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MR Differential Diagnosis of Normal-Pressure Hydrocephalus and Alzheimer Disease: Significance of Perihippocampal Fissures

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PURPOSE: **In the older patient with dilated ventricles, it is often difficult to differentiate normal pressure hydrocephalus (NPH) from cerebral atrophy caused by Alzheimer disease (AD). This study was undertaken to see if dilatation of the perihippocampal fissures (PHFs) could be used as a distinguishing characteristic of these two disorders.**

METHODS: **MR images of 17 patients with AD were compared with those from an equal number of patients with NPH who improved after ventriculoperitoneal shunting. The PHFs, lateral ventricles, third ventricle, and temporal horns were graded subjectively. Objective, computer-aided volumetric measurements of the PHFs and lateral ventricles were obtained. The preshunt images of the NPH patients were evaluated.**

RESULTS: **Significant differences between the two groups were found for the PHFs and lateral ventricles by both the subjective and objective methods, with a high degree of correlation between the two methods.**

CONCLUSION: **The degree of dilatation of PHFs appears to be a sensitive and specific marker for differentiating AD from NPH by both subjective and objective means, with a very small overlap between the two groups. This observation may have relevance in day-to-day practice.**

In elderly patients with dilated ventricles, it is often difficult to differentiate normal pressure hydrocephalus (NPH) from cerebral atrophy caused by Alzheimer disease (AD). The difficulty in distinguishing between these two disorders has been recognized since NPH was first described by Hakim and Adams in 1965 (1, 2) and continues in the era of CT and MR imaging (3–7). The distinction is, nevertheless, important, because NPH may respond dramatically to the placement of a ventriculoperitoneal shunt (8–14). AD, on the other hand, is not a surgically treatable condition.

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Patients with AD almost invariably present with atrophy of the hippocampus and resultant dilatation of the fissures that surround it, the perihippocampal fissures (PHFs) (15–20). The PHFs include the lateral aspect of the transverse fissure of Bichat and the choroidal and hippocampal fissures (21). Dilatation of the PHFs has not been described in NPH. This study was undertaken to see if dilated PHFs, as seen on routine MR images, could be used to differentiate patients with clinical AD from those with shunt-proved NPH. The bodies of the lateral ventricles, the third ventricles, and the temporal horns were also compared between the two groups. Computer-aided volumetric analysis was performed on the PHFs and the lateral ventricles. The objective results were compared with the subjective evaluation to see if time-consuming volumetric analysis was necessary to accurately define the degree of dilatation of the PHFs or whether simple visual inspection of the PHFs was sufficient.

Methods

The records of all patients who underwent ventricular shunting at our institution during a 2½-year period were reviewed retrospectively. Patients who met the following criteria were selected for the NPH group: 1) Clinical diagnosis of NPH; 2) preshunt MR study of adequate quality; 3) no identifiable

cause for hydrocephalus; and 4) at least initial improvement after shunting, as documented in the medical chart. Seventeen patients met the above criteria. The mean age ± SD was 72 ± 6 years.

For the control group, we selected an equal number of age- (70 ± 11 years) and cognition-matched AD patients who were diagnosed according to DSM-IV and NINCDS-ADRDA (22) criteria and who did not have a gait disorder. All patients were being followed up at the aging and dementia clinic at our institution, and all underwent initial and follow-up neurologic, psychiatric, neuropsychiatric, neuroradiologic, and medical examinations. To obtain as pure a sample of AD patients as possible, we excluded those with other diseases that could affect brain function. Conditions that warranted exclusion were neuroradiologic evidence of cerebral infarction or any significant cardiac, endocrinologic, hematologic, hypertensive, gastroenterologic, pulmonary, immunologic, metabolic, or neoplastic disorder. In addition, all patients underwent psychometric evaluation and were rated according to the Global Deterioration Scale (GDS) (23). Only patients who scored 4 or 5 on the GDS scale were included in the study. A 4 corresponds to the late confusional phase, a 5 corresponds to the phase of early dementia, and stages 6 and 7 are defined as the middle and late phases of dementia, respectively (23).

