Intracranial Volume and Alzheimer Disease

Evidence Against the Cerebral Reserve Hypothesis

Rhian Jenkins, BSc; Nick C. Fox, MRCP; Alex M. Rossor; Richard J. Harvey, MRCPsych; Martin N. Rossor, FRCP

Background: Total intracranial volume (TIV) measurement commonly is used to correct for variations in premorbid brain size in imaging studies of cerebral structures in Alzheimer disease (AD). This assumes no intrinsic difference in TIV between patients and control subjects and that TIV measurements are unaffected by cerebral atrophy. However, an autopsy study has suggested that a larger premorbid brain may protect against AD onset. A recent computed tomographic study lent support to this by finding a correlation between intracranial size and age at onset of AD in women.

Objective: To investigate the relationship between TIV and sporadic and familial AD.

Design: Retrospective case study.

Setting: Specialist dementia clinic.

Patients: Eighty-five patients with AD and 52 healthy volunteers.

Main Outcome Measures: Age at symptom onset and TIV measured using a semiautomatic interactive thresholding technique on magnetic resonance imaging spanning the entire intracranial cavity.

Results: Reproducibility measurement was high (intrarater coefficient of variation, 1.2%; interrater coefficient of variation, 0.7%). Unlike brain atrophy in the patients with AD, TIV did not vary over time. Mean TIV did not differ significantly between any of the subject groups. There was no association between TIV and age or age at symptom onset. The only significant predictor of TIV was sex.

Conclusions: Measurements of TIV are independent of atrophy and can be used safely to adjust for differences in head size in studies of cerebral structure in AD. Premorbid brain size does not differ between patients with familial and sporadic AD and controls and does not delay disease onset.

Arch Neurol. 2000;57:220-224

It has been suggested previously that a larger brain volume provides a greater cerebral reserve against the effects of Alzheimer disease (AD), maintaining cognitive function in the presence of neurodegeneration and thereby delaying the onset of symptoms. This hypothesis was based on the observation that nonmented elderly subjects with histological evidence of AD at autopsy had larger brains and a greater number of large neurons than elderly control subjects without such histopathological change.

Other studies have provided in vivo support for this hypothesis by finding a significant positive correlation between intracranial area on computed tomography (CT) and age at onset in women with AD. Two recent, large cross-sectional studies examined head circumference in AD, with one reporting a significant association.

Intracranial size measurements provide an estimate of maximum premorbid brain size and, unlike cerebral volume, should not be affected by atrophy due to neurodegeneration or ageing. The suggestion of a relationship between age at onset and intracranial size is important for our understanding of the pathophysiological features of the disease. In addition, if the association is significant, then total intracranial volume (TIV) may have to be considered a potential confounder in epidemiological studies of risk factors in AD and in future disease prevention studies. Furthermore, TIV commonly is used to correct for head size in studies of global and regional atrophy in AD with the assumption that it is unaffected by disease status. Care should be taken, therefore, to ensure that this assumption is correct.

Early-onset autosomal dominant familial AD (FAD) may be caused by mutations in at least 3 separate genetic loci. The mutations in the amyloid precursor protein (APP) and in the presenilin 1 and 2 genes result in alterations in proteins that are thought to be important in maintaining neuronal integrity. Abnormalities in these proteins could alter brain development and affect maximal brain size achieved. The age at onset in these subjects is usually very different from that in subjects with sporadic AD (SAD); therefore, any assessment of the relationship between age at onset and TIV should control for whether AD is familial or sporadic.
PATIENTS AND METHODS

PATIENTS

Eighty-five patients with a clinical diagnosis of AD who had undergone an adequate MR brain study were identified from the patient database of a specialist dementia clinic. All subjects had undergone comprehensive clinical and neuropsychological assessments and were included in the study only if they fulfilled criteria of the National Institute of Neurological and Communication Disorders and Stroke-Alzheimer’s Disease and Related Disorders Association for probable AD. Alzheimer disease was classified as FAD if subjects had a clear family history of early-onset (<65 years of age) AD with an autosomal dominant pattern of inheritance, and at least 2 affected family members, including a first-degree relative. Of the 22 patients with FAD, 18 were from families where pathologic mutations in the APP (n = 7) or presenilin 1 (n = 11) genes have been identified. Fifty-two healthy controls who had also undergone MR brain scans were identified from the patient database and matched for sex and age at scanning to the AD group. This group consisted of healthy spouses of patients and other volunteers. Details of patients and controls are given in Table 1. All individuals or their legal representatives gave informed consent to the study, which had local ethical approval.

