MRI Study of Intracranial Hydrodynamics and Ventriculoperitoneal Shunt Responsiveness in Patient with Normal Pressure Hydrocephalus

Theerapol Witthiwej MD*, Pathomlirk Sathira-ankul MD*,
Orasa Chawalparit MD**, Wattanachai Chotinaiwattarakul MD***,
Nanthasak Tisavipat MD****, Panida Charnchaowanish MD**

** Department of Surgery, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand*
*** Department of Radiology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand*
**** Department of Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand*
***** Bangkok General Hospital, Bangkok, Thailand*

Objective: *To determine the predictor for shunt responsive cases in patient with normal pressure hydrocephalus (NPH) by means of magnetic resonance imaging (MRI) cerebrospinal fluid (CSF) flow study at Siriraj hospital.*
Material and Method: *The retrospective study was performed in patients suspected NPH and underwent MRI CSF flow measurement. 2D-phase contrast technique (Achieva, 3 Tesla Philips system) was used as CSF flow analysis. The preoperative and postoperative clinical outcomes were collected and analyzed to determine predictive value of MRI CSF flow measurement in shunt responsive patients.*
Results: *Between 2006 and 2011, twenty NPH patients underwent MRI CSF flow study and were treated by ventriculoperitoneal shunt placement. Fourteen of 20 cases had improved, at least in gait score. Of these, 10 were defined as significant responsive group for overall improvement of outcome (sum of iNPHGS ≥ 3). The mean velocity of the CSF flow through the aqueduct of Sylvius was significant difference between shunt-responsive and non- responsive groups ($p < 0.05$). The peak velocity was a significant difference between gait responsive and non-responsive groups ($p < 0.05$). Using a mean velocity threshold 26 mm/sec to identify the significant responsive group, the sensitivity is 50%, specificity 83.3%, positive predictive value 87.5%, and accuracy 70%. In order to identify the gait responsive group by using a threshold of peak velocity 70 mm/sec, the sensitivity was 60%, specificity 83.3%, positive predictive value 81.5%, and accuracy 60%.*
Conclusion: *Using available commercial software in the authors' institute, the mean velocity as well as the peak velocity was a specific value that predicted significant shunt responsiveness in NPH patients.*

Keywords: *Normal pressure hydrocephalus (NPH), MRI CSF flow study, Idiopathic NPH grading scale (iNPHGS)*

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The diagnosis of normal pressure hydrocephalus (NPH) is made on clinical grounds, *i.e.*, an elderly patient with the classic clinical trial of gait disturbance, dementia, and incontinence in the setting of ventricular dilatation without CSF flow obstruction on neuroimaging. However, the clinical picture is frequently obscured by advanced age and concomitant medical and neurological disease. Primary or idiopathic normal pressure hydrocephalus (iNPH) usually occurs in old age patients without a history of meningitis, subarachnoid hemorrhage, and previous cranial surgery as found in secondary NPH patients. The standard treatment of NPH is a ventriculoperitoneal (VP) shunt placement. Unfortunately, not all patients respond to shunt placement[1]. Patients in early stage of NPH seem to respond to VP shunt better than late stage of the disease as a result of changes of cerebrospinal fluid (CSF) dynamic parameters[2]. Over the years, several investigators have noted elevated CSF flow through the aqueduct in patients with clinical NPH who subsequently responded to VP shunting[3]. The earliest magnetic resonance image (MRI) studies noted an increased aqueductal CSF flow void on proton density weighted conventional SE images without flow compensation[4]. More recent studies of CSF motion in NPH have made direct measurements of velocity of CSF flowing through the aqueduct by using cine phase

