Magnetic Resonance Imaging Findings of Idiopathic Normal Pressure Hydrocephalus and Cognitive Function Before and After Ventriculoatrial Shunt

Abstract

Background: The idiopathic normal pressure hydrocephalus (iNPH) is characterized by the triad of gait impairment, incontinence, and dementia. Cases that do not comply with the diagnostic criteria of ventriculomegaly have increased. It has led to the questions about the current criteria of guidelines. As the number of patients with dementia increases with aging, iNPH is importantly placed as a treatable dementia. The purpose of this study was to verify the validity of radiological diagnostic criteria of ventriculomegaly in iNPH. Materials and Methods: A board-certified neuroradiologist retrospectively examined 80 patients with definite iNPH about magnetic resonance imaging (MRI) findings of Evans index (EI) and disproportionately enlarged subarachnoid space hydrocephalus (DESH). The score of mini-mental state examination (MMSE) was measured to represent the cognitive function. The presurgical score of MMSE (pre-MMSE) and postsurgical best score of MMSE (best-MMSE) were compared statistically between patients dichotomized by either EI >0.3 or DESH. Results: The pre-MMSE was not different regardless of dichotomization by EI >0.3 or DESH. The MMSE score (median) increased significantly (P < 0.0001) by shunt from 20.0 to 26.0 in patients with EI >0.3 and from 21.5 to 25.5 with EI ≤0.3. No difference in the best-MMSE was observed between EI >0.3 and EI ≤0.3. The MMSE score increased significantly (P < 0.0001) by shunt from 21 to 27.5 with DESH and from 20 to 24.5 with non-DESH. Regardless of fulfilling or not fulfilling Japanese radiological diagnostic criteria (combination of EI >0.3 and DESH), cognitive function was significantly (P < 0.0001) improved to the same level. Only 24 cases (30%) fulfilled Japanese radiological diagnostic criteria. Conclusion: Cognitive function of iNPH patients was significantly improved by shunt regardless of MRI-findings. Radiological diagnostic criteria of iNPH may need careful reconsideration.

Keywords: Cognitive function, idiopathic normal pressure hydrocephalus, mini-mental state examination, ventriculomegaly

Introduction

Idiopathic normal pressure hydrocephalus (iNPH) is a disease of the elderly population, comprising the triad of gait disturbance, dementia, and urinary incontinence that can be improved by shunting of cerebrospinal fluid (CSF).[1] Besides the clinical trial, there are various opinions regarding the pathophysiology of iNPH. The most popular diagnosis of iNPH has been denoted on magnetic resonance imaging (MRI) findings of ventriculomegaly that is indicated by Evans index (EI) >0.3.[2,3] In addition to EI, another morphological feature of disproportionately enlarged subarachnoid space hydrocephalus (DESH)[4] has been addressed in the Japanese diagnostic guideline.[5] In our recent study, iNPH patients with EI ≤0.3 was observed at 30% and with non-DESH at 55% of 84 definite iNPH patients.[6] Similar results have been reported from other laboratories suspecting the reliability of DESH.[7,8] Regarding EI, 29% of healthy elderly people have EI >0.3,[9] and there is no clear basis for using EI >0.3 as an index of ventriculomegaly, and it is inconsistent. The cases have been also reported that the symptoms were improved by CSF shunting despite EI ≤0.3. These reports have led to the questions about the validity of the current diagnostic criteria in the guidelines.

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As for ventriculomegaly in iNPH, no correlations were reported between the change of midbrain size and change of gait function,\(^{(1)}\) and some correlations were observed between corpus callosum size and cognitive function.\(^{(1,2)}\) However, little is known about the direct relationship between diagnostic ventriculomegaly and clinical symptoms of iNPH. Although gait disturbance is the most prominent symptom, cognitive impairment is also common at about 80% of iNPH patients.\(^{(1,3)}\) In contrast to gait improvement in a short term, recovery of cognitive function often requires a relatively long period of time. Since we can ask the pros and cons of the diagnostic criteria of ventriculomegaly over a long term, the significance of measuring cognitive function would be even greater. This could be the advantage of cognitive function to examine into iNPH patients.

