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Clinical impact of the callosal angle in the diagnosis of idiopathic normal pressure hydrocephalus

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Abstract The utility of measuring the corpus callosal angle (CA) for the diagnosis of idiopathic normal pressure hydrocephalus (INPH) was investigated. Three-dimensional magnetic resonance imaging (MRI) was performed in 34 INPH patients, 34 Alzheimer's disease (AD) patients, and 34 normal control (NC) subjects. Measurement of the CA on the coronal MR images of the posterior commissure perpendicular to the anteroposterior commissure plane was performed for all subjects. The CA of the INPH group (mean±SD, 66±14°) was significantly smaller than those of the AD (104±15°) and NC (112±11°) groups. When using the threshold of the mean−2SD value of the NC group (= 90°), an accuracy of 93%, sensitivity of 97%, and specificity of 88% were observed for discrimination of INPH from AD patients. Measuring the CA helps in differentiating INPH patients from AD and normally aged subjects.

Keywords Callosal angle · Idiopathic normal pressure hydrocephalus (INPH) · Magnetic resonance imaging (MRI) · Alzheimer's disease

Introduction

Idiopathic normal pressure hydrocephalus (INPH) is a syndrome characterized by gait disturbance, mental deterioration, and urinary incontinence, and is associated with normal cerebrospinal fluid (CSF) pressure [1–3], but it should be discriminated from secondary normal pressure hydrocephalus (SNPH). The etiology of INPH is unknown, although SNPH has known causes such as subarachnoid hemorrhage, meningitis, cranial trauma, and intracranial surgery. Using X-ray computed tomography (CT) [3, 4] and magnetic resonance imaging (MRI) [5–8], the patterns of the morphological findings of INPH have been investigated and revealed specific morphological changes including enlarged Sylvian fissures and tight medial parietal sulci [8].

In the treatment guidelines for INPH, "a callosal angle of 40° or more" is described as a supportive feature of suspected INPH [9], but no reference has been cited from the literature. In this study, we investigated whether the callosal angle is a useful marker for the diagnosis of INPH,

and analyzed other previously reported markers including periventricular hyperintensity (PVH), deep white matter intensity (DWMH), and aqueductal ventricular flow void.

Materials and methods

Subjects

In this study, we used MR images of the following patients who were previously selected for analysis by voxel-based morphometry: 34 consecutive patients with INPH, 34 age-matched and cognitive impairment-matched AD patients, and 34 age-matched normal healthy subjects, as described previously [8]. The patients were admitted to the infirmary of our institution for the evaluation of dementia from April 1994 to March 2005. The 34 INPH patients fulfilled the criteria for probable INPH in the INPH guidelines [9]. The diagnosis of probable INPH is based on clinical history, brain imaging, physical findings, and physiological criteria:

1. History must include (a) insidious onset, (b) origin after 40 years, (c) a minimum duration of at least 3 to 6 months, (d) no evidence of antecedent events, (e) progression over time, and (f) other neurological, psychiatric, or general medical conditions.
2. Brain imaging must show evidence of (a) ventricular enlargement (Evans index>0.3 or comparable measure), (b) no macroscopic obstruction to CSF flow, (c) at least one of the following supportive features: (i) enlargement of the temporal horns of the lateral ventricles not entirely attributable to hippocampus atrophy, (ii) a callosal angle of 40° or more, (iii) evidence of altered brain water content including periventricular signal changes on CT and MRI not attributable to microvascular ischemic changes or demyelination, and (iv) an aqueductal or fourth ventricular flow void on MRI.
3. Clinical findings of gait/balance disturbance must be present, plus at least one other area of impairment in cognition, urinary symptoms, or both.
4. Physiological findings of CSF opening pressure in the range of 5–18 mm Hg (or 70–245 mm H_2O) as determined by a lumbar puncture or a comparable procedure.

The patients also fulfilled the criteria for probable INPH in the Japanese clinical guidelines for idiopathic normal pressure hydrocephalus [10], which are summarized below.

Possible INPH is diagnosed in patients:

(a) More than 60 years old.
(b) Having one or more symptoms of gait disturbance, dementia, and urinary incontinence.
(c) With ventricular dilatation (Evans index>0.3) and a narrow CSF space in the superior convexity.
(d) With a CSF pressure lower than 200 mm H_2O with a normal CSF cell count and protein level.
(e) Having no other diseases that may account for the symptoms.
(f) With no other previous illness that causes ventricular dilatation.

Probable INPH is diagnosed if the spinal tap test is positive with possible INPH.

