Brain atrophy in chronic alcoholic patients: a quantitative pathological study

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SUMMARY There are essentially no objective neuropathological data on brain atrophy in chronic alcoholic patients despite numerous neuroradiological studies which show a high incidence of shrinkage or atrophy. Therefore measurements were made of the intracranial volume (ICV) and brain volume (BV) in a necropsy study of 25 chronic alcoholic patients and 44 controls. The pericerebral space (PICS) was calculated according to the formula PICS = \( \frac{ICV - BV}{ICV} \times 100 \) %.

The PICS will increase in patients with brain atrophy since the ICV remains constant throughout life. The mean PICS value was 8.3% in controls, 11.3% in the alcoholic group, 14.7% in alcoholics with superimposed Wernicke's encephalopathy (thiamine deficiency) and 16.2% in those alcoholics with associated liver disease. Thus there was a statistically significant loss of brain tissue in chronic alcoholic patients which appeared to be more severe in those with associated nutritional vitamin deficiencies or alcoholic liver disease.

Brain shrinkage in chronic alcoholic patients as demonstrated by pneumoencephalographic studies\(^1\) and computed tomography\(^2\) is now a well accepted fact. That some of this shrinkage is reversible following prolonged abstinence from alcohol is also well documented.\(^5\) Abnormalities of brain function including specific cognitive deficits\(^7\) and a more generalised global dementia may well relate directly to chronic alcohol abuse.\(^8\) Pathological data on the cerebral cortex of these cases are somewhat sparse and continual pleas have been made by many authors in the last decade for more detailed neuropathological studies of the brains of alcoholic patients.\(^8\)\(^-\)\(^10\) Courville\(^11\) commented on widespread cortical atrophy with preferential involvement of the frontal lobes in chronic alcoholics. Victor, Adams and Collins\(^12\) noted cerebral cortical atrophy in 27% of their cases of Wernicke's encephalopathy. Although most cases of Wernicke’s encephalopathy are associated with chronic alcoholism,\(^13\) pathological studies of these cases have been directed at the more traditional periventricular lesions. Studies of the cerebral cortex have not extended beyond the subjective assessment of the presence or absence of cerebral atrophy macroscopically and comments such as “patchy cortical neuronal loss” at the microscopic level.\(^11\)\(^-\)\(^13\) An additional complication in studying cases of Wernicke’s encephalopathy is that these patients may have a mixture of pathological entities. They have a proven nutritional vitamin deficieny (thiamine), often chronic liver disease (fatty liver or cirrhosis) as well as a long history of ethanol abuse. Fortunately, those patients with hepatic encephalopathy and/or Wernicke's encephalopathy can be identified at necropsy by detailed microscopic neuropathological studies.

There is some indirect objective pathological evidence that brain atrophy occurs in chronic alcoholic patients. It has been shown that the mean brain weight of chronic alcoholic males is significantly less than that of a control group.\(^14\)\(^-\)\(^15\) However, the interpretation of any brain weight study is difficult because of the wide range of normal values.\(^14\) The results would be far more meaningful if a reduction in the brain weight and volume could be documented in relation to the time span of alcohol abuse. This can be achieved by measuring both the brain volume (BV) and the intracranial volume (ICV). During childhood the growth of the brain determines the growth and expansion of the skull\(^16\) and the ICV remains unchanged during life.\(^17\) In the

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normal population there is a close correlation between BV and ICV.\textsuperscript{17,18} There are very few large studies of these parameters in either normal populations or pathological states. This probably relates to the logistic and mechanical difficulties of obtaining these measurements during routine necropsies. The authors have recently described a new technique for measuring the ICV by making polyurethane foam casts (fig 1) of the intracranial cavity.\textsuperscript{19}

The most useful parameter which can be derived from the ICV and BV measurements has been termed the pericerebral space (PICS).\textsuperscript{17}

\[
PICS = \frac{ICV - BV}{ICV} \times 100 \%
\]

In effect the PICS is a measure of the volume of cerebrospinal fluid (CSF) covering the surface of the brain and lying within the various cisterns (fig 2). This does not include ventricular or spinal CSF. As the brain becomes atrophic or shrinks the PICS value will increase.\textsuperscript{17,19} This study compares the PICS values of alcoholics and controls.

Materials and methods

One hundred and fifteen cases were studied in conjunction with the Forensic Pathologist of the Perth City Coroner's Department. One of the authors (JK) attended the necropsies and carried out the procedures as described herein.

