Association between the Onset of Idiopathic Normal Pressure Hydrocephalus Symptoms and Reduced Default Mode Network Connectivity

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Keywords
iNPH (idiopathic normal pressure hydrocephalus) · DMN (default mode network) · DESH · AVIM · FDG-PET/CT · Cerebral glucose metabolism

Abstract
Objective: The aim was to examine the association between connectivity changes in the default mode network (DMN) and the progression of idiopathic normal pressure hydrocephalus (iNPH).

Methods: We retrospectively recruited cases of preclinical and clinical iNPH from 2,196 patients who had received whole-body 18F-fluorodeoxyglucose-positron emission tomography/computed tomography (FDG-PET/CT) scanning. We included 31 cases with asymptomatic ventriculomegaly with features of iNPH on MRI (AVIM; reported as preclinical iNPH) and 12 with iNPH. We performed a voxel-based analysis of the brain FDG-PET images of the AVIM and iNPH groups as well as for each background-matched normal control (NC) group, using Statistical Parametric Mapping 12. Volume of interest (VOI)-based analysis was also performed. We set the VOI as the region from the precuneus to the posterior cingulate cortices (PCC), and compared the mean regional standardized uptake value ratio (SUVR) between the AVIM and iNPH group FDG-PET/CT images and each corresponding NC group.

Results: The voxel-based analysis showed a greater decreased FDG uptake in the PCC in the iNPH group than in the AVIM group. The VOI-based analysis revealed no significant difference in the mean SUVR of the AVIM group and the corresponding NC group, but that of the iNPH group was significantly lower than that of its corresponding NC group.

Conclusions: DMN connectivity was reduced in the clinical iNPH group but not in the preclinical group. These data suggest that alterations in the functional connectivity of the DMN are related to the onset of iNPH symptoms.

Introduction

Idiopathic normal pressure hydrocephalus (iNPH) is a syndrome that often develops in older people and is characterized by a classic triad of symptoms: cognitive impairment, gait disturbance, and urinary incontinence, accompanied by ventricular enlargement [1–3]. The prevalence of iNPH in the older population is around 1% [4–6], and it is treatable with a simple surgery called ce-
rebrospinal fluid (CSF) shunting. However, both the pathophysiological mechanisms and the brain regions related to the classic triad remain unclear.

It has been reported that iNPH has a characteristic radiological brain feature known as disproportionately enlarged subarachnoid-space hydrocephalus (DESH) [7, 2]; DESH findings differentiate it from other types of hydrocephalus (secondary and adult-onset congenital hydrocephalus) [8]. The DESH findings consist of ventriculomegaly, tightness of the medial subarachnoid spaces with/without tight high convexity sulci (TMC), and enlarged Sylvian fissures (ESF). The presence of these findings is reported to be a good predictor of favorable outcomes following shunt surgery [7, 9–11]. Thus, because the disease-specific deformation of the brain can be used to predict treatment outcome, DESH findings may be related to the as-yet-unknown pathophysiology of iNPH. Iseki et al. [4] reported that the appearance of DESH findings precedes the onset of symptoms. They described a group of asymptomatic cases with complete DESH findings as being in the preclinical stage of iNPH, which they termed asymptomatic ventriculomegaly with features of iNPH on MRI (AVIM). We believe that research into the early stages of iNPH, including AVIM, will provide information about the pathophysiology of the disease.

In a 2016 study on the pathophysiology of iNPH, reduced default mode network (DMN) connectivity was reported in patients with this disorder [12]. The DMN is a large-scale brain network that interacts with various other brain regions and is considerably active when the brain is at rest [13]. The clinical utility of this network is currently a popular topic in neuroscientific research because it has been implicated in a number of neurological and neuro-psychiatric diseases (including Alzheimer’s disease (AD), Parkinson’s disease (PD), and depression) over the past decade [14–16]. If there is a link between the pathogenesis of iNPH and DMN connectivity changes, it will not only be useful for future research into iNPH and DMN but may also provide a novel approach for iNPH diagnosis.

