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Cerebrocerebellar relationships in normal subjects and patients with dementia of the Alzheimer type: a SPECT study

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The relationships between blood flow in the cerebrum and the cerebellum was investigated in 21 normal subjects and 21 patients with dementia of the Alzheimer type (DAT). In normal subjects, only asymmetry in the frontal cortical blood flow was significantly correlated with asymmetry in the contralateral cerebellar blood flow. However, a significant correlation between asymmetry in the cerebral cortical blood flow in many areas and the blood flow in the contralateral cerebellum in DAT patients was observed. These results suggest the existence of a functional relationship between the cerebrum and the cerebellum in both normal and DAT groups, mediated by neuronal mechanisms through crossed fiber pathways. However, there are regional differences in the cerebrocerebellar relationship in normal resting and pathological states.

Key words: cerebrum, cerebellum, normal subjects, dementia of the Alzheimer type, SPECT

INTRODUCTION

SINCE THE VARIOUS REGIONS of the central nervous system are functionally interconnected, one would also expect a functional relationship between them. Recent studies with positron emission tomography (PET) and single photon emission CT (SPECT) have demonstrated that the impairment in regional hemodynamics and metabolism observed following focal cerebrovascular disease involves not only the site of the primary lesion but also other areas due to functional suppression of neuronal pathways.[1] It has been reported that supratentorial lesions due to cerebrovascular disease and brain tumors can cause a decrease in blood flow and metabolism in the contralateral cerebellar hemisphere. This phenomenon, termed "crossed cerebellar diaschisis" by Baron et al.,[2] has been hypothesized to be a result of the disruption of the cerebrocerebellar connections, including the corticopontocerebellar tract. To date, functional depression in the contralateral cerebellum has been described in patients with frontal lesions,[3,4] parietal lesions,[5,6] and multilobar or deep lesions in the middle cerebral artery territory.[7] However, Broich et al.[8] have described a patient with a right cerebellar infarction who demonstrated left frontal hypoperfusion on SPECT imaging, suggesting a functional depression of the cerebellorubrothalamic and thalamocortical pathways.

These studies suggest that a close functional relationship exists between the cerebrum and the opposite cerebellum in various pathological states. We investigated whether this cerebrocerebellar relationship was present in normal subjects and in patients with dementia of the Alzheimer type (DAT) by using SPECT to demonstrate asymmetry in cerebral blood flow.

MATERIALS AND METHODS

Subjects

Twenty-one normal subjects (aged 72.6±11.4 years, 12 males and 9 females) and 21 patients with DAT (aged 74.7±8.1 years, 9 males and 12 females) were studied. All subjects were right-handed. The normal subjects were without abnormalities on careful neuro-

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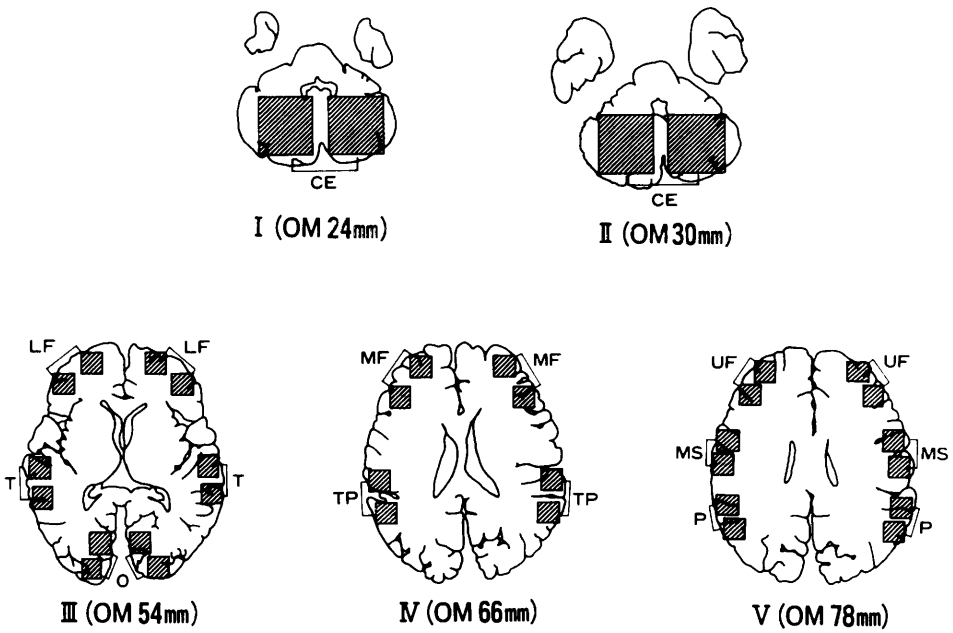

