Age, senile dementia and ventricular enlargement

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SUMMARY Necropsy measurements of cerebral ventricular volume and pericerebral space in senile dementia patients and age-matched controls indicate that ventricular enlargement is not an accurate diagnostic marker for cerebral atrophy. Furthermore, ventricles are of normal size for age in about 40% of all senile dementia patients including those with Alzheimer's disease.

The clinical diagnosis of Alzheimer type senile dementia (SDAT), the most frequent cause of intellectual deterioration in old age[1][2] rests with the exclusion of other causes of organic dementia. A definite diagnosis is usually achieved only at necropsy for brain biopsy is seldom performed, but SDAT may be inferred if cerebral atrophy can be shown radiologically. Computed tomography (CT) has provided a safe non-invasive means of examining the size of the cerebral ventricles[3][4] and has been advocated as a screening procedure for elderly demented patients to find those without cerebral atrophy, some of whom may have treatable conditions such as hypothyroidism or pernicious anaemia,[5] drug intoxication, benign cerebral neoplasms or psychiatric disturbances other than dementia.[6] However, it remains uncertain how accurately ventricular enlargement in old age and senile dementia reflects cerebral atrophy since direct assessment of the pericerebral space by CT is technically difficult. Furthermore, on pathological examination some SDAT brains show comparatively little atrophy[2][7] or have selective atrophy of the temporal lobes[8] which does not affect the body of the ventricles so that a proportion of false negative results might be predicted if the diagnosis of SDAT were based on CT measurement of the main part of the cerebral ventricular system.

It was the aim of this morphometric investigation to examine the range of sizes of the cerebral ventricular system occurring in elderly persons, some severely demented during life and others non-demented, and to find how closely ventricular

enlargement is associated with other pathological changes of SDAT.

Material and methods

The volume of the cerebral ventricles was measured in brains from 55 routine necropsy cases. Twenty-nine (nine males, 20 females, aged 64–92 years) had been severely demented, but none had affective disorders or schizophrenia; 27 were from long-stay psychogeriatric wards and two were awaiting admission. The 26 controls were from general medical and surgical wards and were selected after careful scrutiny of case records including nursing notes; no patient who had abnormal neurological signs or mental illness was included. Twenty-two of the controls (11 males, 11 females) were aged 65–95 years; four younger subjects (two males, two females, aged 23, 38, 42 and 44 years) were also examined.

Brain volume was determined by displacement of 0·15 N saline from an Archimedes vessel. To avoid distortion of the ventricles, brains were suspended by a thread under the basilar artery during fixation in 15% formalin for 4 to 5 weeks. The cerebral hemispheres were cut into 25–30 coronal slices using an electrical slicing machine at a constant setting of 7 mm. The volume proportion of the ventricular system was found by point-counting the brain slices on the Delesse principle[9] using a cellulose acetate sheet with points at the angles of equilateral triangles of side 10 mm. The absolute volume of the cerebral ventricles was then derived from the following formula:

Cerebral ventricular volume =

$$\frac{\text{No of points over the ventricles}}{\text{Total points over the cerebrum}} \times \frac{\text{Cerebral weight}}{\begin{array}{c}\text{Specific gravity}\\\text{of fixed brain}\end{array}}$$

A minimum of 1500 points was counted over each brain so that the percentage standard error incurred was 12–18% depending on the size of the ventricles.

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This was deemed an acceptable error in view of the large range (11 to 99 ml) of ventricular sizes in this investigation; it compares favourably with the estimated 20% error in the measurement of ventricular volume by CT scan.[10] The effect of fixation on the volume of the brain was relatively small (mean increase 3·3%) and post-mortem delay did not significantly affect the mean ventricular size (mean value for controls <24 h postmortem 24·0 ml, 24–48 h 36·0 ml; dements <24 h postmortem 36·0 ml, 24–48 h 48·0 ml) and so no corrections were attempted.

In 41 cases the cranial cavity volume was measured by the method of Davis and Wright.[11] In this procedure a rubber balloon is placed in the skull cavity after removal of the brain, dura of the vault, falx and tentorium. The calvarium is held in place by a coronet clamp. The balloon is inflated with water to a pressure of 150 mmHg, tied off and removed. The water content corresponds to the internal volume of the skull. The difference between the cranial cavity volume and the fresh brain volume is referred to as the pericerebral space; a ratio of the pericerebral space to the cranial capacity is taken as a measure of brain atrophy since cranial cavity volume remains unchanged during life.[11] Similarly, a ratio of the volume of the temporal lobes, found by point-counting brain slices as described above, to the cranial capacity gives a measure of temporal lobe atrophy.

For the diagnosis of SDAT the percentage of neurones bearing neurofibrillary tangles was determined using Ball's[12] counting method on the subiculum of the hippocampal gyrus, an area of predilection for Alzheimer changes.[13] A tangle count was preferred to measurement of senile plaques for it has been shown that hippocampal neurofibrillary change discriminates better between age change and Alzheimer senile dementia.[2 7 14] Twenty-three dements had more than 5% of tangled neurones and were classified as SDAT. Of the six other dementia patients, one showed the selective temporal lobe sclerosis of Pick's disease and two had multiple microinfarcts indicating arteriopathic damage. Three cases remain undiagnosed.

