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MR cisternography: is it useful in the diagnosis of normal-pressure hydrocephalus and the selection of "good shunt responders"?

Oktay Algın, Bahattin Hakyemez, Gökhan Ocakoğlu, Müfit Parlak

PURPOSE
The aim of this study was to evaluate the efficiency of MR cisternography (MRC) in the diagnosis of idiopathic normal-pressure hydrocephalus (INPH) and in the prediction of the response to shunt treatment.

MATERIALS AND METHODS
Thirty-six patients with the diagnosis of "probable INPH" were included in the study group and 15 asymptomatic age-matched individuals were included in the control group. Pre-contrast T1-weighted (T1W) imaging was followed by intrathecal administration of 1 ml gadopentetate dimeglumine. Post-contrast T1W images were taken at the 12th, 24th and 48th hours. The presence of contrast material in the lateral ventricles for more than 24 hours was accepted as a positive diagnosis of INPH. Data from both groups were compared statistically. Statistical significance was accepted for $P < 0.05$.

RESULTS
All of the INPH patients had remaining contrast material in their lateral ventricles at the 12th and 24th hours, while only 28 (78%) patients had contrast material remaining at the 48th hour after MRC. Only 3 (20%) of the control cases had remaining contrast material in their lateral ventricles at the 24th hour. No contrast material was present in the control cases at the 48th hour. The contrast material was found to be significantly more prevalent in the INPH patients at the 24th and the 48th hours compared with the control cases ($P < 0.001$). Shunt placement was performed in 14 INPH patients, and eight improved after shunt placement. All patients (100%) who improved after shunt placement had remaining contrast material in their lateral ventricles at the 24th and at the 48th hours. The sensitivity and specificity of MRC in the prediction of the response to shunt treatment were 100% and 17%, respectively.

CONCLUSION
MRC does not use ionizing radiation and is generally a useful procedure to diagnose NPH and to predict a positive response to shunt treatment; thus, we recommend MRC after routine MRI in patients with the presumed diagnosis of NPH.

Key words: • *cerebrospinal fluid* • *magnetic resonance imaging* • *normal-pressure hydrocephalus* • *contrast media*

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Normal-pressure hydrocephalus (NPH), a rare disease in the general population, is usually seen in elderly people. NPH may be either idiopathic (INPH) or occur secondary (SNPH) to subarachnoid hemorrhage, meningitis, cranial trauma and intracranial surgery (1–4). Many diagnostic measures for NPH, such as the measurement of CSF pressure, intrathecal saline infusion test, intermittent CSF drainage, measurement of the cerebral blood flow and even brain biopsy, have been suggested in the literature (5–9). Radionuclide cisternography (RC), computerized tomography (CT), magnetic resonance imaging (MRI), CT cisternography (CTC), phase-contrast MRI (PC-MRI) and perfusion MRI are among the imaging techniques used in the diagnosis of NPH (5, 8, 9). However, all diagnostic work-up described yield false-positive and false-negative results; additionally, surgical treatment carries significant short- and long-term risks, and the cause or pathogenesis of many NPH cases is not known (8). Differential diagnosis of NPH from other types of dementia is important because the clinical improvement of symptoms of NPH is possible after CSF diversion (8–10). However, not all patients undergoing the shunt operation improve after the operation (9, 10). Despite research on this subject for more than 40 years, there is still no test that can accurately diagnose NPH patients or predict their response to treatment (5, 8–10).

In patients with NPH, there is an impairment of the re-absorption of CSF by arachnoid granulation (9). Intrathecally applied radioactive material remaining in the ventricles for more than 24 hours suggests NPH (8, 10). This finding is related to ventricular reflux resulting from the hyperdynamic flow (10). Ventricular reflux that persists for 24 hours or more was found to have 88% sensitivity in the prediction of a good response to shunt treatment (11). RC, which was previously accepted as a convenient tool to evaluate CSF dynamics, has lost its importance in the diagnosis of NPH because of its low accuracy at predicting the outcome of shunt surgery, the radiation risk and invasiveness (10). RC is now accepted as a diagnostic tool that complements the clinical picture and laboratory and radiological findings (8–12).