In a modern society where the number of patients with dementia increases with aging, iNPH is importantly placed as a treatable dementia. The purpose of this study is to examine the effects of shunt surgery on the cognitive function of iNPH patients with and without diagnostic MRI findings of ventriculomegaly. Then, the goal is to verify the validity of the current diagnostic criteria of the neuroimaging features (EI >0.3 and DESH) on the evaluation of cognitive function of iNPH patients after shunt surgery.

**Materials and Methods**

**Definite idiopathic normal pressure hydrocephalus patients**

A total of 330 probable iNPH cases received ventriculoatrial shunt (VA shunt) at NPH Center of Kashivatanaka hospital in the period of 2010 through 2014. All patients received lumbar tap test with positive response and were evaluated functionally by a neurologist and physical therapists before and after VA shunt by using the Modified Rankin Scale (mRS),\(^{(14)}\) Japanese iNPH Grading Scale (iNPHGS) for gait, continence, and cognitive function,\(^{(1,3)}\) mini-mental state examination (MMSE),\(^{(1,16,17)}\) and Three-meter timed up and go test (TUG).\(^{(19)}\) A patient was denoted as the shunt responder (definite iNPH) when he or she showed at least one of the following postsurgical improvements in mRS ≥1, MMSE ≥3, iNPHGS ≥1, or cessation of urinary incontinence. Then, 288 cases (87%) proved to be definite iNPH, and 80 patients who had clear presurgical axial and coronal brain MRI scans were selected finally for this study on the detailed postsurgical evaluation that was conducted at the 1st, 3rd, 6th, and 12th months after VA shunt.

**Cognitive function**

Gait disturbance and urinary incontinence are easier to improve than cognitive impairment among the iNPH triad. Long-term observation is usually required to confirm postsurgical improvement of cognitive function. Cognitive function was measured by using the score of MMSE.\(^{(1,16,17)}\) Since the prognostic timing varied from patient to patient and depended on the functional modality, the postsurgical best score of MMSE (best-MMSE) was used as representing the cognitive improvement by shunt.

**Neuroimaging of ventriculomegaly**

We verified the accuracy and usability of radiological criteria for iNPH diagnosis.\(^{(2,4)}\) Considering the interobserver variation in the assessment of EI and DESH,\(^{(14)}\) we adopted the measurement results of a board-certified neuroradiologist about the radiological features that were determined by blind to the clinical information. EI was computed using the axial section of MRI-T1 image\(^{(1,3)}\) which was modified from the original method.\(^{(19)}\) DESH was judged according to the original description of by Kitagaki et al.\(^{(4)}\) DESH was described as disproportionately enlarged subarachnoid space, tight high convexity, and enlarged Sylvian fissure [Figure 1]. Although we followed the Japanese guidelines\(^{(15)}\) barring the radiologic diagnostic criteria, patients with EI ≥0.3 and non-DESH were also included in the present study.

**Statistical analysis**

To analyze the effects of CSF shunting on patients, the paired Student’s t-test was applied to the paired Student’s t-test was applied to the parametric data (age, EI) and Wilcoxon matchedpairs signed rank test to the nonparametric data (mRS, iNPHGS, MMSE, and TUG). To analyze the validity of dichotomizing the patients by the radiological diagnostic criteria, the unpaired Student’s t-test was applied to the parametric data (age, EI) and Mann-Whitney’s Utest to the nonparametric data (MMSE, TUG). All statistical analyses were preformed using Prism 8 (version 8.4.1; GraphPad Software LLC., San Diego, CA, USA).

All the measured data were shown as the median (the lower quartile and the upper quartile) throughout the text and tables, but for abstract as the median only. In the figures, data were shown by box plot (the minimum, the lower quartile, the median, the upper quartile, and the maximum).

