Positron emission tomography with \([^{18}F]\)Fluorodeoxyglucose differentiates normal pressure hydrocephalus from Alzheimer-type dementia

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SUMMARY Because diagnostic criteria for normal pressure hydrocephalus have not been clearly determined, it is often difficult to differentiate patients with this potentially treatable condition from those with Alzheimer-type dementia. We have studied three patients with normal pressure hydrocephalus, 17 patients with Alzheimer-type dementia, and seven healthy elderly controls using positron emission tomography and \([^{18}F]\)Fluorodeoxyglucose (FDG). Both Alzheimer-type dementia and normal pressure hydrocephalus groups showed lower cortical rates of FDG utilisation than controls. However, the patterns of metabolic abnormality were distinctly different in the two dementia groups, with Alzheimer-type dementia subjects demonstrating bilateral temporo-parietal hypometabolism while normal pressure hydrocephalus subjects showed globally diminished glucose use.

Normal pressure hydrocephalus is recognised as an important cause of treatable dementia,¹ but there is considerable confusion regarding clinical and radiographic criteria necessary to ensure a good outcome with cerebrospinal fluid shunting procedures.²³ The generally disappointing results of therapy are in large part due to the problem of separating patients with normal pressure hydrocephalus from those with the more common but untreatable Alzheimer’s disease. We have found that noninvasive imaging with positron emission tomography (PET) using \([^{18}F]\)Fluorodeoxyglucose (FDG) is capable of assisting in the differentiation of these two illnesses.

Patients and methods

Three male patients aged 55, 58, and 62 years met clinical criteria for the diagnosis of normal pressure hydrocephalus.⁴ All experienced a gradual generalised decline in cognitive function, associated with gait difficulty and urinary incontinence. X-ray revealed dilated ventricles with minimal cortical atrophy, and radionuclide cisternography in all cases demonstrated ventricular reflux and delayed passage of isotope over the cerebral convexities. At the time of lumbar puncture, opening cerebrospinal fluid pressures were 120, 91, and 100 mm H₂O in patients 1, 2, and 3 respectively.

Patient 1 developed the syndrome 6 months after suffering a subarachnoid haemorrhage and right frontal intracerebral haematoma following rupture of a saccular aneurysm of the right anterior communicating artery. Patient 2 was an alcoholic who developed a gradually progressive dementia over the course of a year with no clear precipitant. Patient 3 had experienced 3 years of difficulty with memory prior to initial evaluation and had been diagnosed as having Alzheimer’s disease. Over the next six months he developed urinary incontinence and a gait disorder characterised by a wide base and magnetic stepping. An internuclear ophthalmoplegia was noted and laboratory examination showed bilaterally delayed pattern reversal visual evoked potentials and oligoclonal banding in the cerebrospinal fluid. He was presumed to have the coincidental occurrence of normal pressure hydrocephalus and multiple sclerosis. All three patients underwent lumbo-peritoneal shunting, and all demonstrated marked
improvement in gait with follow-up ranging from 3 months to 2 years after operation. In addition, all underwent pre- and post-operative neuropsychological testing and demonstrated improvement on tests measuring sensory-motor coordination, memory, and attention (Digit-symbol substitution from the Wechsler Adult Intelligence Scale, Trail-making A and B, rapid thumb press, and memory for stories from the Wechsler Memory Scale).

Seventeen patients, eight men and nine women, aged 55 to 75 years, of varying disease severities met current research criteria for the diagnosis of Alzheimer-type dementia. Scores on the Mattis dementia scale were available for 16 of the patients and ranged from 55 to 129 with a mean of 93-9 (maximum 144, normal 140-144). All patients showed the gradual onset of generalised intellectual decline most marked by memory loss with the specific absence of alcoholism, hypertension, diabetes mellitus, evidence of cerebrovascular disease, previous head trauma, seizures, drug intoxication and history of psychiatric illness. All had Hachinski ischaemia scores of less than 4, and have undergone follow-up neurological and neuropsychological examinations every six months for 8 months to 2 years.