MR cisternography (MRC) is a new technique and alternative to CTC and RC (13). Its advantages include the absence of radiation, high soft tissue resolution and capacity for multi-planar imaging (14). MRC is generally used to diagnose CSF fistulae and identify the communication of arachnoid cysts (ACs) with neighboring CSF areas by showing CSF dynamics (14, 15). MRC can evaluate the CSF circulation physiologically and can be performed with other MR studies, such as PC-MRI, so we believe that it can show a blockage in the CSF absorption if it exists (13). To the best of our knowledge, no data are available about the use of MRC in the diagnosis of NPH in the literature. In this study, we aimed to evaluate the efficiency of MRC in the diagnosis of INPH and in the prediction of the response to shunt treatment.

Materials and methods

This study was performed between March 2006 and December 2008, and 51 cases (the control and the patient groups) referred to our department were included. All patients gave informed consent. The faculty ethical committee approved our study protocol.

Study groups

The control group (group 1) was composed of 15 cases (6 women and 9 men) with a mean age of 63 years (range, 46–75). Because of the invasiveness and the need for a contrast agent in the MRC technique, patients with a pre-diagnosis of intracranial AC and no co-existing diseases or symptoms (except headache) other than AC or mega cisterna magna (MCM) constituted the control cases. Patients under the age of 40 and patients with intraventricular or periventricular AC were excluded from the study because INPH is seen in the elderly and because the localization of the ACs might have affected the CSF flow (15).

The NPH group (group 2) was composed of 36 patients (22 women, 14 men; mean age, 63 years; range, 40–78) who were diagnosed with probable INPH according to the clinical guidelines for NPH (8–10, 16). The diagnosis of dementia was confirmed in the NPH group with a neuropsychological test [the mini-mental state examination test (MMSE)]. An experienced neurologist, neurosurgeon and neuroradiologist grouped the patients together in consensus. Patients with CSF opening pressure >20 mmHg were excluded from the NPH group. Nine patients with the presumed diagnosis of NPH were also excluded from the study due to the presence of head trauma, intracranial hemorrhage, cerebral infarction, meningitis, primary malignancy, leptomeningeal carcinomatosis and coexisting disease.

MR imaging protocol and statistical analysis

The examinations were performed with a 1.5-Tesla MR device (Magnetom Vision Plus, Siemens, Erlangen, Germany). The patients were in a supine position during the examinations. T1-weighted (T1W) SE images were obtained in three planes (TR/TE/NEX, 650/14/2; matrix, 192x256; FOV, 230 mm; slice thickness, 5 mm; and slice gap, 1 mm) before the administration of contrast media. Axial-sagittal plane T2W turbo gradient SE (TGSE) sequences (TR/TE, 7400/115 ms; FA, 160°; NEX, 1; FOV, 230 mm; matrix, 345×512; slice thickness, 2 mm) and axial plane fluid attenuated inversion recovery (FLAIR) sequences (TR/TE, 8400/114; TI, 2150 ms; FOV, 230; matrix, 256x256) were obtained. The acquisition time of pre-contrast MRC, TGSE and FLAIR sequences was approximately 15 minutes. The Evans' indices (the maximum distance between the lateral margins of both the anterior horns divided by the maximum width of the inner table of the cranium) of all the patients in Group 2 were calculated (3). Patients with Evans' indices <0.30 were excluded from the INPH group.

After acquisition of the pre-contrast images, 1 ml (0.5 mmol) gadolinium-DTPA (Gd-DTPA) (Magnevist, Schering, Germany) was injected with a 26-gauge Chiba needle to the lower lumbar region (L4–L5) intrathecally under sterile conditions. The patients were observed clinically after intrathecal Gd-DTPA injection for 48 hours. T1W SE (the same parameters with the pre-contrast T1W images) sequences in 3 planes were acquired 12, 24 and 48 hours after the intrathecal Gd-DTPA injection. The duration of each post-contrast MRC examination was 5 minutes. The presence of contrast material in the lateral ventricles for more than 24 hours was accepted as a positive MRC evaluation (8, 9, 17). If the lateral ventricular contrast enhancement was uncertain, we measured the increase of signal intensity and compared its value with pre-contrast images. The signal intensity of the lateral ventricle was measured by a circular ROI placed on the frontal horn of the lateral ventricle without extending past the edges of the lateral ventricle. A two-fold increase of signal intensity on post-contrast imaging was recognized as a sign of lateral ventricular contrast enhancement.