Definite INPH is diagnosed if a shunt operation is effective in improving the symptoms of a patient with probable INPH.

A spinal tap test was performed and symptomatic improvement was confirmed in all patients. The mean age of the INPH group was 76.0±5.3 years, and the mean mini-mental state examination (MMSE) score was 19.8±4.8. The group consisted of 16 females and 18 males. All patients showed gait disturbance, 27 patients had cognitive disorders, and 21 patients had urinary incontinence. Thirty-four patients with probable AD, who were diagnosed using the criteria from the National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association (NINCDS/ADRDA) [11], were selected from our institute's dementia registry. The mean age of the AD group was 75.9±4.6 years, and the mean MMSE score was 20.1±4.3. This group comprised 16 females and 18 males. None of the AD patients had gait disturbance or urinary incontinence. Finally, 34 healthy volunteers (NC) (female/male=13:21; mean age±SD, 75.7±4.8; mean MMSE±SD, 29.6±0.8) were selected randomly from our institute's normal registry. All control subjects had no evidence of focal brain lesions on MR images except for age-related brain atrophy and hyperintensities on T2-weighted images; a normal physical and neurological examination; and no history of psychiatric disorders. All procedures of this study adhered to the clinical study guidelines of the ethics committee of our institute and were approved by the internal review board, and written informed consent was obtained from the subjects and/or patients' relatives.

MR procedure

A 1.5-T Signa Horizon MR system (GE Medical Systems, Milwaukee, WI) was used for MRI. Three-dimensional spoiled gradient echo (SPGR) imaging (TR, 14 ms; TE, 3 ms; flip angle, 20°; thickness, 1.5 mm; 124 slices; field of view, 220 mm; matrix, 256×256: 0.86 mm×0.86 mm) was performed to obtain three-dimensional T1-weighted coronal images. Axial fast spin-echo T2-weighted images (TR, 3,000 ms; TE, 105 ms; excitations, 4) were obtained in 14 locations parallel to the anteroposterior commissure plane with a section thickness of 5 mm and intersection gap of 2.5 mm, covering the area from the base of the cerebellum to the vertex.

Data analysis

The Evans index and corpus callosal angle were calculated on the individual T1-weighted axial images reconstructed from the SPGR images: the SPGR images were reconstructed to axial images which were parallel to the anteroposterior commissure plane consisting of 1.0-mm isotropic voxels. The Evans index was calculated as the maximal width of the frontal horns/maximal width of the inner skull [12] (Fig. 1).

Because the callosal angles vary on each plane (Fig. 2), the corpus callosal angle was measured on the coronal plane in this study. The coronal image which was perpendicular to the anteroposterior commissure plane on the posterior commissure of each subject was reconstructed (Fig. 3) and two radiologists who were blinded to the subjects' clinical data measured the callosal angle, separately.

The white matter intensity was evaluated by visual inspection from the T2-weighted images. Two radiologists reviewed the images without knowledge of the clinical status. They classified the white matter hyperintensity into periventricular hyperintensity (PVH) and deep white matter intensity (DWMH), and rated the severity into four grades according to Fazekas et al. [13]. For PVH, "absent" = grade 0, "caps or pencil-thin-lining" = grade 1, "smooth halo or thin band" = grade 2, and "irregular periventricular hyperintensity extending into the deep white matter or broad band" = grade 3. For DWMH, "absent" = grade 0, "punctate" = grade 1, "beginning of confluence" = grade 2, and "confluent" = grade 3.

Aqueductal ventricular flow void was evaluated on T2-weighted images, and the flow void in the aqueduct of the midbrain and in the fourth ventricle was expressed as "none" or "visible".

Each subject's index, angle, and scores were shown as average values of the two observers. Differences among groups were analyzed using the Kruskal–Wallis one-way analysis of variance (ANOVA) test followed by the post hoc Tukey test for the original data obtained by visual inspection, and using one-way (ANOVA) and Tukey post-hoc analysis for the Evans index and the callosal angle. The statistically significant level was set at $p<0.05$. Intraclass correlation coefficient and kappa statistic were performed to examine the inter-operators reliability of Evans index, callosal angle, and visual inspection. Correlation between