Seven healthy elderly subjects, two men and five women, aged 59 to 68 years, served as controls. These individuals had normal medical and neurological exams and neuropsychological tests documented an average level of functioning. Results of PET studies in Alzheimer-type dementia and control subjects in our laboratory have been presented in previous publications.

PET was performed between two and six months prior to surgery and within one month of x-ray CT in all normal pressure hydrocephalus patients. Using the Donner 280-crystal tomograph (resolution 8 mm full width at half maximum), subjects were placed in the supine position and given 45 minutes to acclimatise to the testing environment. During this time transmission studies using an external 68Ga source were performed to facilitate attenuation correction. Subsequently 5–10 mCi of FDG were injected intravenously followed by sampling of arterialisued venous blood from a warmed hand. Concurrently, dynamic tomographic data were collected for 45 minutes from one transverse section. Data were collected at 5 s intervals for 0–120 s, 15 s intervals for 120–300 s, 60 s intervals for 300–900 s, and 300 s intervals thereafter. After 45 min, tomographic data were obtained for one to four additional levels with a scanning time of 300 s per section. All patients were studied in the eyes-open state in a quiet room. Sections were performed in a plane parallel to the canthomeatal line, with a slice thickness of 10 mm.

Data were studied from the midventricular level (approximately 6 cm above the canthomeatal line) for all subjects by drawing regions of interest using a standard brain atlas for reference to neuroanatomical structures. Regions sampled were anterior frontal, temporoparietal, and entire cortex of both hemispheres. The relatively high resolution of the system allowed for sampling of activity in small regions of cortex. Regional activity concentrations were determined (counts/cm^2/s) for each region of interest using data obtained from 40–70 minutes after injection. Percentage differences for activity density in frontal and temporoparietal regions were calculated as the frontal-temporoparietal difference divided by the mean of the two values multiplied by 100. These percentages provide an index of the difference between metabolic rates in frontal and temporoparietal regions, and are valid indicators of regional metabolic activity, as the concentration of 18F 40 minutes after injection is related to relative regional rates of glucose use.

Regional cerebral metabolic rates of glucose (rCMRglu) were calculated for 10 Alzheimer-type dementia patients, seven controls, and two normal pressure hydrocephalus patients (blood input data were not available for seven Alzheimer-type dementia patients and normal pressure hydrocephalus patient 3). Rate constants were determined with a three-compartment model using an iterative least-squares fitting method and the Marquardt algorithm. Values for k_1*, k_2*, k_3*, and k_4* were derived from brain and blood time-activity curves for six control subjects and for nine of the 10 Alzheimer-type dementia subjects. Mean values of the rate constants for cortex from the Alzheimer-type dementia subjects were used with the operational equation of Phelps et al to determine metabolic rates in this group, while the mean values of control rate constants were used with the operational equation to determine metabolic rates for the control and normal pressure hydrocephalus subjects. For the Alzheimer-type dementia group these values were k_1* = 0.123, k_2* = 0.225, k_3* = 0.107, k_4* = 0.012; while for the control group they were k_1* = 0.131, k_2* = 0.214, k_3* = 0.113, k_4* = 0.009 min^-1. Use of the operational equation minimises errors due to inaccuracies in the rate constants. Although the value for the lumped constant has not been studied in diseased human brain, we used the value of 0.52 as recently measured by Reivich and coworkers in nine normal young males. The metabolic rates reported here can be compared to the work of other laboratories by multiplying by the ratio of lumped constants.

### Results

PET images at the mid-ventricular level for each normal pressure hydrocephalus patient are presented in fig 1, along with representative images from an Alzheimer patient and control subject. The obvious temporoparietal hypometabolism observed in the Alzheimer-type dementia patient is not seen in the images from normal pressure hydrocephalus patients. This temporoparietal hypometabolism was found in all Alzheimer-type dementia patients regardless of disease severity, age, or sex. The image for patient 1 shows diminished activity in the right frontal region resulting from the haematoma and resultant infarction. All other normal pressure hydrocephalus patients show an even distribution of cortical activity.