Fig. 1 Schema for ROI positioning in each brain slice. CE: cerebellar hemisphere, LF: lower frontal cortex, MF: middle frontal cortex, UF: upper frontal cortex, T: temporal cortex, TP: temporoparietal cortex, MS: motor-sensory cortex, P: parietal cortex O: occipital cortex.

logical examinations and had no history of neurological disorders. None of the normal subjects was taking medications with central nervous system effects. Brain CTs of the normal subjects were without focal abnormalities except for mild brain atrophy. Twenty-one patients with DAT met the NINCDS-ADRDA criteria[9] for probable Alzheimer's disease. None of the DAT patients had cerebrovascular lesions or other obvious lesions on CT or MRI that were thought to be factors contributing to the dementia. All DAT patients had scores of less than 4 on the Hachinski Ischemic Scale.[10] All subjects gave informed consent for SPECT studies.

SPECT study procedure

Regional cerebral blood flow was assessed by SPECT with N-isopropyl-p-[^{123}I]iodoamphetamine (^{123}I-IMP). The SPECT study was performed in the resting state. Fifteen to 20 minutes prior to the injection of ^{123}I-IMP, each subject was placed in the supine position in a darkened room. The subject's eyes were covered by a mask, but their ears were not plugged. During the study external stimuli were reduced to a minimum. The imaging was started 15 minutes after the injection of 222 MBq (6 mCi) of ^{123}I-IMP. The images were obtained with a rotating gamma camera equipped with a low-energy, high-resolution collimator (Siemens ZLC/75 ROTA camera). The SPECT acquisition was undertaken in 60 steps and each step collected counts for 20 seconds. Data were collected in 64×64 matrices and the computer (Shimadzu Scintipac 2400) was able to reconstruct axial sections with filtered back projection. A Shepp and Logan filter was used without attenuation or scatter correction. Transverse slices 6 mm thick and parallel to the orbitomeatal line were obtained. The spatial resolution was 15 mm full width half maximum on the transverse planes.

Figure 1 shows the nine regions of interest (ROIs) on 5 planes selected at 24, 30, 54, 66 and 78 mm above and parallel to the orbitomeatal line. Two square ROIs were symmetrically set in each area identified on the axial CT images according to Matsui and Hirano's atlas of the human brain.[11] The dimensions of the ROIs were 30×30 mm (5×5 pixels) in the cerebellar hemisphere and 18×18 mm (3×3 pixels) in the lower frontal, middle frontal, upper frontal, temporal, temporoparietal, motor-sensory, parietal and occipital corticies. Two smaller adjacent ROIs were chosen in each area to minimize any contribution from a partial volume effect due to the widening of cortical sulci and gyri.

Calculation of asymmetry index

As an indicator of asymmetry in the cerebral blood flow, an asymmetry index (AI) was calculated as follows: $AI=(R-L)/(R+L)/200(\%)$ where R and L represent count values from the right and left sides, respectively. The AI for each cerebral cortex and mean cerebral hemisphere (which was the average for each cerebral cortex) was then compared with the AI for the cerebellum by Pearson's correlation analysis.