All the MR data were evaluated by two radiologists who were blind to the clinical findings of the patients. Clinical resolution of at least one of the symptoms after CSF diversion was accepted as a "positive response to the shunt." MRC data of the patients and the control group were compared with the clinical, laboratory and CSF diversion response to evaluate the contribution of these parameters to the diagnosis and treatment of NPH.

Statistical analysis was performed with SPSS 13.0 (SPSS Inc., Chicago, USA). Concordance of the normal distribution of all continuous variables was calculated by the Shapiro-Wilk test. If the data were not normally distributed, non-parametric tests for dependent variables were used. Symptoms were compared between groups by the chi-square test. For continuous variables, differences among groups were analyzed using the Kruskal-Wallis test, and comparisons of data between the two groups were performed with the Mann-Whitney U test. Statistical significance was accepted for $P < 0.05$.

Results

Control group

None of the control cases had symptoms of gait disturbance, dementia or urinary incontinence. The control group included 2 MSM, 3 posterior fossa AC, 7 temporal AC, 2 cerebellopontine angle (SPA) AC and 1 convexity AC. Intrathecally applied contrast material distributed homogeneously in the posterior fossa in MSM cases. There was communication with the surrounding CSF in 5 ACs. There was no communication in the remaining 8 ACs. The demographic characteristics and the MRC results of the control group are given in Table 1. The lateral ventricles of individuals in the control group were free of contrast material at the 48th hour after injection (all controls were MRC-negative) (Fig. 1). Only 3 (20%) of the control cases showed minimal contrast material in their lateral ventricles at the 24th hour after injection.

Patient group

The Evans' indices of all the patients in the patient group were >0.3. The MMSE score in the patient group was 17.3 (range, 15–22). During the 48-hour follow-up period, none of the patients experienced any neurological disorder, epilepsy or allergic reaction. Ten patients (10/36, 27%) had a postural headache that was responsive to conventional analgesics. The complaints of these patients resolved spontaneously in 72 hours. The demographic characteristics, MRC findings, symptoms and results of the shunt operations are given in Table 2. There was no statistically significant difference between the presence of symptoms and the response to the shunt surgery in the NPH group ($P > 0.05$).

