Reduction of Cerebellar Glucose Metabolism in Advanced Alzheimer's Disease

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Although regional cerebral metabolism and blood flow in Alzheimer's disease (AD) have been studied extensively with PET and SPECT, few reports have been concerned with cerebellar metabolism or perfusion in Alzheimer's disease. To evaluate cerebellar glucose metabolism in Alzheimer's disease patients, we studied the cerebellar and cerebral metabolic rate for glucose (CMRglc) using 2[^{18}F]fluoro-2-deoxy-D-glucose (^{18}F-FDG) and PET. **Methods:** Sixty-eight patients with Alzheimer's disease and 13 age-matched normal control subjects were examined. According to scores obtained on the Mini-Mental State Examination (MMSE), Alzheimer's disease patients were classified into three groups: severe (n = 9), moderate (n = 33) and mild (n = 26). **Results:** The cerebellar glucose metabolism in the severe Alzheimer's disease group was significantly lower (cerebellar glucose metabolism: 5.71 ± 0.62 mg/100 g/min) than that of the control group (6.85 ± 0.66 mg/100 g/min), while temporal and parietal CMRglc were much more decreased. The cerebellar glucose metabolism in the mild and moderate Alzheimer's disease groups also showed lower levels than that of the control group, but the differences did not reach significant levels. Like other cortical CMRglc, the cerebellar glucose metabolism correlated with cognitive impairments. **Conclusion:** In severe Alzheimer's disease, cerebellar glucose metabolism is significantly reduced. The method of analysis using normalization of regional metabolic data to cerebellar values may be liable to err in severe Alzheimer's disease patients.

Key Words: Alzheimer's disease; PET; fluorine-18-fluorodeoxyglucose, cerebral glucose metabolism; cerebellum

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Alzheimer's disease is a progressive neurodegenerative disease, and neuroimaging is of some value, as are neurologic and neuropsychologic examinations, in studying Alzheimer's disease. Functional neuroimaging with PET, which is still largely a research investigation, has demonstrated bilateral temporoparietal and medial temporal hypoperfusion in Alzheimer's disease patients (*1,2*). Similar findings have been supported by perfusion pattern diagnosis in routine SPECT (*3*). In most of the PET and SPECT studies of Alzheimer's disease, cerebellar perfusion or metabolism is used as a reference region on the assumption that cerebellar cortices are less involved in Alzheimer's disease. In mild-to-moderate Alzheimer's disease patients, cerebellar perfusion and oxygen metabolism did not decrease when compared with those of age-matched normal control subjects (*2*). On the other hand, in routine clinical SPECT examinations for Alzheimer's disease, reduced radioactive tracer accumulations have been detected in the parietal and temporal regions, whose activities are normalized using the cerebellum as a reference region. However, histopathological studies have revealed that the cerebellum is also affected in severe Alzheimer's disease patients (*4,5*). Few previous PET studies in Alzheimer's disease evaluated cerebellar metabolism, although there have been many studies on cerebral metabolism and perfusion. The purpose of this study was to evaluate regional cerebellar and cerebral metabolic ratio for glucose (CMRglc) in patients with Alzheimer's disease using 2[^{18}F]fluoro-2-deoxy-D-glucose ([^{18}F]FDG) and PET.

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MATERIALS AND METHODS

Patient Selection

We studied 81 subjects, including 68 patients with Alzheimer's disease (52 women, 16 men; age range 70.6 ± 7.9 yr; mean ± s.d.) and 13 age-matched healthy volunteers (9 women, 4 men; age range 67.9 ± 7.4 yr; mean ± s.d.). According to the following criteria, patients with Alzheimer's disease were selected from those who were admitted to our hospital for an examination. All patients were examined by both neurologists and psychiatrists and given magnetic resonance (MR) imagings of the brain, MR angiographies of the neck and head, an electroencephalography and standard neuropsychological examinations during periods of admission of more than 1 mo.

The inclusion criteria included: (a) the National Institute of Neurological Disease and Stroke/Alzheimer's Disease and Related Disorders Association (NINCDS/ADRDA) criteria for probable Alzheimer's disease (*6*); (b) brain atrophy predominantly involving parietal and/or medial temporal regions and no evidence of focal brain lesions on MR images; and (c) mild-to-severe functional disorders (grades 0.5–3 on Clinical Dementia Rating (CDR) scores (*7*)).