Many patients at the AD clinic at our institution met the above criteria. We therefore further selected those with the largest lateral ventricles, since these patients would presumably present the greatest diagnostic dilemma for the interpreting radiologist.

In all cases, MR imaging was performed at 0.5-T or 1.5-T, and a minimum of axial proton density–weighted (2000–2500/30 [TR/TE]) and T2-weighted (2000–2500/70–80) sequences and sagittal T1-weighted (550–700/20–30) sequences were obtained. Section thickness varied from 5 to 8 mm, with an intersection gap of 0.7 to 2.4 mm. The axial images were obtained parallel to the plane of the hippocampus.

Findings in the two groups were compared both subjectively and objectively. Initially, two blinded, fellowship-trained neuroradiologists reviewed all the images and graded the lateral ventricles, temporal horns, third ventricle, and PHFs for size as follows: 0 = normal, 1 = mildly dilated, 2 = moderately dilated, 3 = markedly dilated.

Next, computer-quantified objective measurements of the volumes of the PHFs and the lateral ventricles were obtained using a method that corrects for partial volume averaging. Only the patients whose images were in digitized form on an optical disc were evaluated objectively. This included 13 patients from both groups. The method used here is a slight modification of the method described by Rusinek and Chandra (24).

In a voxel consisting of two types of tissue (A and B), the partial volume of each of the tissues (a and b) can be determined by solving the following two equations for two unknowns:

1) $$p_a + p_b \times b = s$$

2) $$a + b = v$$

This is provided one knows the following values for the region of interest (ROI) being studied: p_a and p_b represent the signal intensity of an ROI of "pure tissue" A and B, respectively, s is the signal intensity, and v is the volume of the ROI being studied.

An ROI was drawn around the structure under investigation (either the PHFs or the lateral ventricle) on every section in which that structure was present. For the PHFs, the ROI was defined as follows: the lateral border of the ROI was the medial-most aspect of the temporal horn, which corresponded to the lateral-most edge of the hippocampus. This demarcation was always well seen. The medial border of the ROI was defined as the medial-most extent of the hippocampus, which corresponded to the lateral-most extent of the perimesencephalic cistern. Even in cases of severe hippocampal atrophy, the lateral-most extent of the perimesencephalic cistern was definable. The anterior aspect of the ROI of the PHFs was defined as the anterior border of the hippocampus. The posterior border of the ROI of the PHFs was defined as a line drawn 1 cm posterior to the posterior-most extent of the pons.

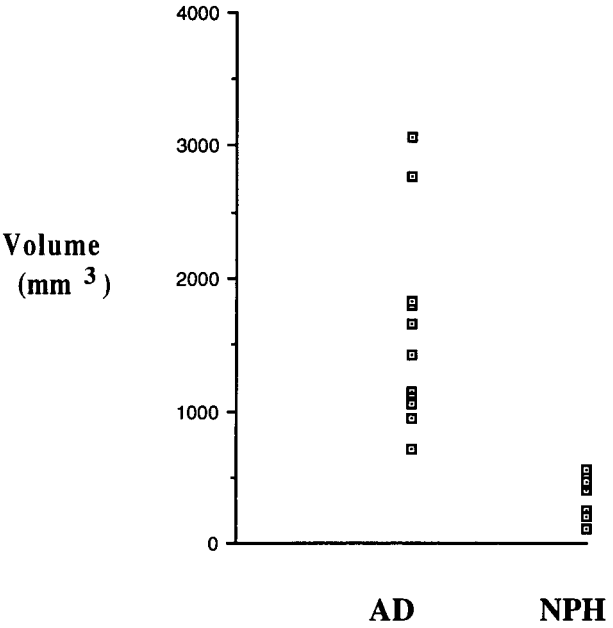


FIG 1. Objective measurement of the volume of the PHFs in patients with Alzheimer disease (AD) and normal pressure hydrocephalus (NPH). The mean volume of the PHFs for the AD group is 1503 ± 720 mm^3; for the NPH group, it is 423 ± 179 mm^3.