Correspondence to:
Witthiwej T, Department of Surgery, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok 10700, Thailand.
Phone: 0-2419-8003
E-mail: twitthiwej@yahoo.com

contrast (PC) MRI techniques. Integration over the area of aqueduct then allows calculation of volumetric flow rate. Bradley W et al demonstrated higher accuracy by using stroke volume (SV) measured by cine-phase contrast (PC) MRI technique instead of CSF flow void score in predicting shunt responsive cases[5]. They also suggested the threshold of 42 μL for stroke volume (SV) in predicting shunt responsive cases. Dixon GR et al repeated the study and found no significant correlation between average MRI flow and degree of improvement[6]. They could not identify any threshold for low CSF flow values below which patients did not improve. Kahlon B studied CSF stroke volume (SV) for predicting outcome after shunt surgery in suspected NPH[7]. His study showed no evidence that cine-PC MRI measurements of SV in the cerebral aqueduct were useful for selecting patients with NPH symptoms for shunt surgery. Luetmer PH found CSF flow rate greater than 18 ml/min (with average flow rate 27.4 ml/min) suggesting idiopathic NPH[8]. Sharma AK studied a change of peak CSF flow velocity after lumbar drainage, which was also a sensitive method to select patients that would benefit from VP shunt surgery[9]. In their study, the shunt responsive group had change of peak CSF flow velocity 14.40 cm/sec. Egeler-Peerdeman SM studied a flux difference-MRI CSF flow parameter in NPH patients,and found the flux difference of a shunt responsive patient was twice of normal range[10]. Through evaluating these controversies, the authors found that many reports might support the usefulness of cine-PC MRI in the study of CSF flow dynamics predicting shunt responsiveness[8,9].

The purpose of the present study was to determine the threshold of MRI CSF flow measurement in identifying shunt-responsive NPH patients by using 3 Tesla MRI machine and available commercial software in the authors' institution.

Material and Method

A retrospective review was performed between 2006 and 2011 in patients with clinically suspected normal pressure hydrocephalus (NPH).

The clinical information was collected for demographic data, duration of symptoms, idiopathic normal pressure hydrocephalus grade before and after VP shunt (Table 1)[11], type of VP shunt, and result of surgery by reviewing in-patient and out-patient data collection. An improvement of overall outcome idiopathic Normal Pressure Hydrocephalus grading scale (iNPHGS) less than 3 was considered as a non-significant responsive group and a sum of iNPH grading scale (iNPHGS) more than 3 was considered as the significant responsive group. Gait disturbance in NPH patients are usually the major initial clinical symptoms that suffers the patient and family. Gait severity based on iNPHGS start from normal gait (grade 0), dizziness or unsteadiness only (grade 1), unstable but independent gait (grade 2), walking with any support (grade 3) and walking not possible (grade 4) orderly. Therefore, any improvement of gait score (> 1 grade) was considered as gait response group and the other score was considered as gait non-response group.

All patients underwent MRI CSF flow study in addition to conventional MRI axial T1 weighted image (T1wi), FLAIR and T2wi (Achieva, 3Tesla Philips system). In the authors' institute, 2-dimensional – phase contrast (2D-PC) was performed as one of the routine pulse sequences in the protocol for CSF flow study. The flow study is acquired in axial plane perpendicular to the long axis of aqueduct of Sylvius.

Table 1. iNPH grading scale(iNPHGS)[11]

Grade	Gait disturbance	Cognitive impairment	Urinary disturbance
0	Normal	Normal	Normal
1	complaints of dizziness of drift and dysbasia but no objective gait disturbance	Complaint of amnesia or inattention but no objective memory and attention impairment	Pollakiuria or urinary urgency
2	Unstable but independent gait	Amnesia or inattention, but no disorientation of time and place	Occasional urinary incontinence (1-3 or more times per week but less than once per day)
3	Walking with any support	Disorientation of time and place, but no impairment of conversation	Continuous urinary incontinence (1 or more times per day)
4	Walking not possible	Disorientaiton for the situation or impaired meaningful conversation	Almost or perfectly impaired bladder function

It routinely begins with velocity encoding (VE) of 10 cm/sec with foot-head direction and reports suggestive hyperdynamic flow if the VE higher than 15 cm/sec has to be used to eliminate aliasing artifact. The sequence of velocity encoding without aliasing artifact was used for quantitative analysis.

