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Predictive value of preoperative statistical parametric mapping of regional glucose metabolism in mesial temporal lobe epilepsy with hippocampal sclerosis

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ABSTRACT

Objective: This study was designed to use statistical parametric mapping of interictal positron-emission tomography using [$_{18}$F]Fluorodeoxyglucose (FDG-PET) to compare the brain metabolisms of patients with mesial temporal lobe epilepsy (MTLE)/hippocampal sclerosis and controls. Another aim of this study was to analyze the potential differences among patients in terms of epilepsy duration, side of hippocampal sclerosis, histopathological findings, insult in their history, and postoperative outcomes.
Methods: We analyzed FDG-PET scans from 49 patients with MTLE/hippocampal sclerosis and 24 control subjects. We analyzed the differences in regional glucose metabolism between the patients and the control group and within the patient group using multiple variables.
Results: We observed widespread hypometabolism in the patient group in comparison with the control group in temporal and extratemporal areas on the epileptogenic side (ES). On the nonepileptogenic side (NES), we observed the most hypometabolism in the thalamus and the anterior and middle cingulate gyrus. In the group of patients with more severe hippocampal sclerosis, we observed statistically significant hypometabolism in the insula on the ES. In patients with poor postoperative outcomes, we found statistically significant hypometabolism in the insula on the ES and the temporal pole (TP) on the NES. Patients with any insult in their history showed hypermetabolism in the TP on both sides.
Conclusion: Our study showed that there are widespread changes in metabolism in patients with MTLE in comparison to controls, either inside or outside the temporal lobe. There are significant differences among these patients in terms of postoperative outcomes, degree of hippocampal sclerosis, and insults in their history.

1. Introduction

The value of Positron-emission tomography (PET) using [$_{18}$F]fluorodeoxyglucose (FDG-PET) in the presurgical evaluation of patients with mesial temporal lobe epilepsy (MTLE) associated with hippocampal sclerosis (HS) [MTLE/HS] is well established [1,2]. In some earlier papers, the visual analysis of PET was found to be reliable both in lateralizing the seizure onset zone and in predicting excellent postoperative outcomes in temporal lobe epilepsy (TLE) [3,4]. However, visual analysis is associated with large variability among investigators. For that reason, methods of quantitative PET analysis have been developed. The first approach is based on glucose metabolic rate calculations in predefined regions of interest (ROIs). These values are compared with the rates from the contralateral side homologous ROI or with the normalized metabolic values from a control group. The definition of the ROI, and its size, shape, and position varies among studies, making data comparison very difficult [2]. Voxel-based approaches such as statistical parametric mapping (SPM) [5] and the asymmetry index [6] do

Abbreviations: SPM, statistical parametric mapping; ES, epileptogenic side; NES, nonepileptogenic side; FDR, false discovery rate; MTLE, mesial temporal lobe epilepsy; TLE, temporal lobe epilepsy; HS, hippocampal sclerosis; TP, temporal pole; FCD, focal cortical dysplasia; ROI, region of interest.

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not depend on the selection of the ROI. The SPM method assesses the null hypothesis at each voxel with univariate statistics and constructs an image from its results. Statistical parametric mapping does not require a priori hypotheses about the location and extent of effects.

We conducted this study with interictal FDG-PET using SPM analysis in order to compare regional glucose between patients with MTLE/HS and a group of control subjects and to analyze the potential differences among patients in terms of epilepsy duration, side of HS, histopathological findings, insult in their history, and postoperative outcomes.

2. Methods

2.1. Case selection, demographics, and history data

We retrospectively reviewed all of the patients with histopathologically proven HS who underwent anterior-medial temporal lobe resection at the Brno Epilepsy Center between 2005 and 2011. The review included patients with a well-documented postoperative outcome for at least 3 years after the surgery and comprehensive results of the histopathological investigation. Patients with other pathologies including dual pathology on magnetic resonance imaging (MRI) and/or without a histopathological investigation were excluded from the study unless there was a finding of focal cortical dysplasia (FCD) of the pole of the resected temporal lobe, which was associated with HS. Clinical data included personal disease history, age at epilepsy onset, epilepsy duration, age at the time of the evaluation, and the postoperative outcome according to the International League Against Epilepsy (ILAE) classification [7].

2.2. Presurgical evaluation

The patients were epilepsy surgery candidates who underwent a comprehensive presurgical evaluation at the Brno Epilepsy Center. Magnetic resonance imaging scans were obtained using the Siemens 1.5 T MRI scanner. Video-EEG monitoring was performed on the 64-channel and 128-channel Alien Deymed systems. All patients had a neuropsychological evaluation targeting memory functions, and patients with language-dominant TLE underwent Wada testing in order to predict the postoperative memory outcome. If the noninvasive evaluations provided discordant data concerning the potential epileptogenic zone, invasive Electroencephalography (EEG) was performed. In all patients, functional neuroimaging techniques (FDG-PET) were performed; and in most patients, interictal/ictal Single-photon emission computed tomography (SPECT) were also performed. Standard anterior-medial temporal lobe resection was based on the results of a presurgical evaluation.