Exclusion criteria included: (a) complication of other neurological diseases or ill physical conditions; (b) presence of severe language, attention or behavioral disorders that would make PET scans difficult; (c) lack of obtaining informed consent from patients and their relatives.

The mean Mini-Mental State Examination (MMSE) (*8*) score was 18.5 ± 4.8 and the mean Alzheimer's Disease Assessment Scale (ADAS) (*9*) score was 22.2 ± 8.6. Patients receiving a MMSE score of 0–11, 12–20 or 21–30 were categorized as having severe, moderate or mild Alzheimer's disease, respectively. Healthy volunteers, who served as normal control subjects, had no neurological signs or significant medical antecedents and no abnormal findings on MR images.

Before PET scans, MR images were obtained for all subjects for diagnosis, anatomical reference and PET positioning. Detailed MR procedures have been reported elsewhere (*10*). Immediately before the PET examination, sagittal gradient-echo images were obtained to determine the coordinates for positioning of the head on the PET table.

PET Procedure

Prior to the PET study, written informed consent was obtained from all patients and their relatives and from all volunteers according to the Declaration of Human Rights, Helsinki, 1975. The PET study was strictly followed according to the PET Drug Usage Manual in our institute and was approved by the internal Ethical Committee.

TABLE 1
Regional Cerebral Glucose Metabolism in Each Group

	n	Age (yr)	Cerebellum	Temporal	Occipital	Frontal	Sensorimotor	Parietal
Severe AD	9	67.8 ± 8.9	5.71 ± 0.62*	4.57 ± 0.79‡	6.16 ± 1.01†	5.43 ± 0.81‡	6.33 ± 0.81*	4.71 ± 1.01‡
Moderate AD	33	72.0 ± 7.9	6.32 ± 0.95	5.64 ± 1.00‡	6.85 ± 1.03*	6.29 ± 1.00‡	6.97 ± 0.94	5.63 ± 1.09‡
Mild AD	26	69.7 ± 7.5	6.71 ± 0.87	6.35 ± 0.86	7.37 ± 0.91	6.82 ± 0.89*	7.37 ± 0.75	6.47 ± 1.01‡
Normal	13	67.9 ± 7.4	6.85 ± 0.66	7.10 ± 0.79	7.90 ± 0.90	7.73 ± 0.84	7.72 ± 0.73	7.80 ± 0.99

*Significantly different from normal control values ($p < 0.05$).
†Significantly different from normal control values ($p < 0.01$).
‡Significantly different from normal control values ($p < 0.001$).
Values are expressed as mean ± 1 s.d. AD = Alzheimer's disease.

PET images were obtained with a tomograph that has four rings located 13 mm apart and yield a transverse resolution of 4.5 mm FWHM (*11*). The slice thickness was 11 mm, and the slice interval was 6.5 mm when the z-motion mode was used. The subject's head was placed horizontally on the table of the PET scanner, and the gantry and the table of the PET scanner were adjusted according to the coordinates determined with MR imaging so that the scans were taken parallel to the AC-PC plane (*12*).

A transmission scan was obtained using a $^{68}Ga/^{68}Ge$ pin source for absorption correction after each subject was positioned. PET studies were performed under resting conditions with eyes closed and ears unplugged. All subjects had fasted for at least 4 hr before PET scanning. One hundred and eighty five to 259 MBq [^{18}F]FDG was injected into an antecubital vein. Arterial blood sampling was done from a catheter inserted into a radial artery just after administration and later at 15, 30, 45, 60, 75, 90, 105 and 120 sec and at 2.5, 3, 3.5, 4, 4.5, 5, 6, 7, 8, 9, 10, 12, 14,16, 18, 20, 25, 30, 40, 50, 60 and 70 min. Brain scanning was started at 60 min after the injection, and emission data were collected for 12 min.

Values of regional cerebral metabolic rate of glucose (CMRglc) were calculated according to a model based on the autoradiographic technique proposed by Sokoloff et al. (*13*) and revised by Phelps et al. (*14*) and Reivich et al. (*15*) for human studies.

