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Cerebral perfusion patterns in vascular dementia of Binswanger type compared with senile dementia of Alzheimer type: a SPECT study

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Summary. Cerebral perfusion patterns in 18 cases with vascular dementia of Binswanger type (VDBT) (8 moderate and 10 severe cases) were compared with 25 cases with senile dementia of Alzheimer type (SDAT) (16 moderate and 9 severe cases) and 14 controls by single photon emission computed tomography using *N*-isopropyl-*p*-^{123}I iodoamphetamine (IMP) as a tracer. The cerebral: cerebellar IMP uptake ratio (%) (CCR) was used as a measure of relative cerebral perfusion. The CCRs were about 85–90% in all areas in controls. Moderate VDBT patients showed a remarkable decrease of CCRs in the basal grey region (thalamus and basal ganglia) (right 79%, left 77%) and in the frontal area (right 79%, left 80%) ($P<0.01$). In severe VDBT patients a significant decrease of the CCR was noted in all regions ($P<0.01$). The decrease of mean CCRs in the hemispheres was significantly correlated with the severity of disease determined by psychometric testing. Patients with SDAT showed a significant decrease of the CCR in the parietal (right 71%, left 74%) and right temporal (78%) areas in the moderate stage ($P<0.01$), and further progression of dementia was associated with low perfusion areas extending to the frontal areas (78%, $P<0.01$). These differences in the perfusion patterns and their changes with progression of the illnesses may be reflected in characteristic clinical features.

Key words: Cerebral blood flow – Single photon emission tomography – Vascular dementia of Binswanger type – Sensile dementia of Alzheimer type

Introduction

Previous studies on regional cerebral blood flow (rCBF) in vascular dementia (VD) have reported various findings; while some have reported reduced CBF in specific areas of the brain, such as the frontal lobe [25] and subcortical regions [2], others have described patchy, asymmetrical reduction of CBF [41, 46, 49]. On the other hand, rCBF findings in senile dementia of Alzheimer type (SDAT) have demonstrated reduced CBF mainly in parietotemporal regions [3, 8, 16, 25], or in the posterior hemispheres [20, 22, 37, 44]. Other studies on SDAT, however, have reported the decrease of CBF in the frontal lobes [10, 14, 38], or in almost all areas of the brain [17, 29, 30, 49]. Such incosistency among reported findings has derived most probably from the heterogeneity of patients due to different sizes and distribution of infarcts in VD, and also from the difference in the severity of stages of the diseases.

We therefore studied cerebral perfusion patterns in a homogeneous group of patients with vascular dementia of Binswanger type (VDBT) as compared with those in SDAT, using single photon emission tomography (SPECT). We also correlated the results with the severity of dementia determined by psychometric testing.

Patients and methods

We studied 18 cases (73, SD 7.5 years) with VDBT, 25 cases (69, SD 9.4 years) with SDAT and 14 controls (67, SD 7.4 years). Informed consent was obtained from all patients.

All subjects underwent computed tomographic (CT) scanning and magnetic resonance imaging (MRI). The diagnosis and classification of dementia were made essentially according to the revised third edition of the American Psychiatric Association Diagnostic and Statistical Manual [1], Hachinski's Ischemic Score [18], and NINCDS-ADRDA criteria for probable Alzheimer's disease [33]. Patients with SDAT with white matter lesions on CT were excluded. Patients with VDBT were diagnosed based upon Hachinski's Ischemic Score [18] and CT and MRI findings showing extensive and diffuse white matter changes (leuko-araiosis [19]) with multiple lacunes associated with hypertension. Patients with infarcts larger than 1.5 cm were excluded. The degree of cognitive impairment was assessed with a simple dementia scale developed by Hasegawa et al. [21], which is similar to the Mini-Mental State Examination (MMSE) [13], consisting of tests of memory, orientation, general knowledge, and calculation (0–32.5 points). The scores were below 21.5 points in all dementia patients. We had confirmed significant correlation between the dementia scores and

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MMSE scores ($\gamma = 0.88$, $P < 0.01$, $n = 24$). We subdivided patients into moderate (11–20 points) and severe cases (less than 10 points) of VDBT and SDAT, respectively. There were 8 moderate cases (72, SD 10 years) and 10 severe cases (77, SD 4.9 years) of VDBT, and 16 moderate cases (69, SD 10.6 years) and 9 severe cases (66, SD 10.2 years) of SDAT. Controls were composed of patients with normal intelligence presenting no appreciable change in CT and MRI.

