Original Research Article

Dementia
and Geriatric
Cognitive Disorders

Dement Geriatr Cogn Disord 2004;18:32–36
DOI: 10.1159/000077732

Accepted: September 23, 2003
Published online: April 6, 2004

Region-Specific Decline of Cerebral Glucose Metabolism in Patients with Frontotemporal Dementia: A Prospective ^{18}F-FDG-PET Study

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Key Words

Frontotemporal dementia · Fluoro-2-deoxy-*D*-glucose-positron emission tomography · Mini-Mental State Examination · Thalamus · Caudate nucleus · Frontal lobe

Abstract

Objective: The aim of this study was to examine the pattern of glucose uptake and the changes over time of metabolic deficits in patients with frontotemporal dementia (FTD). ***Methods:*** 10 patients who had received the clinical diagnosis of FTD underwent positron emission tomography scanning at the time of their first examination (baseline) and at follow-up (after 17.1 ± 6.0 months). For statistical analysis, we used the SPM 99 software. First, we compared the data of the patients at baseline with an age-matched healthy control group. Second, we compared glucose uptake at follow-up with baseline measurements. ***Results:*** Compared with normal controls, FTD patients showed significant metabolic deficits primarily in frontal cortical areas, but also in the caudate nuclei and the thalami. At follow-up, a significant progression of metabolic deficit was exclusively observed in the orbitofrontal parts of the frontal lobe and in the subcortical structures. ***Discussion:*** These findings demonstrate that the clinical progression in patients with FTD is accompanied by a region-specific decline in cerebral glucose metabolism.

Introduction

Frontotemporal dementia (FTD) is a clinical syndrome caused by bilateral although often asymmetric lobar atrophy, which particularly involves the orbitobasal frontal lobe, the temporal polar region and the amygdala, as well as the adjacent white matter and several basal ganglia nuclei [1].

In FTD, there is prominent bilateral and usually symmetric involvement of the frontal lobes [2]; however, the patterns of atrophy are not established clearly [3]. Recent studies suggest that the frontal lobes are the main area of damage in FTD [4, 5]. Positron emission tomography (PET) is a useful instrument for the detection of brain regions with reduced metabolic activity at the early stages of progressive neurodegenerative diseases, even at a stage before atrophic brain changes become apparent on structural (CT or MR) imaging [6]. However, systematic investigations of the pattern of regional glucose metabolism in FTD using PET are rare [7, 8]. Furthermore, to our knowledge, there is no information from longitudinal studies on the course of cerebral metabolic changes, apart from a few case reports [9].

The aim of this study was to examine the pattern of glucose uptake and the changes over time of metabolic deficits in patients with FTD using a prospective study design.

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Methods

The study refers to 10 patients who were consecutively examined at our memory clinic (7 male, 3 female; mean age 59.9 ± 7.9 years) and were diagnosed with FTD according to the Lund-Manchester criteria [10]. Patients with progressive aphasia and semantic dementia were excluded. The diagnosis was based on information gathered from psychiatric assessment, neurological examination, informant interview, laboratory screening and cranial CT or MR imaging. Patients were excluded who fulfilled diagnostic criteria for Alzheimer's disease (AD) according to the NINCDS-ADRDA criteria [11], Lewy body disease according to McKeith et al. [12] or cerebrovascular disease according to the NINDS-AIREN criteria [13]. Cognitive function was assessed using the Consortium to Establish a Registry for Alzheimer's Disease Neuropsychological Battery [14], which incorporates the Mini-Mental State Examination (MMSE).

The control group was recruited at the same unit and consisted of the patients' healthy caregivers (n = 15; male: 7; female: 8; age: 61.8 ± 9.1 years).

