBF reduction with frontal dominant or diffuse cerebral hypoperfusion accompanying severe hypoperfusion around the corpus callosum and Sylvian fissures with artifacts.

Key words: idiopathic normal pressure hydrocephalus, cerebral blood flow, single photon emission computed tomography (SPECT), dementia, Alzheimer disease

INTRODUCTION

NORMAL PRESSURE HYDROCEPHALUS (NPH) was first described by Adams et al. in 1965.[1] This syndrome is characterized by gait disturbance, mental deterioration and urinary incontinence, in association with normal cerebrospinal fluid (CSF) pressure.[2] The symptoms are reversible with a ventricular shunting operation.[1,3] NPH is divided into two subcategories: idiopathic NPH (iNPH) and secondary NPH. Secondary NPH has a known cause, such as subarachnoid hemorrhage, meningitis, cranial trauma and intracranial surgery.

The pattern of regional cerebral blood flow (CBF) in NPH has been investigated by means of positron emission tomography (PET) and single photon computed tomography (SPECT). Although frontal CBF reduction has been emphasized in the majority of NPH cases, no report has been able to demonstrate a typical CBF pattern. Heterogeneity in the reduction of CBF has also been reported.[4–6] This may be because while many previous reports have described diagnostic criteria for NPH, there has been no

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consensus regarding the classification of the disease. Therefore, the inclusion of iNPH and secondary NPH in previous reports has led to heterogeneous CBF patterns. In April 2004, the Guideline Committee for Idiopathic Normal Pressure Hydrocephalus of the Japanese Society of Normal Pressure Hydrocephalus proposed Clinical Guidelines for Idiopathic Normal Pressure Hydrocephalus, for clinical diagnosis and treatment.[7] According to these guidelines, iNPH is divided into three subcategories: possible iNPH, probable iNPH and definite iNPH. In this study, we investigated probable iNPH patients based on these criteria.

Recently, voxel-wise comparison of PET and SPECT brain images has been used as a powerful analysis tool to elucidate disease-associated functional changes in Alzheimer's disease (AD), other degenerative dementias and cerebrovascular disease.[8–10] In order to elucidate the distribution pattern of CBF in iNPH diagnosed as a homogeneous entity, excluding secondary NPH, we performed *N*-isopropyl-*p*-[^{123}I]iodoamphetamine (IMP) SPECT in patients with probable iNPH and analyzed it by means of three dimensional stereotactic surface projections (3D-SSP).[11]

SUBJECTS AND METHODS

Subjects

Thirty patients with iNPH were retrospectively selected from those admitted to our hospital for examination and treatment consecutively. They underwent IMP SPECT before a spinal tap test and fulfilled the criteria for diagnosis of probable iNPH according to the Clinical Guidelines for Idiopathic Normal Pressure Hydrocephalus[7] (Table 1).

The diagnostic criteria of possible iNPH are: (a) more than 60 years old; (b) having one or more symptoms of gait disturbance, dementia and urinary incontinence; (c) ventricular dilatation (Evans Index > 0.3) and narrow CSF space in the superior convexity[12]; (d) a CSF pressure lower than 20 cm H_2O with a normal CSF cell count and protein level; (e) having no other diseases that may account for the symptoms; and (f) no other previous illness that causes ventricular dilatation. Probable iNPH is diagnosed if the spinal tap test is positive with possible iNPH[13] and definite iNPH is diagnosed if shunt operation is effective in improving the symptoms of a patient with probable iNPH.

The 30 patients who met the criteria of probable iNPH consisted of 14 men and 16 women. A spinal tap test was performed and symptomatic improvement was confirmed in all patients. The mean age of the iNPH group was 76.8 ± 5.3 years and the mean MMSE score was 19.6 ± 5.0. All patients showed gait disturbance, 27 patients had cognitive disorders and 19 patients had urinary incontinence. Twenty-one of the 30 patients underwent shunt operation and 19 of them were verified as having definite iNPH. The remaining two patients had shunt dysfunction and a subdural hematoma.