AGE AT ONSET

Age at onset was defined as the age at which symptoms of progressive memory loss or other cognitive decline were first noted. This was documented by physicians during the patients’ initial evaluation, having been estimated from reports of family members and other close informants.

INTRACRANIAL MEASUREMENT

Each subject within the study underwent at least 1 MR brain scan (GE 1.5T Signa unit; General Electric, Milwaukee, Wis). Scans included a routine T1-weighted scout sequence followed by proton density and T2-weighted axial dual-echo sequence (field of view, 240 mm; matrix, 256 × 192 pixels, 4 × 5-mm slices with 2.5 interslice spacing).

The MR images were transferred to a workstation (Sun Microsystems Inc, Mountain View, Calif) where measurements were performed retrospectively, unaware of subject diagnosis. Measurements of TIV were calculated using MIDAS image analysis software with the T2-weighted dual-echo images (Figure 1). The inner boundary of the calvarium, which includes the brain, meninges, and cerebrospinal fluid, was outlined using a semiautomatic interactive grey level thresholding technique. The grey-level threshold for the cutoff between calvarium and cerebrospinal fluid was standardized at 60% of mean intracranial signal intensity on an axial slice immediately superior to the ventricles. This threshold value was then applied to the TIV. The inferior plane through brainstem of the TIV was taken arbitrarily to be at the level of the lowest slice that included cerebellar tissue.

REPRODUCIBILITY

Reproducibility was assessed by performing 3 separate TIV measurements on scans from 10 subjects. The measurements were performed over several weeks in a randomized and blinded manner. Means and SDs were then calculated for the 3 volumes acquired on each scan. Interrater reliability also was assessed using a single scan from 19 subjects measured by 2 investigators. Reproducibility was expressed as the coefficient of variation (SD divided by the mean). To assess whether TIV measurements are independent of increasing cerebral atrophy, 9 subjects with AD who had each undergone 3 scans acquired during a period of 2 or more years (thereby spanning a range of disease progression) had TIV and brain volume measured on each scan. These measurements were examined using regression models clustered on individuals to account for observations not being independent within each subject, with TIV or brain volume as the dependent variable and sequential scan number as the predictor.

DATA ANALYSIS

Data were analyzed using commercially available software (Statistical Package for the Social Sciences [SPSS], version 8.0; SSPS Inc, Chicago, III, and Stata; release 6.0; Stata Corporation, College Station, Tex). Sample size calculations were undertaken to confirm the power of the study based on data from the controls, with significance set at 1%. Differences between the control and AD groups were investigated using analysis of variance (ANOVA). When the ANOVA indicated a significant between-group difference, linear regression models were fitted to investigate these differences. The validity of these models was assessed by examining residuals, fitted values, and Cooks distances (a measure of the influence of a single data point on the regression line). The effect of outliers in the model was examined by removing any points with large Cooks distances (>0.03) and refitting the model. Age at symptom onset and age at scan also were included as covariates in the linear regression models, to examine for any confounding effect.

We undertook a magnetic resonance (MR)–based study of intracranial size in FAD and SAD to examine the hypothesis that TIV was related to the risk for AD. This was achieved in the following 2 ways: by comparing subjects with AD with a matched control population, and by comparing TIV with age at symptom onset. We chose to measure TIV from images that spanned the whole intracranial cavity rather than estimating it from 1 or 2 intracranial area measurements. Estimates of premorbid brain size based on 1 or 2 scan slices are sensitive to slice orientation or position and cannot account for differences in individual head shape. We used serial scans in subjects with AD to assess reproducibility and to confirm that the measure was independent of the development of progressive cerebral atrophy.