Regional cerebral glucose metabolism was measured using PET at the time of their first examination (baseline) and at follow-up after a mean interval of 17.1 ± 6.0 months. PET was performed under standard resting conditions (eyes closed, in dimmed ambient light and silent environment). 370 MBq ^{18}F-fluoro-2-deoxy-*D*-glucose (FDG) was injected at rest. Thirty minutes later, PET imaging was performed using a Siemens ECAT/EXACT HR+ PET scanner (CTI, Knoxville, Tenn., USA). A sequence of three frames (10 min; 5 min; 5 min) was started (3-dimensional mode, total axial field of view of 15.52 cm) and later combined into a single frame. Attenuation correction was performed using a transmission scan. Data were corrected for random, dead time and scatter, and images were reconstructed by filtered back-projection with a Hamm filter (cut-off frequency 0.5 cycles/projection element) resulting in 63 slices in a 128 × 128 pixel matrix (pixel size 2.06 mm) and interplane separation of 2.425 mm.

Image analysis was performed on an SGI O2 workstation (Silicon Graphics Inc., Mountain view, Calif., USA). For stereotactical normalisation of the ^{18}F-FDG-PET data, an established automated routine (Neurostat, University of Michigan) was used, which has previously been evaluated for scientific use in patients with dementia [15]. Images were smoothed using a Gaussian kernel (12 × 2 × 12 mm full width at half maximum). For statistical analysis, we used the SPM 99 software (Statistical Parametric Mapping; Wellcome Department of Cognitive Neurology, London, UK).

First, we compared PET data between patients (baseline and follow-up scans) and controls in order to determine the cortical areas affected in the FTD group (SPM 99, two sample t test, $p_{corr} = 0.01$). Region of interest (ROI) analyses for the nuclei caudati and the thalami were performed ($p_{corr} = 0.05$) to identify the involvement of subcortical structures as previously described [16–19].

Second, we compared the glucose uptake in the patient group at follow-up with baseline measurements in order to identify regions in which the cerebral metabolism had changed (SPM 99, paired t test, $p_{corr} = 0.01$, interindividual differences in tracer activity were adjusted using Ancova in the statistical model).

Results

Symptom Progression

At baseline, cognitive impairment was mild in most FTD patients, as shown by a mean MMSE score of 25 ± 3.43. All patients showed a lack of insight, a decline in personal hygiene, emotional blunting and most of them presented with apathy except 2 who presented with aggression. A progression of cognitive impairment and of behavioural disturbance was noted in all patients at follow-up. On the MMSE, patients had declined by 5 points on average (MMSE 20 ± 6.76).

Regional Cerebral Metabolism at Baseline

When compared with normal controls, patients with FTD had significant metabolic deficits at baseline, primarily in frontal cortical areas including the gyrus frontalis superior, medius and inferior (maximum at x/y/z in Talairach space at –38/10/4, $p_{corr} = 0.002$, gyrus frontalis inferior/sulcus lateralis left; submaxima at 9/27/61, $p_{corr} = 0.006$, gyrus frontalis superior right, 10/20/34, $p_{corr} = 0.013$, gyrus frontalis medius right; cluster size: 22,675 voxels of 2.2 × 2.2 × 2.2 mm^3, $p_{corr;\,cluster} < 0.001$). There was no statistically significant decrease in metabolic activity in the temporal lobe or any other cortical area (fig. 1).

In addition, there was reduced metabolic activity in subcortical structures, particularly the caudate nuclei and the thalami. An ROI analysis that includes the regions of both caudate nuclei (20 mm radius around x/y/z: 0/9/4) revealed a significantly lower glucose uptake in both caudate nuclei (maximum at –4/16/11, $p_{corr} = 0.05$) in the FTD group compared with the control group. An ROI analysis which included both thalamic regions (20 mm radius around x/y/z: 0/–18/11) revealed a significantly lower glucose uptake in both thalami (maximum at 2/–10/11, $p_{corr} = 0.05$).

Regional Cerebral Metabolism at Follow-Up Compared with Baseline

The comparison of follow-up scans with baseline scans of patients with FTD showed a significant progression of metabolic deficits in orbitofrontal parts of the frontal lobe (cluster of 4,032 voxels, $p_{corr} < 0.001$; fig. 2). A metabolic decrease was also observed in the dorsal parts of the frontal lobes and in the left inferior parietal lobule, but it did not reach statistical significance after correction for multiple testing.

