The Tight Medial and High Convexity Subarachnoid Spaces Is the First Finding of Idiopathic Normal Pressure Hydrocephalus at the Preclinical Stage

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Abstract

Disproportionately enlarged subarachnoid-space hydrocephalus (DESH) findings are often reported as characteristic radiological features of idiopathic normal pressure hydrocephalus (iNPH). However, the process of development of DESH remains unclear. The aim of the present study was to determine the dynamic deforming process and pathophysiology of iNPH. All patients >50 years of age who underwent whole body FDG-PET/CT scanning at Kindai University Hospital between May 2017 and April 2018 were included in this retrospective study, and their brain image findings and clinical information were assessed. We defined DESH-like findings, which had one or two equivocal features of the three components of DESH findings, as preclinical morphologic features of DESH (PMD). PMD were classified into six subtypes based on their component of DESH findings: PMD-T, only tight medial and high convexity subarachnoid spaces (TMC); PMD-S, only enlarged Sylvian fissures; PMD-V, only ventriculomegaly; PMD-TV, TMC and ventriculomegaly; PMD-TS, TMC and enlarged Sylvian fissures; PMD-SV, enlarged Sylvian fissures and ventriculomegaly. A total of 2196 cases (70.5 ± 9.3 years) were enrolled, with 54 cases (77.1 ± 5.9 years) with DESH findings, and 42 cases (72.9 ± 7.9 years) with PMD (five PMD-T, two PMD-V, 12 PMD-TV, 18 PMD-TS, and five PMD-SV). In each component of DESH, 35 of 42 (83.3%) cases with PMD had TMC. We suggest that the TMC is the first change on DESH findings in most iNPH cases, and may be an important part of the pathophysiology of iNPH.

Key words: hydrocephalus, iNPH, AVIM, DESH, PET/CT

Introduction

Idiopathic normal pressure hydrocephalus (iNPH) is described as symptomatic hydrocephalus with normal CSF pressure, and is treatable with shunt surgery.1–3) The morphology of the ventricles and subarachnoid spaces on brain imaging are important for diagnosing iNPH. Features of iNPH include ventriculomegaly, tightness of the high convexity and medial subarachnoid spaces, and enlarged Sylvian fissures.4,5) These features are termed disproportionately enlarged subarachnoid-space hydrocephalus (DESH), which is an effective predictor of favorable outcomes in shunt surgery.6–8) However, Iseki et al.9) reported cases with DESH findings without any symptoms of iNPH, termed asymptomatic ventriculomegaly with features of iNPH on MRI (AVIM), and suggested that the conversion of AVIM to DESH indicates that AVIM may be a preclinical stage of iNPH. Thus, brain morphological changes may precede the onset of symptoms in iNPH patients. However, the pathological process of evolution to DESH from the prodromal stage of AVIM remains unclear.

Here, we performed a retrospective analysis of brain imaging findings in >2000 elderly patients to know the pathological process of development of primary stage DESH. In this survey, we termed incomplete DESH-like findings, which had one or two equivocal features of the three components of
DESH findings, as preclinical morphologic features of DESH (PMD), and collected cases with PMD in the cohort. We found that all cases with PMD were as asymptomatic as the cases with AVIM, although cases with PMD were different from cases with AVIM in that PMD had incomplete DESH-like findings. Therefore, we considered that cases with PMD were at an earlier stage than cases with AVIM. In particular, we examined the variation of the radiological features of PMD, and examined the process of forming DESH findings and the pathogenesis of iNPH.

Materials and Methods

Patients and clinical data

We retrospectively reviewed data of all patients >50 years of age who underwent whole body FDG-PET/CT scanning at Kindai University Hospital between May 1, 2017 and April 31, 2018. We retrospectively examined the radiological features of brain CT images performed for attenuation correction, and of fusion images with PET, as part of the routine protocol of FDG-PET/CT scanning at our institute. Particularly for patients with suspected iNPH, clinical information was also collected from electronic medical records, and included age at FDG-PET/CT scanning, sex, purpose of PET scanning, main disease, date of scanning, symptoms of iNPH, receiving a shunt operation or not, comorbidity, and past history. If repetitive brain MRI images were available, the progress of brain morphological changes was also assessed. This study was conducted according to the Declaration of Helsinki, and was approved by the Institutional Review Board of Kindai University. The need for written informed consent was waived for this retrospective study.

