Clinical Study of Cerebrospinal Fluid Dynamics Using $^{111}$In-DTPA SPECT in Patients With Subarachnoid Hemorrhage

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Abstract

The ventricle-to-background ratio and clearance rate constant measured by indium-111 diethylenetriaminepenta-acetic acid single photon emission computed tomography ($^{111}$In-DTPA SPECT) were evaluated for predicting hydrocephalus in 16 patients at 2 to 3 weeks after onset of subarachnoid hemorrhage. The activity in the lateral ventricles, basal cistern, and hemispheric convexities was measured at 6, 24, and 48 hours after lumbar injection of radionuclide. In the follow-up study, eight patients developed hydrocephalus, and required ventriculoperitoneal shunting. Radioactivity measured in the hemispheric convexity did not reach peak activity within 48 hours. The clearance rate measured by applying the mono-exponential equation failed to show delayed clearance of radionuclide in hydrocephalus. The ratio between the ventricle and basal cistern measured at 6 hours postinjection was the best predictor of hydrocephalus ($F(1, 30) = 42.84, p < 0.0001$). These results suggest that a single $^{111}$In-DTPA SPECT scan may be sufficient to identify patients at risk of developing hydrocephalus.

Key words: subarachnoid hemorrhage, hydrocephalus, cisternography, single photon emission computed tomography

Introduction

The diagnosis of cerebrospinal fluid (CSF) fistula and idiopathic normal pressure hydrocephalus has been primarily based on radionuclide cisternography. The characteristic findings of normal pressure hydrocephalus are reflux into the ventricle and late ventricular stasis, as well as impairment of flow over the hemispheric convexities. However, these findings are occasionally observed in healthy subjects. CSF outflow is obstructed in patients with subarachnoid hemorrhage (SAH) by the clotted blood and leptomeningeal fibrosis, which is considered to be the mechanism responsible for the hydrocephalus. Leptomeningeal fibrosis induced by microsurgery is also believed to be a causative factor in the pathogenesis of cerebral vasospasm.

Indium-111 diethylenetriaminepenta-acetic acid single photon emission computed tomography ($^{111}$In-DTPA SPECT) provides higher spatial resolution and more accurate quantification of CSF flow than other modalities. $^{111}$In-DTPA was introduced in 1972, and data acquisition has been generally performed at 4 (or 6), 24, and 48 hours postinjection. The number of SPECT scans required to identify abnormal CSF circulation is not always immediately obvious.

The present study used $^{111}$In-DTPA SPECT to investigate the CSF dynamics in patients with SAH to identify the best analytic parameter for predicting hydrocephalus, the optimum scan procedure for $^{111}$In-DTPA SPECT, and the effect of scarring caused by the transsylvian approach on CSF dynamics.
**Table 1  Patient profiles**

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age (yrs)/Sex</th>
<th>Location of aneurysm</th>
<th>WFNS grade</th>
<th>Distribution of blood on CT</th>
<th>Shunt surgery</th>
<th>GOS</th>
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<tr>
<td>1</td>
<td>74/F</td>
<td>AcomA</td>
<td>I</td>
<td>diffuse SAH</td>
<td>yes</td>
<td>GR</td>
</tr>
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<td>GR</td>
</tr>
<tr>
<td>3</td>
<td>75/F</td>
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<td>II</td>
<td>diffuse SAH</td>
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<td>SD</td>
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<tr>
<td>4</td>
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<td>GR</td>
</tr>
<tr>
<td>5</td>
<td>71/F</td>
<td>lt A1, distal</td>
<td>I</td>
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<td>GR</td>
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<td>6</td>
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<td>diffuse SAH</td>
<td>yes</td>
<td>GR</td>
</tr>
<tr>
<td>7</td>
<td>75/F</td>
<td>lt ICA terminal</td>
<td>IV</td>
<td>diffuse SAH and ICH</td>
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<td>SD</td>
</tr>
<tr>
<td>8</td>
<td>79/M</td>
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<td>diffuse SAH</td>
<td>yes</td>
<td>GR</td>
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<tr>
<td>9</td>
<td>49/F</td>
<td>ACA</td>
<td>IV</td>
<td>diffuse SAH</td>
<td>yes</td>
<td>SD</td>
</tr>
<tr>
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<td>67/M</td>
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</tr>
<tr>
<td>12</td>
<td>81/M</td>
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<td>III</td>
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<tr>
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<td>45/M</td>
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<td>diffuse SAH</td>
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<td>no</td>
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</tr>
<tr>
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<td>no</td>
<td>GR</td>
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<td>16</td>
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<td>I</td>
<td>diffuse SAH</td>
<td>no</td>
<td>GR</td>
</tr>
</tbody>
</table>