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**Figure 1:** Magnetic resonance imaging in idiopathic normal pressure hydrocephalus patients with and without feature of disproportionately enlarged subarachnoid space hydrocephalus. The left image (a) shows characteristics of disproportionately enlarged subarachnoid space hydrocephalus as disproportionately enlarged subarachnoid space, tight high convexity, and dilatation of Sylvian fissure. The right image (b) shows non-disproportionately enlarged subarachnoid space hydrocephalus.
Ethical considerations
Data collection was approved by the Institutional Review Board of Kasivatanaka Hospital, and informed consent was obtained in a written form.

Results
Among 288 cases (87%) as proved to be definite iNPH, 80 patients (47 males and 33 females) who had clear presurgical axial and coronal brain MRI scans were selected for this cohort study. The age shown as the median (interquartile range) was 78.0 (75.5–82.0), whereas the age for males and females were 78.0 (75.0–82.0) and 79.0 (74.0–81.5), respectively. There was no gender difference in age of patient [Table 1].

Ventriculoatrial shunt and clinical functions
At first, we examined the effects of VA shunt on the clinical functions of iNPH patients. We noted that all modalities of clinical functions (mRS, iNPHGS (gait, continence, and cognitive function), MMSE, and TUG) were improved significantly by VA shunt [Table 2].

Evans index and cognitive function
We examined pre- and post-surgical cognitive function in relation to ventriculomegaly defined as EI >0.3. We verified the efficiency of the radiological diagnostic criterion of EI for improvement of iNPH patients by VA shunt [Table 3]. The age was not different in patients between with EI >0.3 and with EI ≤0.3. It is of note that 35% of 80 definite iNPH patients showed less than EI ≥0.3. The presurgical score of MMSE (pre-MMSE) of patients with EI >0.3 was not different from that with EI ≤0.3. The postsurgical best-MMSE of patients with EI >0.3 was not different from that with EI ≤0.3. Thus, both pre- and best-MMSE were not different in iNPH patients regardless of EI >0.3 or EI ≤0.3.

Then, as indicated in Figure 2, the score of MMSE was significantly (P < 0.0001) increased by VA shunt from 20.0 (17.0–25.8) to 26.0 (24.0–29.8) in patients with EI >0.3 and from 21.5 (18.0–27.8) to 25.5 (24.0–29.8) in patients with EI ≤0.3. These results suggest that dichotomizing the patients by EI may not have significant meanings in the evaluation of cognitive function of iNPH patients.

Disproportionately enlarged subarachnoid space hydrocephalus and cognitive function
As shown in Table 4, more than half (55%) of the iNPH patients were diagnosed with non-DESH. The pre-MMSE of patients with DESH was not different from that with non-DESH. In addition, EI of the patients with DESH was not different from that with non-DESH. The effects of VA shunt on the cognitive function of patients with DESH and that with non-DESH were shown in Figure 3. The score of MMSE was increased significantly (P < 0.0001) by shunt surgery from 21 (18–26.8) to 27.5 (25–30) in patients with DESH and from 20 (16–25) to 24.5 (22.3–29) in patients with non-DESH. Although DESH or non-DESH did not influence the pre-MMSE and EI, the best-MMSE of patients with DESH was significantly higher (P < 0.01) than that with non-DESH [Table 4].

Japanese radiological criteria and cognitive function
Table 5 outlines the summary of patients with respect to those who fulfilled the Japanese radiologic diagnostic criteria (combination of EI >0.3 and DESH) and who
Since the introduction of the concept of NPH as a cause of surgically treatable dementia by Adams et al.,[20] a number of CSF shunt surgeries for iNPH were performed with undesirable outcomes.[21–23] Klinge et al.[24] and Ishikawa et al.[3] summarized the outcomes and complications of shunt surgery for iNPH performed before the introduction of the guidelines. Although the outcomes were good in some studies, overall outcome was not satisfactory to recommend shunt to elderly patients. They developed the guidelines for iNPH and select candidates for shunt using clinical data and neuroimaging features.[25] The core parts of the guidelines included radiological diagnosis to define ventriculomegaly since the concept of NPH was proposed as an analogy to pediatric hydrocephalus.[20,26] This may be the reason why EI was included into the guidelines for iNPH,[2,3] although EI was originally proposed to define ventriculomegaly of pediatric hydrocephalus.[19]