The subjects were studied in the supine position with their eyes closed. The examination room was quiet and dimly lit. Three millicuries of *N*-isopropyl-P^{123}I iodoamphetamine (^{123}I-IMP) was administered intravenously. Tomographic imaging was started 30 min postinjection using a gamma camera (GCA602A, Toshiba; GS550U). Sixty-four views, each 30 s long, were collected at 360°/64 intervals. Reconstruction was by backprojection of filtered profiles. The pixel size was 2.7 mm. Transverse tomographic images were obtained successively with the slice thickness of 5.4 mm above the orbitomeatal plane. The in-plane resolution was 1.6 cm.

Out of the complete tomographic set for each patient, we considered the slices centred at the orbitomeatal level plus 2.2 cm (5.4 × 4 mm) (OM + 2.2) for the cerebellum and the temporal lobe, at OM + 4.3 (5.4 × 8 mm) for the basal grey region (thalamus and basal ganglia), and at OM + 7.0) (5.4 × 13 mm) for the frontal and parietal lobes. Regions of interest (ROI: 2.4 × 2.5 × 0.54 cm) were drawn on the three orbitometal slices by an operator trained in neuroanatomy with reference to a standard CT brain atlas [32]. Regional radioactive count densities were measured in a total of 10 pairs of bilateral regions. The values from all ROIs in the cerebral hemispheres (frontal, parietal, temporal, and basal grey region) were averaged to give mean hemispheric values.

The cerebral : cerebellar ^{123}I-IMP uptake ratio (%) (CCR) was used as a measure of relative local perfusion, because there was no substantial difference to the cerebellar radioactivity in VDBT, SDAT and controls, and because the cerebellum is not pathologically involved in SDAT. Patients whose CT scans and MRIs demonstrated vascular pathology in the cerebellum and brain stem were excluded. Since none of our patients had a history of recent stroke, nor had cerebellar infarction, the use of cerebellar normalization should not have biased the ratio substantially [35, 39].

Statistical comparisons between CCRs in comparable regions of controls and the dementia groups were analysed with one-way analysis of variance. Correlation between CCRs and dementia scores and their significance were assessed by the Pearson product-moment correlation coefficient. The criterion for statistical significance was $P < 0.05$.

Results

Figure 1 a and b shows the CCR in hemispheric areas in moderate and severe VDBT patients and SDAT patients, respectively, compared with controls. In control subjects, the CCR was about 85–90% in all regions. In patients with moderate VDBT (Fig. 1a), the CCR was significantly reduced compared with controls in the basal grey regions (right 79%, left 77%) ($P < 0.01$) and the frontal areas (right 79%, left 80%) ($P < 0.01$). In severe VDBT, the CCR was decreased significantly in all areas compared with controls. The difference of CCRs between moderate and severe patients was significant in the left frontal, parietal and temporal areas and basal grey regions of both sides ($P < 0.05$). In contrast, patients with moderate SDAT showed a significant decrease of the CCR in the parietal areas (right 71%, left 74%) ($P < 0.01$) and the right temporal areas (right 78%) ($P < 0.01$) (Fig. 1b). The CCRs in severe SDAT patients were significantly decreased in the frontal (right 78%, left 78%), parietal (right 69%, left 70%) ($P < 0.01$), and temporal (right 78%, 77%) areas compared with controls ($P < 0.01$). The differences of CCRs between moderate and severe patients was significant in the frontal areas, but not in parieto-temporal areas and basal grey regions. The representative tomographic images in patients with VDBT and SDAT are demonstrated in Fig. 2, which shows selective involvement of the frontal areas in VDBT, and of the parieto-temporal areas in SDAT.