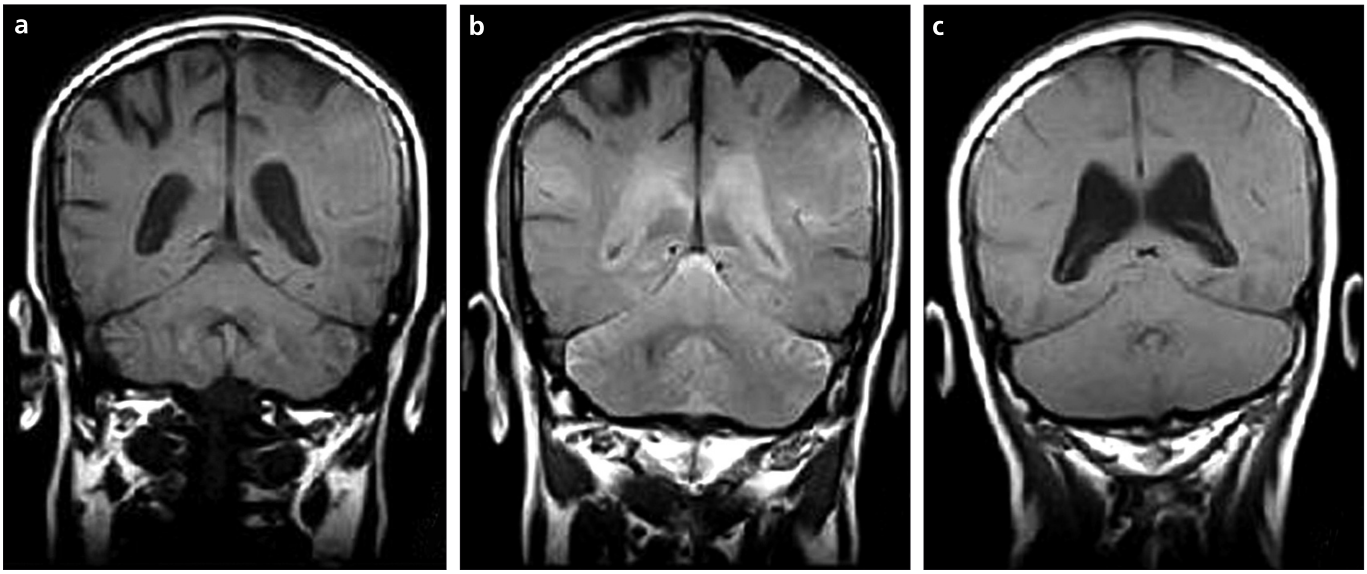


Figure 1. a–c. Pre-contrast **(a)**, 12th hour **(b)**, and 24th hour **(c)** T1A images of a control case. The lateral ventricles were free of the contrast material at the 24th **(c)** and 48th hours (not shown here) after the contrast injection (MRC-negative).

All NPH patients had at least two symptoms of gait disturbance, dementia and urinary incontinence. Gait disturbance was present in 33 patients (33/36, 92%). Urinary incontinence was present in 28 patients (28/36, 78%). Dementia was present in 36 patients (36/36, 100%). CSF diversion was applied to 14 of 36 NPH patients (12 cases underwent ventriculoperitoneal shunting, 2 cases underwent endoscopic third ventriculostomy). Twenty-two patients refused the operation. The clinical symptoms resolved in 8 patients (8/14, 58%) post-operatively, but there was no change in symptoms in 6 of the patients (Fig. 2). All shunt-responding patients who improved after CSF diversion were MRC-positive (Fig. 3). Five of six NPH (83%) patients who had no improvement after shunt treatment had remaining contrast material in their lateral ventricles at the 48th hour. The single remaining patient who did not improve after shunt treatment had a negative MRC result. There was no statistically significant difference between the MRC results and the improvement of symptoms after CSF diversion ($P > 0.05$). The sensitivity and specificity of MRC in the prediction of the response to shunt treatment were 100% and 17%, respectively (positive predictive value 62%, negative predictive value 100%).

Table 1. The clinical and MRC findings of the control group

No	Age	Gender	Lesion-communication	MRC 24th hr	MRC 48th hr
1	63	M	MCM	-	-
2	58	M	PF AC (non-communicating)	-	-
3	60	M	PF AC (communicating)	-	-
4	66	F	PF AC (non-communicating)	-	-
5	72	M	MCM	-	-
6	58	F	Temporal AC (non-communicating)	-	-
7	72	M	Temporal AC (communicating)	+	-
8	57	M	Temporal AC (non-communicating)	-	-
9	63	F	Convexity AC (non-communicating)	+	-
10	46	F	Temporal AC (communicating)	+	-
11	70	M	Temporal AC (communicating)	-	-
12	75	F	Temporal AC (non-communicating)	-	-
13	61	M	Right CPA AC (non-communicating)	-	-
14	75	F	Temporal AC (communicating)	-	-
15	52	M	Left CPA AC (non-communicating)	-	-

MRC, MR cisternography; MCM, mega cisterna magna; AC, arachnoid cyst; PF, posterior fossa; CPA, cerebellopontine angle.

There was contrast material in the lateral ventricles in 36 patients (36/36, 100%) at the 24th hour and in 28 patients (28/36, 78%) at the 48th hour, respectively (28 patients, MRC +) (Fig. 3). The contrast materials (at the 24th and 48th hours) remained for significantly longer periods of time in the lateral ventricles of NPH patients compared with the control group ($P < 0.001$).