**Patients and Methods**

Sixteen patients with ruptured aneurysms, 10 females and six males aged from 45 to 90 years, underwent craniotomy and clipping (Table 1). The anterior interhemispheric approach was employed for ruptured anterior communicating artery aneurysm, and the transsylvian approach for internal carotid artery, middle cerebral artery, and distal A1 aneurysms. A lumbar spinal drainage catheter was inserted after surgery and was left in place for 2 weeks to prevent the development of hydrocephalus.

The diagnosis of hydrocephalus was based on the following symptoms occurring after the removal of spinal drainage: deterioration of consciousness after removal of spinal drainage, gait disturbance, dementia, or urinary incontinence. These clinical symptoms were consistent with enlargement of the ventricle on computed tomography. The diagnosis of hydrocephalus was established in eight patients, who were subsequently treated by ventriculoperitoneal shunting. Both clinical and radiological improvements were confirmed at follow-up evaluations.

111In-DTPA SPECT was performed at 2 to 3 weeks after the onset of SAH. 111In-DTPA (1 mCi) in 1 ml solution (Nihon Mediphysics Co., Tokyo) was injected into the CSF through the spinal drainage catheter. The catheter was removed immediately after the injection. SPECT (E-CAM; Siemens, Germany) was performed at 6, 24, and 48 hours postinjection. Images were reconstructed and displayed as a 64×64 matrix (pixel size 4.0×4.0 mm with an interslice distance of 8.0 mm). Attenuation correction was performed with reslicing parallel to the orbitomeatal line. The regions of interest (ROIs) were placed along the major pathway of CSF flow and included the basal cistern, left and right lateral ventricles, left and right rostral hemispheric convexities, and left and right caudal hemispheric convexities. SPECT provides limited spatial resolution, so the size of each ROI was 150 pixels in the basal cistern, 70 pixels in the lateral ventricles, and 110 pixels in the rostral and caudal hemispheric convexities (Fig. 1A).

Emission computed tomography numbers (mean values for each pixel) at these ROIs were considered to represent radioisotope (RI) counts/acquisition time(s), and were corrected according to the corresponding decrease in radioactivity over time. A calculated time-activity plot was produced for each ROI. Ventricle-to-background ratio and clearance rate are used as analytic parameters in RI cisternography.8,10,17,18,20 This study measured three parameters considered to reveal abnormal CSF circulation.

1) Clearance rate constant: the mono-exponential decay curve was applied to the two points at 24 and 48 hours. This decay curve gave the constant value of k.
Fig. 1 A: Regions of interest (ROIs) were placed on the coronal image including the anterior horns of the lateral ventricles (1), basal cistern (2), and caudal (3) and rostral (4) hemispheric convexities. B–D: Indium-111 diethylenetriaminepenta-acetic acid single photon emission computed tomography images obtained at 6 (B), 24 (C), and 48 hours (D) after the injection in a patient (Case 14) who underwent the left transsylvian approach for clipping of a ruptured left internal carotid-posterior communicating artery aneurysm, demonstrating reduced hemispheric accumulation on the left side, but the ventricle accumulation is not remarkable. The patient recovered without developing hydrocephalus.

2) Ratio between ROIs and basal cistern: the count levels at 6, 24, and 48 hours were normalized to the count level in the basal cistern at 6 hours. We speculated that this normalization may allow comparison between patients with and without hydrocephalus at different intervals, since the amount of radionuclide that reaches the cranial cavity is highly specific to the individual.

3) Ratio between ROIs and total radioactivity in a measured slice: the count levels at 6, 24, and 48 hours were normalized to the total radioactivity in a measured slice. Because a single scan procedure may be sufficient for the diagnosis of hydrocephalus, this normalization was employed for the comparison of images obtained at 6, 24, and 48 hours, given that the abnormal accumulation of the ventricle can be used as an indicator of hydrocephalus.