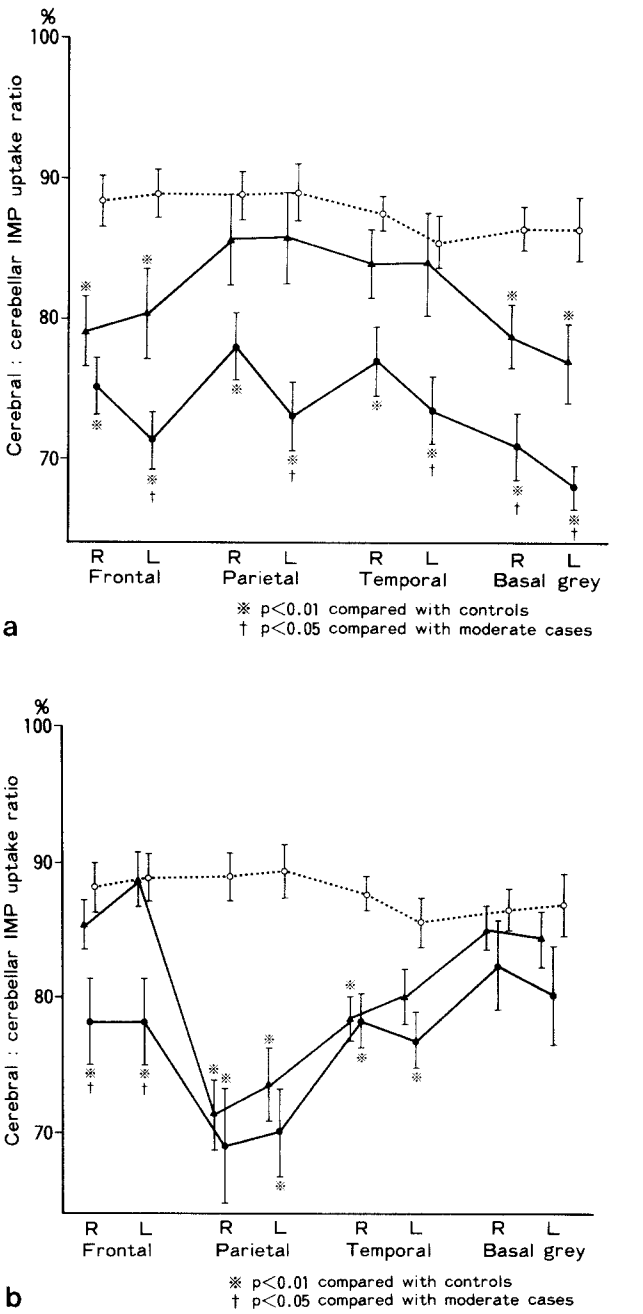

Fig. 1a, b. Cerebral : cerebellar ratios of ^{123}I-IMP uptake (mean ± standard error) in hemispheric areas in vascular dementia of Binswanger type (VDBT) (**a**) and senile dementia of Alzheimer type (SDAT) (**b**). Perfusion patterns of moderate (—▲—), and severe (—●—) cases are compared with those of controls (····○····)

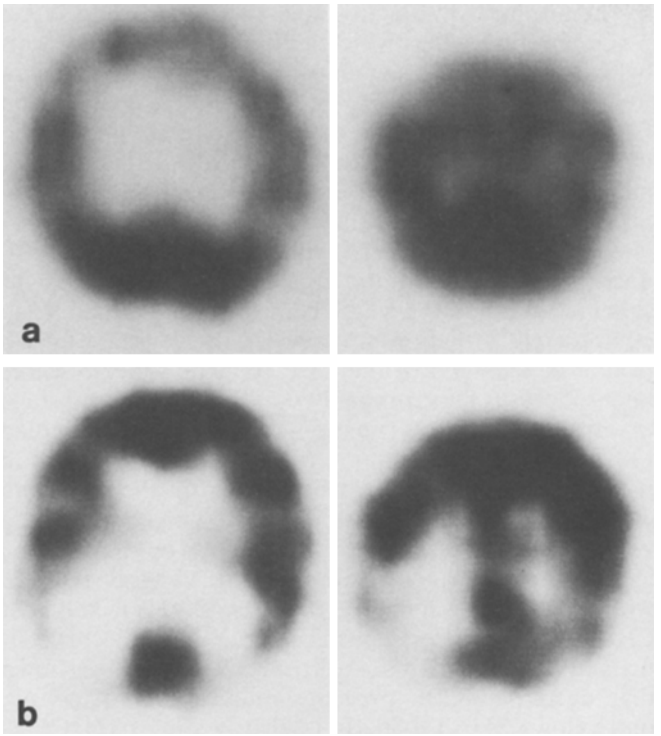

Fig. 2a, b. Representative SPECT findings in patients with (**a**) VDBT and (**b**) SDAT. *Left:* Level of basal ganglia [orbitomeatal level (OM) + 4.3 cm], *right*: OM + 7.0 cm

Table 1. Correlation coefficients between dementia scores and cerebral : cerebellar ratios of ^{123}I-IMP uptake in hemispheric areas. * $P < 0.05$; ** $P < 0.01$ significantly positive correlation; 95% confidence limits in parentheses. VDBT, Vascular dementia of Binswanger type; SDAT, senile dementia of Alzheimer type

