Brain FDG-PET changes in ALS and ALS-FTD

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Abstract

Background: FDG-PET in ALS most typically demonstrates a primary (and sometimes also supplementary) motor cortex hypometabolism, often associated with more diffuse cortical hypometabolism involving mostly the dorsolateral prefrontal cortex, the medial and lateral premotor cortices, and the bilateral insular cortex involvement. In ALS-FTD, extensive temporal hypometabolism is seen in addition to severe diffuse frontal hypometabolism.

Methods: This study analyses FDG-PET findings in 6 ALS patients and 4 ALS-FTD patients.

Results: In addition to earlier described areas of hypometabolism in ALS, we found also reduced FDG-PET metabolism in the medial frontal cortex, the orbitofrontal cortex, and the anterior temporal lobe in our ALS patients. The anterolateral area was the best preserved part of the frontal lobe in ALS patients. In ALS-FTD, frontal and temporal hypometabolism was severe (and parietal hypometabolism was often also present) with relatively preserved perirolandic metabolism.

Conclusion: In ALS, more diffuse frontal and temporal FDG-PET hypometabolism was seen than earlier reported, with the anterolateral area as the best preserved part of the frontal lobe. In ALS-FTD, relatively preserved perirolandic metabolism was seen, associated with severe frontal and temporal hypometabolism.

Key words: [18F]2-fluoro-2deoxy-D-glucose; FDG; positron emission tomography; PET; amyotrophic lateral sclerosis; frontotemporal dementia.

Introduction

Amyotrophic lateral sclerosis (ALS) is characterized by progressive degeneration of both UMN and LMN. ALS is sometimes associated with frontotemporal dementia (FTD). Both hereditary and sporadic ALS-FTD patients have been described. ALS and the most frequent form of FTD (i.e. frontotemporal lobar degeneration with ubiquitinated inclusions) share the presence of accumulation of common abnormal intracellular protein aggregates (TAR DNA binding protein 43 [TDP-43] and fused in sarcoma protein [FUS]) (Mackenzie *et al.*, 2010).

Relatively few series on [18F]2-fluoro-2deoxy-D-glucose (FDG) positron emission tomography (PET) and ALS have been reported, demonstrating most typically a primary (and sometimes also supplementary) motor cortex hypometabolism, often associated with more diffuse cortical hypometabolism involving mostly the dorsolateral prefrontal cortex, the medial and lateral premotor cortices, and the bilateral insular cortex involvement (Abrahams *et al.*, 1996; Jeong *et al.*, 2005; Dalakas *et al.*, 1987; Hatazawa *et al.*, 1988; Ludolph *et al.*, 1992). Other authors (Lloyd *et al.*, 2000; Turner *et al.*, 2005) used different PET tracers to analyse brain metabolism in ALS, and found abnormalities also outside of the motor cortex. In one study, using GABA$_A$ ligand [11C]flumazenil, decrease in relative flumazenil volumes of distribution was found in the bilateral prefrontal, parietal, and visual association cortex, and in the left motor/premotor cortex. Another study used [11C]-WAY100635 PET, and found marked reduction in both global and raphe binding potential in ALS patients.

In FTD patients, temporal (especially anteromedial) and parietal hypometabolism is most often seen in addition to severe diffuse prefrontal hypometabolism (Jeong *et al.*, 2005). Very few FDG-PET data exist in ALS-FTD patients, showing similar findings as in FTD patients (Chio *et al.*, 2010).

We analyzed FDG-PET data of 6 ALS patients and 4 ALS-FTD patients.

Methods

All included ALS and ALS-FTD patients met the revised El Escorial Criteria for definite ALS. When, in addition to the presence of definite ALS features,

anamnesis -apart from pathological emotional lability often seen in pure ALS- was suggestive of FTD, neuropsychological tests, including classical tests of executive function (e.g. Wisconsin Card Sorting Test, verbal fluency tests, Trail Making Test) and behavioural assessment (e.g. Executive and Social Cognition Battery), were performed. When neuropsychological testing confirmed findings suggestive of FTD, a diagnosis of ALS-FTD was made. Genetic analyses were not performed in our patients. Family history was negative (for motor neuron disease and FTD) in our patients.

