Correlation between regional cerebral blood flow and brain atrophy in dementia

Combined Study with $^{133}\text{Xenon}$ Inhalation and Computerised Tomography

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SUMMARY Measurement of the regional cerebral blood flow (rCBF) by the $^{133}\text{xenon}$ inhalation method and computerised tomography were performed in 25 patients with presenile and senile dementia. Reduction of rCBF and various degrees of ventricular enlargement and cortical sulcal widening were demonstrated in the majority of demented subjects. However, there was no correlation between rCBF values and the severity of ventricular dilatation or cortical atrophy. These findings suggest that loss of brain substance is not an important factor in the reduction of rCBF in dementia.

It is well known that both ventricular dilatation and cortical atrophy may be observed in most patients with presenile and senile dementia (Engset, 1970; Fox *et al.*, 1975; Roberts and Caird, 1976). Many studies have also shown reduction in total and regional cerebral blood flow (rCBF) in subjects with dementia of early and late onset (Lassen *et al.*, 1960; Ingvar and Gustafson, 1970; O'Brien and Mallett, 1970; Obrist *et al.*, 1970; Simard *et al.*, 1971; Hachinski *et al.*, 1975). Several possible mechanisms may underlie the cerebral flow reduction in patients with mental deterioration and have been discussed in detail by Lassen (1959). Diminished cerebral metabolic rate of oxygen has been demonstrated in demented patients and was attributed, in part, to reduction in brain weight (Lassen *et al.*, 1960). The rCBF is controlled and regulated by cerebral metabolism (Lassen, 1959). Therefore, cerebral atrophy, through loss in the mass of metabolically active neuronal tissue, was suggested as one of the causes for decreases of rCBF in dementia (Lassen, 1959; Lassen *et al.*, 1960; Simard *et al.*, 1971).

However, systematic investigations of a possible correlation between degree of rCBF decline and severity of cerebral atrophy in demented patients

were not performed. The lack of such studies is most probably related to the nature of the methods which were commonly available for measurement of rCBF and for evaluation of cerebral atrophy in man. For instance, the intracarotid injection of $^{133}\text{xenon}$ for determination of rCBF is an invasive technique limited to patients in hospital and is usually carried out only in conjunction with cerebral angiography. In addition, pneumoencephalography (PEG) and ventriculography were the only methods for demonstration of the ventricular system and subarachnoid space during life. Both are invasive and risky, and are frequently associated with discomfort and morbidity. Understandably, combined studies using these techniques could not be performed easily and, therefore, loss of brain substance as an important mechanism underlying rCBF reduction in demented subjects remains hypothetical.

The advent of non-invasive methods for study of these parameters permits a new and more widely applicable approach to this problem. The development of the atraumatic $^{133}\text{xenon}$ inhalation method (Veall and Mallett, 1966; Obrist *et al.*, 1967, 1975; Wyper *et al.*, 1976) safely enables simultaneous estimation of rCBF in both cerebral hemispheres. In addition, computerised tomography is a relatively new technique (Hounsfield, 1973) which provides direct visualisation of the

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intracranial contents (Gawler *et al.*, 1975) without risk (Perry and Bridges, 1973) or discomfort to the patient. It readily demonstrates widening of the cortical sulci and permits accurate measurements of ventricular size (Gyldensted and Kosteljanetz, 1965, 1976; Huckman *et al.*, 1975; Gawler *et al.*, 1976; Roberts *et al.*, 1976). In the present investigation we have performed computerised tomography and measured rCBF by the inhalation method in a series of demented patients in order to determine if a correlation exists between cerebral blood flow and loss of brain substance.