The commercial software for flow analysis (Easy Vision, Philips) was used separately by one experienced neuroradiologist and one well-trained technologist. The magnitude images were selected for drawing region of interest (ROI) over the aqueduct. Before drawing, the authors adjusted window width and chose the image showing biggest diameter (which was "white flow") of the aqueduct. The ROI was traced free handed around the border of the aqueduct (Fig. 1). The software calculated stroke volume, forward flow, backward flow, percentage of regurgitation, absolute stroke volume, flux, maximum velocity, minimum velocity, mean velocity, and peak velocity. The highest point/phase of each flow measurement was selected as the value of recorded data.

The clinical outcome (iNPHGS), Evans' index, and MRI CSF flow parameters were analyzed for evaluating relationship by using independent samples t test (SPSS 13). The statistical significant difference was set at $p < 0.05$. The present study was approved by the Ethics Committee of the institution.

Results

Between 2006 and 2011, 20 patients with MRI CSF flow study and VP shunt (VPS) placement were included into the present study. Eleven were men and nine were women. Mean age was 66.3 years old (range 44-80 years old). Mean duration of symptoms was 10.5 months. The patients were diagnosed as primary NPH in 12 cases (seven cases improved, and five cases did not improve after VPS) and secondary NPH eight cases (seven cases improved and one case did not improve after VPS). The programmable VP shunt was performed in 14 cases and the non-programmable in six cases. There was no statistically

Table 2. Pre and postoperative change of iNPHGS and number of patients

	Number of cases
Change of gait (compared with preoperative iNPHGS)	
0	6
1	8
2	6
3	0
Change of memory function (compared with preoperative iNPHGS)	
0	12
1	8
2	0
3	0
Change of urinary function (compared with preoperative iNPHGS)	
0	8
1	7
2	4
3	1

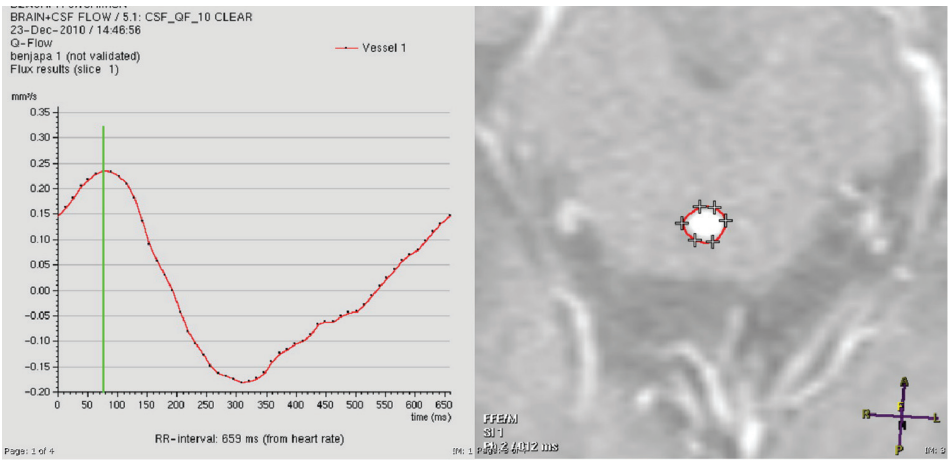

Fig. 1 Graph shows flow velocity and time (left), drawing a region of interest (ROI) over aqueduct of Sylvius (right). Note the vertical line was placed at the highest point of the curve. The value (flux in this curve) at this phase of the series was recorded

significant relationship between type of VP shunt and improvement. Ten of 20 cases had an overall outcome of significantly improved (sum of iNPHGS ≥ 3) after treatment (mean duration of follow-up 6.6 months). Fourteen out of 20 cases had gait improvement (six cases had no change, eight cases improved 1 score, and six cases and improved 2 score), eight out of 20 cases had cognitive improvement (12 cases had no change, eight cases improved 1 score) and 12 out of 20 cases had urinary improvement (eight cases had no change, seven cases improved 1 score, four cases improved 2 score, and one case improved 3 score). The details of improvement are shown in Table 2.