This work was performed on a Sun 3/180 workstation using our proprietary software. To improve the accuracy of the ROIs, the digital images were enlarged three times and displayed on a 1023 × 767 computer monitor. The signal intensity, s, and the volume of the ROI, v, were determined. For every image, an ROI of "pure CSF" and "pure brain" were obtained, thereby determining p_a and p_b. Using equations 1) and 2), one is able to determine the volume of the CSF-filled structures on every section. The volume obtained for each section was summed to obtain the total volume of each structure. The ROI measurements were obtained from the axial images, using either the T1- or T2-weighted sequence, depending on such factors as motion artifacts or better approximation of the long axis of the hippocampus. The T1-weighted sequence was used in four of the 13 cases of NPH and in seven of the 13 cases of AD. A previous study using a phantom and the method described here found no difference in the accuracy of determining the volume of CSF (or water in the phantom model) whether a T1- or a T2-weighted sequence was used (25). Significance was calculated by means of Student's t-test.

Results

A significant difference in the size of the PHFs was found between the NPH and the AD groups. This distinction was seen in both the subjective (Fig 1) and objective (Fig 2) data. By using the subjective data, $P = .0001$. In addition, all the patients in the AD group had enlarged fissures and 13 (77%) of 17 had moderate (Fig 3) or marked (Fig 4) enlargement. Most of the NPH patients (nine, or 53%, of 17) had normal-sized fissures (Fig 5), seven had mildly dilated

fissures (Fig 6), only one had moderate enlargement, and none had marked enlargement. If the patients in whom the PHFs were normal or mildly enlarged were considered to have NPH, and if those with moderate of marked enlargement were considered to have AD, by this criteria alone, the positive predictive value of this test would be 86%. By comparison, the subjective evaluation of the difference in the size of the temporal horns of the lateral ventricles was much less striking ($P = 0.153$) (Fig 7).

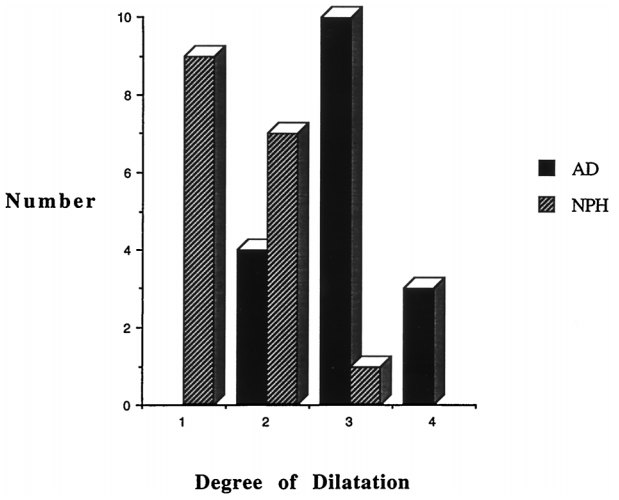
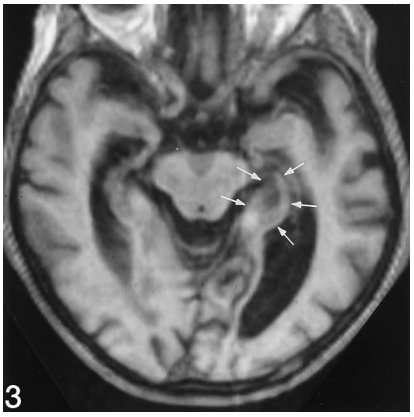


FIG 2. Subjective evaluation of the size of the perihippocampal fissures in patients with Alzheimer disease (AD) and normal pressure hydrocephalus (NPH). 0 = normal, 1 = mildly dilated, 2 = moderately dilated, 3 = markedly dilated.

In terms of the objective analysis, the mean volume of the PHFs for the AD group was 1503 ± 720 mm^3. For the NPH group, the value was 423 ± 179 mm^3 ($P = .0001$). There was no overlap between the two groups; nevertheless, the two largest values for the NPH group were within 10% of the lowest value of the AD group. There was a high degree of correlation between the subjective and objective evaluations of the size of the PHFs (correlation coefficient, $r = .835$).