These 30 probable iNPH patients were then divided into two groups, with and without urinary incontinence. The urinary incontinence group consisted of 19 patients, 10 men and 9 women, with a mean age of 78.1 ± 4.6 years and a mean MMSE score of 18.3 ± 4.9. The group without urinary incontinence consisted of 11 patients, 4 men and 7 women, with a mean age of 74.6 ± 5.9 years and a mean MMSE score of 21.7 ± 4.7. We also wanted to focus on other features of the other clinical symptoms of NPH; however, since the numbers of patients without gait disturbance or dementia were two small, we could not classify other subgroups.

Thirty patients with probable AD were selected from

Table 1 Criteria for the diagnosis of iNPH (Clinical Guidelines for Idiopathic Normal Pressure Hydrocephalus, Guideline Committee for Idiopathic Normal Pressure Hydrocephalus, Japanese Society of Normal Pressure Hydrocephalus)

Possible iNPH
(a) More than 60 years old
(b) Having one or more symptoms of gait disturbance, dementia and urinary incontinence
(c) Ventricular dilatation (Evans Index > 0.3) and narrow CSF space in the superior convexity
(d) CSF pressure lower than 20 cm H_2O with normal properties of CSF cell counts and protein level
(e) Having no other diseases that may account for symptoms
(f) No other previous illness that causes ventricular dilatation
Probable iNPH
Positive spinal tap test with possible iNPH
Definite iNPH
Improvement of symptoms after CSF shunt operation

Table 2 CBF reduction patterns in iNPH and AD patients. Data show the numbers of CBF reduction types

Type	iNPH	AD
N	0	0
F	0	0
TP	0	0
FD	10	3
TPD	8	21
D	12	6
OR	0	0
Sylvian fissure	19	2
Pericallosal area	30	6

F: Reduction in frontal cortex only; TP: reductions in temporal and/or parietal and/or occipital cortex only; FD: reduction in the frontal dominant cortex with additional reductions; TPD: reductions in temporal and/or parietal dominant cortex with additional reductions; D: diffuse cortex reductions or reductions in both frontal and temporoparietal cortices are almost equivalent; OR: other regional reductions.

Fig. 1

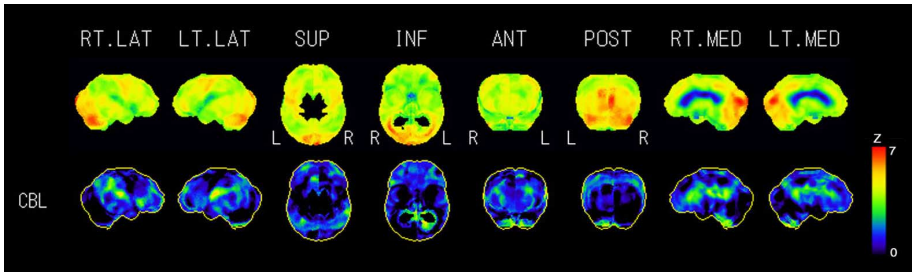

Fig. 2

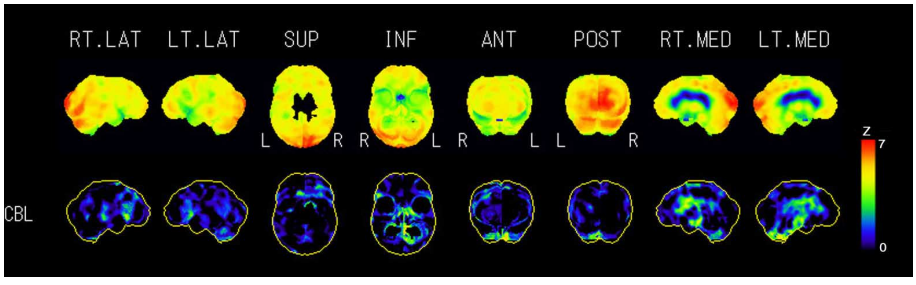

Fig. 1 Representative case showing diffuse relative CBF reduction (type D) using 3D-SSP and the Z score map. This is the case of a 74-year-old female with iNPH. She had gait disturbance, dementia (MMSE = 19) and urinary incontinence. The 3D-SSP and the Z score map demonstrate diffuse perfusional reduction and an especially severe decrease in the peri-callosal area and Sylvian fissures.

