Cerebral Glucose Metabolism in Patients with Frontotemporal Dementia

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Frontotemporal dementia (FTD) is a dementia syndrome characterized by peculiar behavioral changes arising from frontotemporal involvement and distinct from Alzheimer's disease (AD). The purpose of this study was to elucidate the specific patterns in cerebral glucose metabolism in patients with FTD and to compare them with the patterns in patients with AD and normal elderly subjects using fluorodeoxyglucose (FDG) and PET. **Methods:** Twenty-one patients with a clinical diagnosis of FTD [mean age 67.0 ± 7.0 yr, Mini Mental State Examination (MMSE) score 18.7 ± 5.7], 21 age-, sex- and dementia-severity-matched patients with probable AD (mean age 66.9 ± 7.1 yr, MMSE score 20.2 ± 5.5) and 21 age- and sex-matched normal control subjects (mean age 66.8 ± 5.7 yr) were studied. The cerebral metabolic rate for glucose (CMRglc) was measured with FDG and PET. Absolute measures of regional CMRglc were compared among the three groups. One-way ANOVA and the posthoc Tukey HSD test were used for statistical analyses. **Results:** In the FTD group, CMRglc was preserved only in the left cerebellum, right sensorimotor area and occipital lobes. The CMRglc was significantly lower in the FTD group as opposed to the AD group in the hippocampi, orbital gyri, anterior temporal lobes, anterior cingulate gyri, basal ganglia, thalami, middle and superior frontal gyri and left inferior frontal gyrus. **Conclusion:** Although metabolic abnormality in FTD is predominant in the frontal and anterior temporal lobes and the subcortical structures, it is more widespread than has been previously stressed. These findings document an FTD-specific cerebral involvement and facilitate differential diagnosis of degenerative dementias.

Key Words: frontotemporal dementia; Alzheimer's disease; cerebral metabolic rate for glucose; fluorodeoxyglucose; PET

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Frontotemporal dementia (FTD) is a comprehensive clinical entity of primary degenerative dementia that is characterized by peculiar behavioral changes arising from frontotemporal involvement (*1*). FTD was formerly designated as frontal dementia, dementia of the frontal lobe type and Pick's disease (*2–4*). Recent studies have focused on the clinical (*5,6*), neuropsychological (*7,8*) and neuroimaging features of this disorder (*1,9*). In 1994, the Lund/Manchester groups proposed clinical and pathological criteria for FTD (*1*). According to these criteria, three types of histologic change (Pick-type, frontal lobe degeneration type and motor neuron disease type) underlie the atrophy and share an identical anatomical distribution in the frontal and temporal lobes.

Systematic studies using MRI or spectroscopy have been performed to document differential patterns of cerebral degeneration in FTD and Alzheimer's disease (AD) that may facilitate the study of brain-behavior relationships and the differential diagnosis of dementia. We previously reported that frontotemporal white matter in patients with FTD showed an increased MRI signal intensity that appeared to represent increased white matter gliosis (*10*). Kaufer et al. (*11*) reported that structural alterations in the anterior corpus callosum and pericallosal CSF space reflect differential patterns of cerebral degeneration in AD and FTD. Ernst et al. (*12*), using H-1 MRI spectroscopy, demonstrated that, in FTD patients, levels of N-acetyl compounds and glutamate/glutamine were reduced in the frontal lobe, suggesting neuronal loss and increased glial content. However, in the field of nuclear medicine, there have been few systematic studies on FTD. Several anecdotal single cases or case series studies, using SPECT or PET, have stressed frontotemporal hypoperfusion or hypometabolism (*13–27*). The purpose of this study was to elucidate specific changes in the cerebral glucose metabolism in patients with FTD and to compare them with the changes in patients with AD and normal control subjects using fluorodeoxyglucose (FDG) and PET.

MATERIALS AND METHODS

Subject Selection

All patients who were admitted to our hospital for investigation of cognitive disorders were screened. All eligible patients were examined by both neurologists and psychiatrists and received routine laboratory tests, brain MRIs, MR angiography of the neck and head, electroencephalography and neuropsychological examinations including the Mini-Mental State Examination (MMSE) (*28*).