Results

The control values showed a modest but significant rise in ventricular volume with age (fig 1); an exponential curve gave the best fit (r=0·63 p<0·001) which suggests that there is normally an acceleration of ventricular enlargement in old age (cerebral ventricular volume/brain volume% = 0·633e[0·017age]). By comparison, ventricular volume was normal or less than normal in nine (31%) of the dementia patients, three (10%) were close to the upper limit of normal, and just 17 (59%) were well above the upper limit. Of the 23 dements showing histological changes of SDAT only 13 (57%) had a ventricular volume above the upper limit of normal.

Comparison of the pericerebral space with ventricular size (fig 2) showed a linear correlation (r=0·45 p<0·01) but this was not so close as
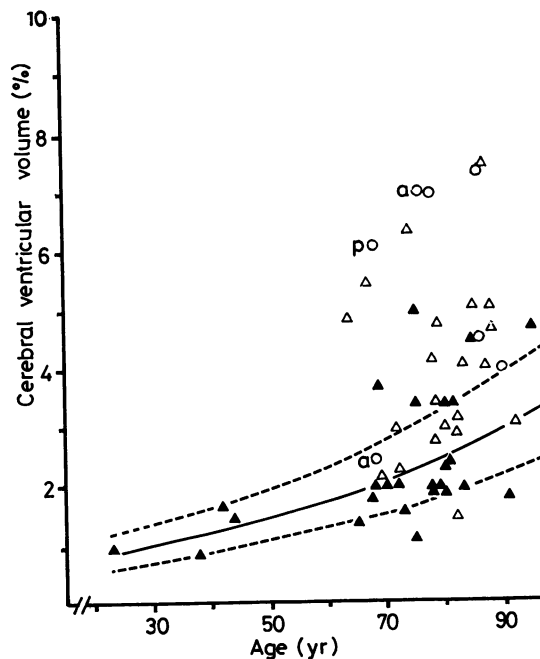

Fig 1 *Plot of cerebral ventricular volume (% of brain volume) against age showing an exponential increase in controls (   ). The broken lines show the normal limits of the control range. In SDAT (△) and in other types of senile dementia (○) about one-third of patients have normal-sized ventricles. a=arteriopathic dementia; p=Pick's disease.*
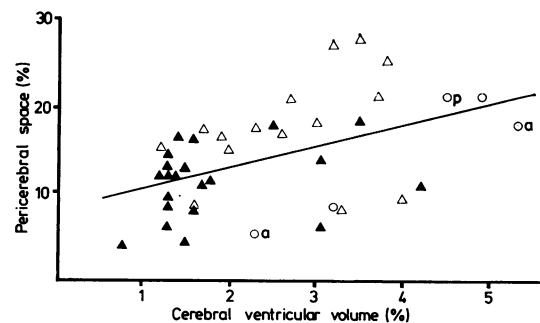

Fig 2 *Plot of the pericerebral space expressed as a proportion of the cranial capacity (an index of cerebral atrophy) against cerebral ventricular volume showing a linear correlation but not close enough to suggest that ventricular enlargement is entirely due to cerebral atrophy (r=0·45). a=arteriopathic dementia; p=Pick's disease. (Symbols as fig 1.)*

might be expected if ventricular enlargement in old age and senile dementia was entirely due to cerebral atrophy. The disparity between cerebral atrophy and ventricular enlargement is further emphasised by fig 3 which shows that ventricles
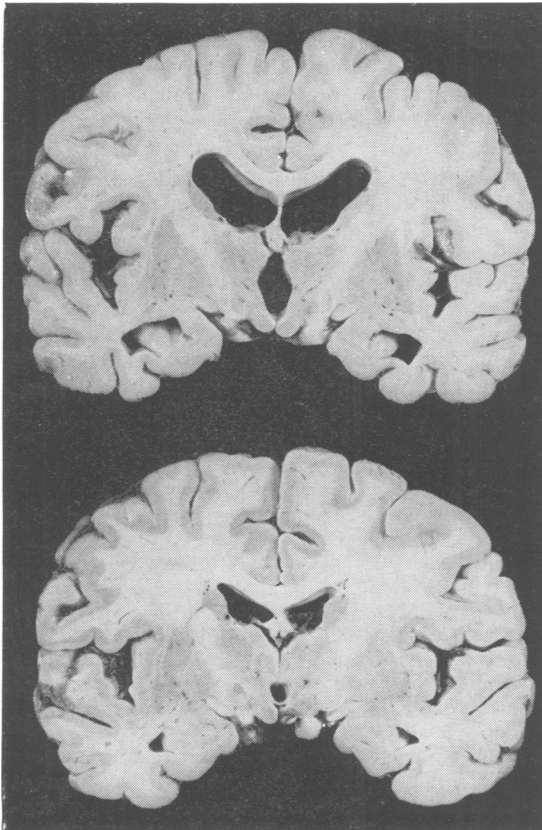

Fig 3　*Cerebral atrophy is advanced in both of these SDAT brains (note the wide Sylvian fissures) but only one shows ventricular enlargement.*

may be large or small in the presence of cerebral atrophy. In addition, temporal lobe atrophy was not accurately reflected by ventricular enlargement. Although 15 out of 20 dements had a reduced temporal lobe volume (that is temporal lobe volume/cranial capacity ratio <9%; mean control value for persons aged over 65=10·1%) this did not correlate closely with ventricular size (r=0·39).