Methods

PATIENTS AND TYPES OF DEMENTIA

Measurement of regional cerebral blood flow and computerised tomography were carried out in 25 patients with progressive intellectual deterioration, 11 men and 14 women, aged 39 to 79 years, mean 60 years. Informed consent to the procedures, after their nature had been fully explained, was given by next of kin. Some demented patients from this series were included in a study on other aspects of rCBF in dementia (Lavy *et al.*, 1978). Duration of dementia ranged from approximately five months to five years with a mean of approximately two years and three months. Each patient underwent a thorough study which included a detailed history and complete physical and neurological examination. Mental state was assessed clinically by standard psychometric tests of memory functions, orientation, judgment, ability to abstract, attention span, and calculation, and by evaluation of the ability to carry out daily activities such as dressing, self-care, and so on. Dementia was mild in four cases, moderate in 11, and severe in 10. Extensive laboratory investigations included sedimentation rate, blood count and biochemical parameters, serology, serum T₄, vitamin B₁₂ and folic acid levels, chest and skull radiographs, electroencephalographic recordings, lumbar puncture, ^{99m}Tc brain scan, and computerised tomography. Cerebral angiography and isotope cisternography were performed in some patients. Because of the basic requirements of the ¹³³xenon inhalation technique, patients with pulmonary dysfunction were not included in the study. After all the diagnostic procedures, we excluded subjects in whom mental impairment was associated with head trauma, toxic, endocrine, or deficiency states, obstructive or low pressure hydrocephalus, Huntington's chorea, Jakob-Creutzfeldt disease, and ischaemic or haemorrhagic strokes with or without residual focal neurological findings. After ruling out the various causes of dementia and since cere-

bral biopsies or necropsies were not available, it was difficult to determine the pathological process underlying the mental impairment in the present series of patients. The 10 subjects aged 39 to 53 years were considered to have primary degenerative dementia, probably Alzheimer's disease (Smith *et al.*, 1966). None had evidence of hypertension or vascular disease. The 15 patients aged 62 to 79 years were generally considered to have senile dementia. Six patients showed evidence of hypertension or coronary and peripheral vascular disease or both. However, from data obtained in neuropathological studies in patients with senile dementia (Tomlinson *et al.*, 1970; Wisniewski and Terry, 1976), it is likely that most of these subjects had a primary degenerative process with neurofibrillary changes and senile plaques similar to Alzheimer's disease (Woodard, 1966), and only a few patients might have had multiple cerebral softenings leading to "multi-infarct" dementia (Hachinski *et al.*, 1974). In fact, computerised tomography disclosed possible old cerebral infarcts in only two patients with senile dementia and none in those with mental impairment of the presenile type.

MEASUREMENT OF rCBF

The ¹³³xenon inhalation method, described in detail by Obrist *et al.* (1967, 1975), was used to determine the rCBF. Briefly, the investigation was performed in the resting state in a quiet and darkened room, with the subject lying comfortably on a bed, with plugged ears and closed and covered eyes. Each patient breathed ¹³³xenon, 2.5 mCi per litre mixed with air, for a period of one minute through a close-fitting face mask with a one-way valve in a non-rebreathing system. The washout of the radioisotope from the brain was followed by eight pairs of NaI collimated scintillation detectors applied over homologous regions in both cerebral hemispheres with the head relating to the probes in a standard position. The detectors are incorporated into an online computerised system. In order to determine concentration of the radioisotope in the expired air, the latter was drawn directly from the mask through a thin unshielded catheter connected to a vacuum pump, and was monitored continuously by a separate detector. The "air" curve, made up from the end-tidal concentrations of ¹³³xenon was used to correct the "head" curves for the recirculation of the inhaled isotope. The expired air was also monitored for CO₂ content, and arterial blood pressure was measured by auscultation immediately before the study. The rCBF was computed as the initial slope index (ISI) derived from the initial slope of the washout curves be-

tween the second and third minute according to Risberg *et al.* (1975). This method of computation was chosen because the ISI is reportedly more stable than other flow indices obtained by the inhalation technique. In addition, it consists mainly of flow in the fast clearing compartment which may be analogous to grey matter, less of white matter flow, and the contribution of flow in extracerebral tissues is negligible (Risberg *et al.*, 1975). The blood-brain partition coefficient of ^{133}Xe was chosen arbitrarily as 1.0 for the whole group of demented patients, and the ISI values are given in ml/100g/min. In agreement with other investigations (Ingvar and Gustafson, 1970; O'Brien and Mallett, 1970), the ISI data were not normalised for PaCO_2 levels.