With respect to the lateral ventricles, the findings were also significant in both the subjective (Fig 8) and objective (Fig 9) evaluations ($P = .0001$). Using the objective data, there was an overlap of seven patients. Using the same criteria as for the PHF patients (if those with normal or mildly dilated ventricles were considered to have AD and if those with moderately or markedly enlarged ventricles were considered to have NPH), the positive predictive value of this test would be 79%. For the objective data, the mean volume for the AD group was 40.1 ± 20.7 cm^3; for the NPH group it was 158.1 ± 75.2 cm^3. There was an overlap of one patient. Again, there was excellent correlation between the two methods of evaluation ($r = .824$).



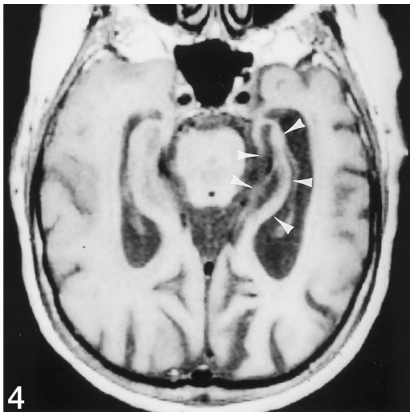
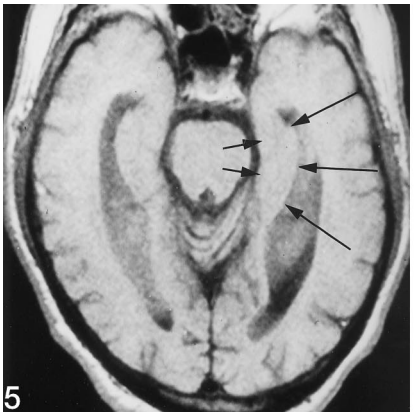


FIG 3. Reverse-angle axial T1-weighted (550/20) MR image in a woman with clinical AD (GDS score = 5). Note decreased signal intensity between the temporal horns and the perimesencephalic cistern (*arrows*), representing dilatation of the PHFs and atrophy of the structures of the medial temporal lobe, including the hippocampus. The size of the PHFs was assessed as moderately dilated.

FIG 4. Reverse-angle axial T1-weighted (640/20) MR image in a 78-year-old woman in the AD group (GDS score = 5). Note marked dilatation of the PHFs on the left (*arrowheads*). There is significant asymmetry between the degree of dilation of the PHFs on the two sides.



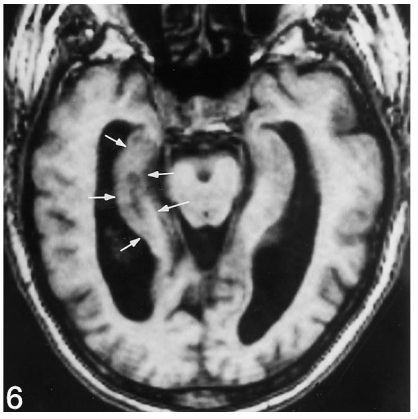


FIG 5. Reverse-angle axial T1-weighted (700/30) MR image of an 80-year-old man with the clinical diagnosis of NPH who improved after placement of a ventriculoperitoneal shunt. There is no abnormally decreased signal intensity of the structures of the medial temporal lobes (*arrows*); therefore, there is no dilatation of the PHFs or atrophy of the structures of the medial temporal lobe, including the hippocampus. The size of the PHFs was graded as normal, in contrast to the patients from the AD group in Figures 3 and 4. The degree of dilatation of the temporal horns is similar to that in patients from the AD group.

FIG 6. Reverse-angle axial T1-weighted (700/30) MR image in a patient with NPH. Note mild degree of decreased signal intensity of the structures of the medial temporal lobes (*arrows*). Therefore, the size of the PHFs was graded as mildly dilated.