Discussion

Cranial MR evaluation is needed in patients with the presumed diagnosis of NPH to differentiate between NPH

Table 2. The clinical and MRC findings of patients with NPH

No	Age	Gender	Ataxia	UI	Dementia	MRC 24th hr	MRC 48th hr	Shunt outcome
1	63	F	+	+	+	+	+	Refused the operation
2	60	M	+	+	+	+	+	No improvement
3	64	F	+	+	+	+	+	Refused the operation
4	75	F	+	+	+	+	+	Improvement
5	63	F	+	+	+	+	+	No improvement
6	65	M	+	+	+	+	+	No improvement
7	59	F	+	+	+	+	+	Refused the operation
8	70	M	+	-	+	+	+	Improvement
9	54	M	+	-	+	+	-	Refused the operation
10	66	M	+	+	+	+	+	Improvement
11	40	M	+	+	+	+	+	Refused the operation
12	66	M	+	+	+	+	+	Improvement
13	62	M	+	+	+	+	+	Refused the operation
14	46	F	+	-	+	+	+	No improvement
15	68	M	+	+	+	+	+	Refused the operation
16	73	M	+	-	+	+	+	Refused the operation
17	70	F	+	-	+	+	+	Improvement
18	74	F	+	+	+	+	-	Refused the operation
19	75	M	+	+	+	+	+	Refused the operation
20	53	F	-	+	+	+	-	Refused the operation
21	73	M	+	+	+	+	+	No improvement
22	59	M	+	+	+	+	-	No improvement
23	60	F	+	+	+	+	+	Refused the operation
24	44	F	+	+	+	+	+	Refused the operation
25	76	M	+	-	+	+	+	Refused the operation
26	54	M	-	+	+	+	-	Refused the operation
27	73	M	+	+	+	+	+	Improvement
28	40	M	+	+	-	+	+	Refused the operation
29	67	M	+	+	+	+	+	Refused the operation
30	46	M	+	-	+	+	+	Refused the operation
31	60	M	-	+	+	+	-	Refused the operation
32	57	F	+	+	+	+	+	Improvement
33	72	F	+	+	+	+	+	Improvement
34	60	F	+	+	+	+	-	Refused the operation
35	62	M	+	+	+	+	-	Refused the operation
36	78	M	+	-	+	+	+	Refused the operation

UI, urinary incontinence; MRC, MR cisternography.