Informed consent was obtained from each patient. FDG-PET (Philips GEMINI XL PET/CT) was performed 30 minutes after intravenous injection of 200 MBq of 18-FDG, with a field of view (FOV) of 180 mm for PET and 500 mm for CT. Attenuation correction of axial slices was done by CT and 3D images generated on NEUROGRAM software (Segami Corp.). Z-score comparison with a normal, age-matched, control population (n = 14, 28, 33, and 31 for control patients aged 40-50, 50-60, 60-70, and 70-80 respectively) without neurological disease was performed. Brain regions with Z-scores below 2 standard deviations of the mean Z-score values for the control group were called hypometabolic. The same FDG-PET scan and parameters were used in our patients. The interpretation of the FDG-PET data was done by a nuclear medicine physician blinded to the clinical information of the patients.

Results

We included 6 ALS patients and 4 ALS-FTD patients. Patient characteristics are summarized in Table 1.

In our 6 ALS patients, hypometabolism was predominantly seen in the prerolandic cortex, the medial frontal cortex, the orbitofrontal cortex, the anterior temporal lobe, and the anterior cingulated cortex. Regional hypometabolic predominance inside of the frontal and temporal lobes was seen, with orbitofrontal hypometabolism most severe in the medial part, and anterior temporal lobe involvement most severe in the anterior and medial part. The anterolateral area was the best preserved part of the frontal lobe.

When comparing hypometabolism between the different ALS patients, hypometabolism seemed not to be related to the disease duration. No difference was seen in FDG-PET metabolism between patients with bulbar onset and patients with symptom onset in the limbs. When present (3 out of 6 ALS patients), asymmetry in reduced prerolandic metabolism did not correspond necessarily to the (crossed) lateralization of the predominant clinical involvement. Sample size, however, did not permit to analyse statistical significant differences between ALS patients differing in disease duration, localisation or asymmetry of symptom onset.

In our 4 ALS-FTD patients, 3 (patient 7, 8, 10) had initial cognitive signs, followed by lower motor neuron signs (with an interval between cognitive and lower motor neuron signs of respectively 12 months, 6 months, and 24 months). Patient 9 had initial motor neuron signs, followed by cognitive signs 12 months later. In these 4 ALS-FTD patients, severe diffuse prefrontal, temporal (especially anteromedial), and parietal hypometabolism was seen. One patient had relative mild hypometabolism (patient 7). In all four ALS-FTD patients, surprisingly, there was a relative preservation of the prerolandic cortex. This was even

Table 1

Patient characteristics

Patient	Sex	Age	Diagnosis	Disease duration (years)
1	M	61	ALS	4
2	M	61	ALS	4
3	M	71	ALS	6
4	F	49	ALS	1
5	F	50	ALS	1.5
6	M	63	ALS	2
7	M	61	ALS-FTD	1.5
8	M	55	ALS-FTD	1
9	F	55	ALS-FTD	1
10	F	48	ALS-FTD	2