Figure 2 presents data for frontal-temporoparietal percentage differences for each hemisphere in each group. Values from normal pressure hydrocephalus patient 1 are excluded in the analysis of the right hemisphere data since the right frontal lesion produced markedly lowered activity counts in...
Positron emission tomography with ["F"]Fluorodeoxyglucose

Fig 1  PET images obtained at the mid-ventricular level for normal pressure hydrocephalus patients (patients 1, 2, and 3), and representative images from an Alzheimer-type dementia and control subject.

the right frontal lobe which are not reflective of the pathology of normal pressure hydrocephalus. The values are significantly different for the normal pressure hydrocephalus and Alzheimer-type dementia groups, although control and normal pressure hydrocephalus groups are different only for left hemisphere values. Alzheimer-type dementia subjects are also significantly different from the control subjects.

Mean values of rCMRglu for each group are shown in the table. Both the normal pressure hydrocephalus and Alzheimer subjects have lower metabolic rates than controls. The Alzheimer-type dementia patients show hypometabolism relative to control subjects which is most marked in temporoparietal cortex, while the disturbed metabolism in normal pressure hydrocephalus is evenly distributed.

Discussion

The diagnosis of normal pressure hydrocephalus is only certain retrospectively by demonstrating improvement following CSF shunting. Research has thus been concerned with delineating clinical and laboratory criteria which predict a good response to shunting. Nevertheless, overall success rates have been disappointing, ranging from 24 to 60% in clinical series.19-22

Exclusion of patients unlikely to respond to CSF
Differences in activity density for right and left hemispheres of normal pressure hydrocephalus (NPH), Alzheimer-type dementia (ATD) and control (C) subjects. Percent difference = 100 \times (\text{frontal} - \text{temporoparietal/frontal + temporoparietal})/2. Error bars are standard error of the mean.

For Right Hemisphere
NPH N = 2, ATD N = 17, C N = 7, Student's t test, two tailed
NPH vs ATD \( p < 0.05 \)
NPH vs C = NS
ATD vs C \( p < 0.001 \)

For Left Hemisphere
NPH N = 3, ATD N = 17, C N = 7, Student's t test, two tailed
NPH vs ATD \( p < 0.001 \)
NPH vs C \( p < 0.05 \)
ATD vs C \( p < 0.001 \)

Table: Means and standard deviations (SD) of regional glucose utilisation rates in cortex (mg glucose/100 cc/min) for normal pressure hydrocephalus, Alzheimer-type dementia, and control groups

<table>
<thead>
<tr>
<th>Patients</th>
<th>RF</th>
<th>LF</th>
<th>RTP</th>
<th>LTP</th>
<th>R Ent</th>
<th>L Ent</th>
</tr>
</thead>
<tbody>
<tr>
<td>NPH</td>
<td>3.81</td>
<td>4.46</td>
<td>4.37</td>
<td>4.58</td>
<td>4.35</td>
<td>4.71</td>
</tr>
<tr>
<td>(N = 2)</td>
<td>(2.25)</td>
<td>(1.12)</td>
<td>(1.38)</td>
<td>(1.67)</td>
<td>(1.71)</td>
<td>(1.10)</td>
</tr>
<tr>
<td>ATD</td>
<td>6.27</td>
<td>5.81</td>
<td>4.54</td>
<td>5.31</td>
<td>5.83</td>
<td>5.46</td>
</tr>
<tr>
<td>(N = 10)</td>
<td>(1.40)</td>
<td>(1.46)</td>
<td>(1.21)</td>
<td>(1.19)</td>
<td>(1.23)</td>
<td>(1.42)</td>
</tr>
<tr>
<td>Control</td>
<td>7.23</td>
<td>6.88</td>
<td>7.37</td>
<td>6.85</td>
<td>7.37</td>
<td>6.94</td>
</tr>
<tr>
<td>(N = 7)</td>
<td>(0.94)</td>
<td>(0.88)</td>
<td>(1.02)</td>
<td>(0.96)</td>
<td>(0.94)</td>
<td>(0.96)</td>
</tr>
</tbody>
</table>

RF—right frontal cortex, LF—left frontal cortex, RTP—right temporoparietal cortex, LTP—left temporoparietal cortex, R Ent—right entire cortex, L Ent—left entire cortex.