The aim of this study was to investigate the association between DMN connectivity changes and the development of iNPH. Here, focusing on the progression from AVIM to iNPH, we evaluated alterations in cerebral glucose metabolism in regions related to the DMN using 18F-fluorodeoxyglucose-positron emission tomography/computed tomography (FDG-PET/CT).

### Materials and Methods

**Subjects**

We retrospectively reviewed the medical records of brain imaging and clinical features in all patients >50 years of age who underwent whole-body FDG-PET/CT scanning at Kindai University Hospital between 1 May 2017 and 31 April 2018. A total of 2,196 patients were enrolled in the study. From this cohort, 46 cases with AVIM or iNPH were identified. However, 1 AVIM case was excluded from the imaging data analysis because of severe ventriculomegaly in the volume of interest (VOI) used in the analysis. Furthermore, 2 patients with iNPH had already received shunt surgery prior to the FDG-PET/CT scanning and were thus also excluded. We analyzed the FDG-PET/CT data from the remaining 43 patients (31 with AVIM and 12 with iNPH). The demographic data are shown in Table 1.

Over 90% of these 43 cases had malignancies, because the main purpose of the FDG-PET/CT was for cancer staging and the detection of recurrence or metastases. In the iNPH group, all cases had gait disturbance, while 66.7% also had cognitive impairment and 41.7% had urinary incontinence.

<table>
<thead>
<tr>
<th>Age, years</th>
<th>NC for AVIM (n=31)</th>
<th>AVIM (n=31)</th>
<th>NC for iNPH (n=24)</th>
<th>iNPH (n=12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male/female</td>
<td>76.4±5.3</td>
<td>76.4±5.3</td>
<td>78.8±6.0</td>
<td>78.8±6.0</td>
</tr>
<tr>
<td>Cases with malignancy</td>
<td>29 (93.5)</td>
<td>29 (93.5)</td>
<td>22 (91.6)</td>
<td>11 (91.6)</td>
</tr>
<tr>
<td>Evans index</td>
<td>0.276±0.027</td>
<td>0.338±0.026</td>
<td>0.277±0.018</td>
<td>0.349±0.021</td>
</tr>
<tr>
<td>Cases with DESH findings</td>
<td>0 (0)</td>
<td>31 (100.0)</td>
<td>0 (0)</td>
<td>12 (100.0)</td>
</tr>
<tr>
<td>Cases with gait disturbance</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>12 (100.0)</td>
</tr>
<tr>
<td>Cases with cognitive impairment</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>8 (66.7)</td>
</tr>
<tr>
<td>Cases with urinary incontinence</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>5 (41.7)</td>
</tr>
</tbody>
</table>

Values express n, n (%), or mean ± SD. NC, normal control; AVIM, asymptomatic ventriculomegaly with features of iNPH on MRI; iNPH, idiopathic normal pressure hydrocephalus; DESH, disproportionately enlarged subarachnoid space hydrocephalus.
Reduced DMN Connectivity Appears at the Onset of iNPHs Symptoms

To compare the FDG-PET/CT data between the pathogenetic groups (AVIM and iNPH groups), we recruited a separate normal control (NC) for each, because they each had a different background. For the 2 NC groups, 55 cases were randomly selected from the cohort of 2,196 subjects, and the age, sex, and presence/absence of malignancies were matched to the cases with AVIM and iNPH. Accordingly, the 2 NC groups were also demographically different (Table 1).

All 98 cases were checked for comorbidities, i.e., other neurodegenerative and/or neuropsychiatric diseases. Based on their electronic medical records (EMR), there were no comorbid diseases in any of the 98 cases according to their past history, present illness, or symptoms.