To compare the effect of the transsylvian approach, the asymmetry of radioactivity in the hemispheric convexity was expressed as the ipsilateral to contralateral percentage.

Data are expressed as mean ± SD. Differences between groups with and without hydrocephalus were evaluated by two-way analysis of averages using Student’s t-test. Probability values less than 0.05 were considered significant. Discriminant analysis for hydrocephalus was performed using the ventricle-to-background (Vbg) and ventricle-to-basal cistern (Vbc) radioactivity ratio using the F-test associated with Wilk’s λ.

Results

Typical SPECT images obtained in patients with and without hydrocephalus are demonstrated in Figs. 1 and 2.

Fig. 2 Indium-111 diethylenetriaminepenta-acetic acid single photon emission computed tomography images obtained 6 (A), 24 (B), and 48 hours (C) after the injection in a patient (Case 8) who underwent the right transsylvian approach for clipping of a ruptured left internal carotid-posterior communicating artery aneurysm, showing remarkable accumulation in the lateral ventricle even after 6 hours. This patient later developed hydrocephalus.
The mean total radioactivity measured in the slices was $1438 \pm 1405$ at 6 hours, $852 \pm 520$ at 24 hours, and $334 \pm 213$ at 48 hours. The mean value decreased linearly with time. No significant differences in total radioactivity in measured slices were found between the patients with and without hydrocephalus. Figure 3 shows time activity plots in an illustrative case without hydrocephalus. The relative amount of radionuclide in the basal cistern and lateral ventricles was higher at 24 hours than at 6 hours. The relative amount of radionuclide in the rostral hemispheric convexity did not peak within the study period.

The clearance rates measured were $0.05 \pm 0.01$ in the basal cistern in the patients without hydrocephalus and $0.06 \pm 0.02$ in the patients with hydrocephalus, $0.05 \pm 0.03$ and $0.06 \pm 0.01$ in the lateral ventricles, $0.04 \pm 0.01$ and $0.03 \pm 0.02$ in the caudal hemispheric convexities, and $0.03 \pm 0.04$ and $0.03 \pm 0.03$ in the rostral hemispheric convexities, respectively. There were no significant differences in these values.

The ratio between the ROIs and the basal cistern showed the normalized counts in the lateral ventricles at 6, 24, and 48 hours were higher in the patients with hydrocephalus than without hydrocephalus ($p < 0.001, 0.01,$ and $0.05$, respectively) (Table 2). No other regions showed significant differences in the normalized count between the two groups.

The ratio between ROIs and the total radioactivity in a measured slice showed the normalized counts in the basal cistern at 6 hours were higher in the patients without hydrocephalus than with hydrocephalus ($p < 0.01$) (Table 3). The normalized count in the lateral ventricles at 6 hours was higher in the patients with hydrocephalus than without hydrocephalus ($p < 0.001$). The normalized count in the rostral hemispheric convexities at 48 hours was higher in patients without hydrocephalus than with

**Table 2** Regional radioactivity normalized using basal cistern level measured at 6 hours

<table>
<thead>
<tr>
<th></th>
<th>Basal cistern</th>
<th>Lateral ventricle</th>
<th>Caudal convexity</th>
<th>Rostral convexity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>6 hrs</td>
<td>24 hrs</td>
<td>48 hrs</td>
<td>6 hrs</td>
</tr>
<tr>
<td>Non-hydrocephalus</td>
<td>0.53</td>
<td>0.15</td>
<td>0.38***</td>
<td>0.33**</td>
</tr>
<tr>
<td>Hydrocephalus</td>
<td>0.30</td>
<td>0.11</td>
<td>0.16</td>
<td>0.24</td>
</tr>
</tbody>
</table>

*p<0.05, **p<0.01, ***p<0.001 by t-test.