Frontotemporal Dementia Group

The Lund and Manchester group proposed clinical diagnostic criteria for FTD (*1*). These criteria have been used in recent studies (*10,12,27*), and Miller et al. (*13*) substantiated the usefulness of these criteria by reporting that loss of personal awareness; hyperorality; stereotyped, perseverative behavior; and progressive reduction of speech are the signs of FTD that most distinguish it from AD. In this study, we used the following criteria to select patients with FTD. The inclusion criteria were: (a) ICD-10 diagnostic criteria for dementia (*29*); and (b) the core diagnostic (behavioral, affective, speech, spatial orientation/praxis, physical, investigational) features of the Lund/Manchester clinical criteria for FTD (*1*) with special emphasis on the symptomatic features (loss of personal awareness; hyperorality; stereotyped, perseverative behavior; progressive reduction of speech and preserved spatial orientation) identified by Miller et al. (*13*). The exclusion criteria were: (a) diagnostic exclusion features of the Lund/Manchester clinical criteria for FTD (*1*); and (b) advanced stage of FTD with severe deficits or rude behaviors that would make assessments difficult. Although there is one neuroimaging item in the Lund/Manchester criteria, i.e., predominant frontal or anterior temporal abnormality, or both, we did not conduct a cerebral metabolic/perfusion investigation when selecting the FTD patients. The FTD

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TABLE 1
Regional Cerebral Metabolic Rate for Glucose in Each Group

Region	FTD	AD	NC	Among	FTD vs. NC	AD vs. NC	FTD vs. AD
R. orb	4.84 ± 1.28	6.05 ± 1.06	7.02 ± 0.90	<0.001	<0.001	0.015	0.002
L. orb	4.81 ± 1.45	6.02 ± 1.07	7.04 ± 0.89	<0.001	<0.001	0.008	0.008
R. inffro	5.88 ± 1.45	6.79 ± 1.34	7.65 ± 0.96	<0.001	<0.001	ns	ns
L. inffro	5.90 ± 1.25	6.99 ± 1.12	7.70 ± 0.90	<0.001	<0.001	ns	0.006
R. midfro	5.41 ± 1.69	6.85 ± 1.36	7.64 ± 0.92	<0.001	<0.001	ns	0.003
L. midfro	5.54 ± 1.35	6.91 ± 1.16	7.62 ± 0.92	<0.001	<0.001	ns	<0.001
R. supfro	5.14 ± 1.47	6.68 ± 0.98	7.19 ± 0.81	<0.001	<0.001	ns	<0.001
L. supfro	5.08 ± 1.14	6.74 ± 1.18	7.25 ± 0.77	<0.001	<0.001	ns	<0.001
R. sm	6.85 ± 1.11	7.23 ± 1.01	7.53 ± 6.68	ns	na	na	na
L. sm	6.90 ± 1.16	7.39 ± 0.94	7.65 ± 0.74	0.040	0.034	ns	ns
R. infpar	6.08 ± 1.26	5.98 ± 1.77	7.68 ± 1.05	<0.001	0.001	0.001	ns
L. infpar	6.32 ± 1.31	6.15 ± 1.74	7.67 ± 1.00	0.001	0.007	0.002	ns
R. suppar	6.26 ± 1.07	6.14 ± 1.57	7.40 ± 0.72	0.001	0.007	0.003	ns
L. suppar	6.17 ± 1.07	6.10 ± 1.41	7.37 ± 0.81	<0.001	0.003	0.002	ns
R. anttem	4.49 ± 0.78	5.43 ± 1.27	6.37 ± 0.68	<0.001	<0.001	0.006	0.006
L. anttem	4.37 ± 1.05	5.43 ± 1.18	6.25 ± 0.72	<0.001	<0.001	0.027	0.003
R. postem	6.24 ± 1.20	5.92 ± 1.78	7.35 ± 0.67	0.002	0.021	0.002	ns
L. postem	5.85 ± 1.39	5.76 ± 1.64	7.17 ± 0.69	0.001	0.005	0.003	ns
R. latocc	7.12 ± 1.33	7.08 ± 1.21	7.59 ± 0.89	ns	na	na	na
L. latocc	6.89 ± 1.35	6.91 ± 1.36	7.52 ± 0.72	ns	na	na	na
R. medocc	7.44 ± 1.17	7.50 ± 1.12	7.97 ± 0.90	ns	na	na	na
L. medocc	7.32 ± 1.27	7.59 ± 1.03	7.98 ± 0.96	ns	na	na	na
R. hip	3.87 ± 0.68	4.52 ± 0.91	5.13 ± 0.50	<0.001	<0.001	0.022	0.012
L. hip	3.81 ± 0.85	4.79 ± 0.84	5.13 ± 0.42	<0.001	<0.001	ns	<0.001
R. antcin	4.92 ± 1.28	6.57 ± 1.02	7.19 ± 0.82	<0.001	<0.001	ns	<0.001
L. antcin	4.84 ± 1.23	6.54 ± 1.17	7.11 ± 0.77	<0.001	<0.001	ns	<0.001
R. poscin	5.69 ± 1.19	5.84 ± 1.50	7.34 ± 1.04	<0.001	<0.001	<0.001	ns
L. poscin	5.68 ± 1.13	6.07 ± 1.54	7.04 ± 0.98	0.003	0.002	0.038	ns
R. bg	7.37 ± 1.13	8.41 ± 1.09	8.40 ± 1.28	0.007	0.017	ns	0.015
L. bg	7.33 ± 1.37	8.28 ± 1.09	8.34 ± 1.03	0.011	0.021	ns	0.030
R. tha	6.82 ± 0.90	7.66 ± 1.13	7.68 ± 1.03	0.012	0.024	ns	0.029
L. tha	6.58 ± 0.90	7.62 ± 1.12	7.57 ± 1.04	0.002	0.008	ns	0.005
R. cb	5.92 ± 0.88	6.51 ± 0.99	6.63 ± 0.71	0.021	0.025	ns	ns
L. cb	6.13 ± 0.91	6.74 ± 1.03	6.74 ± 0.79	ns	na	na	na