Data Analysis

PET and MR image datasets were directly transmitted to a workstation from the PET and MR imaging units. T1 and T2 axial MR images were reviewed by one investigator who was blind to the knowledge of the subjects' clinical data, and the cerebellar atrophy was assessed by visual evaluation.

MR images of three-dimensional scales and coordinates that were identical to those of the PET images were made for anatomical references of the PET analysis. Both PET and MR images were displayed side by side on a display monitor, and two or three circular regions of interest (ROIs), 10 mm diameter, were determined on the cortical ribbon of each region on the CMRglc image. ROIs were placed on the cerebellar cortices, lateral temporal lobe, occipital lobe, frontal lobe, primary sensorimotor region and parietal lobe. The value of each regional CMRglc was shown as the average of the right and left regional values.

Statistical Analysis

The regional CMRglc of the three Alzheimer's disease groups were compared with those of normal controls. For CMRglc measures, one-way analysis of variance (ANOVA) was used for group comparisons, and Scheffé's test was used for multiple post hoc comparisons. To estimate the difference between the quantitative and qualitative evaluations, we calculated the following ratios in the parietal lobes of the subjects, where the glucose metabolic reduction is the severest in Alzheimer's disease:

$$\text{Ratio A} = \frac{\text{each individual parietal CMRglc}}{\text{mean parietal CMRglc of 13 normal controls}}.$$

$$\text{Ratio B} = \frac{\text{each individual parietal CMRglc/ each individual cerebellar CMRglc}}{\text{mean parietal CMRglc of 13 normal controls/ mean cerebellar CMRglc of 13 normal controls}}.$$

The Ratios A and B were compared with a paired Student's t-test in each group.

For each patient, we analyzed the relation between each regional CMRglc value and the cognitive function (MMSE and ADAS score) using Pearson's correlation coefficient. Differences were considered significant when the p value was <0.05.

RESULTS

There was no apparent cerebellar atrophy even in a patient with severe Alzheimer's disease, though there was apparent diffuse cerebral atrophy. The average values for regional CMRglc in each group are shown in Table 1. There was a significant group difference in the cerebellar glucose metabolism ($F = 4.30$; $p = 0.0074$). The cerebellar glucose metabolism in the severe Alzheimer's disease group was significantly lower than that of the control group ($p < 0.05$). There were significant decrements in CMRglc in all of the neocortical regions in the severe Alzheimer's disease group. The moderate Alzheimer's disease group also showed significant reductions of CMRglc in the parietal, temporal, frontal and occipital lobes when compared with normal controls.

Figure 1 shows representative CMRglc images from each group. All patients had Alzheimer's disease reduction patterns (temporal and parietal CMRglc reduction), but the CMRglc value of the severe Alzheimer's disease patients was the lowest.

As shown in Figure 2, the average ratio A of the severe group was 60%, the moderate group was 72% and the severe group was 83%. The average ratio B of the severe group was 72%, the moderate group was 78% and the mild group was 85%. The difference between ratio A and ratio B became significantly larger in accordance with the severity of Alzheimer's disease.

Each regional CMRglc correlated with the MMSE score and ADAS score when Pearson's correlation coefficient was used (Table 2). The magnitude of the correlation in the temporal and parietal cortices was larger than those in the other cortices. However, there was a significant correlation between the MMSE/ADAS score and the CMRglc even in the cerebellum, occipital and sensorimotor cortices.

DISCUSSION

A decline in CMRglc in the temporal and parietal cortices in Alzheimer's disease group was demonstrated in our study,