Evans ratio, stroke volume, and flux had no significant relationship with improvement of NPH score. The peak velocity and mean velocity were the only MRI CSF flow parameters, which showed statistically significant difference between patients with shunt responsive and non-responsive groups ($p < 0.05$). Patients in the responsive group had higher mean of peak velocity and mean velocity than in the non-responsive group (Table 3). The gait response group had peak velocity value significantly different from gait non-response group (Table 4).

To find out the best threshold for selecting significant VP shunt responsive patients using statistical analysis, when mean velocity above 26 mm/sec was used, the sensitivity was 60%, specificity 80%, positive predictive value 75%, and accuracy 70%. Accordingly, the peak velocity value above 70 mm/sec was also the best threshold for gait response group with the sensitivity 50%, specificity 83.3%, positive predictive value 87.5%, and accuracy 60% (Table 5-7).

Discussion

Diagnosis for normal pressure hydrocephalus is one of the difficult clinical problems, not only because of overlapping with other syndromes but also because of the heterogeneity of the treatment response that influences the study designs. Studies of CSF flow analysis by using normal subjects were not successful because when hydrocephalus had developed, the dilated aqueduct resulted in change of area and volume of region of interest (ROI), which in turn influenced the measured flow values[13]. Bradley WG et al suggested stroke volume as the critical predictor for the reason of total volume of CSF flow through the aqueduct in one cardiac cycle[6]. With the threshold of

Table 3. Overall outcome improvement

Overall outcome improvement (cases)	Mean velocity (mm/s) ± SD, $p < 0.05$	Peak velocity (mm/s) ± SD, $p < 0.05$
Significant improve group (10)	32.64 ± 17.38	87.91 ± 27.64
Non significant improve group (10)	18.21 ± 7.24	49.56 ± 18.89

Table 4. Gait outcome improvement

Gait outcome improvement (case)	Mean velocity (mm/s) ± SD, $p = 0.057$	Peak velocity (mm/s) ± SD, $p < 0.05$
Gait responsive group (14)	28.77 ± 16.09	77.46 ± 29.90
Gait non responsive group (6)	17.61 ± 8.27	48.36 ± 21.30

Table 5. When mean velocity (MV) > 26 mm/sec is considered test positive

	Significant improve	Non significant improve	Total
MV > 26 mm/sec	6	2	8
MV ≤ 26 mm/sec	4	8	12
Total	10	10	20

Table 6. When peak velocity (PV) > 70 mm/sec is considered test positive

	Gait improve	Gait not improve	Total
PV > 70 mm/sec	7	1	8
PV ≤ 70 mm/sec	7	5	12
Total	14	6	20

Table 7. Diagnostic performance of MRI CSF flow measurement

MRI parameters	Sensitivity	Specificity	Accuracy	PPV	NPV
Mean velocity > 26 mm/s	60%	80.0%	70%	75.0%	66.7%
Peak velocity > 70 mm/s	50%	83.3%	60%	87.5%	41.7%

42 μL, their method of measurement was not repeatable and the software they used was not commercially available[6]. Parkkola et al used fixed ROI to calculate the flow values and found 10 ml/min of caudal and rostral velocity encoding value in their report[14]. In the present study, the authors tried to simplify the proper technique so that it was easy to understand and repeatable with the available commercial software. The velocity encoding parameter is one important factor that influences the measured flow. The measurement will not be accurate if aliasing artifact occurs in the images. The area of ROI also influences the measurement. The parameter concerning steady technique is an important factor for setting down one's own method of measuring the CSF flow study.