Brain image evaluation

Each individual brain CT image from PET/CT data was checked for radiological features of ventricles and subarachnoid spaces, and the Evans’ index (EI) was measured by a neurosurgeon and two neuroradiologists. PET/CT imaging was performed on a Discovery PET/CT 710 (GE Healthcare, Milwaukee, WI, USA). 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, and a display field-of-view of 500 mm. The voxel size was 0.977 × 0.977 × 3.75 mm. Subjects who had all or a part of DESH findings were enrolled following a criterion of DESH or PMD, as described below.

This survey was conducted in two steps. First, we selected cases with DESH findings or incomplete DESH-like findings from all subjects who underwent FDG-PET/CT scanning. This first step was repeated twice to improve diagnosis. Next, enrolled subjects from the first step were independently classified into DESH or each subtype of PMD by a neurosurgeon and a radiologist without knowing the clinical features of iNPH, and discordant cases were determined by another radiologist to make a consensus agreement between three raters. The κ-coefficient was calculated to show inter-rater reliability of the second step.

Determination of DESH findings and PMD

Disproportionately enlarged subarachnoid-space hydrocephalus findings were defined as ventriculomegaly (EI > 0.3), with tightness of the medial subarachnoid spaces and with/without tight high convexity sulci (TMC), and enlarged Sylvian fissures. In a previous report, incomplete DESH findings were observed when reviewing imaging data collected before onset of iNPH. In the present study, we noted incomplete DESH-like findings that had one or two equivocal features of three components of DESH findings, which we considered a feature of the prodromal stage of AVIM. We then defined the features of these cases as PMD, and classified into subtypes according to their components of DESH (Fig. 1). For separating TMC and enlarged Sylvian fissures into positive or equivocal, we used Narita’s visual rating scale. In the scale, severity of TMC was visually rated as follows: 0, dilated; 1, normal; 2, mildly tight; and 3, severely tight. Likewise, enlarged Sylvian fissures were rated as: 0, narrowed; 1, normal; 2, mildly dilated; and 3, severely dilated. A score of 2 or 3 indicated a positive feature of DESH, while 1 was considered as equivocal. The EI was used to determine the presence or absence of ventriculomegaly. The cutoff value of EI was adopted as 0.3 according to international and Japanese guidelines for iNPH.

In present study, we defined DESH or each subtype of PMD as follows. DESH: TMC rating = 2 or 3, enlarged Sylvian fissures rating = 2 or 3, and EI > 0.3; PMD-T: TMC rating = 2 or 3, enlarged Sylvian fissures rating = 1, and EI < 0.3; PMD-S: TMC rating = 1, enlarged Sylvian fissures rating = 2 or 3, and EI < 0.3; PMD-V: TMC rating = 1, enlarged Sylvian fissures rating = 1, and EI > 0.3; PMD-TV: TMC rating = 2 or 3, enlarged Sylvian fissures rating = 2 or 3, and EI > 0.3; PMD-TS: TMC rating = 2 or 3, enlarged Sylvian fissures rating = 2 or 3, and EI < 0.3; PMD-SV: TMC rating = 2 or 3, enlarged Sylvian fissures rating = 2 or 3, and EI < 0.3.
The Progress of the DESH Findings

Assessment of clinical symptoms and diagnosis of iNPH

The clinical symptoms of all patients were assessed based on medical records of our institute. Patients’ medical records contained a review of systems (ROS) that was assessed by their physicians and nurses, and which provides general state and symptoms. We mainly focused on the symptoms of iNPH in the ROS, linked the symptoms to radiological features, and diagnosed as iNPH or AVIM in patients with DESH findings according to possible iNPH criteria in the second edition guideline for iNPH.5) The criteria include presence of >1 of the iNPH triad (gait disturbance, cognitive impairment, and urinary incontinence), dilated ventricles with an EI > 0.3, and an age of onset >60 years.

For evaluating the clinical symptoms, we excluded cases without clinical information of the iNPH triad on medical records, or cases for whom it was not unequivocal that the symptoms of the triad were caused by hydrocephalus. For example, a case with cancer who showed bedbound activities of daily living was excluded from classification into asymptomatic or symptomatic to avoid ambiguity of judgement, because we were unable to directly evaluate the clinical symptoms. For gait disturbance, we focused on the presence or absence of a small-step gait, magnet gait, and/or a broad-based gait. For cognitive impairment, we checked for a clinical history of dementia and the results of neuropsychological tests, and ensured that medical records showed that at least one modified cognitive test was performed. Cases with other dementia diseases including Alzheimer’s disease were not classified as presence of cognitive impairment caused by iNPH. For urinary incontinent, we examined the urine frequency during the night in the ROS. In the present study, we used the term AVIM to indicate asymptomatic patients with DESH findings detected by CT scanning, although the AVIM was originally defined by MRI (defined not to include the presence of enlarged Sylvian fissures).

