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Noninvasive MRI Assessment of Intracranial Compliance in Idiopathic Normal Pressure Hydrocephalus

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Running Title:

Intracranial Compliance Assessment in I-NPH

ABSTRACT

Purpose: To assess the state and dynamics of the intracranial system in idiopathic normal-pressure hydrocephalus (I-NPH), we determined intracranial compliance using magnetic resonance imaging (MRI).

Materials and Methods: The intracranial compliance index (ICCI), which was defined as the ratio of the peak-to-peak intracranial volume change ($ICVC_{p-p}$) to the peak-to-peak CSF pressure gradient (PG_{p-p}) during the cardiac cycle, was obtained from the net transcranial blood and CSF flow measured with phase-contrast cine MRI. ICCI was determined in patients with I-NPH (n=7), brain atrophy or asymptomatic ventricular dilation (VD, n=6), and in healthy volunteers (control group; n=11). The changes in ICCI indices were also analyzed after a CSF tap test (n=2).

Results: The ICCI in the I-NPH group was significantly lower than in the control and VD groups, whereas no difference was found between the control and VD groups. The $ICVC_{p-p}$ was also lower than in the control and VD groups. However, no significant difference was found in the PG_{p-p} between groups. The ICCI increased after the tap test.

Conclusion: intracranial compliance analysis with MRI makes it possible to noninvasively obtain more detailed information of intracranial biomechanics in the I-NPH and to assist in the diagnosis of I-NPH.

Key Words: intracranial compliance; idiopathic normal pressure hydrocephalus; pressure gradient; intracranial volume loading; brain atrophy; tap test

INTRODUCTION

For diagnosing a normal-pressure hydrocephalus (NPH), clinical symptoms (gait disturbance, dementia, and incontinence) and their follow-up observations are crucial, but there are still many unsolved problems with this syndrome in terms of the diagnostic criteria and selection of appropriate patients for shunt surgery (1). In particular, diagnosis of idiopathic NPH (I-NPH) without a known cause of communicating hydrocephalus is more difficult (2-6) than that of secondary NPH with evidence of previous subarachnoid haemorrhage, meningitis, head injury, or numerous other conditions. Therefore, cerebrospinal fluid (CSF) flow studies with magnetic resonance imaging (MRI) (7-11) and some invasive examinations (2-6) such as tap test or CSF outflow resistance via an infusion test have been performed in addition to clinical findings and conventional image diagnosis with X-ray computed tomography or MRI. The MRI CSF flow studies (e.g., analysis of CSF flow velocity or volumetric flow rate in the aqueduct) noninvasively obtained information about changes in intracranial mechanical properties, i.e., intracranial compliance (defined as the ratio of intracranial volume change to pressure change) due to decreased CSF resorption in NPH (8, 10-13). However,

there is a limitation that the CSF flowmetry does not always show changes in intracranial compliance because CSF flow is modulated by the hemodynamics of the brain (14). Therefore, in the present study, we directly analyzed the intracranial compliance in I-NPH using cine-MRI to noninvasively assess the state and dynamics of the intracranial system and to assist in diagnosis. The intracranial compliance index (ICCI) was calculated with change of volume loading to the cranium, i.e., net intracranial volume change, and CSF pressure gradient during the cardiac cycle, based on the MR-ICP method of Alperin et al (15). We describe the characteristics of the ICCI in I-NPH, and the usefulness of its analysis.

MATERIALS AND METHODS

ICCI Determination

The ICCI, which is defined as the ratio of the maximal intracranial volume change to the maximal craniospinal CSF pressure gradient change during the cardiac cycle, was obtained from the net transcranial blood flow, CSF flow, and displacement of the cord measured with phase-contrast (PC) cine MRI. For details

of these measurements, the reader is referred to reference 15. In short (flow chart in Fig. 1), we first set the vertical slice plane at the mid-C2 level against the cerebrospinal axis (Fig. 1a-c), and twice obtained velocity-mapped phase images with different velocity encoding gradients for CSF flow and cord displacement as well as for transcranial blood flow, respectively (Fig. 1d and e).