Based on clinical symptoms and conventional imaging of ventricular enlargement (Evans' index > 0.3), no macroscopic obstruction of CSF flow, and presence of at least one of following supportive features (temporal horn enlargement, callosal angle > 40 degree, periventricular edema, aqueductal or fourth ventricular flow void on MRI), normal pressure hydrocephalus was suspected. Diagnosis of NPH is still highly controversial. VP shunt placement in NPH has an non-homogeneous response due to many causes, such as other co morbidity, *e.g.* Alzheimer's disease, cervical spinal stenosis, primary or secondary NPH, duration of symptoms, and stage of the disease. Ordinarily, in the authors' institution, a high volume tap test for diagnosis and predicting who would likely respond to VP shunt placement was used. Most of the patients did not get MRI CSF flow study due to high volume of patients on the MRI waiting list and the requirement of general anesthesia for some patients. However, in some patients who were questioned about diagnosis and needed conventional MRI, 2D-PC MRI flow study was added as a supportive investigation and found a correlation between flow parameters and clinical improvement.

In the present study, there were significant relations between peak velocity, mean velocity, and overall outcome; peak velocity also had significant relation to gait response. Some patients had improvement of stride and increased step height. Despite their improvement, there was no change of iNPHGS.

Many studies attempted to predict who would be likely to respond to VP shunt placement. From guidelines for management of iNPH, the high volume tap test is recommendation A (strongly recommended) according to a multicenter class II study with 100% positive predictive value, but has low specificity and is not able to exclude a patient from surgery if tap test was negative[15]. External lumbar drainage (recommendation B) could increase sensitivity and negative predictive value but may also increase complications such as meningitis and the requirement of hospital admission[16]. There were many studies of cine PC MRI but results remain inconclusive. The guidelines for management of iNPH considered a cine PC MRI as recommendation C[12].

Limitations of the present study were a retrospective study, including a small number of cases, using a more subjective grading score, little analysis of gait improvement, and permitting inclusion of secondary normal pressure hydrocephalus. Although the present study showed a significant relationship between CSF flow parameters and postoperative improvement, PC MRI CSF flow study could not replace other diagnostic tests, such as tap test or external lumbar drainage, as in previous inconclusive studies and also within the present study limitations.

Conclusion

With the authors' technique and software analysis, cine-PC MRI CSF flow study might be used as a tool to predict outcome of VP shunt placement in normal pressure hydrocephalus patients. The mean velocity more than 26 mm/sec predicted significant overall outcome improvement and peak velocity more than 70 mm/sec predicted gait response to treatment.

Potential conflicts of interest

None.

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การศึกษาคลื่นแม่เหล็กไฟฟ้าการไหลเวียนของน้ำหล่อเลี้ยงสมองและไขสันหลังและการตอบสนองต่อการผ่าตัดใส่ท่อระบายจากโพรงน้ำในสมองลงสู่ช่องท้องในผู้ป่วยที่มีภาวะน้ำคั่งในโพรงสมองชนิดความดันปกติ

ธีรพล วิทธิเวช, ปฐมฤกษ์ สถิรอังกูร, อรสา ชวาลภาฤทธิ์, วัฒนชัย โชตินัยวัตรกุล, นันทศักดิ์ ทิศาวิภาต, พนิดา ชาญเชาว์วานิช

วัตถุประสงค์: *เพื่อหาค่าการทำนายการตอบสนองต่อการผ่าตัดใส่ท่อระบายจากโพรงน้ำในสมองสู่ช่องท้อง (ventriculoperitoneal shunt) ในผู้ป่วยที่มีภาวะน้ำคั่งในโพรงสมองชนิดความดันปกติ (normal pressure hydrocephalus) โดยใช้การตรวจคลื่นแม่เหล็กไฟฟ้าของการไหลเวียนน้ำหล่อเลี้ยงสมองและไขสันหลัง (MRI CSF flow study)*