Morphological progress detected by serial MRI

We enrolled subjects with DESH findings or PMD who had repetitive MRI before PET scanning, and estimated the progression of DESH findings or PMD.
Statistical analysis

To compare characteristics of age and EI between the three groups of subjects (all subjects, DESH subjects, and PMD subjects), we performed a Kruskal–Wallis rank sum test as the data were not normally distributed (Bartlett test). The P-value was calculated by a post-hoc Mann–Whitney U-test corrected with the Bonferroni method. The ratio of malignancy of the three groups was compared with a χ²-test. A P-value <0.05 was considered statistically significant. Data are reported as mean ± standard deviation. All these statistical analyses were performed using statistical software (R version 3.4.1; downloadable at https://cran.r-project.org/bin/windows/base/old/3.4.1/). Interrater reliability in the classification of DESH was assessed using Kappa coefficients (SPSS version 22.0; SPSS Inc., Chicago, IL, USA).

Results

Patients and clinical data

A total of 2196 patients (1264 men, 932 women; mean age 70.5 ± 9.3 years) were enrolled in this study (Table 1). A 1910 (85.3%) patients underwent FDG-PET/CT scanning for diagnosing cancer, 364 (14.6%) were normal healthy patients who had a medical check, and two (0.1%) were vasculitis patients. The main disease diagnosed after scanning was lung cancer (16.8%), with 76.3% of all patients having a malignancy.

Cases with DESH findings or PMD

We found 54 (2.5%) cases with DESH findings and 42 (1.9%) cases with PMD (Fig. 2). As the DESH cases consisted of symptomatic cases with iNPH and asymptomatic cases with AVIM, we classified cases with DESH findings into two groups (iNPH and AVIM) based on their symptoms of NPH. We found 14 (0.6%) cases with iNPH and 32 (1.5%) cases with AVIM. Unfortunately, eight (0.3%) cases with a DESH finding were not determined as their symptoms of malignant disease were too severe to be evaluated for iNPH. In 14 cases with iNPH, three cases already had had a shunt operation. In 42 cases with PMD, we found no cases with symptoms of iNPH, although nine of 42 cases were not evaluated for symptoms because of the severity of illness related to the main diseases or lack of sufficient clinical information on their symptoms and clinical histories. We found five cases with PMD-T, two cases with PMD-V, no cases with PMD-S, 12 cases with PMD-TV, 18 cases with PMD-TS, and five cases with PMD-SV. No cases with PMD-S were observed. The inter-rater reliability in the classification of DESH and PMD was assessed as κ = 0.823.

Characteristics of the DESH and PMD groups

The mean age of the DESH group (77.1 ± 5.9 years) was significantly higher than that of the PMD group (72.9 ± 7.9; P = 0.03; Table 1). The mean age was lowest (70.5 ± 9.3 years) in all subjects, although there were no differences in the mean age between all subjects and the PMD group. The mean EI was highest in the DESH group (0.339 ± 0.024), followed by the PMD group (0.312 ± 0.033), and then all subjects (0.278 ± 0.032), with significant differences between the groups (P <0.01 for all). The rate of malignant disease was similar between

| Table 1 Characteristics of the patients | All patients | DESH | PMD |
|----------------------------------------|-------------|-----|-----|
| Sex (male/female)                      | 1264/932    | 34/20 | 30/12 |
| Age (years)                            | 70.5 ± 9.3  | 77.1 ± 5.9* | 72.9 ± 7.9 |
| Evans index                            | 0.278 ± 0.032 | 0.339 ± 0.024 | 0.312 ± 0.033 |
| Purpose of undergoing FDG-PET/CT scanning | 1910 (85.3%) | 53 (98.1%) | 40 (95.2%) |
| Diagnosing cancer                      | 285 (14.6%) | 1 (1.9%) | 2 (4.8%) |
| Medical examination                    | 0 (0%)      | 0 (0%) | 0 (0%) |
| Diseases                               |             | | |
| Cancer                                 | 1676 (76.3%) | 46 (76.7%) | 30 (71.4%) |
| Benign tumor                           | 111 (5.1%)  | 3 (5.6%) | 4 (9.5%) |
| Inflammatory diseases                  | 17 (0.8%)   | 1 (1.9%) | 2 (4.8%) |
| No disease                             | 248 (11.3%) | 1 (1.9%) | 2 (4.8%) |
| Not determined                         | 144 (6.6%)  | 3 (5.6%) | 4 (9.5%) |

*Significant between the DESH and PMD groups (P = 0.03). DESH: disproportionately enlarged subarachnoid-space hydrocephalus, PMD: preclinical morphologic features of DESH.
the all subjects, DESH, and PMD groups (76.3%, 76.7%, and 71.4%, respectively; Table 1).