Fig. 2 Representative case of frontal dominant relative CBF reduction (type FD) shown by the 3D-SSP and the Z score map. This is the case of an 83-year-old female with iNPH. She had gait disturbance and urinary incontinence but no cognitive disorders (MMSE = 29). The 3D-SSP and the Z score map demonstrate frontal dominant relative CBF reduction and a severe decrease in the peri-callosal area.

Fig. 3 Z score map of significantly decreased relative CBF area in the iNPH group compared with the normal control group. In the frontal, parietal and temporal lobes, Sylvian fissure and peri-callosal areas, the relative CBF of iNPH is significantly decreased ($z > 2.0$) (*upper row*). Z score map of significantly decreased relative CBF area in the Alzheimer group compared with the normal control group (*middle row*). Z score map of significantly decreased relative CBF area in the iNPH group compared with the Alzheimer group. In Sylvian fissure and peri-callosal areas, the relative CBF of iNPH is significantly decreased ($z > 2.0$) compared with that of Alzheimer (*lower row*).

Fig. 3

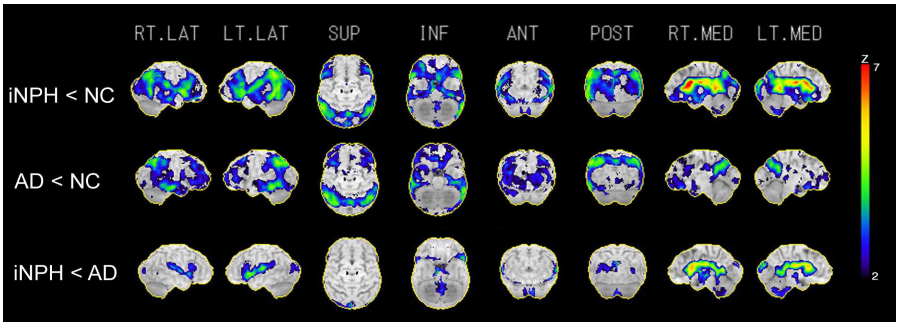

Fig. 4

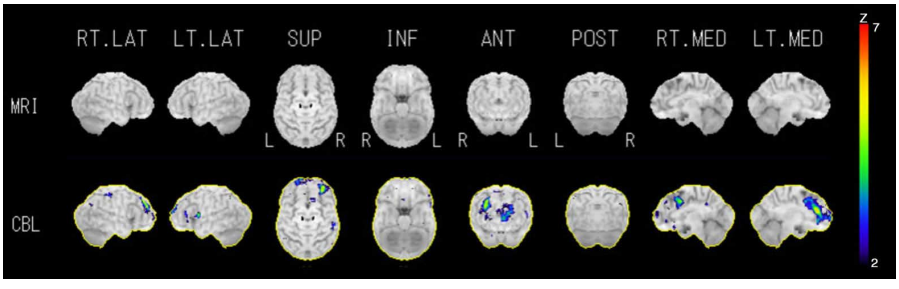

Fig. 5

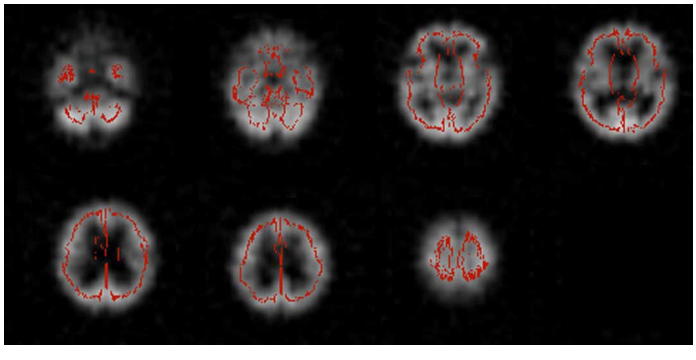

Fig. 4 Z score map of the significantly decreased relative CBF area in the iNPH group with urinary incontinence compared with the group without. In the medial and lateral frontal lobe, the relative CBF is significantly decreased ($z > 2.0$).

Fig. 5 Peak pixels extracted by 3D-SSP were overlaid on the original SPECT of a patient with iNPH.

our institute's Dementia Registry. Diagnosis of probable AD was based on the criteria from the National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association (NINCDS/ADRDA). The patients with iNPH and AD were matched for age and MMSE score. The mean age of the AD group was 76.9 ± 5.2 years and the mean MMSE score was 19.6 ± 4.5. None of the patients in the AD group had gait disturbance or urinary incontinence.

The control group consisted of 15 neurologically and cognitively normal controls who complained of headache or vertigo and requested a SPECT examination. They had no abnormal findings on SPECT and MRI or CT, except for age related changes. This group consisted of 7 men and 8 women with a mean age of 69.2 ± 9.9 years.

SPECT procedure