**Table 3** Regional radioactivity normalized using background radioactivity

<table>
<thead>
<tr>
<th></th>
<th>Basal cistern</th>
<th>Lateral ventricle</th>
<th>Caudal convexity</th>
<th>Rostral convexity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>6 hrs</td>
<td>24 hrs</td>
<td>48 hrs</td>
<td>6 hrs</td>
</tr>
<tr>
<td>Non-hydrocephalus</td>
<td>0.45**</td>
<td>0.23</td>
<td>0.06</td>
<td>0.16***</td>
</tr>
<tr>
<td>Hydrocephalus</td>
<td>0.13</td>
<td>0.13</td>
<td>0.04</td>
<td>0.07</td>
</tr>
</tbody>
</table>

*p<0.05, **p<0.01, ***p<0.001 by t-test.
Fig. 4 Discriminant analysis in patients with hydrocephalus (●) and without hydrocephalus (○) using the ventricle-to-background ratio at 6 hours (V_{bg-6h}), and ventricle-to-basal cistern ratio at 6 (V_{BC-6h}), 24 (V_{BC-24h}), and 48 hours (V_{BC-48h}). Significant between-group differences were obtained with all these parameters (V_{bg-6h}: p < 0.001; V_{BC-6h}, V_{BC-24h}, and V_{BC-48h}: p < 0.0001, 0.01, and 0.05, respectively). A discriminant line (dots) based on V_{bg-6h} correctly identified seven of eight patients with hydrocephalus.

hydrocephalus (p < 0.05). No other regions showed significant differences in the normalized count between the two groups.

Discriminant analysis found the V_{bg} at 6 hours significantly discriminated the groups with and without hydrocephalus (F(1, 30) = 20.55, Wilk’s λ = 0.593, p < 0.001) (Fig. 4). The V_{BC} at 6 hours discriminated the groups with and without hydrocephalus more accurately (F(1, 30) = 42.84, Wilk’s λ = 0.41, p < 0.0001) than that at 24 and 48 hours (F(1, 30) = 8.86 and 6.61, Wilk’s λ = 0.77 and 0.82, p < 0.01 and 0.05 for 24 and 48 hours, respectively).

Patients who underwent the transsylvian approach had asymmetry of radioactivity in the hemispheric convexity with a median of 72.3% (range 41–1748) in the caudal convexity and 75.5% (range 25–310) in the rostral convexity at 6 hours, 71.2% (range 20–419) in the caudal convexity and 37.4% (range 7–410) in the rostral convexity at 24 hours, and 72.4% (range 18–222) in the caudal convexity and 55.7% (range 4–473) in the rostral convexity at 48 hours.

Discussion

The present study found characteristic ventricular accumulation and impaired flow over the convexity as determined by 111In-DTPA SPECT in patients with post-SAH hydrocephalus. These findings were clearly seen, even in images taken at 6 hours postinjection. The circulation of CSF was variably impaired on the side of hemispheric convexity where the transsylvian approach was employed. Quantitative measurement, such as the constant calculated using mono-exponential curve-fitting, failed to show delayed clearance of CSF across the regions, as well as between the patients with and without hydrocephalus.

I. CSF circulation theory

The proliferation of arachnoid cells, triggered by the inflammatory reaction or blood clotting
products, may result in obstruction of CSF flow through the arachnoid villi into the venous sinuses in patients with SAH.\textsuperscript{12} The generalized fibrosis in the subarachnoid space occurring from 1 week after the bleeding may be the cause of hydrocephalus.\textsuperscript{16} CSF is generally considered to flow from the production site in the choroid plexus, and is absorbed in the Pachionian granulations as originally proposed by Key-Retzius-Weed.\textsuperscript{13,14} However, recent investigations suggest that CSF can be produced everywhere, and absorbed everywhere, in the subarachnoid space.\textsuperscript{5} A phantom study indicated that convexity accumulation of radionuclide is not due to a bolus transport but rather to dilution of the CSF in the basal part of the intracranial subarachnoid space.\textsuperscript{5} CSF circulation is driven by the pulsating flow which causes effective mixing.\textsuperscript{5} \textsuperscript{111}In-DTPA SPECT showed that the RI injected from the lumbar region will accumulate primarily in the basal cistern in normal CSF circulation at 6 hours. Subsequent RI accumulation may still be an indicator of transport and clearance of CSF.\textsuperscript{3,8,10,11,18,20} Therefore, several analytic parameters have been considered to assess CSF dynamics.\textsuperscript{8,10,18,20}