วัสดุและวิธีการ: *ได้ทำการศึกษาย้อนหลังในผู้ป่วยที่มีอาการภาวะน้ำคั่งในโพรงสมองชนิดความดันปกติและได้รับการผ่าตัดใส่ท่อระบายจากโพรงน้ำในสมองสู่ช่องท้อง โดยการตรวจคลื่นแม่เหล็กไฟฟ้าของการไหลเวียนน้ำหล่อเลี้ยงสมองและไขสันหลัง ใช้เทคนิค 2D-phase contrast โดยเครื่องสแกนคลื่นแม่เหล็กไฟฟ้าชนิด 3 เทสลา รุ่น Achieva ของบริษัทฟิลิปส์ ข้อมูลทางคลินิกก่อนและหลังผ่าตัดได้ถูกการรวบรวมและวิเคราะห์เพื่อหาค่ากำหนดของคลื่นแม่เหล็กไฟฟ้าของการไหลเวียนน้ำหล่อเลี้ยงสมองและไขสันหลังในการทำนายการตอบสนองต่อการผ่าตัดใส่ท่อระบายน้ำจากโพรงสมองสู่ช่องท้อง*

ผลการศึกษา: *ในช่วงเวลา 5 ปี ระหว่าง พ.ศ. 2549 และ พ.ศ. 2554 มีผู้ป่วย 20 ราย ที่ได้รับการผ่าตัดใส่ท่อระบายจากโพรงน้ำในสมองลงสู่ช่องท้อง โดยผู้ป่วย 14 ราย มีตอบสนองดีขึ้นโดยเฉพาะด้านการเดิน ในจำนวนผู้ป่วย 14 ราย ที่มีอาการดีขึ้นนี้ ผู้ป่วย 10 ราย ถูกกำหนดให้เป็นกลุ่มที่มีการตอบสนองดีขึ้นอย่างชัดเจน ซึ่งมีคะแนนรวมมากกว่าหรือเท่ากับ 3 โดยใช้แบบประเมินภาวะน้ำคั่งในโพรงสมองชนิดความดันปกติชนิดปฐมภูมิ (idiopathic normal pressure hydrocephalus grading scale) ผลที่ได้พบว่าค่าความเร็วเฉลี่ยของการไหลน้ำหล่อเลี้ยงสมองและไขสันหลังผ่าน aqueduct of Sylvius มีค่าแตกต่างอย่างมีนัยสำคัญทางสถิติระหว่างกลุ่มที่มีการตอบสนองชัดเจนและกลุ่มที่ไม่ค่อยตอบสนองต่อการผ่าตัดรักษา ส่วนค่าความเร็วสูงสุดมีแตกต่างอย่างมีนัยสำคัญทางสถิติระหว่างกลุ่มที่มีการตอบสนองด้านการเดินและกลุ่มที่ไม่ค่อยตอบสนองต่อการผ่าตัดรักษา เมื่อใช้ค่าเพดานเฉลี่ยที่ 26 มิลลิเมตรต่อวินาที ในกลุ่มตอบสนองอย่างชัดเจนต่อการผ่าตัดพบว่ามีความไว ร้อยละ 60 ความจำเพาะ ร้อยละ 80 ค่าทำนายผลบวก ร้อยละ 75 ความแม่นยำ ร้อยละ 70 สำหรับในกลุ่มตอบสนองด้านการเดินโดยใช้ค่าเพดานความเร็วสูงสุดที่ 70 มิลลิเมตรต่อวินาที พบว่ามีความไวความจำเพาะค่าทำนายผลบวกความแม่นยำเป็นร้อยละ 50, 83.3, 87.5 และ 60 ตามลำดับ*

สรุป: *จากการศึกษาคลื่นแม่เหล็กไฟฟ้าของการไหลเวียนน้ำหล่อเลี้ยงสมองและไขสันหลังโดยใช้ซอฟท์แวร์เชิงพาณิชย์ในโรงพยาบาลศิริราช พบว่าค่าความเร็วเฉลี่ยและค่าความเร็วสูงสุดเป็นค่าจำเพาะที่ใช้ทำนายการตอบสนองอย่างชัดเจนต่อการใส่ท่อระบายน้ำในโพรงสมองสู่ช่องท้องในผู้ป่วยที่มีภาวะน้ำคั่งในโพรงสมองชนิดความดันปกติ*