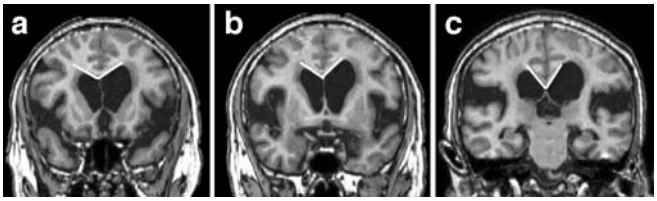

Fig. 2 Variation of the callosal angle measurement. The callosal angle varies depending on which plane it is measured from and is *A* 118°, *B* 103°, and *C* 70° on this patient with idiopathic normal pressure hydrocephalus. We defined the callosal angle as the measurement on the coronal plane just on the posterior commissure (**c**)

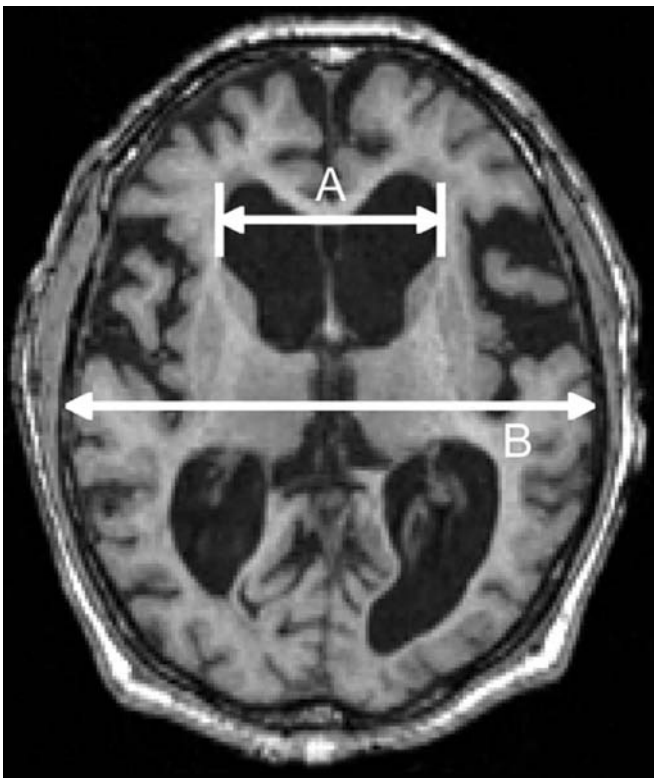

Fig. 1 Measurement of Evans index calculated as the maximal width of the frontal horns (*A*)/maximal width of the inner skull (*B*)

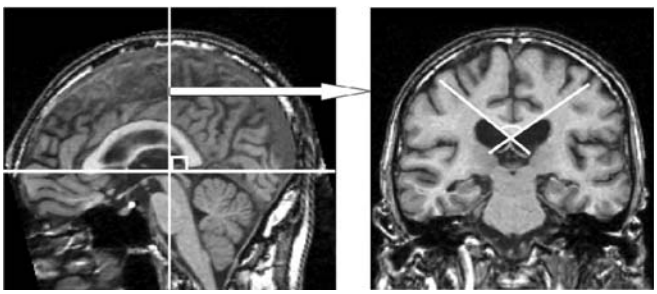

Fig. 3 The coronal section where callosal angle is measured. The callosal angle was measured on the coronal plane, which was perpendicular to the anteroposterior commissure plane on the posterior commissure of each subject

MMSE score and Evans index or callosal angel was evaluated with Spearman rank correlation test.

Results

The inter-observer reproducibility values for Evans index and callosal angle were 0.937 and 0.975. The kappa coefficient of the inter-observer reliability of the visual rating was 0.81 for DWMH and 0.89 for PVH.

The mean Evans index and callosal angle of all groups are shown in Table 1. The Evans index of the INPH group was significantly larger than those of the AD and NC groups; and the callosal angle of the INPH group was significantly smaller than those of the AD and NC groups. The Evans index of the AD group was also larger than that of the NC group; however, there were no significant differences between the callosal angle of the AD group and the NC group (Table 1). When using the guideline criteria of an Evans index of 0.3, an accuracy of 86%, sensitivity of 100%, and specificity of 74% were demonstrated for discrimination between INPH and AD patients. When using the threshold of the NC group's mean−2SD value of the callosal angle (= 90°), an accuracy of 93%, sensitivity of 97%, and specificity of 88% were demonstrated for discrimination between INPH and AD patients. When using a combination of Evans index and callosal angle (threshold Evans index > 0.3 and callosal angle < 90°), an accuracy of 96%, sensitivity of 97%, and specificity of 94% were demonstrated for discrimination between INPH and AD patients (Fig. 4).