Cases for the study were selected on the basis of a negative neurological history apart from alcohol related disorders such as Wernicke's encephalopathy or epilepsy (a significant proportion of alcoholics are also epileptic\textsuperscript{20}). Cases in which brain swelling was likely to have occurred (for example head injuries) and cases which had macroscopic evidence of swelling were excluded. Assessment of "alcoholic" or "control" status was based on clinical notes available from the major teaching hospitals in Perth as a result of previous admissions. These were available in 70\% of cases. The next of kin were interviewed when possible to assess the duration and quantity of alcohol consumption and the person's nutritional status. All cases were subject to a complete necropsy with microscopic examination of tissues. Relevant findings such as fatty liver or cirrhosis were helpful indicators of the extent of alcohol abuse. Reports concerning the circumstances surrounding the death were also helpful. In many cases liver function tests were available and in six cases, CT scans had been done during previous hospital admissions (fig 3).

After consideration of all the available data, 69 of the 115 cases were selected for this study. There were 25 alcoholic patients and 44 controls.

The necropsies were carried out in a standard fashion as was removal of the brains. The dura mater was left attached to the skull. The brain was dried and weighed immediately on a standard balance which has a nominal error of
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Fig 2  Schematic representation of the pericerebral space (PICS) which is calculated according to the equation:

\[
PICS = \frac{\text{Intracranial volume} - \text{fresh brain volume} \times 100}{\text{Intracranial volume}}
\]

and represents the "space" between the skull and the brain.

±5 grams. The fresh brain volume was determined by the fluid displacement method (Archimedes' principle) using 0.15 N saline as the immersion fluid. A polyurethane foam cast (fig 1) was then made of the intracranial cavity according to the method described recently by the authors. The volume of the cast and hence the intracranial volume was determined by the fluid displacement technique. Anatomical parameters including head circumference and maximum internal skull length and width were measured. The brains were fixed in 10% formol saline for two weeks. The brains were then embedded in a 3% agarose block and cut into 3 mm coronal slices using an electric meat slicer. This allowed detailed macroscopic examination of the cases. (This material will be the subject of further quantitative morphometric analyses). Sections were taken for histological examination to identify those patients with Wernicke's encephalopathy and/or hepatic encephalopathy and to exclude diagnoses such as Alzheimer's disease which could cause cerebral cortical atrophy. PICS values were determined according to the equation

\[
PICS = \frac{\text{ICV} - \text{BV}}{\text{ICV}} \times 100
\]

carried out using the Student t test when variances of the two groups were equal. The Cochran and Behrens mod-

ifications of the t test were applied when the variances were unequal. The p values were almost identical for both of these tests. Because we were only interested in PICS values which exceeded the upper limit of the normal range, the one tailed p value was determined.

Results

Of the 69 selected cases there were 44 controls and 25 alcoholics, ten of whom had chronic Wernicke's encephalopathy (microscopic diagnosis). The results of this latter group were analysed separately (alcoholic/Wernicke's encephalopathy group). The clinical details for each of the alcoholic groups of patients are summarised in table 1. As is generally the case in any study of an alcoholic population, the males outnumbered the females (5:1). The mean age of the control group was 58 years which was the same as the alcoholic/Wernicke's encephalopathy group. However, the mean age of the alcoholic group was 50 years. Six of the alcoholic cases were epileptic, but none had histologic evidence of hypoxic brain damage.

There was a poor correlation between the intracranial volume (ICV) and body height, weight or skull width. There was some correlation between the ICV and skull length and a less significant correlation with head circumference. However, these measurements are of little practical value in the accurate determination of ICV.

Fig 3  (a, b) CT scan of a 52-year-old female alcoholic (case 29) with Wernicke's encephalopathy and a PICS value of 13.7%. Note widening of cortical sulci and ventricular enlargement and compare with CT scan of control case. (c, d) A 54-year-old male (case 38) with a PICS value of 8.3%.
Table 1  Clinical details of 69 cases studied

<table>
<thead>
<tr>
<th>Group</th>
<th>Number of cases</th>
<th>Mean Age (yr)</th>
<th>Sex</th>
<th>Epilepsy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls</td>
<td>44</td>
<td>58</td>
<td>37</td>
<td>7</td>
</tr>
<tr>
<td>Alcoholics</td>
<td>15</td>
<td>50</td>
<td>14</td>
<td>1</td>
</tr>
<tr>
<td>Alcoholics/Wernicke's encephalopathy</td>
<td>10</td>
<td>58</td>
<td>7</td>
<td>3</td>
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</table>