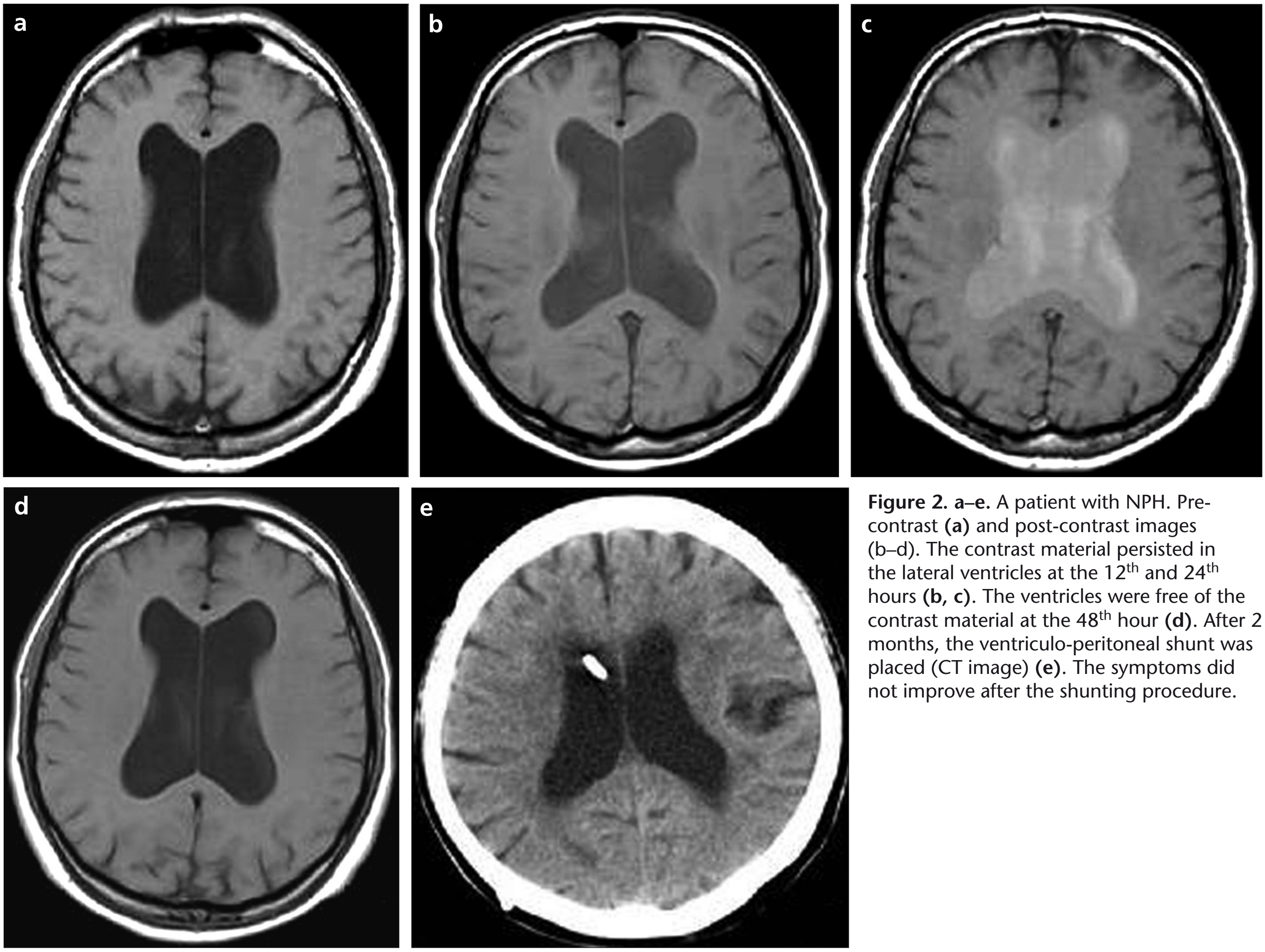


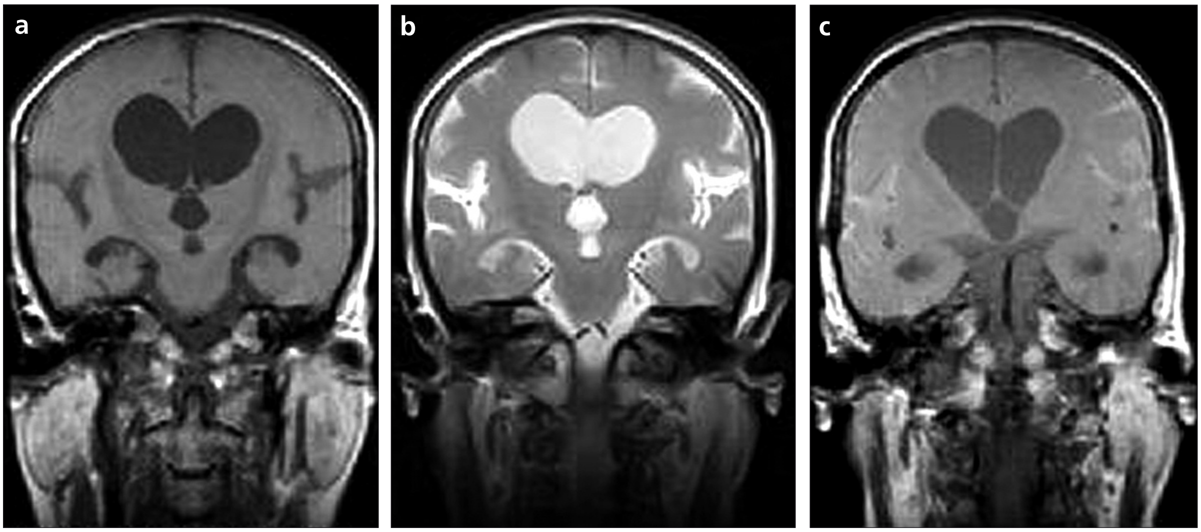
Figure 2. a–e. A patient with NPH. Precontrast **(a)** and post-contrast images (b–d). The contrast material persisted in the lateral ventricles at the 12th and 24th hours **(b, c)**. The ventricles were free of the contrast material at the 48th hour **(d)**. After 2 months, the ventriculo-peritoneal shunt was placed (CT image) **(e)**. The symptoms did not improve after the shunting procedure.