To obtain the net transcranial flow, we measured the flow or displacement during the cardiac cycle in each region; CSF flow [$V_c(t)$], displacement of cord [$V_s(t)$], arterial inflow (the sum of both internal carotid arteries and both vertebral arteries) [$V_a(t)$], and venous outflow (the sum of both internal jugular veins) [$V_v(t)$] (Fig. 1d and e). At this time, we corrected the baseline offset due to eddy currents by a subtraction process (14). After venous outflow was scaled up so that mean intracranial volume change was zero (14-16), and the intracranial volume change was obtained from following Equation:

$$ICVC(t) = \int [V_a(t) + V_v(t) + V_c(t) + V_s(t)]dt, \quad \text{---(1)}$$

where the measured volumetric flow in each region was positive in the cranial direction.

Next, we obtained the craniospinal CSF pressure gradient during the cardiac

cycle, which was calculated from the above measured CSF flow velocity using a following simplified Navier-Stokes Equation (17):

$$\nabla P = \frac{\partial P}{\partial z} = -\rho \frac{\partial w}{\partial t} + \mu \left(\frac{\partial^2 w}{\partial x^2} + \frac{\partial^2 w}{\partial y^2} \right), \quad \text{---(2)}$$

where *x*, *y*, and *z* are coordinates, and *z*-direction is a canal axis. *P* and *w* are the pressure and the axial velocity, and ρ and μ are the fluid density (CSF: 1.0007 g/cm^3) and viscosity (CSF: 1.1 cP), respectively. Then the CSF pressure gradient was normalized by multiplying the CSF flow area (15).

Finally, the ICCI was obtained by dividing the peak-to-peak normalized CSF pressure gradient change ($PG_{p\text{-}p}$) into the peak-to-peak intracranial volume change ($ICVC_{p\text{-}p}$) during the cardiac cycle.

Study Subjects

ICCI analysis was performed in patients with I-NPH (four men and three women, 73±7 years) and asymptomatic ventricular dilation or brain atrophy (VD; three men and three women, 79±3 years), and in healthy volunteers (control group; nine men and two women, 36±13 years). All patients with I-NPH showed improvement with a CSF tap test (6), i.e., symptom analysis after lumbar puncture

and removal of CSF (30 mL or CSF pressure fell to zero). In two cases of I-NPH, the ICCI, $ICVC_{p\text{-}p}$, and $PG_{p\text{-}p}$ were compared before and after the tap test. The rate (R) of change was calculated by

$$R\ (\%) = 100\ (S_a\text{-}S_b) / S_b\ , \qquad \text{--- (3)}$$

where S_b and S_a indicate each value before and after tap test.

The purpose and procedures of all our investigations were fully explained to all patients, and the studies were performed only after obtaining informed consent from each patient. The Mann-Whitney U test was used to determine the significance between the groups.

Imaging Conditions

Measurements were done using retrospective cardiac gated PC cine-MRI on a 1.5 T MR system (Gyroscan Intera; Philips Medical Systems International, Best, The Netherlands), and 32-phase images were obtained in a cardiac cycle. A gradient echo pulse sequence (T1-FFE) was used with shortest echo time, flip angle of 25 degrees (for CSF flow and cord displacement) and 20 degrees (for blood flow), first-order flow compensation gradients, 6 mm slice thickness, 2 signals averaged,

140×140 mm rectangular field of view, and 256×128 acquisition matrix. The raw data matrix was zero padded to 512×512 to easily trace the contour of each region. Velocity encoded gradient was set at 7 cm/s for CSF flow and cord displacement and at 80 cm/s for blood flow along the cranio-caudal axis, respectively. The precision flow measurements under these imaging conditions correspond very well with the measured values obtained using an electromagnetic flow meter as described in reference 18.