Morphological progress detected by serial MRI

In 96 DESH or PMD subjects, 16 subjects had repetitive brain MRI scans, and six of the 16 subjects showed morphological changes in brain proportion over the scans (Fig. 3). In cases 1–3, TMC was obvious, and the width of the anterior horns gradually increased. In particular, cases 2 and 3 showed slight enlargement of the Sylvian fissures. In case 4, enlargement of Sylvian fissures appeared after

Fig. 2 A flow chart of case classification and results.

Fig. 3 Brain MRI findings of six cases with morphological changes over time. Case 1 had TMC at 71 years of age, with progressive enlargement of the anterior horns of the lateral ventricles. Cases 2 and 3 had TMC at first MRI examination, with progressive enlargement of the anterior horns of the lateral ventricles and Sylvian fissures. Case 3 showed only a small increase in the Sylvian fissures, although the right Sylvian fissure was enlarged at 74 and 75 years of age. Case 4 had TMC and ventriculomegaly at first examination, with progressive enlargement of the Sylvian fissures. Case 5 already exhibited DESH findings at first MRI examination, but showed progressive enlargement of the anterior horns. Case 6 developed sudden DESH findings at 20 months from the first scan (at 63 years of age).
occurrence of TMC and ventriculomegaly. Case 5 had full DESH findings at 67 years of age, but the size of the lateral ventricles increased over subsequent scans. Case 6 showed dynamic changes in the brain, although the subject only had two MRI scans taken at 63 and 64 years of age, with a span of 20 months. Nevertheless, full DESH findings appeared over this period.

With respect to iNPH, cases 1 and 5 had gait disturbance (the exact time of onset was not obvious), while cases 3 and 4 were judged as asymptomatic. The symptoms of cases 2 and 6 remain unknown, because there was insufficient information on their symptoms in our medical records. None of these six cases had undergone shunt surgery.

**Discussion**

Previous reports showed a prevalence of iNPH, diagnosed with Japanese criteria, of 0.3–2.8% of elderly subjects in Japan. In the present study, the prevalence of iNPH was 0.63%, consistent with these previous findings. Furthermore, we found a prevalence of cases with AVIM of 32 (1.45%) in 2196 enrolled patients, which corresponds with the prevalence of eight (1.0%) in 790 cases reported by Iseki et al. This correspondence with previous epidemiology reports confirms the appropriateness of our study. Nevertheless, we found a difference in the shunt surgery rate, with reports of approximately 50% of probable iNPH patients undergoing shunt operations in Japan, compared with only three (20%) of 15 patients in the present study. These differences may reflect the high rates of malignant disease in the present study (13 out of 14 cases; 93%), who received prioritized treatment rather than shunt surgery.

In the present study, we focused on the early stage of iNPH, as this dynamic stage may be important in the pathophysiology of iNPH. We found 42 asymptomatic cases with PMD, which is considered the prodromal stage of DESH. The lower mean age of PMD patients compared with DESH patients suggests that PMD may precede DESH. In the PMD group, there was a range of PMD (five types). However, our finding [35 cases (83.3%) had TMC] suggests that TMC may be the first morphological change in the course of DESH findings. This hypothesis was supported by the cases that showed morphological development on serial brain MRI, with five of six cases showing TMC at first MRI scan, followed by other features at later scans, and one case showing rapid morphological changes over 20 months.

In a prospective 10-year follow-up study of three 70-year-old subjects, Iseki et al. reported that a tight high convexity proceeded AVIM and iNPH, which is similar to our prospective study findings. However, we suggest that not all cases begin the deformation to DESH from TMC, because we found seven PMD cases with ambiguous TMC out of 42 cases with PMD. Furthermore, it is feasible that the three components of the DESH findings appear almost simultaneously. Cases 1–5 in our serial MRI dataset showed that multiple components of DESH findings were simultaneously deforming from anatomically normal to DESH findings over a period of 2–12 years. Future long-term sequential studies with a larger number of cases are required to determine the exact progression of DESH findings.

Recently, Engel et al. described the transition of radiological features in the pre-symptomatic phase of iNPH, with an increase in EI being the most evident compared with TMC, an enlarged Sylvian fissure, or other parameters. Furthermore, features of PMD were observed at the first MRI in nine of 10 cases, although TMC fluctuated between positive and ambiguous. Our findings of an increase in EI and the appearance of TMC at the early stage of iNPH are consistent with the study by Engel et al., although once the features of TMC appeared, they remained consistent. This discrepancy is likely caused by the TMC evaluation method, which can be under- or over-estimated using scanned slices.