RESULTS

REPRODUCIBILITY

Coefficients of variation were 1.2% within measurers and 0.7% between measurers, confirming high reproducibility.
Regression models clustered on individuals with AD showed a significant linear decrease in brain volume of 27.4 cm³ with each additional scan ($t = -5.5; P = .001$) but a nonsignificant increase in TIV of 6.1 cm³ ($t = 2.2; P = .06$).

DEMOGRAPHIC DATA

The patient characteristics are given in Table 1. There was no significant difference in the proportions of men and women in each group. The FAD group was 15 years younger (95% confidence interval, 12-19 years) than the SAD group ($t = 8.7; P < .001$).

TOTAL INTRACRANIAL VOLUMES

Mean TIV for each group can be seen in Table 2. We based our power calculations on a previous study of brain volume in AD where differences of 8.5% and 11% were found between groups. For an equivalent difference between patient and control groups, our study has power of 98% and 99%, respectively, with significance set at 1%. The study therefore has a less than 2% chance of type II statistical error.

The fitted linear regression models are shown in Table 3. When all variables were included in the model, only sex was found to influence TIV ($F = 24.6; P < .001$). This finding was checked for robustness by removing the outlying individuals (n = 8) with Cooks distances of greater than 0.03 from the model. This had no effect on the interpretation ($F = 36.1; P < .001$).

The influence of age at symptom onset on TIV was examined by adding age at onset as a covariate in the model. This did not contribute significantly to the model, with sex remaining the only significant predictor of TIV (Table 3, Figure 2, and Figure 3).

Comment

Total intracranial volume is determined during childhood by the volume of brain, meninges, and cerebrospinal fluid contained within it. Brain volume is maximal by early childhood and appears to decline from early adulthood. Our measure of TIV is likely to correlate closely with premorbid brain size and be relatively invariant to disease onset or advancing age.

The technique used to measure TIV had high reproducibility and was shown to be independent of increasing atrophy. This is important for its use in studies of AD, where structures such as the hippocampus are normalized for intersubject head size differences. We did not find any significant differences in TIV between the

Table 1. Demographics of Groups

<table>
<thead>
<tr>
<th>Group*</th>
<th>No. of Subjects</th>
<th>Sex, No. M/F</th>
<th>Age at Scan, Mean ± SD (Range), y</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls</td>
<td>52</td>
<td>24:28</td>
<td>56.1 ± 12.1 (36-85)</td>
</tr>
<tr>
<td>AD group as a whole</td>
<td>85</td>
<td>41:44</td>
<td>60.8 ± 10.2 (38-82)</td>
</tr>
<tr>
<td>Sporadic AD</td>
<td>63</td>
<td>33:30</td>
<td>65.2 ± 7.0 (51-82)</td>
</tr>
<tr>
<td>Familial AD</td>
<td>22</td>
<td>8:14</td>
<td>48.2 ± 6.7 (38-65)</td>
</tr>
</tbody>
</table>

*AD indicates Alzheimer disease.

Table 2. TIV for Subject Groups and by Sex*

<table>
<thead>
<tr>
<th>Group</th>
<th>No. of Subjects</th>
<th>TIV, Mean ± SD, cm³</th>
<th>Sex, No.</th>
<th>TIV by Sex, Mean ± SD, cm³</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls</td>
<td>52</td>
<td>1407.1 ± 148.9</td>
<td>24 Males</td>
<td>1512.5 ± 128.2</td>
</tr>
<tr>
<td>AD as a whole</td>
<td>85</td>
<td>1403.9 ± 164.7</td>
<td>41 Males</td>
<td>1513.4 ± 127.7</td>
</tr>
<tr>
<td>Sporadic AD</td>
<td>63</td>
<td>1419.5 ± 170.4</td>
<td>33 Males</td>
<td>1517.8 ± 134.9</td>
</tr>
<tr>
<td>Familial AD</td>
<td>22</td>
<td>1359.5 ± 141.5</td>
<td>8 Males</td>
<td>1495.2 ± 97.1</td>
</tr>
</tbody>
</table>

*TIV indicates total intracranial volume; AD, Alzheimer disease.