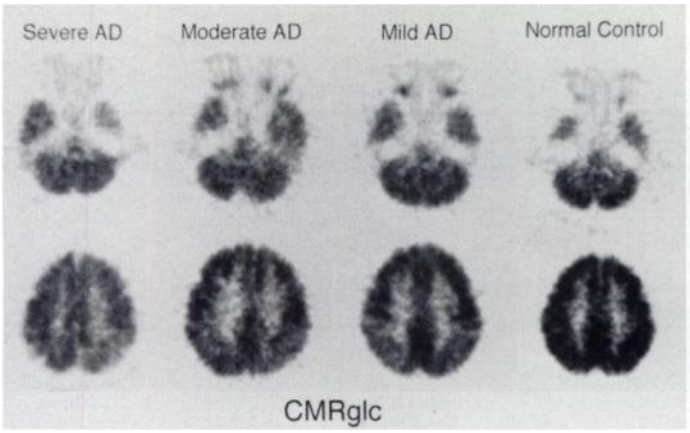

FIGURE 1. Representative CMRglc images from each of three groups of Alzheimer's disease patients and a normal subject. Severe Alzheimer's disease: A 69-yr-old woman with Alzheimer's disease. MMSE score was 7. Both cerebellar and cerebral glucose metabolism were decreased. Moderate Alzheimer's disease: A 73-yr-old woman with Alzheimer's disease. MMSE score was 15. Mild Alzheimer's disease: A 75-yr-old woman with Alzheimer's disease. MMSE score was 22. Normal control: A 73-yr-old normal woman.

which supports the findings of previous studies (*1,16–18*). Our study, however, revealed that cerebellar glucose metabolism in the severe Alzheimer's disease group was significantly reduced compared with that of normal control subjects. The cerebellar glucose metabolism in the mild and moderate Alzheimer's disease groups tended to be lower than that of normal control subjects.

Our results are supported by a neuropathologic study of the autopsied cerebellum from six Alzheimer's disease and 10 non-Alzheimer's disease subjects (*4*). Neither senile plaques nor amyloid angiopathy were observed in the non-Alzheimer's disease subjects, while in four of the six patients with Alzheimer's disease, diffuse plaques were detected in the molecular layer, which were seen as ill-defined areas of fine fibrillar materials. The compact plaques in the Purkinje cell or in the granular cell layers were found in three of the six Alzheimer's disease patients. Amyloid angiopathy was observed in three of the six Alzheimer's disease patients. In one of the Alzheimer's disease patients, the cerebellum, in addition to the cerebral cortices, was affected.

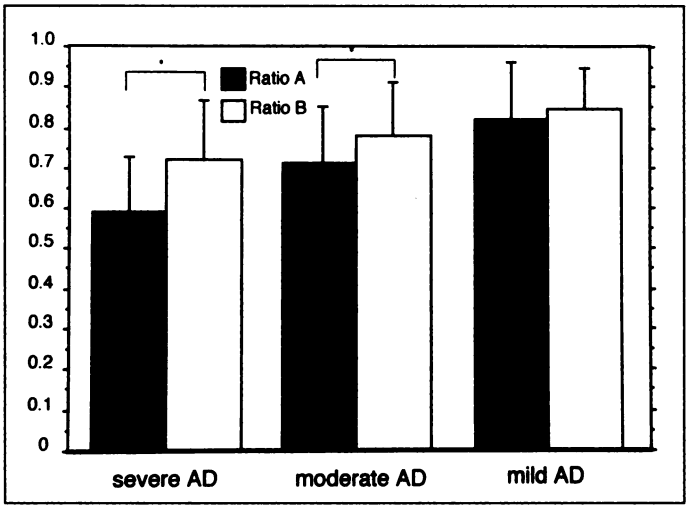

FIGURE 2. Average A and B ratios in each Alzheimer's disease group. Ratio A = each individual parietal CMRglc/mean parietal CMRglc of 13 normal controls. Ratio B = (each individual parietal CMRglc/each individual cerebellar glucose metabolism)/(mean parietal CMRglc of 13 normal controls/mean cerebellar glucose metabolism of 13 normal controls) $^{*}p < 0.05$.

On the other hand, [^{18}F]FDG and PET studies showed that there were no significant differences among the cerebellar glucose values in the control and Alzheimer's disease groups (*16,17*), while the mean cerebellar glucose metabolism in stroke and tumor patients was lower in the hemisphere contralateral to the supratentorial lesion (*18*). Kushner et al. (*18*) compared severe-to-mild Alzheimer's disease patients with a normal group. If they had classified them into three groups, as was done in our study, they might have found a significant difference between the cerebellar glucose metabolism in advanced Alzheimer's disease patients and the control group.

It is important to note that even in the occipital cortices in Alzheimer's disease patients, the CMRglc was lower than that of normal controls. Kumar et al. (*1*) reported that primary sensorimotor regions demonstrated statistically significant reductions in CMRglc even in mild Alzheimer's disease, the CMRglc in the sensorimotor area of Alzheimer's disease patients in our study also tended to be lower than that of the control group. We suppose all the regions are connected with each other, and global neurodegeneration and remote effects from severely affected areas take part in the reduction of whole brain glucose metabolism.