	VDBT		SDAT	
Frontal				
Right	0.21	(−0.29–0.62)	0.22	(−0.19–0.56)
Left	0.49*	(0.03–0.78)	0.44*	(0.05–0.71)
Average	0.40	(−0.09–0.73)	0.35	(−0.05–0.65)
Parietal				
Right	0.42	(−0.06–0.74)	0.08	(0.33–0.46)
Left	0.65**	(0.26–0.86)	0.14	(−0.27–0.51)
Average	0.57*	(0.14–0.82)	0.12	(−0.29–0.49)
Temporal				
Right	0.31	(−0.19–0.68)	0.12	(−0.29–0.49)
Left	0.37	(−0.12–0.72)	0.31	(−0.1 −0.63)
Average	0.52*	(0.7 −0.8)	0.25	(−0.16–0.59)
Basal grey				
Right	0.29	(−0.21–0.67)	0.18	(−0.23–0.54)
Left	0.45	(−0.3 −0.76)	0.21	(−0.2 −0.56)
Average	0.42	(−0.06–0.74)	0.20	(−0.21–0.55)
Mean hemisphere				
Right	0.26	(−0.24–0.65)	0.31	(−0.1 −0.63)
Left	0.52*	(0.07–0.8)	0.41*	(0.02–0.69)
Mean	0.47*	(0 −0.77)	0.38	(−0.02–0.67)

The correlation coefficients between dementia scores and the CCRs for individual hemispheric areas and the mean hemispheres are shown in Table 1, and the correlation between dementia scores and the CCRs of the whole hemispheres is depicted in Fig. 3. In VDBT, the dementia scores had a significantly positive correlation with the CCRs in the left frontal and parietal areas and the left mean hemisphere. The average of right and left CCRs correlated significantly with the dementia scores in the parieto-temporal regions and the mean hemispheres (Fig. 3a). In SDAT, the severity of dementia was significantly correlated with the decrease of the CCRs in the left frontal area and the left mean hemisphere, but not in the right-left average of the mean hemispheres (Table 1, Fig. 3b).

Discussion

Our results showed that in the intial stage of VDBT hypoperfusion appeared in the frontal area and the basal grey region. In the advanced stage, CBF was reduced in all areas, but most markedly in the basal grey region. Such frontal dominance of hypoperfusion in the early phase is consistent with the previous findings in multi-infarct dementia [25]. A similar CBF decrease in the frontal area has also been reported in patients with normal pressure hydrocephalus (NPH) in whom periventricular white matter is severely involved [24, 31, 34]. In normal humans CBF in the frontal areas is 10–20% higher than the average CBF of the whole hemisphere

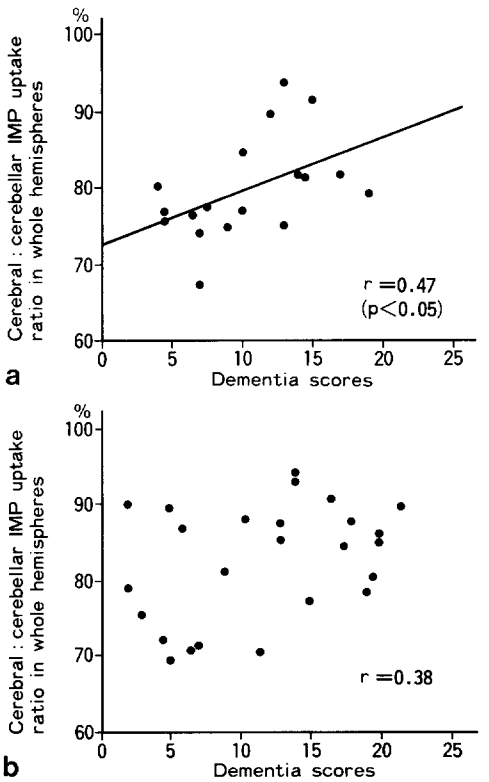

Fig. 3a, b. Correlation between dementia scores and the right-left average of cerebral : cerebellar ratios of ^{123}I-IMP uptake in mean hemispheres. **a** VDBT; **b** SDAT

[22, 47]. This "hyperfrontal pattern" [22] is thought to reflect non-specific arousal reaction by the mediothalamic frontocortical projection system [45]. Our results indicate that this system is impaired most conspicuously in the early period of VDBT, and support the previous reports suggesting that multiple lacunes are more specifically associated with signs of frontal lobe dysfunction [11, 12, 48].