Table 1 Asymmetry indices (AIs) of selected ROIs in each patient with DAT

Case no.	Lower frontal	Middle frontal	Upper frontal	Temporal	Temporo-parietal	Motor-sensory	Parietal	Occipital	Mean hemisphere	Cerebellum
1	−12.73*	−19.38*	−19.30*	+1.22	−14.21*	−6.64*	+3.64	+0.61	−8.35*	+9.97*
2	+6.51	+2.22	+14.50*	+19.16*	+5.64	+14.88*	+18.02*	−2.91	+9.76*	−14.14*
3	+12.31*	+14.78*	+15.77*	+7.06	+16.54*	+3.53	+11.36*	+4.46	+10.72*	−5.23
4	+11.58*	+7.18	+7.77	+18.41*	+5.38	+8.97	+1.59	−2.80	+7.26*	−6.43*
5	+7.99	+0.72	+9.51	−6.32	−3.61	+8.61	+17.96*	−3.00	+3.98	+2.07
6	−1.39	−3.27	−8.47	−8.03	−8.60	−5.28	−13.42	−0.43	−6.11*	+2.50
7	+3.17	+5.54	−1.74	−1.51	−14.31*	−0.97	−6.06	+0.56	−1.92	−0.95
8	−4.52	+2.65	−5.84	+5.12	+2.34	+10.02*	+14.33*	−6.69	+2.18	+0.70
9	−3.92	+10.01*	+5.16	+23.57*	+11.30	+6.51	+20.20*	−2.82	+8.75*	+3.63
10	+1.00	−2.59	−7.62	−5.19	−5.74	−2.90	−7.08	−3.04	−4.14	+0.77
11	+9.53	+1.63	+3.16	−0.78	−2.03	+9.72	+15.24*	−4.53	+3.99	−2.68
12	+12.02*	+12.70*	+17.00*	+13.96*	+15.12*	+13.28*	+14.12*	+3.01	+12.65*	−5.03
13	+2.53	+7.10	+4.23	−8.78*	−2.04	−5.83	−4.68	−1.13	−1.07	+1.09
14	+4.36	+9.14*	+16.89*	+9.55*	+1.92	+3.37	+16.47*	−1.40	+7.54*	+2.23
15	+4.56	+5.80	+5.86	−6.90	−2.74	+11.45*	+3.91	−1.79	+2.52	−1.50
16	−15.32*	−25.21*	−22.79*	−22.60*	−12.82*	−4.59	−21.41*	−1.04	−15.72*	+3.41
17	−3.99	−9.16	−3.34	−7.19	−12.82*	−7.19*	−15.27*	−2.62	−7.70*	+5.49*
18	−12.12*	−14.31*	−5.03	−30.41*	−29.80*	−10.41*	−24.41*	+3.06	−15.43*	+11.12*
19	+1.63	+1.58	−7.98	−17.30*	−3.63	−4.81	−3.21	−0.49	−4.28	−1.62
20	+2.99	+5.91	+0.24	−6.44	+20.63*	−6.51*	−13.33*	+1.67	+0.65	+0.61
21	−1.55	−13.70*	−10.03	+3.12	+5.42	+11.19*	+8.39	−1.47	+0.22	−0.67
Mean ± SD of normal subjects										
Mean	0.06	−0.96	−0.74	0.70	−0.17	1.94	1.70	0.59	0.53	−0.21
S.D.	4.80	4.30	6.22	4.37	5.85	4.00	5.93	4.20	2.70	2.59

* significant hypoperfusion lesions more than 2SD from normal mean

RESULTS

Table 1 gives the AI values for all of the areas examined in the 21 DAT patients and the mean values for each area in the 21 normal subjects. The mean AI values in each of the cerebral sub-regions varied from −0.96 to 1.94 (%) in the normal group. There was also a tendency for the cortical blood flow in the right hemisphere to be slightly, but not significantly, higher than in the left in the resting state.

When significant asymmetry of cerebral blood flow is defined as an AI value beyond the mean ± 2 SDs of normals, significant asymmetries were often demonstrated in DAT patients in each region except the occipital cortex.