RESULTS

The average ICCI of I-NPH group was 4.99 mL/[Pa•m] (SD = 1.88) compared with 11.4 mL/[Pa•m] (SD = 7.27) for control group and 20.5 mL/[Pa•m] (SD = 20.6) for VD group (Fig. 2). The ICCI in the I-NPH group was significantly lower than in the control and VD groups (P values were 0.03 and 0.01, respectively), whereas there was no significant difference in the ICCI between the VD and control groups (P = 0.42) (Fig. 2).

The average $ICVC_{p\text{-}p}$ was also significantly smaller in the I-NPH group (mean ±

SD, 0.422 ± 0.190 mL) than in the control (0.856 ± 0.375 mL) and VD groups (1.32 ± 1.20 mL) (P values were 0.01 and 0.03, respectively), but there was no significant difference (P = 0.76) in the $ICVC_{p\text{-}p}$ between the VD and control groups (Fig. 3).

On the other hand, the average $PG_{p\text{-}p}$ was not significantly different in the I-NPH group (mean ± SD, 0.0837 ± 0.0162 Pa•m) from the control (0.0869 ± 0.0301 Pa•m) and VD groups (0.0743 ± 0.0390 Pa•m) (P values were 0.86 and 0.67, respectively), and there was no significant difference (P = 0.58) in the $PG_{p\text{-}p}$ between the VD and control groups (Fig. 4).

ICCI values in both I-NPH patients after the tap test were greater than those before (Fig. 5). In one patient the increase of ICCI (case A in Fig. 5) was the result of increase in $ICVC_{p\text{-}p}$ and decrease in $PG_{p\text{-}p}$ values after tap test. In another patient the increase of ICCI (case B in Fig. 5) was caused only with an increase in $PG_{p\text{-}p}$.

DISCUSSION

Since the diagnosis and management of I-NPH remains unclear as compared to the secondary NPH, numerous techniques are used to identify patients who are likely to have I-NPH, and various means are used to identify those patients most likely to respond to treatment (6). In particular, CSF tap test or CSF outflow resistance via an infusion test is one of the reliable examinations (6), but these are invasive. It has been reported that a single standard for the prognostic evaluation of I-NPH patients was lacking, and that supplemental tests could increase the predictive accuracy of the prognosis (6). Therefore, we attempted intracranial compliance analysis using MRI as a noninvasive examination. Various reports have indicated that the compliance in patients with NPH declined (8, 10-13). In fact, we recently verified that there is a positive correlation between the ICCI and the pressure-volume response determined by the ICP changes after a bolus injection of saline (1-5 ml) into the lateral ventricle, as an invasive measure of compliance (19). When it is difficult to differentiate VD from NPH on ordinary MRI or X-ray CT, the ICCI analysis with MRI will likely prove useful.

In our ICCI studies, the ages between the I-NPH group and control group were somewhat different. However, a small outflow-resistance with increased age, i.e.,

low negative slope of compliance/age has been reported (20). In fact, there was no significant correlation between ICCI and age (R^2=0.31, P>0.05). This is because the change with age may be included in the determination error such as a reproducibility of ICCI within 20%. Therefore, we took alterations in ICCI induced by age differences as being negligible compared with the large changes by I-NPH (11).

On the other hand, the fact that $ICVC_{p-p}$ in I-NPH was also significantly smaller (Fig. 3) coincided with a recent result (21) indicating that patients with Chiari malformation have low compliance. Our result also can be explained by a theory, according to which, due to the reduced compliance of the intracranial compartment, venous and CSF outflow occur more immediately following the systolic increase in arterial blood inflow, which in turn results in a smaller systolic increase in intracranial volume, i.e., $ICVC_{p-p}$ (21). This $ICVC_{p-p}$ change provides additional diagnostic information on I-NPH. Moreover, the fact that PG_{p-p} in I-NPH did not significantly change in other groups (Fig. 4) would indicate the need for not only CSF flow measurement, i.e., PG_{p-p}, but also ICCI (or $ICVC_{p-p}$) determination.

The increase in ICCIs of both I-NPH patients with positive CSF tap test (Fig. 5) can be explained by an increase in compliance by withdrawing CSF. However, the reason for the ICCI increase is not the same; in one case, $ICVC_{p\text{-}p}$ increased because $PG_{p\text{-}p}$ decreased. In another case, it was due to the fact that mainly the $ICVC_{p\text{-}p}$ increased. The exact reason must be pursued in detail in forthcoming studies of a larger sample.