Unit-mg/100g/min. P values are shown in the Among, FTD vs. NC, AD vs. NC and FTD vs. AD columns.

FTD = frontotemporal dementia; AD = Alzheimer's disease; NC = normal controls, R. = right; L. = left; orb = orbital gyrus; inffro = inferior frontal; midfro = middle frontal; supfro = superior frontal; sm = sensorimotor area; infpar = inferior parietal lobule; suppar = superior parietal lobule; anttem = anterior temporal lobe; postem = posterior temporal lobe; latocc = lateral occipital; medocc = medial occipital; hip = hippocampus; antcin = anterior cingulate gyrus; bg = basal ganglia; tha = thalamus; poscin = posterior cingulate gyrus; cb = cerebellum; ns = not significant by analysis of variance; na = not applicable.

group consisted of 21 patients [10 women, 11 men; mean age 67.0 ± 7.0 (s.d.) yr] and the mean MMSE score was 18.7 ± 5.7. One of the FTD patients also had motor neuron disease.

Alzheimer's Group

Twenty-one patients (12 women, 9 men; mean age 66.9 ± 7.1 yr) who fulfilled National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association criteria for probable AD (*30*) were randomly sampled from the same cohort of patients and were matched for sex, age and MMSE score. All the AD patients were given the same examinations that were given to the FTD group, and the mean MMSE score was 20.2 ± 5.5.

Normal Control Subjects

Twenty-one (12 women, 9 men; mean age 66.8 ± 5.7 yr) age- and sex-matched normal control subjects were selected randomly from healthy volunteers, who were recruited from the community. All subjects had normal brain MRIs, normal findings on the physical and neurological examinations and no history of psychiatric or neurologic disorders. All the subjects in this study were right-handed.

PET Procedure

Before the examination, written informed consent was obtained from all the patients and/or their relatives and from all the normal control subjects according to the Declaration of Human Rights, Helsinki, 1975. The PET procedure was followed strictly according to the *PET Drug Usage Manual* in our institute and was approved by the internal ethical committee. Before PET scans, all subjects received MRIs for diagnosis and PET positioning. The detailed MRI scanning procedure was described elsewhere (*31*).