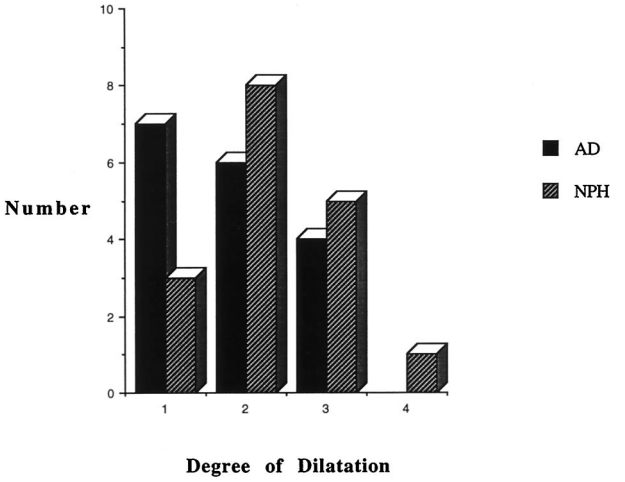


FIG 7. Subjective evaluation of the size of the temporal horns of the lateral ventricles in patients with Alzheimer disease (AD) and normal pressure hydrocephalus (NPH). 0 = normal, 1 = mildly dilated, 2 = moderately dilated, 3 = markedly dilated.

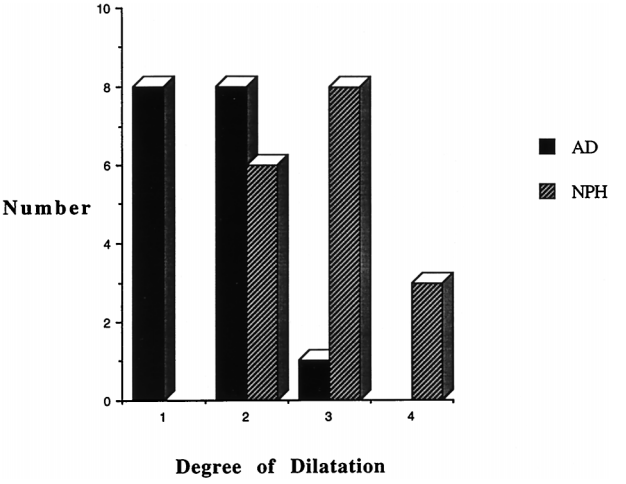


FIG 8. Subjective evaluation of the size of the bodies of the lateral ventricles in patients with Alzheimer disease (AD) and normal pressure hydrocephalus (NPH). 0 = normal, 1 = mildly dilated, 2 = moderately dilated, 3 = markedly dilated.

Subjective evaluation of the size of the third ventricle also showed a difference between the two groups ($P = .0009$) (Fig 10). There was an overlap of seven patients. Using the same criteria as above, the positive predictive value of the third ventricles was 79%. Significant asymmetry of the PHFs was noted in four (23%) of the 17 AD patients (Fig 4) and in none of the NPH patients.

Discussion

NPH was first described by Hakim and Adams (1, 2). Their first reports, based on pneumoencephalography, pointed out that it is often difficult to differentiate NPH from cerebral atrophy. This difficulty continues in the present day. Nevertheless, the distinction is of paramount importance in that patients with NPH can improve after the placement of a ventriculoperitoneal shunt.