The imaging scan was started in the resting state, 15 minutes after the injection of 111 MBq (3 mCi) of ^{123}I-IMP. All SPECT studies were performed in a rotating dual-headed gamma camera (GAMMA View SPECT 2000 H, Hitachi, Tokyo, Japan) with a LEGP collimator. Projection data were obtained at 15 sec/step × 64 view (2 rotations × 360°). A Ramachandran filter was used for SPECT image reconstruction and attenuation correction was performed using Chang's method.

Data analysis with 3D-SSP

All the SPECT image data were transferred to a personal computer and converted to binary format. Data analysis was performed with 3D-SSP.[11,14,15] The relative CBF in each voxel was calculated by normalizing each voxel activity to the cerebellar activity. In this study, we used a freeware "iSSP" (Nihon Medi-Physics, Nishinomiya, Hyogo, Japan) in which a 3D-SSP program with a graphic user interface was developed for clinical use. The Z-score ([normal mean – individual value]/normal standard deviation) image of each subject was produced.

Visual inspection was performed to detect regional CBF reduced areas in iNPH patients on the individual Z score maps. CBF images were classified by one experienced nuclear medicine physician into the following perfusion patterns based on a modified SPECT diagnosis scheme, originally developed by Holman et al.[16] and Ishii et al.[17]:

- N: normal.
- F: reduction in the frontal cortex only.
- TP: reductions in temporal and/or parietal and/or occipital cortex only.
- FD: reduction in the frontal dominant cortex with additional reductions.
- TPD: reductions in temporal and/or parietal dominant cortex with additional reductions.
- D: diffuse cortex reductions or almost equivalent reductions in both frontal and temporoparietal cortices.
- OR: other regional reductions.

Because CBF reductions in the Sylvian fissure regions and pericallosal regions were marked in iNPH patients, these areas were evaluated separately.

Next, group comparisons of the CBF image between iNPH and control groups, between AD and control groups, between iNPH and AD groups and between iNPH groups with and without urinary incontinence were performed with a 2-sample Student's t test on a pixel-by-pixel basis. Obtained t values were converted to Z values using significance integral transformation for comparison and Z-score maps were obtained. In this comparative study, Z-scores over 2.0 were considered significant between control and iNPH subjects and between patients with and without urinary continence. There were no significant differences in mean age or MMSE score between the groups with and without urinary incontinence.