The correlation coefficients between the AIs in each of the cerebral sub-regions and the AI in the cerebellum in both the normal and the DAT groups are given in Table 2. A negative correlation between the AI in the cerebrum and the AI in the cerebellum was observed. The only significant correlation found in normal subjects was between the frontal cortex (lower, middle, and upper frontal cortices) and the cerebellum. However, in the DAT group, AIs in many of the cortical sub-regions (except for the occipital cortex) significantly correlated with the AI in the cerebellum. Therefore, the cerebrocerebellar relationship in cerebral blood flow noted in the normal subjects differs from the relationship seen in the DAT patients.

Table 2 Correlation coefficients between AIs in each cerebral sub-region and AI in cerebellar hemisphere for normal subjects and DAT patients

Region	Normal subjects	DAT patients
Lower frontal cortex	−0.496*	−0.756****
Middle frontal cortex	−0.540**	−0.561***
Upper frontal cortex	−0.571***	−0.581***
Temporal cortex	0.076	−0.559***
Temporoparietal cortex	−0.279	−0.614***
Motorsensory cortex	−0.265	−0.695****
Parietal cortex	−0.293	−0.480*
Occipital cortex	0.096	0.127
Mean hemisphere	−0.536**	−0.708****

*: $p < 0.05$, **: $p < 0.02$, ***: $p < 0.01$, ****: $p < 0.001$

Figures 2 and 3 show the correlation in both normal and DAT groups between the AI in the cerebellar hemisphere and the mean AI in the cerebral hemisphere. A significant cerebrocerebellar relationship is observed in both normal subjects and DAT patients. Significant hypoperfusion in the contralateral cerebellum associated with asymmetric cerebral cortical blood flow, namely crossed cerebellar diaschisis, was observed in five of the 21 DAT patients (23.8%). Figure 4 shows the SPECT of a

patient with DAT (Case 1) which demonstrated crossed cerebellar diaschisis.

DISCUSSION

Following the proposal of the metabolic homeostasis hypothesis by Roy and Scherrington[12] in 1890, a large number of studies have revealed that a tight coupling exists between neuronal activity and cerebral blood flow and metabolism in most situations. While some recent studies have reported an uncoupling of brain function and cerebral perfusion in some circumstances (e.g. in the acute or subacute stages of ischemic cerebrovascular disease),[13,14] a very close correlation between local neuronal activity and cerebral blood flow is likely to be present in the resting state of normal subjects and DAT patients. Therefore, we investigated the functional relationship between the cerebrum and cerebellum by examining asymmetries in cerebral blood flow.

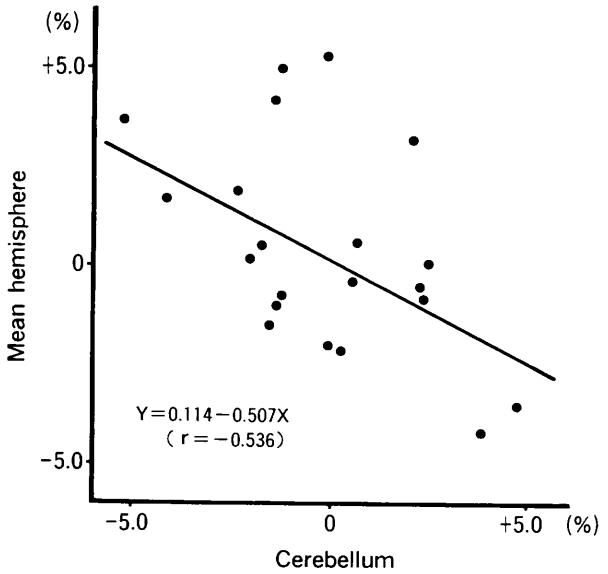

Fig. 2 Correlation between AI in cerebellar hemisphere and AI in mean cerebral hemisphere in normal subjects.

Our data indicate that asymmetry in frontal cortical blood flow is correlated with asymmetry in the blood flow of the contralateral cerebellum in normal subjects. In DAT patients, asymmetry in the cortical blood flow in many areas is correlated with asymmetrical flow in the contralateral corebellum. These results suggest that a functional relationship exists between the cerebrum and cerebellum in both the normal and the DAT groups.