In conclusion, we investigated intracranial compliance using MRI in I-NPH patients and compared with VD and healthy subjects. The ICCI and $ICVC_{p\text{-}p}$ in the I-NPH group were significantly lower than in the control and VD group, but there was no significant difference between the VD and control groups. There was no significant difference in the $PG_{p\text{-}p}$ between groups. ICCI in I-NPH increased after the CSF tap test. ICCI analysis using PC cine MRI makes it possible to noninvasively obtain a more detailed determination of the intracranial state in I-NPH and thereby assist in the diagnosis.

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Figure Legends

Figure 1. Procedure (upper flow chart), and (**a**-**c)** slice and ROI position for obtaining intracranial compliance index (ICCI). (**a**) T1-weighted image in the mid-sagittal plane and (**b**, **c**) thickened phase-contrast (PC) MR angiograms on right and left sides for setting the slice plane (dotted line). (**d**) Velocity-mapped PC cine MRI for determining the CSF flow (†) and spinal cord displacement (*). (**e**) Velocity-mapped PC cine MRI for arterial inflow, i.e., right and left internal carotid arteries (**1** and **2**) and vertebral arteries (**3** and **4**), and venous outflow, i.e., both internal jugular veins (**5** and **6**).

Figure 2. Intracranial compliance indices (ICCI) obtained with MRI in patients with idiopathic normal-pressure hydrocephalus (I-NPH) and asymptomatic ventricular dilation or brain atrophy (VD), and in healthy volunteers (control). Data are shown as mean ± SD. Asterisks indicate significantly different values between these groups ($P<0.05$). NS: not significant.

Figure 3. Peak-to-peak intracranial volume changes ($ICVC_{p\text{-}p}$, means ± SDs) determined with MRI in each group. Asterisks indicate significantly different values between these groups ($P<0.05$). NS: not significant.

Figure 4. Peak-to-peak normalized pressure gradients ($PG_{p\text{-}p}$, means ± SDs) calculated with MRI in each group. NS: not significant.

Figure 5. The changing rates of each of the intracranial volume change ($ICVC_{p\text{-}p}$), peak-to-peak normalized pressure gradient ($PG_{p\text{-}p}$), and intracranial compliance index (ICCI) after tap test in two cases with I-NPH.

1. MRI scan

・Twice obtained axial velocity-mapped images in each cardiac phase at the C2 level (dotted line in **a-c**).
1st : ±80 cm/s velocity encoding for blood flow
2nd : ±7 cm/s velocity encoding for CSF flow and cord

↓

2. Flow and displacement determination

・Flow and motion measurements in each ROI, and correction. Arterial inflow (1-4 in **e),** venous outflow (5 and 6 in **e**), and displacement of cord (⁎ in **d**) and CSF flow († in **d**).

↓

3. Calculation of intracranial volume change (*ICVC*)

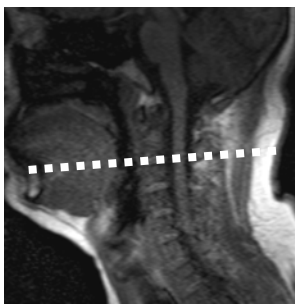
・From the net transcranial flow during the cardiac cycle

4. Calculation of CSF pressure gradient (*PG*)

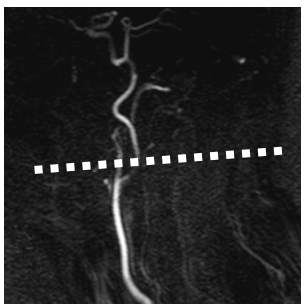
・Using a simplified Navier-Stokes Equation and normalizing by the CSF flow area († in **d**).