Before the publication of the guideline, a number of studies were carried out on the outcome of CSF shunt surgery for iNPH.[14,24] Since the definition of ventriculomegaly for iNPH diagnostic criteria and cognitive function

Table 4: Cognitive functions of idiopathic normal pressure hydrocephalus patients with or without disproportionately enlarged subarachnoid space hydrocephalus before and after shunt

|                      | DESH   | Non-DESH | P   |
|----------------------|--------|----------|-----|
| Number of patients   | 36     | 44       |     |
| Patient age (years)  | 78 (74-81) | 78.5 (76-83) | 0.376 |
| Evans index          | 0.319 (0.293-0.337) | 0.324 (0.290-0.347) | 0.259 |
| Pre-MMSE             | 21 (18-26.8) | 20 (16-25) | 0.133 |
| Best-MMSE            | 27.5 (25-30) | 24.5 (22.3-29) | 0.0054 |

Data are shown by the median (interquartile range). iNPH—Idiopathic normal pressure hydrocephalus; Pre-MMSE—Presurgical score of mini-mental state examination, Best-MMSE—Postsurgical best score of mini-mental state examination.


did not. There were no significant differences in age, EI, pre-MMSE, and best-MMSE between the group of fulfilling Japanese radiological criteria and the group of not-fulfilling the criteria. Only 24 cases (30% of the 80 definite iNPH patients) fulfilled the Japanese radiological diagnostic criteria.

As shown in Figure 4, the score of MMSE was significantly increased ($P < 0.0001$) by VA shunt from 20.5 (18–25.8) to 27 (25–30) in the patients fulfilling the Japanese radiological diagnostic criteria. Similarly, in the patients not-fulfilling Japanese radiological criteria, the score of MMSE was also significantly increased ($P < 0.0001$) from 20 (17–26.8) to 25 (23–29) by shunt surgery. Regardless of fulfilling or not-fulfilling the Japanese radiological diagnostic criteria (combination of EI >0.3 and DESH), cognitive function of iNPH patients was significantly improved to the same level by VA shunt.

Discussion

We demonstrated that all modalities of physiological functions (gait, cognitive function, and urinary continence) associated with iNPH improved significantly by VA shunt. We investigated whether the MRI-based current criteria of ventriculomegaly really capture the pathophysiology of iNPH by focusing on the diagnosis and prognosis of cognitive function. No significant differences were observed in the pre-MMSE nor best-MMSE between the patients with EI >0.3 and those with EI ≤0.3. In addition, the score of MMSE improved significantly by VA shunt in both groups of EI >0.3 and EI ≤0.3. Thus, the current diagnostic criterion of ventriculomegaly by EI may not seem reasonable for defining iNPH patients.

Figure 2: Cognitive function before and after shunt in idiopathic normal pressure hydrocephalus patients with or without ventriculomegaly: Evans index >0.3 or Evans index ≤0.3. In the figure, the left shows data of idiopathic normal pressure hydrocephalus patients with Evans index >0.3, whereas the right shows data of idiopathic normal pressure hydrocephalus patients with Evans index ≤0.3. Pre-MMSE indicates the pre-surgical score of mini-mental state examination, whereas best-MMSE indicates the postsurgical best score of mini-mental state examination. The box plot shows the minimum, the lower quartile, the median, the upper quartile, and the maximum. ****$P < 0.0001$