Diagnosis of AVIM and iNPH
The selection of cases with AVIM and iNPH from the cohort of 2,196 subjects was performed according to the DESH findings on brain CT images from FDG-PET/CT data. In clinical practice, there are also many iNPH patients without DESH findings, and retrospective studies have reported a greater prevalence of non-DESH iNPH patients than DESH patients in some cohorts [17, 18]. However, we adopted DESH findings as the hallmark feature of AVIM and iNPH patients in order to separate these pathogenetic groups from the other groups in the study, because DESH is a radiological feature that could be clearly identified within the retrospective design of our investigation. We defined DESH-positive cases as those with all 3 findings: ventriculomegaly (an Evans index > 0.3), TMC, and ESF. The survey was repeated twice to prevent misdiagnosis, and 53 patients with DESH were recruited. Subsequently, we classified cases with DESH into AVIM and iNPH according to the presence or absence of iNPH symptoms from EMR data. Asymptomatic cases with DESH findings were classified as AVIM, while cases with DESH findings and at least 1 of the classic triad of iNPH symptoms were classified as iNPH (Fig. 1). However, in cases where the presence or absence of symptoms could not be determined because of a lack of clinical information or the influence of comorbidities, no classification of AVIM or iNPH was made, and these cases were classified as unknown-symptom DESH. As a result of this classification, 32 cases with AVIM, 14 cases with iNPH, and 8 cases with unknown-symptom DESH were diagnosed from the 54 cases with DESH findings. The details and results of this classification have been previously reported [19].

FDG-PET/CT Acquisition
After fasting for at least 4 h, each patient was infused with FDG (adjusted for body weight) intravenously for > 2 min. After an uptake phase of 60 min, PET/CT imaging was performed on a Discovery PET/CT 710 (GE Healthcare UK Ltd., Chalfont St. Giles, UK). CT images were acquired in helical CT mode. Helical CT acquisition was performed using a tube voltage of 120 kVp, an automated tube current with a noise index of 23, a rotation time of 0.5 s, a detector configuration of 16 × 1.25 mm, a pitch factor of 1.375 for helical CT, a slice thickness of 3.75 mm, and a display field-of-view of 500 mm. CT data were used for attenuation correction. All PET data were acquired in a 3-dimensional time-of-flight (TOF) mode. The acquisition time per bed position was 2 min.

Voxel-Based Analysis
First, the FDG-PET data were converted to a NIfTI format for processing on MRIcron software (University of South Carolina, Columbia, SC, USA).

The voxel-based analysis was performed using Statistical Parametric Mapping 12 (SPM12; Institute of Neurology, University College London, London, UK) implemented on MATLAB R2013b (The MathWorks Inc., Natick, MA, USA). All FDG-PET data were spatially normalized and smoothed using SPM12. A two-sample t test in SPM12 was used for voxel-wise comparisons between iNPH subjects and age- and sex-matched NC subjects, and between AVIM subjects and age- and sex-matched NC subjects. The cerebellar FDG uptakes were used as covariates. The significance threshold was set to p < 0.05, corrected for family-wise error (FWE) due to multiple comparisons, and the voxel extent threshold was set to 100.
**VOI-Based Analysis**

VOIs were drawn of both the DMN-related region (from the precuneus to the posterior cingulate cortex (PCC) and the cerebellum on spatially normalized FDG-PET images. Both VOIs were drawn avoiding DESH-related brain and CSF space deformations. Using these VOIs, the mean standardized uptake value ratio (SUVR) of the precuneus to PCC region, which was calculated by referring to the cerebellar cortex, was calculated for each subject using MRIcron. The mean SUVRs were determined for both the AVIM and iNPH groups, and these values were compared against each NC group.

**Statistical Analysis**

SUVR values are presented as the mean ± standard deviation (SD). The mean SUVRs of both the AVIM group and the iNPH group were compared with each NC group using a \( t \) test. All statistical analyses were performed using statistical software (R v3.4.1). The threshold for statistical significance was set at \( p < 0.001 \).

**Results**

**Voxel-Based Analysis**

Compared with the NC group, most of the cases with iNPH in this study had decreased FDG uptake on FDG-PET/CT images in the precuneus to PCC region. Images from a representative case are shown in Figure 3. FDG uptake at the medial parietal cortices was higher in the AVIM group than in the NC group; however, there was no region of increased FDG uptake in the iNPH group when compared with the NC group (Fig. 4). There was decreased FDG uptake in both the iNPH and AVIM groups when compared with the NCs inside and around the lateral ventricles. Furthermore, the comparison between the iNPH and its NC group revealed a larger de-
Reduced DMN Connectivity Appears at the Onset of iNPHs Symptoms

The DMN has become a focus of neuroscientific interest, and various neurological and neuropsychiatric diseases have been reported to have a relationship with this network. However, to the best of our knowledge, only a single study has reported DMN functional connectivity in the iNPH brain [12]. This study offers a novel advan-
In the brain, the DMN is a large-scale network consisting of the precuneus, PCC, medial frontal lobe, inferior parietal regions, and medial temporal lobe [20]. This network is detectable on FDG-PET by increased FDG uptake, reflecting increased brain glucose metabolism [21, 22]. The precuneus to PCC area has been reported as one of the major hubs of the DMN, and research into this region is currently receiving a great deal of attention [22–24].