The detailed PET scanning procedure for measuring the cerebral metabolic rate for glucose (CMRglc) was described elsewhere (*32*). In brief, PET images were obtained with a tomograph Headtome IV (Shimadzu Corp., Kyoto, Japan) (*33*). A transmission scan was performed using a $^{68}Ga/^{68}Ge$ pin source for absorption correction after each subject was positioned. PET studies were performed with the subjects under resting conditions with eyes closed and ears unplugged. All subjects had fasted for at least 4 hr before PET scanning. FDG of 185–346 MBq, was injected into the right antecubital vein, and arterial blood sampling was done from a catheter inserted into the left radial artery. Brain scanning was started at 60 min after the injection, and emission data were

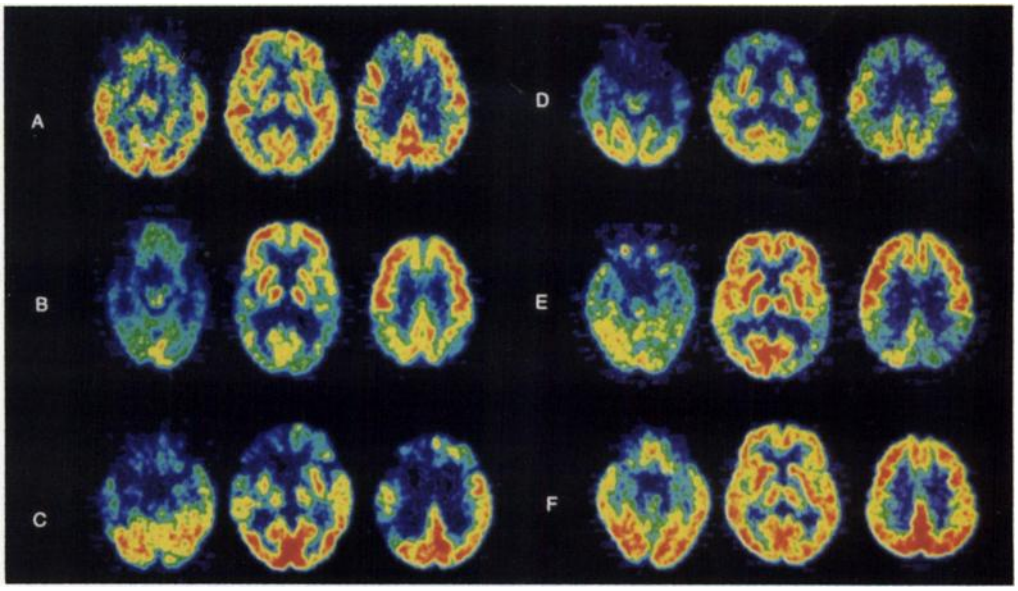

FIGURE 1. Typical cerebral metabolic rate for glucose (CMRglc) images in FTD patients, an AD patient and a normal control subject. (A) A 70-yr-old woman with FTD; MMSE: 21. CMRglc is reduced in right frontal lobe. (B) A 71-yr-old woman with FTD, clinically diagnosed as temporal Pick type; MMSE: 17. CMRglc images demonstrate severely reduced CMRglc in bilateral temporal lobe. In this patient, parietal and occipital CMRglcs were also decreased. (C) A 62-yr-old man with FTD, clinically diagnosed as frontotemporal Pick type; MMSE: 24. CMRglc is severely reduced in frontal and temporal lobe, predominantly in right side. CMRglcs in right basal ganglia and right parietal lobe are also decreased. (D) A 73-yr-old woman with FTD, clinically diagnosed as frontotemporal Pick type; MMSE: 5. CMRglc is severely reduced in temporal and frontal lobe, predominantly in left side. Bilateral parietal CMRglc is also decreased. (E) A 58-yr-old man with Alzheimer's disease; MMSE: 15. Bilateral temporoparietal CMRglc-reduction pattern indicates typical Alzheimer-reduction pattern. (F) A 64-yr-old normal woman. There is no reduction of glucose metabolism.

collected for 12 min. Values of regional CMRglc were calculated by Phelps' autoradiographic method using FDG (*34*).

Data Analysis

PET and MRI datasets were transmitted directly to a workstation (Indigo^2, SGI, Mountain View, CA) from the PET and MRI units, and image analysis was performed on the workstation.

A quantitative analysis was performed with conventional region of interest (ROI) settings. MRIs of three-dimensional scales and coordinates that were identical to those of the PET images were made for anatomical references of the PET analysis. We displayed both PET and MRIs side-by-side on a display monitor and determined two or three circular ROIs (10-mm diameter) on the cortical ribbon of each region on the CMRglc image. ROIs were carefully placed on the cerebellum, orbital gyrus, superior frontal gyrus, middle frontal gyrus, inferior frontal gyrus, anterior temporal lobes, posterior temporal lobes, medial occipital lobes, lateral occipital lobes, inferior parietal lobes, superior parietal lobes, hippocampus, anterior cingulate gyrus, posterior cingulate gyrus, basal ganglia, sensorimotor area and thalamus on the CMRglc image referencing coordinate MRI. One-way analysis of variance and the posthoc Tukey HSD test were used for statistical analysis. The statistically significant level was set at $p < 0.05$.