In order to evaluate how much the dilatation of the ventricle system and the Sylvian fissure affected the individual statistical image, we used a function of the software "iNeurostat" (Nihon Medi-Physics, Nishinomiya, Hyogo, Japan), which indicates the extracted peak count pixels on the original axial SPECT images through the process of 3D-SSP for peak count extraction. By means of visual inspection of each individual image, we checked whether the inverse dotted line, which indicates pixels extracted by 3D-SSP, existed exactly on the cortices or not.

RESULTS

Individual Z-score maps

Severely reduced relative CBF (Z score more than 4) areas were observed around the corpus callosum in 30/30 cases (100%), and in the Sylvian fissure area in 19/30 iNPH patients (63%), which included artifacts referred to dilatations of the ventricles and Sylvian fissures. A mild to moderately reduced relative CBF (Z score more than 2 to less than 4) area in the cerebrum was seen in all iNPH patients: 10 cases were type "FD", 8 cases were type "TPD" and 12 cases were type "D". None of the subjects showed types "N", "F", "TP", or "OR" (Table 2). Figure 1 shows a case with diffuse relative CBF reduction (type D) and severely decreased pericallosal area and Sylvian fissures. Another case showing frontal dominant relative CBF reduction (type FD) is shown in Figure 2. In patients with AD, severely reduced relative CBF areas were observed around the corpus callosum in 6/30 cases, and in the Sylvian fissure in 2/30 subjects. Three cases were type "FD", 21 cases type "TPD" and 6 cases type "D" in AD patients (Table 2).

Group comparison

The two-sample t test revealed relative hypoperfusion areas in the frontal and parietotemporal lobes and severe hypoperfusion areas in the peri-corpus callosum and the

Sylvian fissure in the iNPH group compared with the control group (Fig. 3, *upper row*). However, parieto-temporal and posterior cingulate hypoperfusion and minimal frontal hypoperfusion were demonstrated in the AD group compared with the control group. Hypoperfusion areas in the pericallosal and the Sylvian fissure regions were not shown in the AD group compared with the control group (Fig. 3, *middle row*). Direct comparison between iNPH and AD groups showed significant hypoperfusion areas in the peri-corpus callosum and the Sylvian fissure in the iNPH group (Fig. 3, *lower row*).

As shown in Figure 4, the medial and lateral frontal CBF was lower in the group with urinary incontinence than in the group without.

Inverse evaluation

Dotted lines were seen on the lateral ventricles in all 30 subjects, and on the Sylvian fissures in 19 subjects. Figure 5 demonstrates a case that had an extracted peak pixel of the original SPECT image from both lateral ventricles and Sylvian fissures.

DISCUSSION

We demonstrated regional CBF patterns in iNPH using uniformed diagnostic criteria and voxel-based statistical parametric mappings. This study is the first in which 3D-SSP voxel-based analysis was applied to iNPH to investigate regional CBF reductions. Some previous reports have described regional CBF in iNPH[4–6,18–20]; however, there have been no specific findings regarding the diagnostic value of iNPH. Momjian et al. investigated the white matter regional cerebral blood flow in NPH using $H_2{}^{15}O$ PET and reported that it is reduced with an abnormal gradient from the lateral ventricles towards the subcortical white matter,[18] though they did not refer to the cortical blood flow. Mataro et al. studied the cerebral blood flow changes after surgery in a group of iNPH patients by using a voxel-wise comparison technique (SPM) and found that frontal and parietal CBF was improved after surgery, though they did not show a baseline CBF pattern.[21] Dumarey et al. also studied CBF changes after shunt operation in NPH patients, including both idiopathic and secondary NPH,[22] but, similarly, this study did not refer to the baseline CBF of the iNPH group, compared with the normal control group. Another report demonstrated a change in CBF after spinal tap test in NPH, but did not report the baseline CBF.[23]