In this study, NC cases had high FDG uptake in the precuneus to PCC region on FDG-PET images, consistent with a previous report [21]. However, cases with iNPH showed reduced FDG uptake in this region (Fig. 3). These data suggest there is reduced DMN connectivity in patients with iNPH. This reduction in DMN connectivity in the iNPH is also consistent with a previous report that assessed the same region (precuneus to PCC) using functional MRI [12].

The results of voxel-based analysis using SPM12 to analyze the regions of increased FDG uptake demonstrated a high FDG uptake in the medial parietal cortex in the AVIM group compared with its corresponding NC group; in contrast, there were no regions of increased FDG uptake in the iNPH group (Fig. 4). These results of the AVIM versus NC analysis may be because there is increased gray matter density in the medial parietal area [25] caused by

tage because it assessed DMN connectivity in both the preclinical and clinical iNPH stages.

Table 2. Standardized uptake value ratios of cases with idiopathic normal pressure hydrocephalus

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age, years</th>
<th>Sex</th>
<th>Malignancy</th>
<th>Symptoms of iNPH</th>
<th>SUVR of the precuneus to PCC region</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>71</td>
<td>M</td>
<td>present</td>
<td>gait</td>
<td>1.059</td>
</tr>
<tr>
<td>2</td>
<td>71</td>
<td>M</td>
<td>present</td>
<td>gait and cognitive</td>
<td>1.057</td>
</tr>
<tr>
<td>3</td>
<td>72</td>
<td>M</td>
<td>present</td>
<td>gait and cognitive</td>
<td>0.806</td>
</tr>
<tr>
<td>4</td>
<td>73</td>
<td>M</td>
<td>present</td>
<td>gait</td>
<td>0.890</td>
</tr>
<tr>
<td>5</td>
<td>75</td>
<td>F</td>
<td>present</td>
<td>gait and urinary</td>
<td>0.999</td>
</tr>
<tr>
<td>6</td>
<td>76</td>
<td>M</td>
<td>absent</td>
<td>gait</td>
<td>0.952</td>
</tr>
<tr>
<td>7</td>
<td>81</td>
<td>F</td>
<td>present</td>
<td>gait, cognitive, and urinary</td>
<td>0.961</td>
</tr>
<tr>
<td>8</td>
<td>81</td>
<td>M</td>
<td>present</td>
<td>gait and cognitive</td>
<td>1.071</td>
</tr>
<tr>
<td>9</td>
<td>82</td>
<td>F</td>
<td>present</td>
<td>gait and urinary</td>
<td>1.372</td>
</tr>
<tr>
<td>10</td>
<td>85</td>
<td>M</td>
<td>present</td>
<td>gait, cognitive, and urinary</td>
<td>0.987</td>
</tr>
<tr>
<td>11</td>
<td>87</td>
<td>F</td>
<td>present</td>
<td>gait and cognitive</td>
<td>0.962</td>
</tr>
<tr>
<td>12</td>
<td>88</td>
<td>F</td>
<td>present</td>
<td>gait, cognitive, and urinary</td>
<td>0.810</td>
</tr>
</tbody>
</table>

InNPH, idiopathic normal pressure hydrocephalus; SUVR, standardized uptake value ratio; M, male; F, female; gait, gait disturbance; cognitive, cognitive impairment; urinary, urinary incontinence.
Reduced DMN Connectivity Appears at the Onset of iNPHs Symptoms

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The increased FDG uptake in the medial parietal cortex in AVIM cases corresponds with results from our previous work [26]. However, these data reveal that there are no high levels of neural activity in any brain region linked to the DMN in the development of iNPH.