RESULTS

The mean regional CMRglc in each group is summarized in Table 1. The mean regional CMRglc in patients with FTD and with AD was decreased in every ROI when compared with that in normal control subjects. The differences between patients with FTD and normal control subjects in the front-temporo-parietal association cortex, limbic area, basal ganglia and thalamus were highly significant, and those in the primary sensorimotor cortex and cerebellum were marginally significant. On the other hand, the differences between patients with AD and normal control subjects were significant in the orbital gyrus, temporal and parietal lobes and posterior cingulate gyrus. The mean CMRglc in the hippocampus was somewhat decreased in patients with AD. The reductions of regional CMRglc in the frontal lobe, anterior temporal lobe, basal ganglia and thalamus were significantly larger in patients with FTD than in the patients with AD, and the reduction of regional CMRglc in the parietal lobe and posterior cingulate gyrus was comparable with that in the patients with AD. Figure 1 shows typical CMRglc images for all three groups.

DISCUSSION

Despite being named after the frontotemporal region, FTD was documented in this study to have a more widespread hemispheric metabolic derangement than was previously recognized. The medial temporal region and the subcortical structures including the corpus striatum and thalamus were severely affected. Although the cortical involvement was accentuated in the frontal lobes and anterior temporal lobes, the involvement of the parietal region was also noted and was comparable to that in AD. Glucose metabolism in the sensorimotor cortex and the cerebellar cortex was also decreased in FTD.

Reduced glucose metabolism in the orbital gyrus, anterior cingulate gyrus, frontal cortices, anterior temporal cortices, hippocampus and subcortical structures was consistent with the pathological features of FTD (*15,35,36*). Our results clearly indicated that predominant frontotemporal involvement is a characteristic sign of FTD that is distinct from AD. This further substantiated the preliminary findings indicated in the PET studies of anecdotal cases (*15,16,19,21*) and supported the findings in SPECT studies (*14,17,18,22–25*). Starkstein et al. (*20*) reported that reduced cerebral blood flow in the frontal lobe is a specific feature of FTD. Pickut et al. (*26*) reported that bifrontal hypoperfusion on ^{99m}Tc-hexamethyl propyleneamine oxime SPECT is useful for discriminating frontal lobe-type dementia from AD patients.

The involvement of the parietal lobe, sensorimotor cortex and cerebellar cortex in FTD has not been stressed either in neuropathological or neuroimaging studies. Some of the previous studies, however, have noted some parietal deficits of perfusion or metabolism (*15,17,21–23,27*). Parietal involvement was recognized in postmortem studies of patients with advanced FTD (*35,36*) and was rarely predominant in aberrant patients with Pick's pathology (*37,38*). In addition, the motor cortex is a locus in FTD patients with motor neuron disease. The central and parietal hypometabolisms reflect such changes that may occur earlier and more commonly in milder degrees. The marginal cerebellar hypometabolism may also reflect an early pathologic change in this region. Another possible expla-

nation of cerebellar hypometabolism seen in one side is a crossed cerebellar diaschisis caused by an involvement of the cerebral hemisphere in the opposite side. Although a significant reduction of hippocampal CMRglc was noted in the FTD group when compared with the AD group, this finding should be carefully interpreted. The decreased value may reflect not only the FTD pathology in the hippocampus but also a larger partial-volume effect in FTD, especially in Pick's disease, as opposed to AD, because the hippocampal atrophy in FTD is usually more profound than that in AD (*36,38,39*).

CONCLUSION

A decline of CMRglc in the frontal lobe or anterior temporal lobe is a feature of FTD, although the metabolic involvement was more widespread in the brain than was previously stressed. Another distinctive feature of FTD that distinguishes it from AD is an involvement of the basal ganglia and thalamus. As the degree of glucose hypometabolism in the parietal and medial temporal lobes in FTD was comparable with (or even exceeding) that in AD where these regions were centrally involved, these findings do not exclude the diagnosis of FTD.

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