↓

5. $ICCI = \frac{\text{Peak-to-peak } ICVC}{\text{Peak-to-peak } PG}$



a



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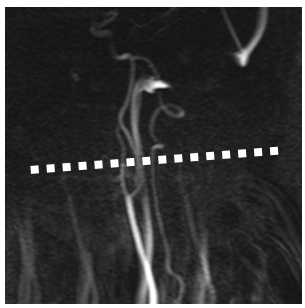
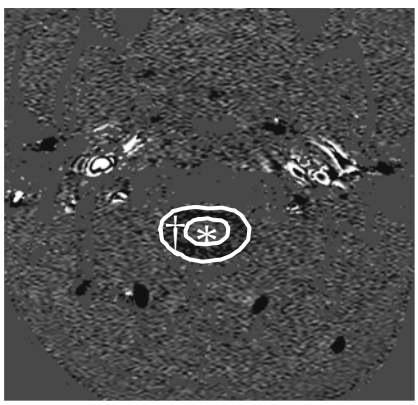


c



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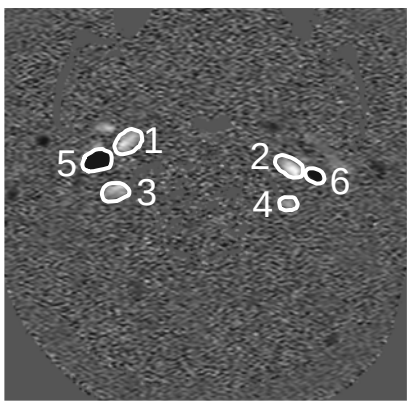
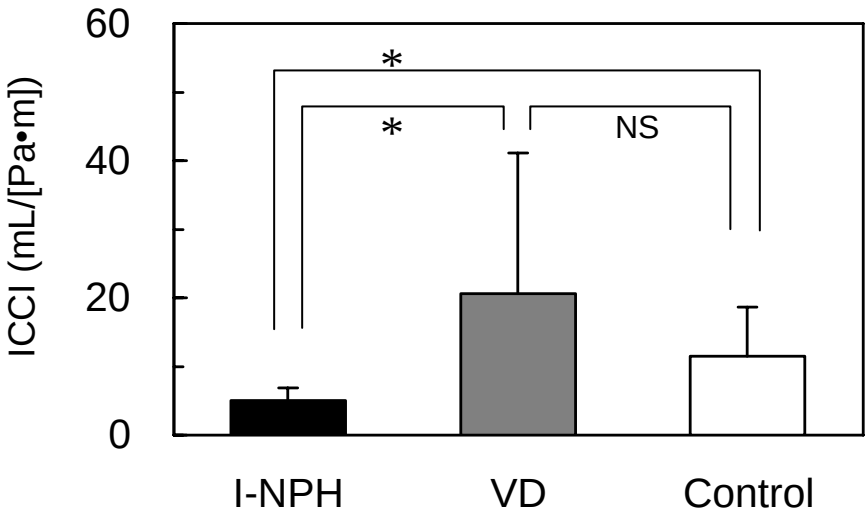