Table 3. Results of Regression Analysis on Total Intracranial Volume*

<table>
<thead>
<tr>
<th>Predictor Variable</th>
<th>Partial Regression Coefficient, cm³</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model 1†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex‡</td>
<td>204 088.5</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Age at scan, y</td>
<td>367.2</td>
<td>.75</td>
</tr>
<tr>
<td>FAD vs controls§</td>
<td>-24 761.2</td>
<td>.45</td>
</tr>
<tr>
<td>SAD vs controls§</td>
<td>-3643.7</td>
<td>.89</td>
</tr>
<tr>
<td>Model 2‡</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex‡</td>
<td>205 914.1</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Age at scan, y</td>
<td>-3146.9</td>
<td>.58</td>
</tr>
<tr>
<td>Age at symptom onset, y</td>
<td>3961.6</td>
<td>.49</td>
</tr>
<tr>
<td>SAD vs FAD¶</td>
<td>7984.2</td>
<td>.87</td>
</tr>
</tbody>
</table>

*FAD indicates familial Alzheimer disease; SAD, sporadic Alzheimer disease.
†Includes patients and control subjects.
‡For the regression analysis, 0 indicates female; 1, male.
§For the regression analysis, 0 indicates control; 1, patient.
¶For the regression analysis, 0 indicates FAD; 1, SAD.
AD and control groups of either sex. Mean TIVs for male and female subjects with AD were within 2% of the mean value for the respective control groups. No significant association was found between age at onset in male or female subjects and TIV in the AD group.

Our findings do not, therefore, support the suggestion by a previous study that a larger brain is protective against AD. The patients with AD we studied were relatively young (mean age of SAD group, 65 years; range, 51-82 years), and our findings should not automatically be extrapolated to older patients. Premorbid brain size may only exert a discernible effect on risk for AD in older individuals. However, other reported studies with older patient groups that incidentally used TIV measurements in their analyses support our findings. In particular Jack et al in a large, carefully conducted study of 126 controls (mean age, 79 years) and 94 patients with AD (mean age, 74 years), found no significant difference in the mean TIVs of both groups, ie, 1393 cm³ and 1369 cm³, respectively. These values were very similar to those found in our study. Furthermore, an early study that directly measured TIV post mortem found very similar values to ours, ie, mean male TIV of 1543 cm³ and mean female TIV of 1351 cm³, with a mean age of 63 years in both groups.

Maternal or childhood nutritional status could have been a confounding factor in our measurements of TIV, with significant changes seen during this century. However, our study failed to find any support for this; no association was found between age or date of birth and TIV (Figure 4). The effect of socioeconomic status on group comparisons should be minimal, as the control group was made up predominantly of the spouses of those affected.

In the study by Katzman et al, the brain weights of 10 apparently cognitively healthy elderly subjects who showed the histopathological changes of AD were compared with those of 19 healthy subjects without such changes. The subjects with AD changes had mean brain weights 10% heavier than the controls. However, these differences are at least partly explained by the higher proportion of men in the group with AD changes (30% compared with only 11% of the healthy subjects). Autopsy studies suggest that, on average, men have brain weights that are almost 20% greater than women; this accords closely with our finding of 16% greater TIV in our male controls. If the male subjects in the study by Katzman et al had 20% greater brain weights, then this explains almost half of the difference found between both groups. More importantly, the power available in the study by Katzman et al is low, ie, 38% when comparing the nondemented groups with and without pathologic changes and 62% when comparing the demented and nondemented groups with pathologic changes, both with significance at the 5% level. In our study, we had power of 98% and 99% at the 1% level. This makes it likely that the differences found by Katzman and colleagues were at least partly the result of a biased sample.