Discussion

In a necropsy study of cerebral ventricular volume it is important to consider the effect of post-mortem decay for CT scans indicate that the

ventricles become smaller after death.[15] In our subjects over 65 years of age the upper limit of normal for the ventricular volume expressed as a percentage of the brain volume was about 5% whereas it is between 10%[16] and 14%[17] when calculated from CT scans in life. This difference probably reflects the shift of cerebro-spinal fluid into the brain tissue after death. Experiments have shown that equilibration of brain and cerebro-spinal water and electrolytes occurs mainly in the first 12 hours after death with only minor changes after 24 hours[18] and sequential CT scans confirm that much of the ventricular contraction has taken place by 5 to 6 hours postmortem.[15] The data in our investigation actually suggest some increase in ventricular size with extended post-mortem interval, although this is not statistically significant and is probably fortuitous. Because only one necropsy was carried out less than 12 hours after the patient's death, we have thought it reasonable to assume that post-mortem changes were comparable throughout.

A ratio of the volume of the ventricles to the volume of the brain was used because this takes account of the normal biological variation in brain size although it may exaggerate the effects of cerebral atrophy. This ratio was employed since the range of normal brain size is considerably greater than the variable loss in brain mass through atrophy. Analysis of the absolute ventricular volumes did not alter the results significantly but, as might be expected, the values were more widely scattered, particularly those of the controls.

Our work reaffirms that there is an age-related increase in ventricular size as do recent investigations by CT scan.[16 17] Early claims that ventricular enlargement occurs normally in old age have not been generally accepted because these were based on air encephalography which is performed only on persons under investigation for neurological disorders.[17] Furthermore, a previous pathological enquiry found little difference in ventricular size between non-demented old people and younger age groups.[19] However, the exponential type of increase in ventricular size with age suggested by our study and also by CT scan measurements[17] is consistent with the similar decline in brain volume during old age described by Davis and Wright.[11] CT scans are carried out on many more patients than were formerly investigated by air encephalography, and a larger proportion are probably free from nervous disease, but the criticism can still be made that these CT observations[16 17] and also our necropsy study relate to

hospital patients who may not be representative of the normal population. Recently, Jacoby *et al*[20] examined 50 psychiatrically and neurologically healthy volunteers from the community to establish genuine normative standards for CT scans in the elderly; they found only a non-significant trend to larger ventricles with age, but this may be due to the lack of any persons under the age of 62 years in their survey.

In our series pathological ventricular enlargement was by no means a reliable marker for senile dementia. No more than 59% of the dements had a definite increase in ventricular size and at most 13 out of 25 patients with SDAT showed this feature (fig 1). This is a much smaller proportion than was suggested by Gosling[21] who found enlarged ventricles in 86% of dements compared with 11% of non-demented patients investigated for neurological disorders, but it should be noted that these patients were mainly in the sixth decade of life and therefore Gosling's findings are not entirely relevant to senile dementia, for cerebral atrophy tends to be more severe in pre-senile dementia.[22] Our results are more in keeping with two CT scan investigations specifically concerned with old people which found very variable ventricular dimensions in senile dementia and a large overlap with the size range in non-demented persons.[5 23]

The volume of the cerebral ventricles and of the pericerebral space were not so closely related (r=0·45) as to suggest that ventricular enlargement in old age and senile dementia is entirely a consequence of cerebral atrophy. This finding has the obvious implication that CT observations on ventricle size cannot be taken as a measure of the degree of cortical atrophy. In particular, ventricular enlargement is unlikely to be of value as a sign of pathological cerebral atrophy in persons over the age of 80 years because senile dementia patients at this age tend to have selective temporal lobe atrophy[8] and we have found no useful correlation between temporal lobe shrinkage and the size of the ventricular system. This conclusion is closely similar to that reached by Jacoby and Levy[23] who found a low level of correlation between CT scan features of cortical atrophy and ventricular size in elderly control subjects (r=0·38) and virtually no correlation in senile dements (r=0·16). These authors also reported that dementia patients over the age of 80 years less frequently showed ventricular enlargement than those below this age. Clearly a CT scan measurement of the pericerebral space might be more useful, but at present this is difficult to

do with accuracy. The unreliability of CT scan measurements of pericerebral space and sulcal width may account for the absence of a clear relationship between these and the degree of intellectual impairment in old people.[24] It is notable that Jacoby and Levy[23] found a subjective assessment of the degree of cortical atrophy to discriminate better between senile dements and elderly controls than either of two objective measurements of ventricular dimensions. It is therefore to be hoped that technical refinement of CT will ultimately make measurement of the pericerebral space a routine matter and so obviate the need for clinical observations on ventricular enlargement in the context of cerebral atrophy.

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