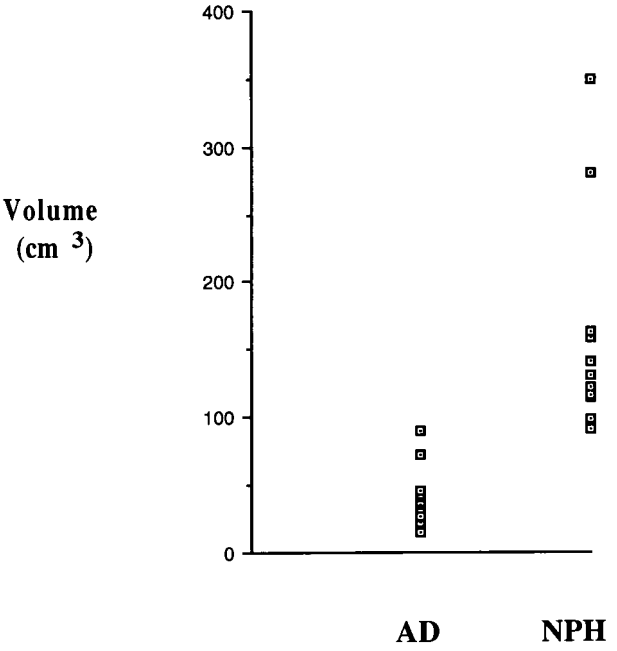


FIG 9. Objective measurements of the volumes of the bodies of the lateral ventricles for patients with Alzheimer disease (AD) and normal pressure hydrocephalus (NPH). The mean volume for the AD group was 40.1 ± 20.7 cm^3; for the NPH group, it was 158.1 ± 75.2 cm^3.

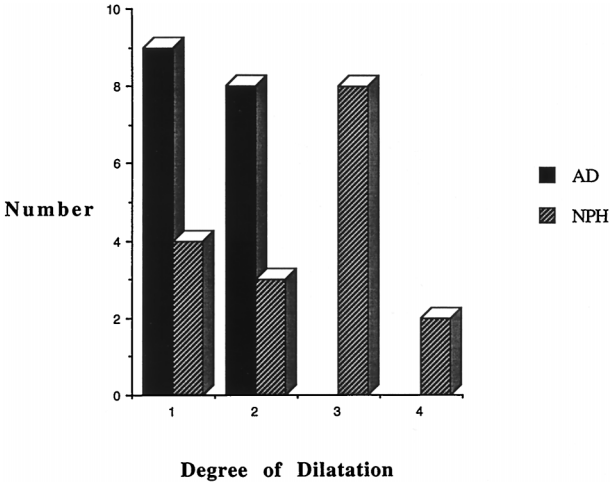


FIG 10. Subjective evaluation of the size of the third ventricles in patients with Alzheimer disease (AD) and normal pressure hydrocephalus (NPH). 0 = normal, 1 = mildly dilated, 2 = moderately dilated, 3 = markedly dilated.

The radiologic criteria for AD on both CT and MR studies are now becoming established. AD patients present with some degree of cerebral atrophy exemplified by sulcal and ventricular dilatation. This finding, however, is seen in a number of conditions, including normal aging (26, 27). Several investigators have reported that a much more sensitive and specific radiologic marker for AD on both CT and MR examinations is atrophy of the hippocampus and resultant enlargement of the PHFs (15–20): the lateral aspect of the transverse fissure of Bichat and the choroidal and hippocampal fissures (21). This radiologic indication of AD is in agreement with current

understanding of the pathogenesis of this disease (28). Pathologic studies have shown that atrophy of the hippocampal formation is the earliest finding in AD and that it is present universally in patients with this disorder (29–31). A number of radiologic studies have found that atrophy of the hippocampus is an early and reliable sign of AD, which can be used reliably to differentiate AD patients from those with other forms of dementia when the clinical diagnosis is in question (15, 17–19, 32, 33). A study by de Leon et al (34) showed that dilated PHFs and the associated hippocampal atrophy can successfully predict which elderly patients with minimal cognitive impairment will progress to AD.

The diagnosis of hydrocephalus resulting from known causes, such as physical obstruction of the CSF pathways, appears to be well established (35). In terms of the temporal lobe structures, dilatation of the temporal horn is one of the earliest signs of hydrocephalus in the adult; however, the radiologic diagnosis of NPH is more elusive. This is especially true when one attempts to predict from the radiologic data which patients will improve with the placement of a ventriculoperitoneal shunt. A number of authors have reported that the outcome of ventricular shunting in patients who apparently fulfill the available clinical and radiologic criteria for NPH has been disappointing (36–40). Such results in large-scale clinical trials indicate a need for better radiologic criteria in defining those patients who will respond to shunting. Conversely, and perhaps even more important, it is necessary to define the radiologic criteria for patients who will not benefit from shunting.