In addition, a significant decrease in metabolic activity relative to baseline was found in the medial n. caudatus

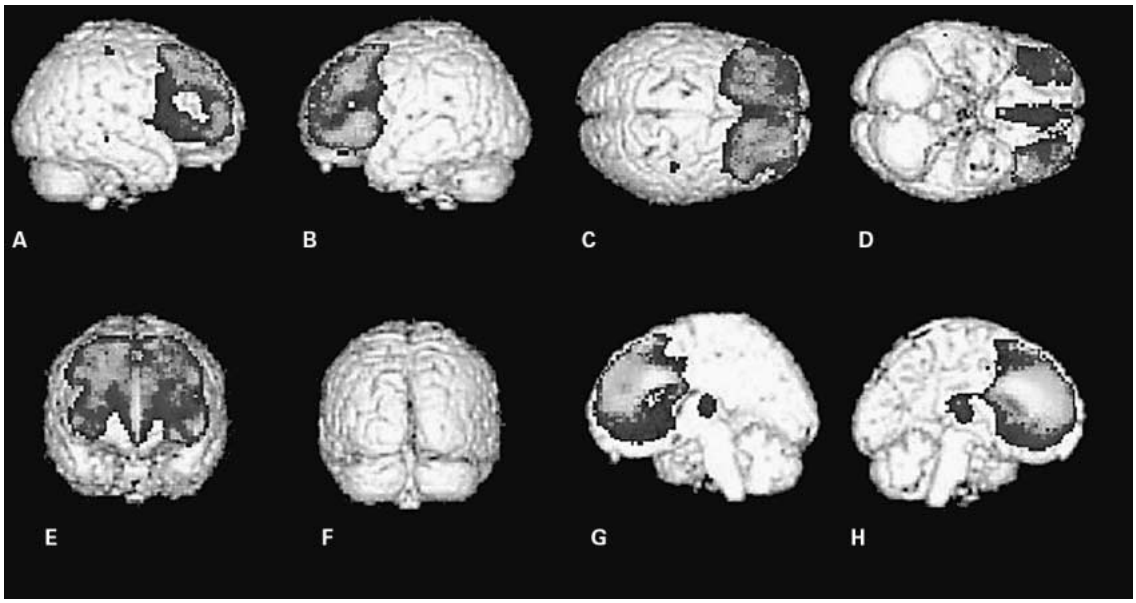

Fig. 1. Group comparison: FTD patients at baseline compared with healthy controls. Projection on a template ('normal brain'); $p_{uncorr} = 0.01$ for illustration; view from lateral right (**A**); lateral left (**B**); top (**C**); bottom (**D**); front (**E**); back (**F**); mesial right (**G**), and mesial left (**H**).