Table 2  Pathological details of 25 alcoholics

<table>
<thead>
<tr>
<th>Case number</th>
<th>Age (yr)</th>
<th>Sex</th>
<th>Liver disease</th>
<th>Cortical atrophy</th>
<th>Ventricular dilatation</th>
<th>Cerebellar atrophy</th>
<th>PICS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>36</td>
<td>50</td>
<td>M</td>
<td>Fatty</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>14-2%</td>
</tr>
<tr>
<td>37</td>
<td>54</td>
<td>M</td>
<td>Nil</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>18-3%</td>
</tr>
<tr>
<td>39</td>
<td>73</td>
<td>M</td>
<td>Nil</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>17-0%</td>
</tr>
<tr>
<td>41</td>
<td>73</td>
<td>M</td>
<td>Cirrhosis</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>16-4%</td>
</tr>
<tr>
<td>52</td>
<td>58</td>
<td>M</td>
<td>Nil</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>3-2%</td>
</tr>
<tr>
<td>55</td>
<td>27</td>
<td>M</td>
<td>Nil</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>9-0%</td>
</tr>
<tr>
<td>65</td>
<td>31</td>
<td>M</td>
<td>Nil</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>12-8%</td>
</tr>
<tr>
<td>69</td>
<td>30</td>
<td>M</td>
<td>Nil</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>2-5%</td>
</tr>
<tr>
<td>71</td>
<td>48</td>
<td>M</td>
<td>Nil</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>7-4%</td>
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<tr>
<td>82</td>
<td>24</td>
<td>M</td>
<td>Nil</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>6-2%</td>
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<tr>
<td>83</td>
<td>68</td>
<td>M</td>
<td>Nil</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>11-2%</td>
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<tr>
<td>84</td>
<td>53</td>
<td>M</td>
<td>Nil</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>8-3%</td>
</tr>
<tr>
<td>90</td>
<td>34</td>
<td>F</td>
<td>Fatty</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>11-0%</td>
</tr>
<tr>
<td>98</td>
<td>72</td>
<td>M</td>
<td>Nil</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>19-3%</td>
</tr>
<tr>
<td>117</td>
<td>55</td>
<td>M</td>
<td>Fatty</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>11-9%</td>
</tr>
<tr>
<td>Group 3</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>42</td>
<td>M</td>
<td>Fatty</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>15-7%</td>
</tr>
<tr>
<td>29</td>
<td>52</td>
<td>F</td>
<td>Fatty</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>13-7%</td>
</tr>
<tr>
<td>56</td>
<td>57</td>
<td>M</td>
<td>Fatty</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>19-5%</td>
</tr>
<tr>
<td>67</td>
<td>58</td>
<td>M</td>
<td>Nil</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>12-1%</td>
</tr>
<tr>
<td>78</td>
<td>57</td>
<td>F</td>
<td>Cirrhosis</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>13-0%</td>
</tr>
<tr>
<td>95</td>
<td>55</td>
<td>M</td>
<td>Nil</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>11-6%</td>
</tr>
<tr>
<td>111</td>
<td>72</td>
<td>M</td>
<td>Fatty</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>23-2%</td>
</tr>
<tr>
<td>113</td>
<td>57</td>
<td>F</td>
<td>Fatty</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>23-0%</td>
</tr>
<tr>
<td>118</td>
<td>71</td>
<td>M</td>
<td>Nil</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>5-1%</td>
</tr>
<tr>
<td>119</td>
<td>62</td>
<td>M</td>
<td>Nil</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>9-9%</td>
</tr>
</tbody>
</table>

Group 2 = Alcoholics
Group 3 = Alcoholics/Wernicke's encephalopathy

*Epileptic

Table 3  Comparison of pericerebral space (PICS)* in control and alcoholic groups

<table>
<thead>
<tr>
<th>Group</th>
<th>Number of Cases</th>
<th>Means PICS*</th>
<th>Standard Deviation</th>
<th>p Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls</td>
<td>44</td>
<td>8-3%</td>
<td>±3-3%</td>
<td></td>
</tr>
<tr>
<td>Alcoholics</td>
<td>15</td>
<td>11-3%</td>
<td>±5-2%</td>
<td>p &lt; 0-02</td>
</tr>
<tr>
<td>Alcoholics/Wernicke's encephalopathy</td>
<td>10</td>
<td>14-7%</td>
<td>±5-8%</td>
<td>p &lt; 0-006</td>
</tr>
<tr>
<td>Alcoholics/liver disease‡</td>
<td>10</td>
<td>16-2%</td>
<td>±4-4%</td>
<td>p &lt; 0-001</td>
</tr>
</tbody>
</table>