and cerebral atrophy and to determine whether the patient would improve if a shunt operation were performed (18). Patients with cerebral atrophy do not improve after CSF diversion, so the differentiation of NPH from cerebral atrophy is important (6, 10). Both dementia and lateral ventricular enlargement are primary findings of NPH, but they can both be seen in patients with cerebral atrophy secondary to Alzheimer's disease or vascular dementia (10, 19, 20). The differentiation of NPH from cerebral atrophy in the elderly with ventriculomegaly may sometimes be so difficult that neither clinical and imaging findings nor brain biopsy is enough to identify the exact diagnosis (6, 12, 18). Dysfunction of the Windkessel mechanism and the decrease in intracranial compliance are thought to play a role in the etiology of NPH (20, 21). Because of these changes, intracranial arterial pulsation leads to an increase in pressure waves, which in turn disturb CSF dynamics. The decrease in the venous absorption of CSF further contributes to the pathology (4, 9, 21, 22).

RC is a technique that is useful in the evaluation of CSF circulation and absorption. It can provide morphological and physiological data (23). Chmielowski et al. defined RC as the most reliable diagnostic procedure in the diagnosis of NPH (24). Serial images are acquired during 48 hours after intrathecal injection of the radiotracer for RC. In normal individuals, intrathecally injected radiotracer reaches the basal cisterns, ventricles and the convexity 2–3, 3–6 and 12–24 hours after the injection, respectively (17, 25). In NPH, a disturbed CSF flow occurs that consists of a so-called "reversed pattern" with stasis of the CSF in the ventricles for 48 hours or longer (10). CTC and RC were also used to demonstrate disturbed CSF circulation with a similarly reversed CSF flow (8–10). The use of RC-CTC is infrequent nowadays due to the use of radiation, low resolution, additional cost and failure to show anatomical details (8, 9).

We performed MRC instead of RC in our study. Intrathecal gadolinium application has not been recognized worldwide. In the literature, it is reported that intrathecal administration of 1 ml (0.5 mmol) Gd-DTPA does not cause neurological or behavioral abnormalities or early or late complications (14, 15, 26). It is also used for evaluation of CSF dynamics, CSF leaks and communication of ACs; the safety of this dose has been verified in other studies (14, 15, 26–28).

In our study, all NPH patients had a more prolonged residence of contrast material in their lateral ventricles compared with the control group ($P < 0.001$). The ventricular retention and deficient ventricular clearance of the contrast agent in NPH patients were possibly due to insufficient absorp-