Because the majority of fiber tract connections linking the cerebrum with the cerebellum are crossed, it is possible that the inverse correlation observed between the blood flow of the cerebrum and cerebellum is mediated by neuronal mechanisms through crossed fiber pathways. Among these tracts, the corticopontocerebellar tract is anatomically the

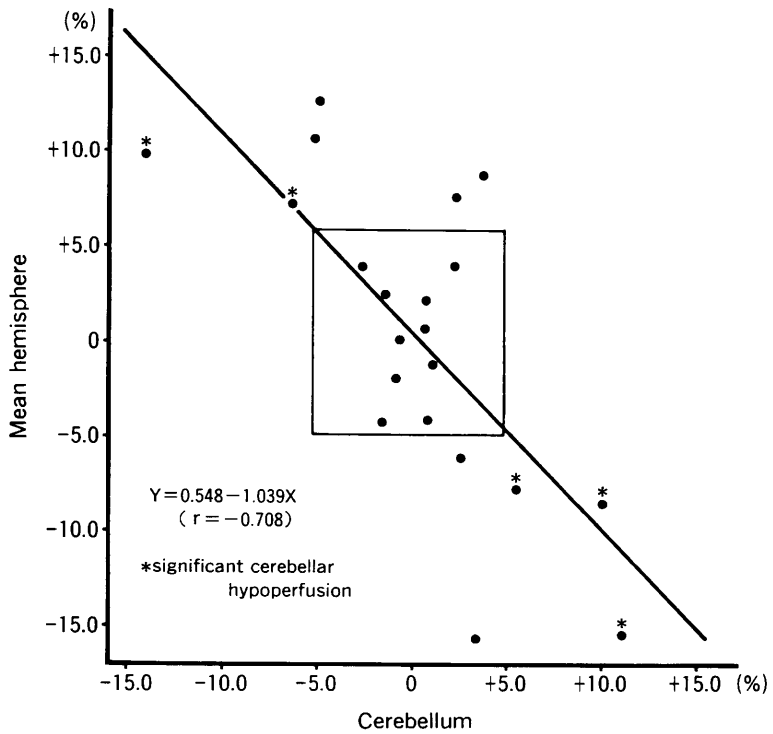

Fig. 3 Correlation between AI in cerebellar hemisphere and AI in mean cerebral hemisphere in DAT patients. The box indicates the normal AI±2SDs.

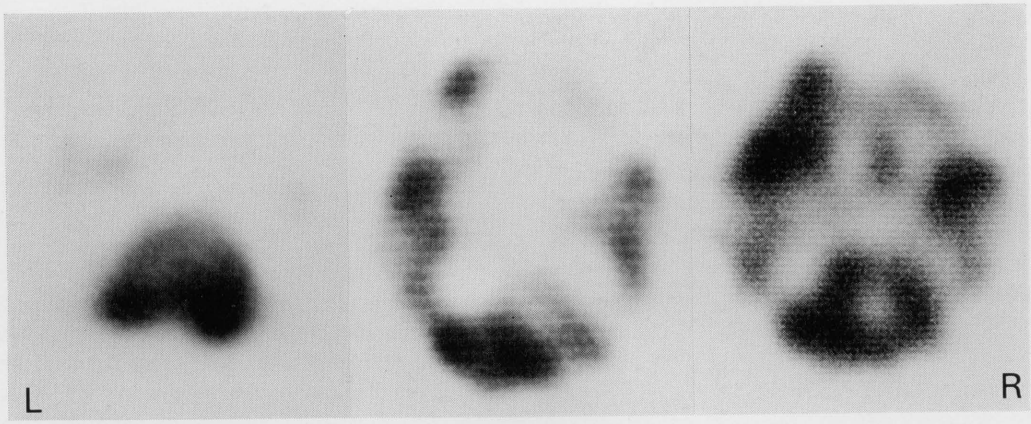

Fig. 4 SPECT findings in a patient with DAT demonstrating crossed cerebellar diaschisis. Transverse views 30 mm (left), 66 mm (middle), and 78 mm (right) above the orbitomeatal line show decreased perfusion in the left cerebellar hemisphere compared with the right, the right frontal and temporoparietal cortices compared with the left side.