shunting would contribute to higher success rates. Alzheimer's disease is the most common form of dementia and as such represents an important diagnostic consideration when contemplating treatment, as these patients are not likely to benefit from shunting. Indeed, neuropathological changes of Alzheimer's disease have been demonstrated in patients failing to respond to shunts. While our report is limited to the study of only three patients, they fit both prospective and retrospective criteria for the normal pressure hydrocephalus syndrome and did not share the same pattern of regional cerebral metabolic alterations as our Alzheimer-type dementia patients. These data suggest that metabolic imaging in a population of subjects suspected of having normal pressure hydrocephalus will allow for identification of those with Alzheimer-type dementia, providing a residual population more likely to respond to CSF shunting.

The two methods of data analysis reported here are complementary. Frontal—temporoparietal percentage differences for activity density provide a quantitative index of the pattern of metabolic activity for a given patient which can be used to compare regional differences between patients. These percentages clearly indicate different patterns of metabolism in normal pressure hydrocephalus and Alzheimer-type dementia, without specifying whether the differences in Alzheimer-type dementia result from depression of temporoparietal metabolism or an increase in frontal metabolism. Absolute values of regional cerebral metabolic rates, however, show a definite depression of cerebral metabolism in all brain regions in normal pressure hydrocephalus, and in temporoparietal cortex in Alzheimer-type dementia. Taken together, these findings indicate that both the dementias of normal pressure hydrocephalus and Alzheimer-type disease are characterised by hypometabolism, while the regional distribution of these metabolic abnormalities is distinctly different.

Our findings in Alzheimer-type dementia are in agreement with other studies of cerebral metabolism which have also found a focal or multifocal nature of metabolic depression in Alzheimer's disease. These data further support the concept that regional glucose utilisation rates in Alzheimer-type dementia can be used to provide information about the distribution of metabolic abnormalities associated with this disorder.
the abnormality, with hypometabolism most marked in temporoparietal and frontal association cortex and less involvement of motor, somatosensory and primary visual cortex.26–28 The global hypometabolism which we found in normal pressure hydrocephalus, however, contradicts the prevailing theories about the pathophysiology of the illness. It has been suggested that symptoms are caused by primary involvement of the frontal lobes, with stretching of leg fibres in the corona radiata29 or selective ischaemia in the distribution of the anterior cerebral artery.30 Our findings of equal involvement of all cortical regions argues against selective involvement of any one cortical area. However, limitations in spatial resolution limits the quantitation of metabolism in white matter. Focal alterations in periventricular white matter caused by transudation of CSF or intermittently increased pressure would not be detected with this procedure. An earlier study by Grubb et al31 evaluated cerebral blood flow and metabolism (by measuring the cerebral metabolic rate of oxygen) in normal pressure hydrocephalus and dementia with cortical atrophy. While these investigators noted diminished flow and metabolism in both groups, neither the regional patterns of flow and metabolism nor the changes in these parameters following removal of CSF differentiated the two groups. These findings might be explained by the poorer resolution of their non-tomographic technique, and because the cortical atrophy group contained patients with several different types of dementia.

The images and the quantitative data presented here are not diagnostic of the normal pressure hydrocephalus syndrome. Nevertheless, it is clear that when confronted with the demented patient who appears to be a candidate for shunting, PET may allow for exclusion of a subgroup with Alzheimer-type dementia and therefore increase the likelihood of a favourable outcome. While the present prohibitive expense and technological support needed for PET studies preclude its use by the general medical community, recent developments in single photon emission computed tomography with new radiopharmaceuticals to measure blood flow allow more practical methods of evaluating cerebral physiology in vivo.32–34 Although flow and metabolism appear to be normally coupled in Alzheimer-type dementia,28 further studies are needed to evaluate this issue in normal pressure hydrocephalus patients. Evaluation of a larger number of well-defined patients are required in order to demonstrate that single photon emission computed tomography studies of cerebral flow will yield equivalent information to that obtained with these PET metabolic studies. Our results suggest that the general availability of such a technique will be of value in the differential diagnosis of dementia.

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