One of the characteristics of NPH appears to be dilatation of the temporal horns of the lateral ventricles (6). Dilatation of the perimesencephalic cistern and its extensions, the PHFs, has not been described in nondemented patients with NPH. Since dilatation of the PHFs appears to be a radiologic marker for AD, it was thought that it might serve to differentiate AD from NPH. We therefore undertook this comparative study between a group of AD patients and a group of NPH patients, with special attention to the PHFs. The results of our study show that there is a significant difference in the size of the PHFs in patients with clinical AD and those with shunt-proved NPH. The difference was evident by either computer-assisted volumetric maps or subjective visual inspection. Nevertheless, there was a small overlap between the two groups.

The high degree of correlation between the subjective and objective findings raises an important point. Volumetric analysis is time-consuming, difficult to perform, and requires special equipment, making it impractical to perform in routine clinical practice. Nevertheless, the difference between AD and NPH is a question that is often raised in such a setting. The data presented here show that simple visual inspection is almost as good as volumetric analysis when it comes to determining whether there is dilatation of the PHFs, provided one understands the radiologic features. This point has been stressed by others. De Leon et al (34) found a high degree of correlation between visual inspection of the PHFs on reverse-angle CT scans and detailed volumetric analysis of coronal MR images. A number of recent studies have emphasized the importance of visual inspection of this area in temporal lobe epilepsy (41–44), another disorder that is known to cause hippocampal atrophy. These findings underline the importance of understanding the anatomy of the PHFs and the necessity of routine inspection of this area on MR images of the brain.

It is well established that dilatation of the temporal horns is a defining characteristic of hydrocephalus. Therefore, a question can be raised as to why the PHFs appear to differentiate AD from NPH better than the temporal horns do. The answer lies in understanding the specific atrophic changes that develop in the hippocampi of patients with AD.

The part of the hippocampus that atrophies most in AD is the CA1 region (44); that is, the part of the hippocampus that projects into the temporal horn. The parts of the hippocampus that project into the PHFs (the CA2, CA3, and CA4 regions) also atrophy, but to a lesser degree (44). Therefore, the temporal horn should dilate proportionally more than the PHFs in patients with AD. This finding was recently confirmed in a study by Frisoni et al (45), who determined that a linear measurement of the size of the temporal horns was a better discriminator between patients with AD and healthy subjects than was a linear measurement of the choroidal fissure. Therefore, it appears that there should be dilatation of the temporal horns in both NPH and AD patients, although to different degrees and for different reasons. On the other hand, only patients with AD should have dilatation of the PHFs. Dilatation of the PHFs has, to our knowledge, never been described in patients with NPH, except in those with concurrent dementia (5). It is for this reason that the PHFs appear to discriminate well between patients with AD and NPH.

Another reason for the discriminating attributes of the PHFs may be the way that the interpreting radiologist views the films. In healthy subjects, the PHFs are very small. Therefore, a small degree of atrophy of the hippocampus creates a large percentage of change in the size of the PHFs, which is easily perceived radiologically. The temporal horn, on the other hand, is much larger than the PHFs. Therefore, atrophy of the CA1 region creates a much smaller percentage of change in the volume of the temporal horn, which is more difficult to perceive radiologically, even if it represents a larger volumetric change.

In evaluating an MR image of an elderly patient with dilated ventricles, the referral often is directly from the primary care physician or from the emergency department (46). In such a setting, the radiologist assumes the important role of raising the possibility of certain diagnoses and suggesting further workup. Based on the results of the present investigation, we think it is prudent for the radiologist to comment on the size of the PHFs in an elderly patient

with dilated ventricles, thereby suggesting the possible origin of the patient's malady as well as the need for further testing to confirm this diagnosis. It should be pointed out that even in the ideal setting, AD and NPH are often difficult to distinguish on the basis of clinical presentation alone (3, 4, 6, 7). The classical clinical triad of NPH, described as gait impairment, incontinence, and dementia, is also frequently seen in patients with AD.