*PICS = Intracranial volume - fresh brain volume × 100%
†p Value—according to student "t" test (single tail)
‡—this subgroup is derived from all alcoholics

Pathologic details including pericerebral space (PICS) values for the two alcoholic groups are listed in table 2. Table 3 compares the PICS values in the control and alcoholic groups. The mean PICS value of the control group was 8-3% compared to the alcoholic group which was 11-3% and the alcoholic/Wernicke's encephalopathy group which was 14-7%. Even though the standard deviation of each of the groups was high, the difference between the PICS values of the controls and the alcoholic groups was statistically significant as shown by the p values in table 3. There was no relationship between PICS values and the time interval between death and necropsy. Linear regression analysis showed a slope of 0-28. Excluding cases with epilepsy (see table 2) did not alter the results.

Each brain was assessed subjectively for macroscopic cortical atrophy, ventricular dilatation and...
cerebellar vermal atrophy.

It can be seen (table 2) that there is some correlation between the PICS values and the subjectively assessed cerebral cortical atrophy and ventricular dilatation. Assuming the upper limit of normal for PICS values to be 14-9% (mean plus two standard deviations), eight (32%) of the 25 alcoholic cases had PICS values above this limit. Of these eight cases, five had cortical atrophy and six had ventricular dilatation. Of the remaining 18 cases only three cases were considered to have cortical atrophy and ventricular dilatation. Cerebellar vermal atrophy was noted in 36% of the alcoholic cases.

Liver disease was present in 40% of the 25 alcoholic cases (table 3). There were only two cases with cirrhosis, the remaining eight having fatty livers. The incidence of liver disease was higher in the alcoholic/Wernicke’s encephalopathy group. Only one case (case 117) had histological evidence of hepatic encephalopathy. The mean PICS value for the alcoholic patients with liver disease was 16-2% compared to a mean PICS of 10-3% for those alcoholics with normal livers.

Discussion

The results of this study provide objective pathological evidence that a significant proportion of chronic alcoholic patients have brain atrophy. The atrophy was reflected by an increase in the volume of the pericerebral space (PICS). PICS values were higher in those alcoholics who had superimposed Wernicke’s encephalopathy caused by thiamine deficiency, and were highest in those with alcoholic liver disease (fatty liver or cirrhosis). The increase in PICS values corresponds to a mean loss of brain tissue of 41 g in the alcoholic group, 89 g in the alcoholic/Wernicke’s encephalopathy group and 109 g in the alcoholic/liver disease group. Similar results were found in our alcoholic brain weight study in that the male alcoholic group who all had cirrhosis had a mean brain weight of 75 g less than controls whereas that of the alcoholic/Wernicke’s encephalopathy group was 65 g less. Torvik and his colleagues documented a mean brain weight difference of 31 g in comparing 545 male alcoholics with 586 controls.

It is important to note that there is a wide scatter of PICS values in the alcoholic groups and in fact only 32% of the cases had a PICS value higher than the normal range (mean plus two standard deviations = 14-9%). Thus the very high incidence (up to 100%) of cerebral shrinkage in alcoholics as demonstrated in several CT scan studies are not reflected in this pathological study.

The accuracy and hence usefulness of the subjective evaluation of macroscopic cerebral cortical atrophy and ventricular dilatation can be readily assessed from this study. There does appear to be a reasonable correlation between the subjective assessment of cortical atrophy and ventricular dilatation and high PICS values (table 2). However, the measurement of the PICS is obviously a far more accurate way of identifying loss of brain tissue. The incidence of cortical atrophy in this study (32%) compares with previous studies of alcoholics with Wernicke’s encephalopathy in which atrophy was noted in 27%12 and 21%13 of cases. Cerebellar verm al atrophy was present in 36% of the alcoholic cases. This is also consistent with other studies in that vermal atrophy was noted in 34% of 131 cases of Wernicke’s encephalopathy.13 The cerebellum is normally about 10% of the brain volume. Thus loss of cerebellar tissue, as in verm al atrophy, would be unlikely to cause a significant increase in the PICS value.