In this study, we first revised the criteria of "iNPH" using the Clinical Guidelines for Idiopathic Normal Pressure Hydrocephalus as described above,[7] in order to exclude secondary NPH and ambiguous iNPH cases. These guidelines regard spinal tap test[13] and MRI findings as important.[7] Then, we found diffuse or frontal dominant CBF reduction in 22 of 30 probable iNPH patients (73%) and severe relative CBF reduction in the Sylvian fissure and peri-callosal area. The majority of probable iNPH cases in this study showed diffuse or frontal dominant CBF reduction, which supports previous findings.[4–6] In addition, our voxel-wise study is the first to demonstrate characteristic findings of severe relative CBF reductions in the Sylvian fissure and peri-callosal areas in probable iNPH patients. We know that these CBF reductions in the Sylvian fissure and pericallosal areas do not reflect pure CBF reductions, but mostly dilatation of the Sylvian fissure and lateral ventricle systems, as shown by the inverse plotting of extracted peak pixels in the original SPECT image. This phenomenon was verified in our study using the inverse technique. The warping technique of 3D-SSP could not match the cortices around the dilated ventricles and Sylvian systems in the iNPH brain to the standard brain. Although these findings are due to artifacts, they seldom appear in any other diseased brains except for severe atrophy, such as in advanced AD.

3D-SSP was designed for functional imaging to obtain the anatomical information and automatically adjust for individual differences in brain atrophy, distortion and rotation into a standardized brain model. Some previous reports verified the accuracy of anatomical standardization using 3D-SSP with normal subjects[24] and atrophied brains.[25] Non-distorted brains and moderately deformed brains may be standardized appropriately; however, functional images occasionally cannot be standardized appropriately, particularly when the subject has excessively severe distortion or atrophy, such as major cerebral infarction or brain atrophy due to AD. Ventricular dilatation is usually recognized in iNPH patients. The relative hypoperfusion area in the corpus callosum explains the ventricular dilatation. The relative hypoperfusion area in the Sylvian fissure can also be explained by the dilatation of the CSF space.

In addition, Z score map of comparison between the iNPH group and the normal control group also showed reduced posterior cingulated and precuneus perfusion (Fig. 3). This may suggest that a complication of AD exists in some of the iNPH patients, or this finding may be one of the features of iNPH perfusion reduction.

Our study demonstrated a more decreased medial and lateral frontal CBF in patients with urinary incontinence than in those without. A previous report described the relationship of urinary incontinence and the relative hypoperfusion area in the medial frontal lobe.[26] The area that we showed to have a more decreased CBF area in the urinary incontinence group matched the area shown as the region particularly important for the control of micturition.[27] Griffiths et al.[28] reported that genuine urge incontinence with reduced bladder filling sensation was associated with a global decrease of the CBF and, more specifically, with hypoperfusion of the frontal areas of the brain, especially on the right, and suggested that their findings are consistent with PET scan observations, which showed that areas in the right anterior cingulate gyrus and

right inferior frontal gyrus were involved in voluntary voiding in normal males.[29] Our finding supports that these medial and lateral frontal hypoperfusions also concern urinary incontinence in iNPH subjects. Although their reports emphasize the right side, our results demonstrated a decrease in both sides. This may be due to various complex pathophysiologies of the iNPH brain.

A limitation of our study was that the NC groups were not age-matched with the iNPH and AD groups. In normal healthy people, blood flow does not decrease with age in the parietal and occipital lobe; however, frontal blood flow significantly decreases with increasing age. In this study there was no problem in evaluating parietal and occipital blood flow. Effect of frontal perfusion decrease with aging cannot be completely excluded; however, in differentiating iNPH from AD there is no problem because hypoperfusion areas in the peri-corpus callosum and the Sylvian fissure is a characteristic finding of iNPH as compared with AD (Fig. 3).

CONCLUSION

The voxel-based statistical mapping method revealed an iNPH CBF reduction pattern. Diffuse or frontal dominant CBF reduction was shown and, additionally, severe relative hypoperfusion around the corpus callosum and Sylvian fissures was demonstrated, which probably reflects dilatation of the ventricle systems and Sylvian fissures and may represent characteristic patterns of iNPH.

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