Ventricular Temperatures in Idiopathic Normal Pressure Hydrocephalus (iNPH) Measured with DWI-based MR Thermometry

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(Received July 22, 2014; Accepted March 25, 2015; published online June 23, 2015)

Purpose: The brain produces intense heat as a result of cerebral metabolism and cerebral blood flow, and the generated heat is removed mainly through circulation of the intracranial blood vessels and cerebrospinal fluid (CSF). Because magnetic resonance (MR) images are constructed from analysis of the spin of various molecules, the diffusion coefficient can be used as a parameter that reflects the temperature of water molecules. We used diffusion-weighted imaging (DWI)-based MR imaging to measure the temperature of the CSF around the lateral ventricles in patients with idiopathic normal pressure hydrocephalus (iNPH).

Methods: Our study included 33 cases of iNPH (Group N, mean age, 75.1 years) and 40 age-matched controls (Group C, mean age, 74.5 years). We calculated CSF temperature in the ventricular domain using the conversion formula to evaluate the feasibility of iNPH study.

Results: The mean temperatures were significantly higher in Group N (37.6°C ± 0.4°C) than Group C (36.7°C ± 0.5°C; P < 0.01). The cut-off value of 37.2°C (more than the mean + 2 standard deviations [SD] of the values in Group C) showed sensitivity of 72.4% and specificity of 77.5% for distinguishing the 2 groups. We confirmed improved CSF temperature in the lateral ventricles in all patients examined both before and after shunting.

Conclusions: Elevated ventricular temperatures in patients with iNPH (Group N) may represent a disturbance in heat balance. Our results showed that thermometry using DWI-based MR imaging can help in the noninvasive and consistent evaluation of CSF temperature and may thus provide a useful supplementary brain biomarker for iNPH.

Keywords: diffusion-weighted imaging (DWI)-based MRI, idiopathic normal pressure hydrocephalus (iNPH), ventricular temperatures

Introduction

Idiopathic normal pressure hydrocephalus (iNPH) is increasingly important among the various disorders associated with the clinical triad of dementia, gait disturbance, and urinary incontinence in the elderly. Its characteristic finding is ventriculomegaly. iNPH is usually diagnosed using noninvasive methods by magnetic resonance (MR) imaging,1–3 and cerebrospinal fluid (CSF) shunt surgery can reverse its symptoms.
iNPH is difficult to distinguish from neurological or nonspecific conditions that cause locomotor, cognitive, and urinary disorders in the elderly. Although half a century has passed since the first report of the disorder, it continues to be described as “idiopathic” in the clinical field because its etiology and pathological mechanism have yet to be elucidated. Against this background, early surrogate markers for detecting iNPH have been sought to facilitate its more accurate diagnosis in the elderly, to select appropriate patients for whom CSF shunt surgery would be effective, and to maintain the long-term effects of shunt surgery.

Recently, MR imaging has provided information about brain physiology within the central nervous system as well as brain structure, and thermometry is expected to be useful for clinical evaluation. Of the various MR imaging methods, post-processing of the diffusion-weighted image (DWI) is clinically useful. MR images are constructed from the encoding spin of molecules, and diffusion is a parameter that reflects the thermal motion of molecules. Based on the MR characteristics of the brain, the diffusion coefficient increases with the elevation of brain temperature and increased activity of free water. The utility of this novel thermometry using DWI-based MR imaging has been reported with regard to the relationship between the diffusivity of water molecules and the measurement of brain temperature. The previous reports suggested that change in brain temperature is characteristic of the hemodynamics of cerebral blood flow and may thus be applicable for the evaluation of diseases that affect the CSF, such as iNPH. The application of this technique to evaluate ventricular temperature is now anticipated in neurological diseases such as iNPH, which results from impairment of CSF circulation with ventriculomegaly.

Using a previously reported method of DWI-based MR imaging to measure CSF temperature around the lateral ventricles in patients with iNPH, we undertook this study to clarify the feasibility of measuring brain temperature in patients with iNPH by determining whether CSF temperatures are higher in iNPH cases than in controls and whether CSF temperatures change in patients with iNPH after shunting.