DETERMINATION OF VENTRICULAR SIZE AND CORTICAL ATROPHY BY COMPUTERISED TOMOGRAPHY
The study was performed within one week, before or after the rCBF measurement. The technical aspects of computerised tomography are described in detail elsewhere (Hounsfield, 1973; Gawler *et al.*, 1975), and will not be dwelt upon here. The ventricular size was determined for each subject as the Evans ratio (Evans, 1942) in percentage from the 160×160 matrix oscilloscopic display of a tomographic cut through the frontal horns at the level of the foramina of Monro. As in other studies using computerised tomography (Fox *et al.*, 1975; Huckman *et al.*, 1975; Gawler *et al.*, 1976; Gyldensted and Kosteljanetz, 1976), it was measured as the maximal distance between the tips of the frontal horns divided by the width between the inner tables of the skull at the same level. Similar results were obtained on attempts to correlate the rCBF with several other indices of ventricular size measured from the tomograms, and so only the Evans ratios are given in this study. Since the methods for quantitative measurement of cortical atrophy are less precise (Roberts *et al.*, 1976), the degree of sulcal widening was

compared and ranked within the series by arranging the tomograms in an ascending order of severity from 1 to 25. The evaluation and comparison between cases were based on the width of the widest sulcus and number of widened sulci observed in the highest tomographic cut showing cortex but no ventricles and where similarities existed, also on the degree of dilatation of the insular cisterns (Huckman *et al.*, 1975; Roberts *et al.*, 1976).

Results

The Table shows the mean brain rCBF values in the whole group of demented patients and in those with presenile and senile dementia. Mean flow was higher in the presenile than in the senile group. In all groups there was a significant reduction of the rCBF from the expected age-matched normal values. In the present series the rCBF decreases in patients with senile dementia significantly exceeded ($P < 0.002$) the flow reductions observed in the presenile group (Table). Mean brain rCBF values were generally lower in patients with severe dementia than in those with mild and moderate mental impairment, but the differences were not significant.

Computerised tomography disclosed various degrees of ventricular enlargement in the majority of demented subjects. Mean ventricular size, measured as the Evans ratio (Evans, 1942), was 38% and exceeded the mean value of 24% reported in normal control subjects (Gawler *et al.*, 1976). Furthermore, in 23 demented patients the Evans ratio was above 30% which was reported as the upper limit in a series of normal subjects (Gawler *et al.*, 1976). Ventricular enlargement occurred in subjects with presenile and with senile dementia, and its degree did not differ significantly between the two groups (Table). There were no significant differences in ventricular size among groups of patients with mild, moderate, or severe

Table Mean brain rCBF values and ventricular size in patients with dementia

Dementia type	Number of cases	Age (yr)		Mean brain rCBF* (ml/100g/min) ± SEM	Expected age-matched normal mean brain rCBF† (ml/100g/min)	Δ % reduction demented versus normal	Ventricular size‡	
		Range	Mean				Range	Mean ± SEM
Presenile	10	39–53	48.1	43.2 ± 2.3	52.8	18.6§	30–47	36.9 ± 1.7
Senile	15	62–79	68.9	35.3 ± 1.2	48.2	25.8§	28–48	38.9 ± 1.6
Whole series	25	39–79	60.0	38.5 ± 1.4	50.2	23.3§	28–48	38.1 ± 1.2

*Calculated from 16 bihemispheric ISI values.

†Calculated from the computed regression line through mean brain rCBF values obtained by the inhalation method from 44 normal control subjects aged 19–76 years, plotted against age. Normal mean brain rCBF = $63.14 - 0.2155 \times \text{age}$ (Melamed *et al.*, 1978). Values were calculated for mean age of demented group.