Disease duration was defined as the time between symptom onset and FDG-PET performance.
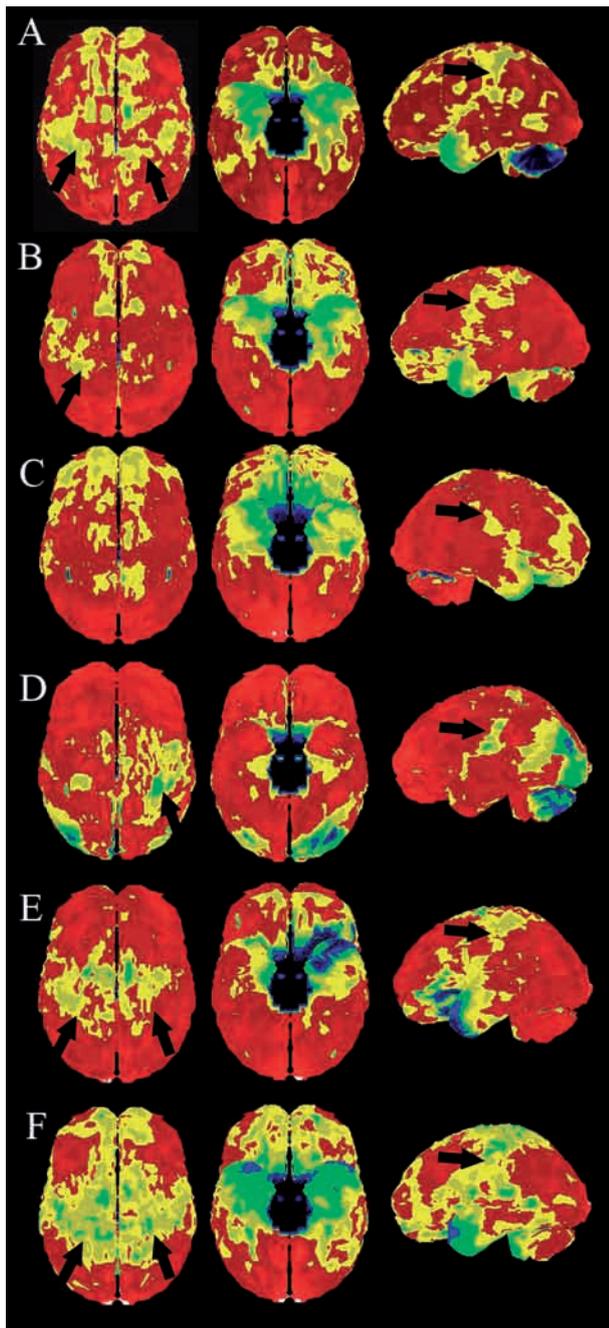
FIG. 1. — In our 6 ALS patients (patient 1 to 6, corresponding to A to F respectively), 3D FDG-PET reconstruction images (each vertical column representing respectively a superior, inferior, and the most representative lateral view) show hypometabolism in the prerolandic cortex (arrows), the medial frontal cortex, the orbitofrontal cortex, and the anterior temporal lobe. In all ALS patients, the anterolateral area was the best preserved part of the frontal lobe.

true in patient 9, who had at time of the FDG-PET performance already lower motor neuron signs since one year and only beginning mild cognitive symptoms.
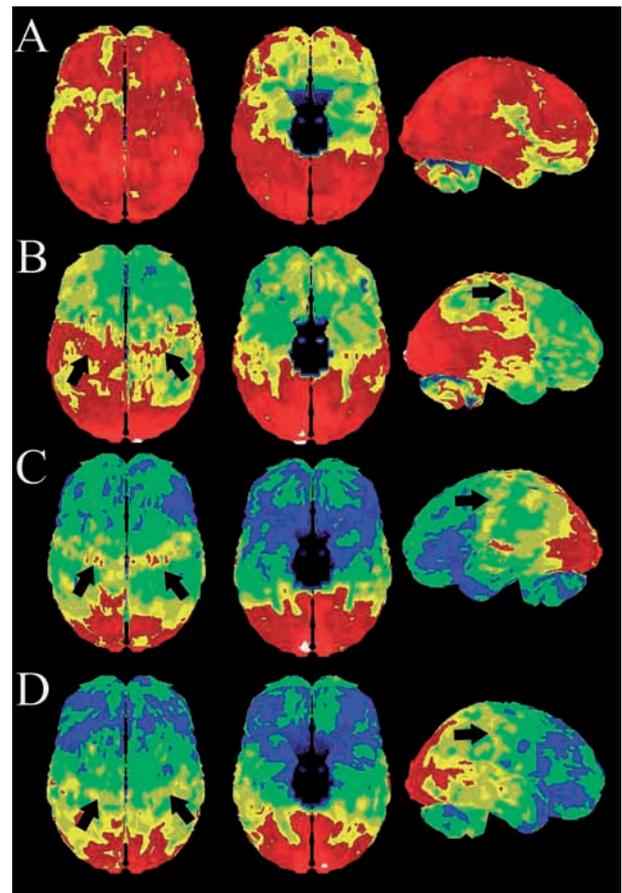

FIG. 2. — 3D FDG-PET reconstruction images (each vertical column representing respectively a superior, inferior, and the most representative lateral view) in our 4 ALS-FTD patients (patient 7 to 10, corresponding to A to D respectively) show frontal, temporal, and parietal (except for patient 7) hypometabolism with relative preservation of the supplementary motor areas (arrows).