Figure 3: Cognitive function before and after shunt in patients with or without disproportionately enlarged subarachnoid space hydrocephalus (DESH). In the figure, the left shows data of idiopathic normal pressure hydrocephalus patients with DESH, whereas the right shows data of idiopathic normal pressure hydrocephalus patients without DESH. Pre-MMSE indicates the pre-surgical score of mini-mental state examination, while best-MMSE indicates the post-surgical best score of mini-mental state examination. The box plot shows the minimum, the lower quartile, the median, the upper quartile, and the maximum. ****$P < 0.0001$
iNPH was not clearly stated in the pre-era of the guidelines, previous studies might have contained shunt-responsive patients with EI ≤0.3. However, no studies compared the shunt outcomes between patients with EI >0.3 and with EI ≤0.3. After the introduction of guidelines, only the patients who fulfilled the radiological diagnostic criteria have been selected for shunt surgery. It has been difficult to verify the validity of EI >0.3 as the radiological diagnostic criteria for iNPH. Naruse and Matsuoka reported the symptoms of all the 14 patients improved remarkably by shunt despite EI ≤0.3. They suggested EI might not be appropriate to evaluate external ventricular enlargement because cerebral ventricles could not enlarge externally. In the present study, the pre- and post-surgical cognitive functions were not different each other between groups of EI >0.3 and EI ≤0.3.

DESH is a different approach to define ventriculomegaly to discriminate iNPH from other causes of dementia such as Alzheimer disease and vascular dementia by the unique configuration of the CSF distribution in iNPH on the coronal section of MRI. In our study, only 36 cases (45%) were with DESH among the finally selected definite iNPH patients. There were no significant differences in age, EI, and pre-MMSE between the patients with DESH and those with non-DESH. However, the best-MMSE of patients with DESH was significantly higher (P < 0.005) than that with non-DESH, whereas the best-MMSE was not different each other regardless of fulfilling Japanese radiological criteria (combination of EI >0.3 and DESH) or not-fulfilling the criteria. Other recent reports support our findings about the low reliability of DESH for iNPH diagnosis. It may be due to the non-objective and non-quantitative definitional explanation for DESH. Nevertheless, the revised Japanese guideline includes DESH as a radiological diagnostic criterion along with EI >0.3. DESH might have some meanings, though details remain unknown. Further studies may be needed to clarify the pathophysiological reality of DESH.

To the best of our knowledge, this is the first large-scaled study on the longitudinal recovering process of cognitive function in the definite iNPH patients who were not selected by the presence or absence of diagnostic ventriculomegaly. Only 30% of definite iNPH patients fulfilled the Japanese radiological diagnostic criteria (combination of EI >0.3 and DESH); however, all of the patients showed significant improvement after shunt. After all, what is the diagnostic meaning of MRI-based ventriculomegaly in iNPH patients? Results of this study strongly suggest that currently proposed radiological diagnostic criteria of iNPH may need careful reconsideration to establish the most appropriate guideline.

**Limitations of the study**

This was a retrospective study and the analyzed patients were only from neurosurgical department of a single hospital. Evaluating cognitive function using the score of MMSE is a sensitive and useful way to examine retrospectively the effects of shunt surgery. Gait disturbance is one of the major symptoms of iNPH but can be a cause of tumble ensuing limb fractures in the elderly people. These patients may not be listed in the differential diagnosis of iNPH as they usually consult orthopedists.
Conclusion

There were no significant differences in the pre-MMSE between the two groups dichotomized by diagnostic criteria of EI >0.3 or DESH. The MMSE score was increased significantly by VA shunt to the same level regardless of dichotomization by EI >0.3 or DESH. Only 24 cases (30% of the 80 definite iNPH patients) fulfilled the Japanese radiological diagnostic criteria (combination of EI >0.3 and DESH). Regardless of fulfilling or not-fulfilling the Japanese radiological criteria, cognitive function of iNPH patients was significantly improved by VA shunt and reached to the same level. Dichotomizing patients by MRI-findings may cloud appropriate pathophysiological judge on the diagnosis of iNPH.

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Conflicts of interest

There are no conflicts of interest.

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