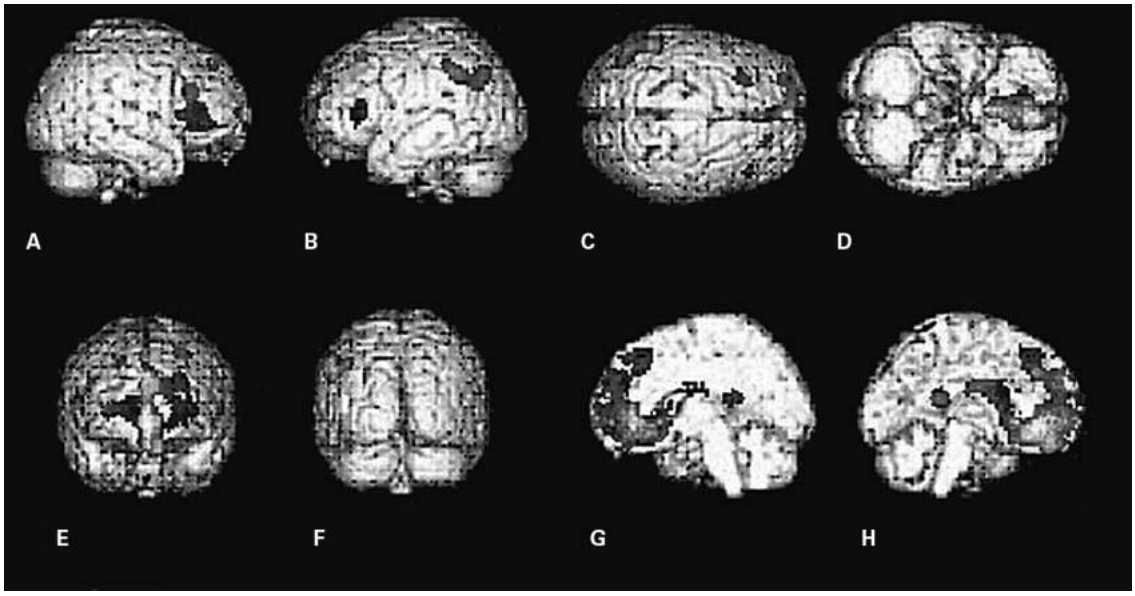

Fig. 2. Group comparison: FTD patients at follow-up compared with FTD patients at baseline. Projection on a template ('normal brain'); $p_{uncorr} = 0.01$ for illustration; view from lateral right (**A**); lateral left (**B**); top (**C**); bottom (**D**); front (**E**); back (**F**); mesial right (**G**), and mesial left (**H**).

on both sides (maximum at x/y/z: 2/10/0, $p_{corr} = 0.01$). Glucose uptake in the thalamus did not show a statistically significant change from baseline.

Discussion

The comparison between the FDG-PET scans of the FTD patients at baseline and PET scans of healthy subjects showed a significant metabolic deficit which was confined to the frontal lobes. This probably reflects the topography of cortical neuropathological changes and is consistent with previous functional imaging findings of other groups [8]. There was no metabolic decrease relative to controls in any other cortical area. This confirms our clinical diagnoses of the frontal variant of FTD. The observation of metabolic deficits in subcortical structures, particularly in the caudate nuclei and the thalami, is consistent with the neuropathological observation that in Pick's disease and in FTD without specific pathology, a degeneration of the caudate nuclei may be present [10, 16, 17]. The co-existence of neurodegenerative changes in the frontal lobe and in subcortical areas is explained by frontal-subcortical circuits [20]. Striatal hypometabolism might partly be a consequence of frontostriatal deafferentation, in a manner similar to that occurring after frontal cortex ablation in monkeys [21, 22]. The thalamus is positioned at the interface of frontal-subcortical circuits and patients with a lacunar infarct in the thalamus show hypometabolism in the frontal cortex [23]. Thus, also thalamic hypometabolism might reflect a disruption of frontal-subcortical circuits.

At follow-up after 17 months, patients with FTD had declined by an average of 5 points on the MMSE. The annual rate of decline was 3.5 points per year. This is comparable with the cognitive decline seen in AD [24]. The comparison of glucose uptake between baseline and follow-up showed a statistically significant decline of metabolic activity exclusively in the orbitofrontal cortex. This suggests that the lobar type of neurodegeneration was maintained, and there was no significant expansion to temporal or parietal cortical areas. It would be of interest to see whether orbitofrontal involvement is associated with an increase in behavioural disturbances. Recently, it has been shown that the orbitofrontal cortex is involved in the expression of aggressive behaviour [25]. Thus, it could be assumed that orbitofrontal involvement in the course of FTD may result in increased aggressiveness. Diehl and Kurz [26] have recently described a positive correlation between severity of dementia and symptoms of aggression.

The present study has several limitations. Diagnoses were not confirmed by post-mortem examination; however, all patients showed metabolic deficits in the frontal lobe, which corroborates the clinical diagnosis. There was a large variation in the interval between baseline and follow-up (SD ± 6), but a decline of frontal metabolic activity was seen in all patients, even in those who were followed up at a shorter interval. In longer intervals of follow-up examination, a spreading of the disease in non-frontal entities was observed. The patient sample was small because FTD occurs relatively rare and the patients are difficult to manage.

In summary, our findings demonstrate that the clinical progression of FTD over 17 months is accompanied by a region-specific decline in cerebral glucose metabolism, which is confined to the frontal lobe and the caudate nucleus, and that the decline in cognitive function assessed using the MMSE occurs at the same rate in FTD as in AD. Our data may be of potential importance for research trials and therapeutic monitoring.

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