Materials and Methods

Subjects

The subjects were 2 groups of patients admitted to our hospital or who received medical care at the outpatient clinic between January 1st 2008 and December 31st 2011. DWI-based MR imaging was performed in all cases in addition to routine MR imaging evaluation for this study. The ethics committee of our university approved this study in conformity with the Declaration of Helsinki, and informed consent was obtained from all subjects.

One group (Group N) consisted of 33 patients (17 men, 16 women; mean age, 75.1 ± 4.2 years) definitively diagnosed with iNPH that responded to the shunt operation. Diagnosis was made according to the clinical management guidelines for iNPH of the Japanese Society of Normal Pressure Hydrocephalus, and patients fulfilled the criteria of the international guidelines for iNPH. We included those patients with iNPH only and excluded patients with secondary hydrocephalus with history of head injury, subarachnoid hemorrhage, or meningitis. Patients underwent ventriculo-peritoneal shunt surgery, and improvement of symptoms after surgery was confirmed. All were in excellent health at the time of their MR scans, which were performed before and approximately one month after shunt surgery.

The control group (Group C) consisted of 40 age-matched normal subjects (21 men, 19 women; mean age, 74.5 ± 3.3 years) who underwent voluntary health examinations, subsequently showed no evidence of supratentorial lesions on head MR imaging, and had no apparent cerebrovascular lesions or history of other neurological abnormalities.

MR imaging and data analysis

All MR imaging examinations were obtained using a 1.5-tesla whole body imager (Philips Medical Systems, Best, The Netherlands). Image acquisition of DWI was approximately 3 min. Six gradient directions were applied for DWI to obtain high spatial resolution. A single-shot echo-planar imaging technique was used for DWI (repetition time [TR]/echo time [TE], 6000/88 ms), with a b value of 1000 s/mm² and image averaging performed twice. Motion-sensitizing gradients were applied in 15 directions. Forty-two 3-mm-thick sections were obtained without intersection gaps.

The other conventional MR imaging examination analyzed in this study included fluid-attenuated inversion recovery (FLAIR) images (delay time, 2200 ms; TR/TE, 8000/100 ms). These sequences were kept similar to the sequence used in the above-mentioned human study.

We extracted the lesions of each lateral ventricle targeted for measurement by outlining the borders of the ventricles to exclude periventricular brain, calculated the temperature of the CSF in the ventricle domain for the analyses in Groups C and N.
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according to the previously published conversion formula, and followed the 2 groups using MR imaging. The mean time between shunt surgery and follow-up MR imaging was approximately 2 months. We retrospectively examined the data for temperature analysis.

We simultaneously evaluated any correlation of the thermography measurements with Evan’s index\(^1,2\) by group as a parameter of ventricular size; the index represents a ratio of the diameter of the maximal anterior horns of the lateral ventricle to the transverse intracranial diameter and indicates ventriculomegaly of 0.3 or greater.

Because body temperature can affect brain temperature, we also compared body temperatures of the patient and control groups. For the patient group, axillary temperatures (axillary thermometer; Terumo, Tokyo, Japan) were measured on the same day as before and after MR imaging evaluations. When the examined subjects had a fever or were not in good medical condition on the examination day, MR imaging evaluation was avoided to minimize the influence of an abnormal core temperature. We simultaneously recorded the temperatures of all subjects before MR imaging evaluation to determine any elevation in temperature, although no case had a fever on the day of imaging.