largest pathway. It includes the corticopontine tract to the ipsilateral pontine nuclei and the ponto-cerebellar fibers to the contralateral cerebellum.[15]

Several PET and SPECT studies have demonstrated that crossed cerebellar diaschisis, which was thought to be caused by the interruption of the corticopontocerebellar tract, is a common finding following unilateral supratentorial lesions.[2–7] However, contralateral cerebral hypoperfusion following unilateral cerebellar lesion, perhaps secondary to a functional depression mediated through the cerebellorubrothalamic and thalamocortical tracts, is throught to be an unusual phenomenon since it has rarely been observed since Broich et al.[8] first reported it. Considering these clinical observations and neuroanatomical fiber connections, we suspect that functional asymmetry in the cerebrum causes a secondary functional asymmetry in the cerebellum, mainly through the corticopontocerebellar tract.

Anatomical studies in monkeys have shown that corticopontine fibers arise predominantly from precentral, premotor, prefrontal, frontal eye fields, and postcentral cortices,[16,17] though the more widespread portions of the cerebral cortex project to the contralateral cerebellar hemisphere via the ipsilateral pontine nuclei. However, our results showed that, in normal subjects, the only significant blood flow correlation is between the blood flows of the frontal cortex and the cerebellum. This correlation does not exactly reproduce the distribution of corticopontine neurons in the cerebral cortex. Therefore, it may be that other crossed fiber systems linking the cerebrum and the cerebellum, including the corticoolivocerebellar tract, contribute to the observed relationship. Moreover, it may be that the functional projections from the frontal cortex are greater than the density of the anatomical projections. A functional predominance of the frontal cortex exists in the resting state of normals, described by Ingvar[18] as a "hyperfrontal" distribution of cerebral blood flow. Junck et al.[19] also reported that with PET, asymmetry in the glucose metabolism of the frontal cortex is strongly correlated with asymmetry in the glucose metabolism of the contralateral cerebellum in normal subjects. However, a PET study by Barker et al.[20] showed a significant relationship between metabolic activation in the sensory-motor region and metabolic activation in the cerebellum when performing verbal memory or tactile somatosensory tasks in normal subjects. These regional differences seem to depend on whether the subjects are in a resting state or are active. In the normal resting state, the frontal cortex is likely to exert an influence on the function of the contralateral cerebellar hemisphere. acting mainly through corticopontocerebellar pathway.

In DAT patients, cerebral function in many areas of the cerebral cortex is correlated with function in the contralateral cerebellar hemisphere. Some investigators maintain that metabolic asymmetries are often demonstrated in the association cortex in DAT patients.[21,22] Our results also indicate that an asymmetry in cerebral blood flow in each cerebral sub-region is greater in patients with DAT than in controls. Because the degenerative processes in the cerebral cortex in DAT are unlikely to progress uniformly and symmetrically, the correlation between asymmetric blood flow in many areas of the cortex and the cerebellum in patients with DAT may contribute to the significant functional asymmetry in the cerebral cortex. We observed significant contralateral cerebellar hypoperfusion in five of 21 patients with DAT (23.8%). Similary, Kushner et al.[23] reported asymmetric cerebellar metabolism in four of 24 Alzheimer cases (16.7%). Akiyama et al.[24] reported

the same results in seven of 26 Alzheimer patients (26.9%). Accordingly, crossed cerebellar diaschisis occurs in a number of conditions associated with asymmetric supratentorial lesions, in addition to focal cerebral lesions.

This study suggests that the cerebrocerebellar relationship differs regionally in DAT patients when compared with normal subjects. The functional relationship observed in normals may be fundamentally different from that in patients with pathological conditions like DAT.

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