The Spearman rank correlation coefficient (R_s) between MMSE score and Evans index was −0.511 ($p<0.001$) and the R_s between MMSE score and callosal angle was 0.510 ($p<0.001$).

The results of the visual inspection are summarized in Table 2. Subjects with no PVH or DWMH were classified as follows: three cases in the INPH group, three cases in the AD group, and nine cases in the NC group. Mean PVH rating scores in the INPH group were higher than those of the AD and NC groups, and mean DWMH rating scores in the INPH group were higher than those of the NC group (Table 2).

Aqueductal flow void was observed in 79%, 88%, and 82% of the INPH, AD, and NC groups, respectively. A fourth ventricular flow void was observed in 47%, 47%, and 44% of the INPH, AD, and NC groups, respectively. There were no significant differences in aqueductal or fourth ventricular flow void frequency among the three groups.

Coronal sections showing representative callosal angles of a patient with INPH, a patient with AD, and a healthy man are shown in Fig. 5.

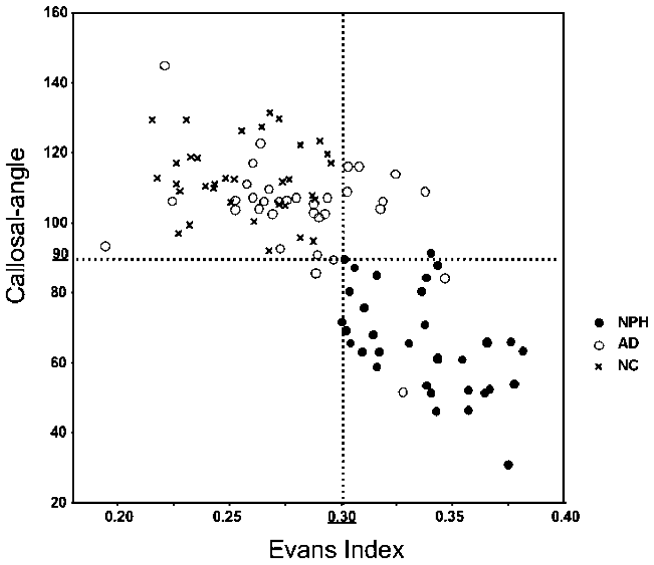

Fig. 4 Scatter plots of the Evans index and the callosal angle of each subject in idiopathic normal pressure hydrocephalus (INPH), Alzheimer's disease (AD), and normal control (NC) group. The *dotted line* indicates the threshold of the callosal angle (mean−2SD of the NC group = 90°) and the threshold of Evans index (= 0.30)

Table 1 Mean values of the Evans index and callosal angle measurements in each group

	Evans index	Callosal angle
INPH	0.338±0.025[a]	66±14[b]
AD	0.283±0.033[c]	104±15
NC	0.259±0.025	112±11

The callosal angles were measured at the level of the posterior commissure, when the slices are oriented perpendicular to the anteroposterior commissure plane.
INPH idiopathic normal pressure hydrocephalus, *AD* Alzheimer's disease, *NC* normal control subject
[a]Significantly larger than NC and AD
[b]Significantly smaller than NC and AD
[c]Significantly larger than NC

Discussion

Our study demonstrated the useful measurement of the callosal angle in INPH patients, providing the first study reporting the measurement of the callosal angle on MR images.

The concept of the callosal angle was first described by Benson et al. [14] for the diagnostic finding of normal pressure hydrocephalus on pneumoencephalography. Thereafter, Sjaastad et al. [15] reported the useful measurement of the callosal angle for NPH diagnosis

Table 2 Mean visual rating scores of white matter lesions in each group

	INPH	AD	NC	Among groups	INPH vs AD	INPH vs NC	AD vs NC
PVH	1.9	1.1	0.7	$p<0.001$	$p<0.05$	$p<0.05$	NS
DWMH	1.6	1.4	0.8	$p<0.001$	NS	$p<0.05$	$p<0.05$

INPH idiopathic normal pressure hydrocephalus, *AD* Alzheimer's disease, *NC* normal control subject, *PVH* periventricular hyperintensity, *DWMH* deep white matter intensity

with pneumoencephalography. To the best of our knowledge, there has been no report on the measurement of the callosal angle on X-ray CT or MRI, so we proposed that the callosal angle should be measured on a coronal plane which is perpendicular to the AC–PC plane on the posterior commissure plane. Our study demonstrated that the callosal angle in the INPH group was much smaller than those in the AD and NC groups. This suggests that the callosal angle is a good indicator of probable INPH: a sharp callosal angle, i.e., less than 90°, is produced by elevation of dilated lateral ventricles and compression by dilated Sylvian fissures. Measuring the callosal angle could be a convenient method for discriminating INPH from neurodegenerative disease with large ventricles due to atrophy.