**Determination of ventricular temperature (temperature estimation)**

The previously reported kinetic theory suggested a direct relationship between the absolute temperature (T) and diffusion coefficient (D). Moreover, several recent studies by the team of Mills and Nagy have shown that CSF temperature can be estimated using this relationship.\(^11,20\) They have proven the relationship between pure water diffusion and diffusivity and the ability of DWI to measure the temperature of CSF. On the basis of previous reports, including those of our collaborators,\(^15,16\) we calculated the diffusion constant (D, mm\(^2\)/s) using a previously reported equation,

\[
D = \frac{\ln (S_0/S)}{b},
\]

in which \(b\) is the applied diffusion weighting (s/mm\(^2\)), \(S_0\) is the voxel signal intensity of the reference, and \(S\) is that of the DWIs, and we then converted the constant to temperature.

The temperature (T, °C) estimation is considered for CSF within the lateral ventricles because this method is only applicable to nonrestricted water. The D value was converted to the corresponding temperature using

\[
T = \frac{2256.74}{\ln (4.39221/D)} - 273.15,
\]

and the mean of the temperature estimates was finally determined.

We applied these formulae for DWI-based MR thermometry of the ventricles according to the method reported previously by our collaborators.\(^15,16\) We performed this study as a feasibility study because this method to estimate absolute CSF temperature using the water diffusion coefficient has not been established.

Diffusion of the CSF is almost equal to the free diffusion of pure water. Therefore, we applied this formula Eq. 2\(^20\) for this pilot study taking into consideration the possible bias in the calculated temperature level from the pulsatile and breathing-related movement of the water molecule, structured water molecules bordering on polymers, and hydrogen-bonding breaking effect by the ion.\(^21\)

Figure 1 shows a typical analysis data sheet from an iNPH case. Although 6 decimal digits are used to display the average temperature value, the effective number of digits may be smaller.

**Statistics**

We analyzed statistics using SPSS software (19.0, SPSS Inc., Chicago, IL, USA). Clinical data are presented as means ± SD. Group comparisons were performed using a nonparametric Wilcoxon rank-sum test or Spearman’s rank correlation coefficient, with \(P < 0.05\) considered significant. Finally, we performed receiver operating characteristic (ROC) curve analysis for each peak of interest and plotted the area under the curve (AUC) for each selected feature.

**Results**

Table presents the clinical characteristics of the subjects enrolled in Groups C and N. In Group N, all 33 patients demonstrated gait disturbance, 31 (93.9%) showed cognitive impairment, and 25 (75.8%) experienced urinary incontinence. These distributions were similar to those in previous reports.\(^22-24\) Body temperature did not differ between the groups and did not differ significantly between the groups before (36.4 ± 0.5°C) and after (36.2 ± 0.4°C) MR imaging. It was not possible to observe the correlation between the changes in body temperature and ventricular temperature examined in this study before and after surgery. The temperature was significantly higher in Group C (37.7°C ± 0.4°C) than Group N (36.7°C ± 0.5°C) (\(P < 0.01\)) (Fig. 2A).
To identify the peaks that would be useful for differential diagnosis between Groups N and C, we analyzed sensitivity and specificity using ROC curve analysis. The cut-off value of 37.2°C (more than the mean + 2 SD in Group C) showed sensitivity of 78.1%, specificity of 77.5%, and positive predictive value of 73.5% to distinguish the 2 groups. Furthermore, the classification efficiency of this cut-off value and the discriminatory power of the data set were proven by ROC curve analysis. ROC curve analysis also proved the diagnostic capability of the peak at 37.2°C. The AUC was 0.818 for distinguishing Group N and Group C, suggesting that the peak at 37.2°C could be used to discriminate Group N with appropriate accuracy (Fig. 2B). We also evaluated the correlation between the thermography measurement and Evan’s index. Although we expected some direct correlations, there were no significant correlations between the groups on the scatter plot. Thus, the Evan’s index is not needed as a parameter of ventricular volume as a covariate in this analysis.