The results of voxel-based analysis to identify regions of low FDG uptake revealed a significant decrease in FDG uptake inside and around the lateral ventricles in both the AVIM group and the iNPH group compared with each corresponding NC group. We consider that this significant decrease may be due to ventriculomegaly in DESH deformation. However, focusing on FDG uptake in the PCC, there was a larger decreased region in the iNPH group than that in the AVIM group. These data suggest that neural activity in the PCC is reduced at the onset of iNPH; however, we cannot completely exclude the influence of ventriculomegaly in these results of voxel-based analysis using SPM12.

Comparing the mean SUVs between groups in the VOI-based analysis revealed decreased brain glucose metabolism in the precuneus to PCC region in cases with iNPH, but not in cases with AVIM. These results suggest that altered DMN connectivity is not observed at the preclinical stage of iNPH, but that DMN connectivity is reduced at the clinical stage. Thus, the reduction of DMN connectivity may appear at the onset of iNPH symptoms. Accordingly, we consider that reduced DMN connectivity is associated with iNPH symptoms.

The neural activity of the PCC has been reported to be linked to autonomic arousal and awareness [23, 27], and the level of consciousness [28]. The hallmarks of cognitive impairment in patients with iNPH have been reported as attention deficits and slowing of psychomotor speed [29]. It is therefore possible that reduced DMN connectivity in the precuneus to PCC region is related to cognitive impairment, 1 of the 3 characteristic iNPH symptoms.

The brain regions linked to the classic triad of iNPH symptoms are still under discussion. The candidate brain regions for cognitive impairment include the frontal cortex [30, 31], striatum [32], corpus callosum [33], and hippocampus [34]. For gait disturbance, frontal lobe dysfunction has been discussed [30, 35], and the mid-cingulate cortex has been reported to be linked to urinary incontinence [36]. Our study suggests that the precuneus to PCC region is a novel brain region that is related to iNPH symptoms. However, which symptom or symptoms of iNPH are related to this region remain unclear; we were unable to analyze image data for each symptom because of our small sample size.

Further studies are therefore needed to determine the brain regions linked to iNPH symptoms.

This study has several limitations. The first is the small sample of iNPH cases. Only 12 cases of iNPH were obtained for analysis from the cohort of > 2,000 patients, and the potential for random error is therefore not able to be excluded. Second, there was some ambiguity in the assessment of comorbidities and of the iNPH triad of symptoms, because the cases for analysis were retrospectively recruited based on EMR. To attempt to control for this, cases with insufficient information for a diagnosis of AVIM or iNPH were excluded from the analysis. Third, most of the subjects in this study had cancer; we cannot exclude that malignancy may have affected their cerebral glucose metabolism. In fact, there are FDG-PET reports that show that cerebral glucose metabolism is altered in patients with malignancy [37]. We therefore created NC groups for both the AVIM and the iNPH groups to adjust the malignancy rate and other backgrounds, and to rule out the effect of cancer on the brain. Fourth, because of the study design, we were unable to totally exclude the possible influence of comorbidities that have been reported to alter DMN connectivity (e.g., AD, PD, depression, and schizophrenia). However, according to the EMR, no subjects in this study had any of these DMN-affecting diseases. Finally, the potential bias caused by deformation of the iNPH brain was unable to be completely avoided. Nevertheless, for each case, we ensured that enlarged lateral ventricles were not included in the VOI, and we excluded 1 patient with AVIM from the analysis due to severe ventriculomegaly in the VOI.

Conclusions

Our study concluded that there was reduced DMN connectivity in the clinical iNPH group, but not in the preclinical iNPH (AVIM) group. The data suggest that reduced functional connectivity of the DMN is possibly related to the onset of iNPH symptoms. Our results provide a new clue into the unknown pathophysiology of iNPH and a novel approach for diagnosing this disease. Prospective evidence is needed to confirm this conclusion and the exact role of the DMN in iNPH pathophysiology.

Statement of Ethics

This study was conducted according to the Declaration of Helsinki and was approved by the Institutional Review Board of Kindai University (approval No. 30-113).
Conflict of Interest Statement
The authors have no conflicts of interest to report in this study.

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References
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