No significant association was found between TIV and age at onset in male or female subjects. This result, therefore, fails to replicate the report by Schofield et al
of a smaller premorbid brain size being associated with an earlier age at onset. The authors measured intracranial area on 2 adjacent axial computed tomographic (CT) sections as their estimate of TIV. They suggest that the intracranial area measurements may not adequately reflect differences in TIV between individuals because of differences in the shape of the calvarium. The areas measured will be sensitive to the CT section chosen. The sections measured were those at the level of the foramen of Monro and of the pineal gland. It has been shown previously that the brain undergoes considerable structural readjustment as atrophy increases. If both chosen landmarks within the brain do not remain fixed relative to the calvarium with increasing age or atrophy, then the measure of TIV may vary with time. Similar concerns apply to the study of Forstl et al,17 who found that patients with AD had a mean intracranial area on CT that was 4% smaller than that of a matched control group. Only a single CT slice was used for this measurement, and ventricular landmarks were used to determine which slice was chosen. Ventricular enlargement may result in a higher slice being chosen, and that slice is likely to have a smaller intracranial area. These considerations argue in favor of using TIV rather than intracranial area as a marker of premorbid brain size.

Mori et al18 used TIV to estimate premorbid brain volume and found that IQ scores correlated positively with premorbid brain volume and negatively with brain atrophy. They concluded that premorbid brain volume was a determinant of reserve against intellectual decline. However, no relationship was found between IQ and memory scores and TIV. It may be that a larger premorbid brain volume does not delay symptoms of disease onset (eg, memory decline), but that IQ scores are simply higher.18

A more recent study by Schofield and colleagues3 examined head circumference in patients with AD and controls. They reported significantly smaller head circumference in their AD group and a significant trend toward increasing frequency of AD in women with the smallest head circumference. This effect, however, was not seen in men. These results contradict those of an earlier study by Graves et al,4 who found that head circumference was not associated with the risk for AD. They also examined disease duration (as measured by age at clinical examination minus age at symptom onset) and head circumference and found no association.

It could be postulated that patients with FAD who have on average an earlier age at onset than those with SAD could have a difference in TIV. The APP and presenilin 1 and 2 mutations cause early-onset autosomal dominant FAD and may affect the function of proteins involved in neuronal development.6 As a result, these mutations theoretically could cause the cranial cavity to be underdeveloped and therefore affect measurements of TIV. In our study, no difference was found between the TIVs for the FAD group when compared with the SAD group or controls. This result suggests that these mutations have no significant effect on gross total intracranial size.

Our study does not disprove the suggestion that a greater cerebral reserve (at least in terms of size) is protective against AD, but it does make it less likely. The method that we have described is simple to perform and has high reproducibility; it should therefore be easy to apply to other AD cohorts to examine further the relationship between premorbid brain size and AD or its risk factors such as apolipoprotein E status. As our understanding of the pathophysiological features of AD increases, we are likely to find further factors that alter an individual's risk for AD. Some individuals are indeed relatively protected against AD, but it is likely to be cellular differences with a molecular genetic basis rather than brain size that really matter.

Accepted for publication August 5, 1999.

This research has been supported by the Medical Research Council (MRC) UK, London, England. Dr Fox holds an MRC Clinician Scientist Fellowship; Dr Harvey, an Alzheimer's Disease Society Research Fellowship, London; and Dr Rossor, an MRC Programme Grant.

Many thanks to William R. Crum, DPhil, for his assistance with this study.

Corresponding author: Nick C. Fox, MRCP, Dementia Research Group, The National Hospital for Neurology and Neurosurgery, 8-11 Queen Square, London WC1N 3BG, England (e-mail: n.fox@dementia.ion.ucl.ac.uk).

REFERENCES


©2000 American Medical Association. All rights reserved.

Downloaded From: http://archneur.jamanetwork.com/pdfaccess.ashx?url=/data/journals/neur/13123/ on 04/15/2017