Table 4 summarises previous intracranial volume studies and derived PICS values in control groups.17 18 23–27 Techniques have varied from filling the base of the skull and skull cap with water,23 sand or even ball bearings to the inflation of a balloon with water inside the cranial vault.27 The ranges of normal values are generally similar to ours. Davis and Wright17 showed a gradual increase in PICS with age. This was also evident in our control data, the increase being about 0-1% per annum after the age of 25 years. This, however, does not enter into the comparative statistical evaluations in this study as the mean age of the controls was the same or higher than that of the alcoholic groups (table 1).

An important question to consider in any necropsy study is the possible changes which might have occurred between the time of death and time at which the necropsy is done. Appel and Appel28 and Sarwar and Mc Cormick29 claim that the brain increases in size after death, possibly due to the absorption of CSF. Hubbard and Anderson30 found that there is an estimated 5-9% decrease in ventricul
lar volume after death due to the shift of CSF into brain tissue. This observation was made by comparing CT scans and ventricular volume measurements after fixation of the brain. Davis and Wright\(^\text{17}\) examined the question of changes in PICS values in relation to the time delay between death and necropsy. They showed that the brain volume did not change significantly up to five days after death. Our results showed a similar lack of correlation. In fact, the mean time delay was 22 hours in the control group compared to 43 hours for the alcoholic groups. According to the authors cited above\(^\text{18, 29}\) this should have caused a greater reduction in the PICS value of the alcoholic group than the control group.

Hubard and Anderson\(^\text{27}\) used the balloon technique\(^\text{17}\) to determine PICS values in 20 cases of Alzheimer's disease. However, to our knowledge there has been no previous study of PICS values in a group of alcoholic patients. Alexander and Looney\(^\text{18}\) included two chronic alcoholic patients in their study. The PICS values of those cases were 12-1% and 15-1%, both well above their stated normal range of 4-9%.

Of some interest is the fact that alcohols with liver disease (fatty liver or cirrhosis) had higher PICS values (16-2%) than those with normal liver histology (10-3%). This finding was unrelated to hepatic encephalopathy which was noted in only one case. It has been previously suggested that cerebral atrophy and associated ventricular enlargement in alcohols could be related to liver disease.\(^\text{30}\) Acker et al\(^\text{31}\) recently addressed the same question and carried out liver biopsies, CT scans and psychometric tests on 41 alcoholic patients. They showed that the degree of liver damage correlated significantly with both sulcal and Sylvian fissure widening. This is contrary to the results of Lee and her colleagues\(^\text{29}\) who carried out a similar study in a group of 37 young alcoholics. They concluded that there was no significant correlation between liver disease and cortical atrophy, although four of their seven cases with cirrhosis had cortical atrophy. They added that a larger study was necessary to confirm their data.

Acker et al\(^\text{31}\) suggested that it would be interesting to study the brains of patients with non-alcoholic liver disease. Of the 115 cases in our original study, there were two cases with cardiac cirrhosis. Their respective PICS values were 15-4% and 23-9%, both well above normal, but obviously no conclusions can be drawn from these isolated cases.

In a separate study of the brains of 150 chronic alcoholic patients (unpublished data), a subjective assessment of cerebral atrophy and ventricular dilatation was made. Three groups of alcohols were identified according to whether they had cirrhosis alone, Wernicke's encephalopathy alone or cirrhosis plus Wernicke's encephalopathy. As shown in table 5 those alcohols with cirrhosis alone had a much lower incidence of cerebral atrophy and ventricular dilatation than the other two groups. In addition, there was no increase in the incidence of cerebral atrophy in patients with Wernicke's encephalopathy when cirrhosis was also present. These findings suggest that the nutritional deficiency state which causes Wernicke's encephalopathy (thiamine deficiency) plays the major role in the causation of cerebral cortical atrophy in chronic alcohols. This is contrary to the results of this study in which PICS values tend to be highest in those alcohols with liver disease.

In summary, as the result of the development of a relatively simple technique for measuring the ICV at necropsy by making a polyurethane foam cast, we have been able to derive some accurate quantitative data concerning loss of brain tissue in chronic alcoholic patients compared to a control group. The loss of brain tissue is significant and likely to be more severe if the patient has Wernicke's encephalopathy (thiamine deficiency) and in those patients with alcoholic liver disease even when there is no histological evidence of hepatic encephalopathy. However, further studies will be necessary regarding the complicated inter-relationships between cerebral atrophy and the potential pathogenetic factors which include alcohol, nutritional vitamin deficiencies and liver disease.

The material used in this neuropathological study will be used for further quantitative morphometric analyses to determine which areas of the cerebral hemispheres are reduced in volume in chronic alcoholic patients.

We have had much assistance and cooperation in this study. In particular we are grateful to the staff of
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