The Evans index is determined by the largest diameter of the frontal horns divided by the diameter of the internal skull, on the same plane. A value greater than 0.3 for the Evans index is the only essential morphologic criterion of probable INPH as reported in the journal *Neurosurgery* and 'the Japanese guidelines'. The Evans index of our INPH cases was above 0.3; the mean Evans index was 0.338 in the INPH group. The mean Evans index of the AD group was 0.283, and 26% (9/34) of the Evans indices in the AD patients were above 0.3. This suggested that if we only used the Evans index, we could not distinguish an INPH patient from an AD patient. However combination of Evans index and callosal angle produced a better performance in discriminating INPH from AD than single use of Evans index or callosal angle.

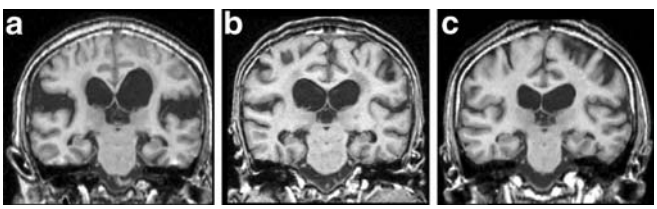

Fig. 5 Representative coronal sections showing callosal angles of idiopathic normal pressure hydrocephalus (INPH), Alzheimer's disease (AD), and healthy man. *A* 64-year-old male INPH patient: MMSE score was 27, Evans index was 0.30, and the callosal angle was 69°. *B* 67-year-old male AD patient: MMSE score was 26, Evans index was 0.29, and the callosal angle was 102°. *C* 70-year-old healthy man: MMSE score was 30, Evans index was 0.24, and the callosal angle was 118°

Evans index and callosal angle have a weak correlation with MMSE score, which means those markers do not directly reflect cognitive impairments of the subjects. When clinicians order MRI for the reason of cognitive impairments of the patients, the possibility of INPH may not have been considered; therefore measuring the callosal angle and Evans index, which reflect the characteristic morphologic change of INPH, would help radiologists to suggest the possibility of INPH.

White matter changes including PVH and DWMH have often been observed in INPH patients compared to aged subjects but they are not sufficient for the diagnosis of INPH [16–18]. Moreover, PVH and DWMH in INPH are supposed to be correlated with the clinical outcome. In particular, in INPH, the severity of the white matter changes may correlate with the clinical symptoms [18], but there is no evidence of a correlation with the response to shunt operation [19, 20]. In our study, the grade of PVH in the INPH group was significantly greater than those in the AD and NC groups. The percentage of positive PVH findings was over 90%. This indicates that most of the INPH patients have PVH, but some AD or NC subjects also have PVH. A positive PVH finding alone does not distinguish INPH patients from AD or NC subjects. Tullberg et al. [21] reported that when comparing INPH and Binswanger's disease, both groups had similar changes in white matter lesions as shown by MRI, indicating a common pathophysiological pattern.

Previous studies have reported CSF flow void in INPH [22–24], although flow voids often occur in both INPH and NC patients [5]. On conventional axial T2-weighted images, an aqueductal ventricular flow void is often observed. Therefore, our results indicate that an aqueductal ventricular flow void is not a useful finding for INPH diagnosis.

Conclusions

INPH patients have a small callosal angle (under 90°) on coronal MR images at the level of the posterior commissure, when the slices are oriented perpendicular to the anteroposterior commissure plane. Measuring the callosal angle on MRI is a convenient and useful technique for the diagnosis of INPH.