Discussion

This study describes FDG-PET findings in 6 ALS and 4 ALS-FTD patients. The prerolandic and the medial frontal cortex hypometabolism we found in our ALS patients confirmed earlier described findings. In addition to earlier reported metabolic abnormalities in ALS, we found also orbitofrontal cortex, anterior temporal lobe, and anterior cingulated cortex hypometabolism in our ALS patients. In contrast to earlier described ALS-associated FDG-PET findings, the medial frontal cortex was more severely involved than the dorsolateral frontal cortex (which was the best preserved frontal area) in our ALS patients.

Frontal, temporal, and parietal hypometabolism in our ALS-FTD patients corresponded to FDG-PET

findings in patients with isolated FTD and to the few available FDG-PET data in ALS-FTD patients. The most striking finding in our ALS-FTD patients, however, was the relative preservation of the perirolandic area despite the presence of motor neuron dysfunction. The pathophysiology of this finding is unclear. FDG-PET hypometabolism related to FTD symptoms might be more profound and/or earlier present then the perirolandic hypometabolism related to motor neuron symptoms in these patients. In order to better analyse FDG-PET metabolism in patients with ALS and/or FTD, a direct comparison should be performed in a study including a larger number of patients with ALS, FTD (with different subtypes, e.g. behavioural variant FTD, semantic dementia, non-fluent aphasia), and ALS-FTD.

The small sample size of our study, and potential differences in control groups used in our study and others series make definite interpretation of the results difficult.

REFERENCES

1. MacKenzie IR, Rademakers R, Neumann M. TDP-43 and FUS in amyotrophic lateral sclerosis and frontotemporal dementia. Lancet Neurol. 2010;9:995-1007.
2. Abrahams S, Goldstein LH, Kew JJ, Brooks DJ, Lloyd CM. *et al.* Frontal lobe dysfunction in amyotrophic lateral sclerosis. A PET study. Brain. 1996;119:2105-20.
3. Jeong Y, Cho SS, Park JM, Kang SJ, Lee JS. *et al.* 18F-FDG PET findings in frontotemporal dementia: an SPM analysis of 29 patients. J Nucl Med. 2005;46:233-9.
4. Dalakas MC, Hatazawa J, Brooks RA, Di Chiro G. Lowered cerebral glucose utilization in amytrophic lateral sclerosis. Ann Neurol. 1987;22:580-6.
5. Hatazawa J, Brooks RA, Dalakas MC, Mansi L, Di Chiro G. Cortical motor-sensory hypometabolism in amyotrophic lateral sclerosis: a PET study. J Comput Assist Tomogr. 1988;12:630-6.
6. Ludolph AC, Langes KJ, Regard M, Herzog H, Kemper B. *et al.* Frontal lobe function in amyotrophic lateral sclerosis: a neuropsychological and positron emission tomography study. Acta Neurol Scand. 1992;85:81-9.
7. Lloyd CM, Richardson MP, Brooks DJ, Al-Chalabi A, Leigh PN. Extramotor involvement in ALS: PET studies with the GABA(A) ligand [(11)C]flumazenil. Brain. 2000;123:2289-96.
8. Turner MR, Rabiner EA, Hammers A, Al-Chalabi A, Grasby PM, Shaw CE, Brooks DJ, Leigh PN. [11C]-WAY100635 PET demonstrates marked 5-HT1A receptor changes in sporadic ALS. Brain. 2005;128:896-905.
9. Chio A, Calvo A, Moglia C, Restagno G, Ossola I. *et al.* Amyotrophic lateral sclerosis-frontotemporal lobar dementia in 3 families with p.Ala382Thr TARDBP mutations. Arch Neurol. 2010;67:1002-9.

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