Motor apraxia or dyscoordination could conceivably alter cerebral-cerebellar metabolic relationships in Alzheimer's disease patients. There is a frontal hypometabolism in progressive supranuclear palsy, where neocortical pathology is minimal (*19*). A similar proposal may be made to explain the decrease in the cerebellar glucose metabolism in Alzheimer's disease. The cerebellar hemispheres demonstrate right-left metabolic asymmetries that correlate with asymmetries in the opposite direction in the contralateral frontal, temporal and parietal cortices, reflecting the phenomenon of crossed cerebellar diaschisis (*20*). We suppose that these reductions are due not only to cerebellar degeneration but also to remote effects from severely affected cortical regions, such as temporal cortices, parietal cortices and so on. Because our patients suffered no motor disorder and were not wheelchair bound or immobilized in spite of reduced cerebellar glucose metabolism, and because there was no obvious cerebellar atrophy even in the severe Alzheimer's disease group, cerebellar degeneration might play a small role.

In a SPECT study of Alzheimer's disease, regional cerebral blood flow (CBF), normalized to the mean activity in a cerebellar reference slice, was assessed (*21*). Talbot et al. (*22*) evaluated the effect of using two different reference regions in the quantification of SPECT. Alzheimer's disease patients, frontotemporal dementia patients and age-matched controls were examined using ^{99m}Tc-HMPAO and SPECT. Regional CBF in each ROI were determined by normalizing the count densities to both cerebellar and occipital cortex reference regions. The number and topographical distribution of ROIs with significant group differences varied depending on the choice of reference region. The magnitude of these differences was greatest when the cerebellum was used as the reference region. Because the disparity between results obtained with the two reference regions was most apparent in the Alzheimer's disease group, Talbot et al. (*22*) concluded that the cerebellum was the more appropriate choice for a reference region in the quantification of SPECT in primary degenerative dementia.

Because there is a good correlation between blood flow and metabolism in most regions of the brain (*23*), the use of the cerebellum as a reference region has the risk of underestimating the magnitude of perfusional or metabolic reduction, especially in a patient with severe Alzheimer's disease. As our data indicated that all regional glucose metabolism correlated with cognitive impairments, there may be no regions in the brains of

TABLE 2
Pearson Correlation Coefficient Between Regional CMRglc and MMSE/ADAS Scores in Alzheimer's Disease Patients

Score	Cerebellum	Temporal	Occipital	Frontal	Sensorimotor	Parietal
MMSE	r = 0.366 ($p < 0.005$)	r = 0.546 ($p < 0.001$)	r = 0.387 ($p < 0.005$)	r = 0.470 ($p < 0.001$)	r = 0.354 ($p < 0.005$)	r = 0.519 ($p < 0.001$)
ADAS	r = −0.377 ($p < 0.005$)	r = −0.594 ($p < 0.001$)	r = −0.364 ($p < 0.005$)	r = −0.556 ($p < 0.001$)	r = −0.465 ($p < 0.001$)	r = −0.620 ($p < 0.001$)

MMSE = Mini-Mental State Examination; ADAS = Alzheimer's Disease Assessment Scale.

Alzheimer's disease patients that could be used as a good reference region for normalizing. The correlation between the cognitive impairments and the glucose metabolism in the cerebellum, occipital cortices and sensorimotor cortices indicates that even in these regions, the CMRglc is not completely preserved in Alzheimer's disease. Moreover, as the role of the cerebellum in the memory process is not insignificant (*24*), this may be one of the causes of cerebellar glucose metabolic reduction in Alzheimer's disease. However, the origin of most of the cerebellar glucose metabolic reduction in Alzheimer's disease would be remote effects from frontal, temporal and parietal lobes affected by the disease and neurodegeneration in severe Alzheimer's disease.

CONCLUSION

We demonstrated a significant cerebellar glucose metabolic reduction in severe Alzheimer's disease with no evident cerebellar atrophy. Although cerebellar glucose metabolism is not as strongly reduced as in the parietal and temporal regions, Alzheimer's disease is a global degenerative brain disease in which the degeneration appears evident in accordance with severity.

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