We also evaluated any significant correlation between the CSF temperatures of the lateral ventricles before and after shunting surgery (Fig. 3). All MR imaging examinations were scheduled to be performed before and after the shunt operation in ac-

| Table. Clinical characteristics of Group C and Group N subjects |
|---------------------------------|-----------------|-----------------|
|                   | Group C (n = 40) | Group N (n = 33) |
| Sex (male:female) | 21:19           | 17:16           |
| Age (y; mean±SD)  | 74.5 ± 3.3      | 75.1 ± 4.2      |
| Gait disturbance (%) | 0 (0)         | 33 (100)        |
| Cognitive impairment (%) | 0 (0)         | 31 (93.9)       |
| Urinary incontinence (%) | 0 (0)         | 25 (75.8)       |
| Body temperature (°C) | 36.1 ± 0.5     | 36.3 ± 0.6      |
| Evan’s index       | 2.3 ± 0.4       | 3.3 ± 0.3       |
cordance with the written protocol, and only one patient who underwent the operation failed to complete the MR imaging schedule, as a result of a change of mind. Ventricular temperatures in patients treated by ventriculo-peritoneal shunting surgery decreased with the implanted drainage tube compared to the temperatures measured before surgery, and symptom improvement was confirmed after surgery.

Discussion

iNPH appears to result from impaired CSF circulation; it develops in elderly patients; and symptoms usually progress slowly. Appropriate CSF shunt surgery can improve symptoms, but preoperative diagnosis using these criteria is usually difficult. A tool is needed for clinical diagnostic discrimination, and a difference in CSF temperature could be such a tool if this variable were to be observed between iNPH patients and control subjects.

In the physiological field of the central nervous system, the brain is the most energy-demanding organ, and the large quantity of energy used for metabolism is subsequently transformed into heat. The generated heat is mainly removed through intracranial blood vessels and cerebrospinal fluid circulation; the balance between the generation of heat and its removal by the circulation ensures an appropriate fixed temperature in the human brain. Because the cerebrospinal fluid circulation is affected and the blood circulation in the brain is decreased in iNPH, we hypothesized that this heat balance was disturbed in patients with iNPH.

Recently, a noninvasive approach for tempera-
though iNPH could be regarded as a circulation with insufficient CSF pulsatility, which could lead to overestimation of the ventricular temperature, which would be problematic in patients with monitoring devices or dentures. It would also be ideal to measure the real ventricular size using MR imaging at the same time, which is currently limited by heterogeneous diffusion of water within the ventricle. We are upgrading the software to be able to trace the ventricular size automatically.

As a next step, more data should be collected and compared with the present data by evaluating other MR imaging-based diagnostic methods, such as phase contrast MR imaging or, more recently, TIME-SLIP (time spatial labeling inversion pulse) MR imaging for shunt-responsive iNPH at the baseline survey. Comparison of these data might explain the increase in temperature from lack of CSF exchange between the lateral ventricles and the rest of the ventricular system and subarachnoid space. As a second priority, poor responders to the shunt operation would be evaluated to assess the applicability of this method as a universal evaluation for all patients with iNPH regardless of shunt treatment. A future study might compare patients with ventriculomegaly from other causes, such as Alzheimer’s disease, to better address the differences with iNPH by this thermometry using DWI-based MR imaging method.

Despite these limitations, we confirmed an apparent difference in temperature within the lateral ventricles of patients with iNPH and controls. Because the brain generates a substantial percentage of total body heat, the lack of CSF exchange between the lateral ventricles, rest of the ventricular system, and subarachnoid space could explain the increased temperature. Whether such an effect has a critical influence on the measurement needs to be assessed in future studies.

Conclusions

Ventricular temperature measured using DWI MR imaging appears to provide useful supplementary information for the diagnosis or sequential evaluation of treatment for iNPH. Our results show that noninvasive measurement of the temperature of the ventricular CSF is clinically feasible and provides information regarding potential lack of CSF exchange between the lateral ventricles and subarachnoid space that could explain the increased temperature.

Disclosure: N. Kuriyama received partial research support from a Grant-in-Aid for Scientific Research (C) (No. 24590809) from the Ministry of Education, Culture, Sports, Science and Technology Japan.
of Education, Culture, Sports, Science, and Technology of Japan. All the other authors report no specific disclosures.

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