Ishikawa et al. reported that symptomatic probable iNPH consists of three groups (DESH, incomplete DESH, and non DESH). The radiological features of incomplete DESH were defined as two definite and one equivocal of the three DESH findings (TMC, enlarged Sylvian fissure, and ventriculomegaly). In the present study, it remains possible that cases with PMD contain incomplete DESH. However, we found no cases with obvious symptoms of iNPH in the PMD cases, suggesting that PMD reflects another stage of incomplete DESH, because incomplete DESH has been reported as symptomatic. Interestingly, Ishikawa et al. also reported that among each subtype of incomplete DESH, cases with TMC were good responders for shunt surgery. Thus, we also suggest that TMC is a primary and important change correlated with symptoms and pathophysiology.

A common conclusion of studies evaluating the correlation of radiological findings and outcomes after shunt surgery in iNPH is that tight high convexity sulci or one of its indices (callosal angle) is a major predictor of shunt responders for all iNPH findings, including ventriculomegaly, enlarged Sylvian fissures with involvement of the temporal horns, and focal enlargement of cortical sulci. These reports also suggest that a tight cortex in the vertex area is an important biomarker.
in differentiating iNPH from other diseases, as well as part of the pathophysiological process of iNPH.

Patients with iNPH frequently show retrograde venous flow in the superior sagittal sinus (SSS) during the Valsalva maneuver. Moreover, the presence of lymphatic vessels of the meningeal lymphatic system running parallel to the SSS were recently reported, with tracer injected into the subarachnoid space of mice being drained through this pathway and the SSS, which likely form part of the drainage of the glymphatic system. We suggest an association of TMC, SSS, and the meningeal lymphatic trunk because of their neighboring positions. Thus, we hypothesize that an unknown cause blocks absorption of CSF in any part of the brain, which causes the meningeal lymphatic system to over-drain CSF around the high convexity to compensate the CSF balance and reduce the peripheral subarachnoid space, causing SSS congestion. Alternatively, a reduced meningeal lymphatic system theory has been suggested, whereby retrograde SSS flow disturbs the surrounding meningeal lymphatic system and reduces CSF inflow to the high convexity and subarachnoid space. Further physiological and clinical studies are required to examine these potential mechanisms.

There are several limitations of our study. First, we cannot exclude the potential for selection bias. To maintain objectivity and replicability in classification of the radiological features, we used rating scales for TMC and enlarged Sylvian fissures in iNPH, and the evaluation was conducted by three independent raters blinded to clinical features. However, we can never exclude the bias completely. Second, the brain CT images were not perfectly clear, as they were only obtained for attenuation correction for PET images as part of the FDG-PET/CT scanning procedure, rather than for diagnosing intracranial diseases. However, the image quality was satisfactory for measuring brain and CSF space morphology, and the evaluation was repeated twice for >2000 cases. Another limitation involves the cut-off value of the Evans’ index. Recently, Brix et al. suggested new cut-off values depending on age and gender, and the consensus for the proper value of EI to define ventriculomegaly remains unclear. In the present study, we adopted a, EI cut-off value of 0.3 according to clinical guidelines for iNPH. Nevertheless, it is possible that the fixed value of EI may have affected our results. Our study was based on retrospective review of electronic medical records, without direct medical examinations. Thus, the clinical data, particularly on symptoms, may not be exact. To reduce ambiguity, we removed some cases without sufficient information for diagnosis (classified as ‘not determined’), although the ambiguity of symptoms cannot be completely eliminated. The influence of malignancy in our study also remains unclear. As our cohort contained approximately 76% of patients with malignant diseases (Table 1), our findings should be applied carefully to the general population. Finally, because of the cross-sectional study design, we were unable to determine whether cases with PMD will develop future DESH findings. Thus, future long-term follow-up studies are required.

In conclusion, we provide novel findings on the morphological changes in the brain during the early stage of iNPH. We suspect that in the majority of cases, TMC is the first change during development of DESH, followed by enlargement of the Sylvian fissure and ventriculomegaly, and may be associated with the pathophysiology of iNPH. These findings further our understanding of the pathophysiology of iNPH, and may be important for development of new treatments, and determining the exact time for interventions, in iNPH.

Conflicts of Interest Disclosure

The authors have no conflicts of interest for this work. The first author who is members of The Japan Neurosurgical Society (JNS) have registered online Self-reported COI Disclosure Statement Forms through the website for JNS members.

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