A number of nonradiologic tests have been described that appear to be sensitive and specific for AD. These include apolipoprotein E4 (47, 48) and neural thread protein (49). In the era of cost containment, one may be tempted to forgo a neuroradiologic examination in an elderly patient with dementia, but this may not be advisable. It is axiomatic that even a 100% sensitive and specific test for AD would not exclude other disorders that can contribute to a patient's dementia, disorders that can be treated and that can only be diagnosed by a neuroradiologic examination. Examples include chronic subdural hematomas, both intra- and extraaxial tumors, and NPH (5–7).

In a study such as ours, it is important to establish criteria to differentiate the populations being compared (NPH versus AD, in this instance) and to construct as pure a sample as possible. Since AD is rather prevalent in the elderly population, it was important for us to avoid inclusion of patients in either group who might be afflicted with both conditions concurrently. To be included in either group, patients had to fulfill the set of criteria described earlier. For the AD group, lack of a gait disorder presumably eliminated subjects with concurrent AD and NPH, since patients with NPH usually evince this sign first (6, 13, 50). Of the three clinical characteristics that define NPH, it has been shown that after shunting, the one that is most likely to improve is the gait disorder; the degree of dementia is rarely improved to a significant degree (6). Consequently, neurosurgeons are reluctant to operate on patients who are more than mildly demented. Therefore, to eliminate the population bias that might arise from this factor, only those patients who were in the early stages of dementia (GDS score of 5 or less) were included in the AD control group. The size of the PHFs increases with the severity of dementia (5, 51). By including only patients in the early stages of dementia in the AD group, we created a bias against the theory being explored in this study.

For the NPH group, a positive response to ventricular shunting according to the patient's chart was used as a criterion for inclusion. A number of reports have emphasized that the long-term improvement rate for patients in whom shunts had been placed for NPH is less than the initial improvement rate (40). Since this study was concerned with the establishment of criteria for diagnosing NPH, it was decided to use initial rather than long-term improvement after placement of an intraventricular shunt as an entry criterion. Long-term failure after initial response may be related to a number of factors not related to the actual diagnosis of NPH, such as shunt failure, development of subdural or subarachnoid hemorrhage, or development of other medical or neurologic problems.

A number of comments should be made regarding the objective analysis. The "pure CSF" ROI was obtained from a ventricle in which visual inspection of the sections above and below eliminated any possibility of partial volume averaging or flow artifacts. The ROI of "pure brain" presented somewhat of a dilemma, since the structures of the mesial aspect of the temporal lobe, including the hippocampus, the parahippocampal gyrus, and the subiculum represent a conglomeration of both white and gray brain structures, the percentage of which is difficult to determine. This is compounded by the fact that in both AD and normal aging, the gray and white structures atrophy at different rates (52). We tested a number of brain structures that contained elements of both gray and white matter without any partial voluming from CSF. In the final analysis, when measuring the size of the PHFs, no significant difference was observed irrespective of which area of "pure brain" was used. None of the *P* values were affected. The numerical data presented were derived from the basis pontis as the ROI of "pure brain."

A number of the images had intersection gaps as high as 30%, which can potentially result in a large error when calculating something as small as PHFs. In the calculations presented, the intersection gap was treated the same way for both populations. The section thickness for the purpose of the calculations was made to be equal to the actual section thickness plus the intersection gap. However, even if one assumes the maximum degree of error to go against the proposition being explored in this paper (ie, if one includes only the thickness of the actual section in calculating the volume PHFs for patients with AD and includes both the height of the section and the intersection gap for the same calculation in patients with NPH), the significance remains unchanged ($P = .0001$). The same is true when determining the significance of the lateral ventricles.

Conclusion

This study has shown, by both subjective and objective means of evaluation, that there is a significant difference in the dilatation of PHFs and in the size of the lateral ventricles in patients with NPH versus those with AD. Patients with NPH had dilated ventricles and small PHFs, whereas patients with AD had dilated PHFs and ventricles that were enlarged but significantly smaller than those in patients with NPH. The findings regarding the PHFs appear highly sensitive and specific, with very small overlap between the two groups.

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