References

1. Adams RD, Fisher CM, Hakim S, Ojemann RG, Sweet WH (1965) Symptomatic occult hydrocephalus with normal cerebrospinal fluid pressure, a treatable syndrome. N Engl J Med 273:117–126
2. Hakim S, Adams RD (1965) The special clinical problem of symptomatic hydrocephalus with normal cerebrospinal fluid pressure. J Neurol Sci 273:307–327
3. Vassilouthis J (1984) The syndrome of normal-pressure hydrocephalus. J Neurosurg 61:501–509
4. Pappadà G, Poletti C, Guazzoni A, Sani R, Colli M (1986) Normal pressure hydrocephalus: relationship among clinical picture, CT scan and intracranial pressure monitoring. J Neurosurg Sci 30:115–121
5. Caruso R, Cervoni L, Vitale AM, Salvati M (1997) Idiopathic normal-pressure hydrocephalus in adults: result of shunting correlated with clinical findings in 18 patients and review of the literature. Neurosurg Rev 20:104–107
6. Holodny AI, Waxman R, George AE, Rusinek H, Kalnin AJ, de Leon M (1998) MR differential diagnosis of normal-pressure hydrocephalus and Alzheimer disease: significance of perihippocampal fissures. AJNR Am J Neuroradiol 19:813–819
7. Kitagaki H, Mori E, Ishii K, Yamaji S, Hirono N, Imamura T (1998) CSF spaces in idiopathic normal pressure hydrocephalus; morphology and volumetry. AJR Am J Roentgenol 19:1277–1284
8. Ishii K, Kawaguchi T, Shimada K et al (2008) Voxel-based analysis of gray matter and CSF space in idiopathic normal pressure hydrocephalus. Dement Geriatr Cogn Disord 25:329–335
9. Relkin N, Marmarou A, Klinge P, Bergsneider M, Black PM (2005) Diagnosing idiopathic normal-pressure hydrocephalus. Neurosurgery 57 (S2):4–16
10. Ishikawa M (2004) Clinical guideline for idiopathic normal pressure hydrocephalus. Neurol Med Chir (Tokyo) 44:222–223
11. McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM (1984) Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's disease. Neurology 34:939–944
12. Orrison WW Jr (1998) Neuroimaging. W.B. Saunders, Philadelphia
13. Fazekas F, Chawluk JB, Alavi A, Hurtig HI, Zimmerman RA (1987) MR signal abnormalities at 1.5 T in Alzheimer's dementia and normal aging. AJR Am J Roentgenol 149:351–356
14. Benson DF, LeMay M, Patten DH, Rubens AB (1970) Diagnosis of normal-pressure hydrocephalus. N Engl J Med 283:609–615
15. Sjaastad O, Nordvik A (1973) The corpus callosal angle in the diagnosis of cerebral ventricular enlargement. Acta Neurol Scand 49:396–406
16. Bradley WG Jr, Whittemore AR, Watanabe AS, Davis SJ, Teresi LM, Homyak M (1991) Association of deep white matter infarction with chronic communicating hydrocephalus: implications regarding the possible origin of normal-pressure hydrocephalus. AJNR Am J Neuroradiol 12:31–39
17. Kristensen B, Malm J, Fagerland M et al (1996) Regional cerebral blood flow, white matter abnormalities, and cerebrospinal fluid hydrodynamics in patients with idiopathic adult hydrocephalus syndrome. J Neurol Neurosurg Psychiatry 60:282–288
18. Krauss JK, Regel JP, Vach W et al (1997) White matter lesions in patients with idiopathic normal pressure hydrocephalus and in an age-matched control group: a comparative study. Neurosurgery 40:491–495
19. Dixon GR, Friedman JA, Luetmer PH et al (2002) Use of cerebrospinal fluid flow rates measured by phase-contrast MR to predict outcome of ventriculoperitoneal shunting for idiopathic normal-pressure hydrocephalus. Mayo Clin Proc 77:509–514
20. Tullberg M, Jensen C, Ekholm S, Wikkelso C (2001) Normal pressure hydrocephalus: vascular white matter changes on MR images must not exclude patients from shunt surgery. AJNR Am J Neuroradiol 22:1665–1673
21. Tullberg M, Hultin L, Ekholm S, Mansson JE, Fredman P, Wikkelso C (2002) White matter changes in normal pressure hydrocephalus and Binswanger disease: specificity, predictive value and correlations to axonal degeneration and demyelination. Acta Neurol Scand 105:417–426
22. Jack CR Jr, Mokri B, Laws ER Jr, Houser OW, Baker HL Jr, Petersen RC (1987) MR findings in normal-pressure hydrocephalus: significance and comparison with other forms of dementia. J Comput Assist Tomogr 11:923–931
23. Bradley WG Jr, Whittemore AR, Kortman KE et al (1991) Marked cerebrospinal fluid void: indicator of successful shunt in patients with suspected normal-pressure hydrocephalus. Radiology 178:459–466
24. Krauss JK, Droste DW, Vach W et al (1996) Cerebrospinal fluid shunting in idiopathic normal-pressure hydrocephalus of the elderly: effect of periventricular and deep white matter lesions. Neurosurgery 39:292–299