The frontal dominance of hypoperfusion in the early phase of VDBT may be due to the tendency for ischaemic changes to involve preferentially frontal subcortical white matter [23]. However, CT and MRI findings in our VDBT patients usually demonstrated evenly distributed white matter changes in periventricular and adjacent tissues. An alternative interpretation therefore is that diffuse subcortical disconnection in VDBT may lead to the disruption of coupling in the frontal and the basal grey regions, particularly the thalamus, because of their close anatomical connections and interdependent functioning. Although thalamocortical fibres connect with practically all parts of the cortex, there is a considerable variation in the richness of connections for specific areas. The projections to the frontal granular cortex, which have reciprocal connections with the dorsomedial thalamic nucleus and neighbouring thalamic nuclei [27], are most abundant [6]. It has also been suggested that the dorsolateral prefrontal cortex is part of a dorsal functional system including anterolateral caudate, lateral pallidum, subthalamic nucleus and hippocampus [43].

Although VDBT is a white matter disease, we were not able to assess the perfusion pattern exclusively of the white matter, because limitations imposed by SPECT resolution did not permit an accurate evaluation, particularly in patients with enlarged ventricles. In a study using positron emission tomography (PET) the decrease in CBF was comparable in the white matter and grey matter, though slightly less conspicuous in the former, in VDBT and SDAT patients as a whole [15]; in a very recent PET study, the reduction in CBF and oxygen metabolism was more marked in the white matter than in the cerebral cortices in patients with VDBT [50].

Our results in SDAT showed a marked reduction of CBF in the parietotemporal region in the milder stage as well as in the advanced stage, and the CBF reduction further involved the frontal regions in the advanced phase. The selective reduction of CBF in the parietotemporal areas is consistent with the previous findings with PET [14–16], and with SPECT [9, 25, 44], and also with the studies on the regional differences in the severity of morphological [4] and neurochemical changes (serotonin recognition site, choline acetyltransferase) [40], which have indicated focal loss of neurons from parietotemporal cortices.

It has been demonstrated that overall CBF reductions in both multi-infarct dementia and SDAT correlate directly with the severity of dementia [5, 26, 28, 46, 49]. We showed that mental disabilities in VDBT were significantly correlated with the mean decrease of CBF in hemispheres. Furthermore, we found a closer correlation between dementia scores and CBF in the left frontal and parietal areas than in the right. This may be because left hemisphere dysfunction is more strongly reflected in psychometric testings which are largely based upon verbal capabilities. A previous longitudinal study of cognitive ability and CBF [36] revealed that cognition and CBF fluctuated to a greater extent in patients with multi-infarct dementia than in those with SDAT. These findings indicate a close relationship between CBF and mental faculties in vascular dementia. In our SDAT patients, intellectual functions were well correlated with the CBF decrease in the left frontal area and the left mean hemisphere, but not in the whole hemispheres. Our failure to demonstrate a relationship between the degrees of intellectual deficits and of the CBF reduction in the whole hemispheres is most probably due to the advanced stage of our SDAT patients (i.e. approximately corresponding to less than 20 points on the MMSE); CBF reduction in the parietal areas was already marked in the moderate cases. Previous SPECT studies on subjects including very mild cases (i.e. more than 20 points on the MMSE) [7, 25] have shown correlation of a focal hypoperfusion with the neuropsychological findings. It is also likely that CBF reduction is less conspicuous than intellectual deficits in SDAT patients. A prospective study has shown that decreased CBF precedes multi-infarct dementia, but follows SDAT [42]. It is also possible that CCRs lower than 70% are less sensitive in reflecting further progression of brain dysfunction in our SPECT study. However, our results indicate that progression from moderate to severe dementia in SDAT is strongly associated with extension of degenerative processes from the parietotemporal areas to the frontal regions.

In conclusion, CBF reduction in VDBT is most prominent in the anterior cerebral hemispheres, and CBF reduction in the whole hemispheres was closely correlated with progression of intellectual impairments; in SDAT, CBF in the moderate stage was reduced selectively in the posterior cerebral hemispheres, and further progression of dementia was closely correlated with the CBF reduction in the frontal areas. Such differences in the perfusion patterns and their changes with progression of the illnesses may be reflected in characteristic clinical features of the diseases.

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