‡Measured from a tomographic cut through the frontal horns at the level of the foramina of Monro as the Evans ratio in percentage: the width between the most lateral extremities of the tips of the frontal horns divided by the distance between the inner tables of the skull at the same level.

§ $P < 0.001$ (*t* test).

dementia. When individual mean brain rCBF values were plotted against ventricular size, it was observed that increasing severity of ventricular dilatation was not associated with lower blood flow levels (Fig. 1). In fact, a statistically significant correlation ($P < 0.02$) was observed even between increasing ventricular size and mean brain rCBF values in the senile group.

Fig. 1 Mean brain rCBF values (calculated for each patient from 16 bihemispheric ISI levels) plotted against ventricular size measured as the Evans ratio in percentage (see Methods). $\circ$ =presenile, $\bullet$ =senile.

Various degrees of widening of the cortical sulci were seen on the computerised tomograms in almost all of the demented subjects. Degree of cortical atrophy, ranged within the series (see Methods), was more or less evenly distributed among the patients with presenile and senile dementia. In only one subject with presenile dementia were no changes detectable. There was no correlation between mean brain rCBF values and the severity of cortical atrophy for the whole series, and for those with presenile and senile dementia (Fig. 2).

Discussion

In the present combined study, rCBF was reduced and cerebral atrophy was demonstrated in the majority of patients with presenile and senile dementia. However, no correlation was found between rCBF levels and the degrees of either ventricular dilatation or cortical atrophy in the whole series and in subjects with presenile or senile dementia. Higher or lower rCBF values

Fig. 2 Mean brain rCBF values plotted against the relative severity of cortical sulcal widening, ranked within the series of 25 demented subjects (see Methods). $\circ$ =presenile, $\bullet$ =senile.

occurred in the demented subjects regardless of the severity of the cerebral atrophy observed in the computerised tomograms. In addition, although rCBF values were generally higher and reduction from normal age-matched rCBF levels were lower in the presenile than in the senile patients, the degrees of ventricular enlargement and widening of cortical sulci did not differ between the two groups. These findings suggest that loss of brain substance does not play an important role in the reduction of rCBF in dementia.

Cerebral arteriosclerosis, through narrowing of vascular calibre and increased resistance, was suggested as an additional cause for the decreases of rCBF, particularly in elderly subjects with mental deterioration (Lassen, 1959; O'Brien and Mallett, 1970; Simard *et al.*, 1971). However, contrary to previous beliefs, it seems that cerebral arteriosclerotic changes are not highly prevalent among patients with senile dementia (Obrist, 1972). Studies of brains from demented old patients indicate that the presence of senile plaques and neurofibrillary tangles is the major pathological phenomenon (Tomlinson *et al.*, 1970; Wisniewski and Terry, 1976). In the present study, patients with a history of stroke or transient ischaemic attacks were excluded. Although some patients with senile dementia had evidence of hypertension and peripheral or coronary vascular disease, we believe that the majority of "senile" subjects in the present series suffered from a primary cerebral degenerative process with changes analogous to Alzheimer's disease. In that respect it is of interest that possible old cerebral infarcts were encountered

only rarely in the computerised tomograms of these patients, in agreement with the study of Fox *et al.* (1975) in a similar series. Likewise, it is highly probable that all or most of the 10 cases with presenile dementia had a primary neuronal degeneration caused by Alzheimer's disease (Smith *et al.*, 1966). In both presenile and senile dementia, mental processes are depressed not only because of cerebral atrophy but because of reduced activity of the diseased malfunctioning neurones (Wisniewski and Terry, 1976). Since rCBF is coupled to cerebral metabolism, it may be reduced in dementia mainly because of its adaptation to the diminished metabolic rate of neurones affected by the degenerative process (Lassen, 1959; Ingvar and Gustafson, 1971). It seems, therefore, that not the loss of brain substance but rather the remaining abnormal cerebral tissue is the most important factor producing rCBF reduction in dementia.

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