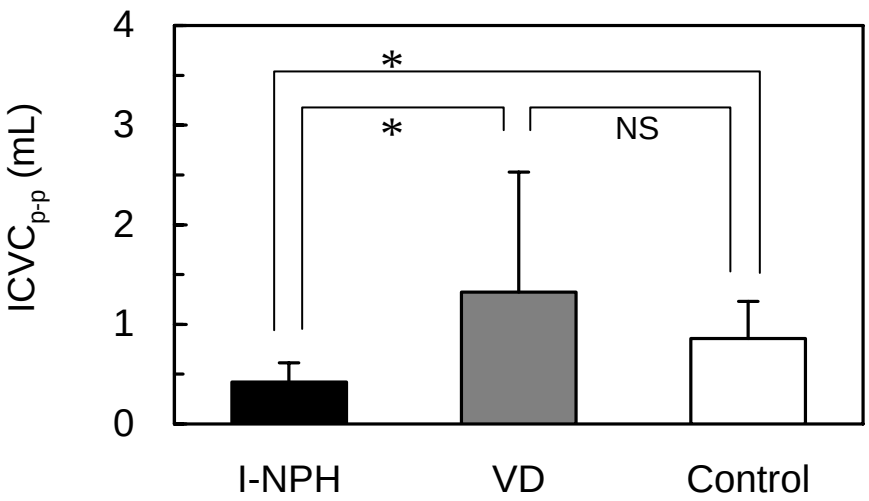
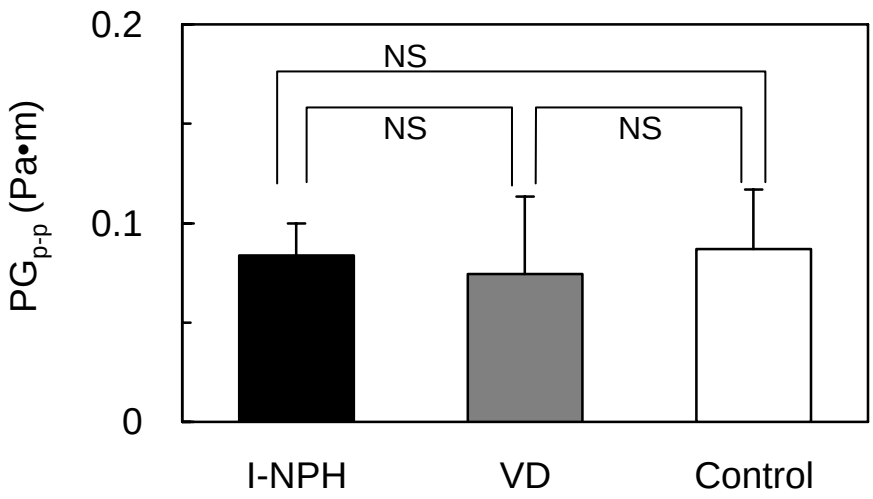
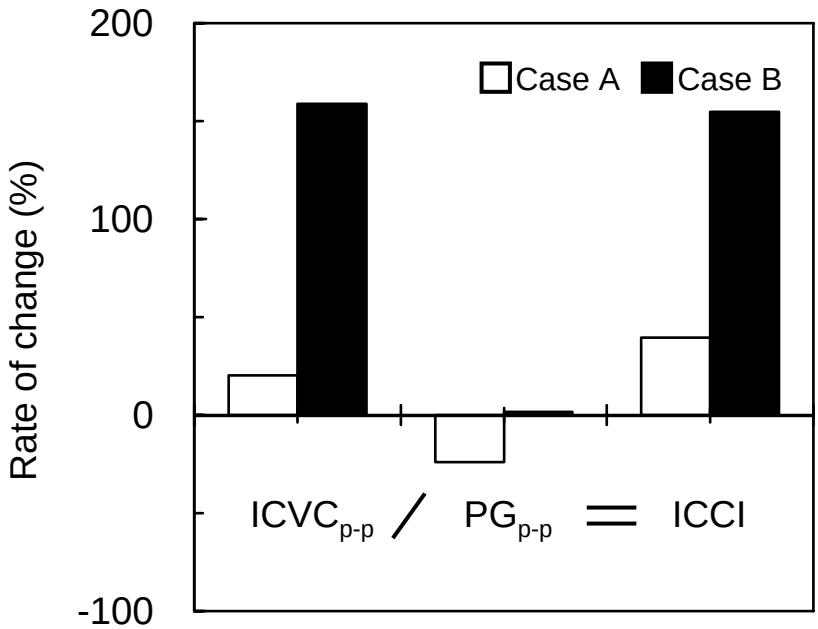


e


60
40
20
0
ICCI (mL/[Pa•m])
*
*
NS
I-NPH
VD
Control


4
3
2
1
0
ICVC$_{p-p}$ (mL)
*
*
NS
I-NPH
VD
Control


0.2
0.1
0
PG_{p-p} (Pa•m)
NS
NS
NS
I-NPH
VD
Control


200
100
0
-100
Rate of change (%)
Case A
Case B
ICVC$_{p-p}$ / PG$_{p-p}$ = ICCI