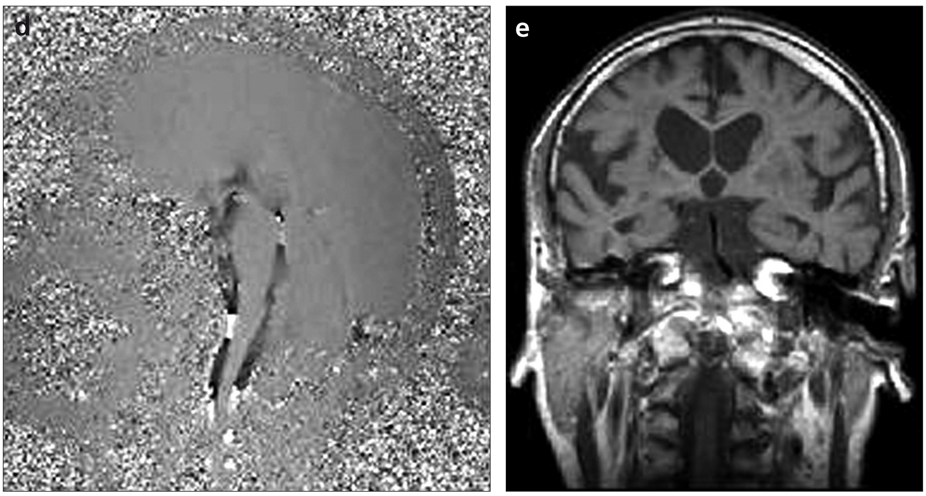


Figure 3. a–e. Positive MRC examination of a patient with definite NPH. Pre-contrast **(a)** and post-contrast images **(b, c)**. The contrast material persisted in the lateral ventricles at the 24th **(b)** and 48th hours **(c)**. This case was treated with endoscopic third ventriculostomy after 3 months. The patient's complaints improved after the operation. The sagittal phase-contrast image **(d)** of the control MRI one year after the operation showed patent third ventriculostomy (velocity encoding, 2 cm/s). Coronal T1W image **(e)** showed that the lateral ventricles were smaller compared with the pre-operative size.

tion at the arachnoid granulation level or to CSF malabsorption secondary to increased venous pressure (17, 21, 25). The ventricular reflux secondary to "to and fro" jet flow at the aqueductal level may also delay the clearance of contrast agent from the ventricles (8, 29, 30).

We did not find a significant correlation between improvement after shunt surgery and MRC findings. However, all 8 patients who improved after shunt surgery had positive MRC results, leading to a sensitivity of 100% and a negative predictive value of 100%. The sensitivity of RC in predicting the shunt response was previously reported to be 88% (11). MRC has a higher sensitivity than RC because the persistence of intraventricular contrast material can be more clearly identified with MRC secondary to its higher soft-tissue resolution or CSF-to-brain contrast. In our study, 1 ml contrast medium diffused in the ventricular system, and details of the ventricular system and other CSF spaces became clearly visible. We concluded that patients with positive MRC findings are more likely to improve after shunt surgery. In accordance with our results, Black showed that positive RC imaging was useful in predicting the shunt response, but a negative or equivocal result could not predict the shunt response (23).

Aqueductal CSF flow increases in NPH patients (1, 18). The blockage of CSF absorption of NPH patients increases CSF pulsatility, which may explain the high aqueductal CSF flow in these patients (9). Another advantage of MRC is its user-friendly nature (27, 28). MRC provides a simultaneous, quantitative evaluation. Our departments are currently conducting another study to evaluate the role of MRC and PC-MRI together in the diagnosis of NPH. Another advantage of MRC is that it is easier and less invasive to perform than RC and CTC, leading to fewer side effects, such as post-procedure postural headaches (15). MRC could be acquired with routine MR and other MR techniques simultaneously, and it costs less than additional RC or CTC.

The major limitation of our study was the lack of a gold standard test in the diagnosis of definite NPH, which prevented the calculation of the false-negative and false-positive values of MRC in the diagnosis of NPH (16, 31). The second limitation of the study was the subjectivity of the criteria used to evaluate improvement after shunt surgery.

Although there have been many studies on NPH, its clinical presentation is difficult to differentiate from that of other types of dementia. Cases of obstructive hydrocephalus, aqueductal stenosis and increased intracranial pressure in the elderly may present with symptoms mimicking NPH, but different treatment algorithms with this presumed diagnosis necessitate a careful diagnostic work-up with radiological imaging. Timely diagnosis can lead to the reversal of symptoms through ventricular shunting, but no routine test predicting the potential response to shunt surgery has been validated. There have been no publications about the use of MRC in the diagnosis of NPH and the selection of patients with good outcomes after shunting. MRC provides useful data in the diagnosis of NPH. We can predict that patients with positive MRC results will improve after the shunt treatment. In light of our results, we suggest the use of MRC with other MRI findings to diagnose NPH and to select shunt responders.

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