II. Parameters calculated in SPECT

The clearance rate determined for exponential curve-fitting is an indicator of the disappearance of CSF.\textsuperscript{6,8,20} This value can be calculated as a constant, regardless of the amount of radionuclide that reaches the cranial cavity and the timing of the scan. Delayed CSF circulation in patients with hydrocephalus was demonstrated using mono-exponential curve-fitting.\textsuperscript{8} Furthermore, the normal RI clearance curve may fit the bi-exponential curve.\textsuperscript{6,20} The present study is consistent with the previous findings that peak activity in the lateral ventricle and basal cistern is 9–10 hours after lumbar injection.\textsuperscript{20} The clearance rate can be calculated as long as the scan is performed twice after the peak, but the present scan procedure is not responsible for the failure to identify impaired CSF circulation in hydrocephalus. In the hemispheric convexity, the radioactivity did not always reach the peak value within 48 hours. Although the physical half-life of 2.81 days is considered to suit studies over a period of up to 72 hours, only low amounts of radioactivity can be administered due to the high radiation dose to the spinal cord.\textsuperscript{1} Although the hemispheric convexity is the main region responsible for impaired CSF clearance, our study indicates that the clearance rate measured at the hemispheric convexity may not reveal delayed CSF disappearance.

The present study normalized the regional radioactivity to the level of the basal cistern measured at 6 hours. Since the amount of radionuclide that reaches the cranial cavity is highly individual, the radioactivity at the level of the basal cistern measured at 6 hours is used as a standard to assess subsequent distribution of the radionuclide. The major accumulation of RI in patients with hydrocephalus at 6 hours is mainly located in the ventricle rather than in the basal cistern. Accordingly, normalization fails to show the decrease in the hemispheric convexities in patients with hydrocephalus. We found that the V\textsuperscript{BC} at 6 hours was the best predictor of subsequent hydrocephalus. We also used normalization using total radioactivity in a measured slice to compare the V\textsuperscript{BG}. The V\textsuperscript{BG} was also highest in the images at 6 hours. These results suggest that a single scan procedure performed at 6 hours postinjection may be sufficient to predict the development of hydrocephalus in patients with SAH.

III. Evaluation of postoperative CSF circulation

Clotting after SAH could result in obstruction of CSF circulation.\textsuperscript{12,16} In addition, craniotomy and microsurgery may impair CSF circulation by postoperative scar formation. The impaired CSF circulation is involved in the development of vasospasm, which can be modified by cisternal irrigation or intravascular surgery. In this study, the distribution of RI ipsilateral to the approach was reduced by approximately 70% in the caudal hemispheric convexity, and to a larger extent in the rostral hemispheric convexity.

IV. Conclusions

The major conclusions of the present study are as follows. The V\textsuperscript{BC} measured at 6 hours is the most accurate predictor of hydrocephalus. The clearance rate constant can be calculated using data at 24 and 48 hours from the ventricle and basal cistern. However, this parameter failed to show the delay in CSF disappearance. Impaired CSF dynamics in the hemispheric convexity may be calculated either by using ROI to background ratio or right to left asymmetry. The scan procedure can be shortened to a single data acquisition run performed at 6 hours postinjection. Postoperative impaired CSF dynamics are variable in the transsylvian approach. The rostral convexity appears more impaired than the caudal convexity.

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References


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Commentary

111In-DTPA can provide accurate quantification of CSF flow. The authors investigated the CSF dynamics in patients with SAH to identify the analytic parameter for predicting hydrocephalus, and found characteristic ventricular accumulation and impaired flow over the convexity in patients with symptomatic hydrocephalus. These findings were seen in images taken at 6 hours post RI intrathecal injection. This study may provide a key to diagnose idiopathic NPH in the early stage.

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This is a valuable study about clinical application for prediction of hydrocephalus. Subarachnoid hemorrhage is one of the important causes of hydrocephalus, but the pathological and physiological mechanisms of hydrocephalus induced by subarachnoid hemorrhage remain unclear, especially the change of CSF dynamics. The authors applied $^{111}$In DTPA SPECT for predicting the risk of hydrocephalus development after subarachnoid hemorrhage. The results showed a distinct relationship with both the time and location following subarachnoid hemorrhage and hydrocephalus. This is very valuable work in which the quantitative analysis on the development of hydrocephalus will promote application in clinics. It is also hoped that more cases will be investigated with this kind of observation and analysis to get more significant data for predicting the risk of hydrocephalus after subarachnoid hemorrhage in the future.

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