2.3. Histopathology

Standard histopathological examination of hippocampal and temporal pole (TP) resection specimens was performed on formalin-fixed paraffin-embedded tissues. For the grade of HS, the grading system by Wyler was used [8]. For FCD in the TP, the classification system reported by Palmini et al. [9] was used.

2.4. Patient population, surgery, outcome, and histopathology

We included 49 patients (27 female, 22 male) in the final analysis. The age of the patients at the time of the preoperative investigation ranged from 16 to 59 years with a median of 40 years. The active epilepsy duration ranged from 4 to 58 years with a median of 25 years. Of the 49 patients, 21 (42.9%) had some type of insult in their history (12 patients had encephalitis/meningoencephalitis, and 9 patients had febrile seizures). Of the 49 patients, 27 (55.1%) had left-sided (language-dominant) MTLE/HS, and 22 patients (44.9%) had right-sided (language-nondominant) MTLE/HS.

The time after surgery ranged from 2 to 7 years with a median of 4.5 years. At the last follow-up visit, according to the ILAE outcome classification [7], 31 out of 49 patients (63.3%) were classified as Outcome Group 1 (completely seizure-free since the surgery), 7 (14.3%) as Outcome Group 2 (only auras since the surgery), 6 (12.2%) as Outcome Group 3 (one to three seizure days per year), 3 (6.1%) as Outcome Group 4 (from 4 seizure days per year to 50% seizure reduction from baseline seizure days), and 2 (4.1%) as Outcome Group 5 (less than 50% seizure reduction from baseline seizure days).

Precise grading of HS (Wyler grading system) [8] was available for 34 patients. Of those 34 patients, 6 (17.6%) were classified as Wyler I/II (low-grade HS) and 28 (82.4%) as Wyler III/IV (high-grade HS). Patients classified as low-grade HS did not differ significantly from the patients classified as high-grade HS in terms of postoperative outcome (ILAE I + II in 55.5% of patients with low-grade HS and 67.6% in high-grade HS respectively; Fisher's exact test, $p = 1.0$). Histolopathological evaluations revealed FCD of type I a/b in the TP in 13 patients (26.5%) (type Ia in 8 patients and type Ib in 5 patients).

All patients signed informed consent forms. The study was approved by the local ethics committee.

2.5. Control group

For the control group, we selected 24 (13 female, 11 male) patients with FDG-PET images acquired within oncological screenings. The age of the control subjects at the time of imaging ranged from 16 to 54 years with a median of 34.5 years. The control subjects were without any findings on their MRI scans and without any neurological or psychiatric diagnoses. No disorder in the central nervous system was found, and no drugs influencing brain metabolism were taken by these control subjects. Their FDG-PET findings were assessed as normal.

2.6. FDG-PET image acquisition

[$_{18}$F]Fluorodeoxyglucose PET scans were available for SPM analysis in all 49 (27 female, 22 male) patients and in the 24 (13 female, 11 male) control subjects. Both patients and controls underwent the same procedure. Patients were imaged as outpatients in the interictal state. The PET images for both groups were acquired using a Siemens ECAT ACCEL PET scanner (three detection rings with lutetium orthosilicate type crystals and 16.2 cm axial field of view (FOV); Erlangen, Germany) in 3-D mode using the “Brain” protocol. The intrinsic spatial resolution of the scanner was 6.3 mm at full width at half maximum (FWHM) 1 cm from the center of the FOV, and 6.7 mm at FWHM 10 cm from the center of the FOV. Subjects prepared by fasting for 6 h before the scan and resting in a quiet, darkened room for 50–60 min after FDG administration. The dose of FDG administered was 200 MBq ± 15% per subject with no weight differentiation. The emission acquisition time in 3-D mode was 10 min. Forty-seven tomographic slices with a 3-mm slice thickness were reconstructed with a 128 × 128 iteration matrix with 6 iterations and 16 subsets, and a 6 mm FWHM Gaussian filter was applied.

2.7. Image preprocessing for SPM analysis

Spatial preprocessing and statistical analysis were performed using SPM8 (Wellcome Department of Cognitive Neurology, Institute of Neurology, University College London, U.K.) and MATLAB version 2011b (MathWorks Inc., Natick, MA, USA). All FDG-PET images, both patient and control scans, were spatially normalized into the standardized stereotactic Montreal Neurological Institute space using our in-house FDG-PET template. This template was created following instructions introduced by Soma et al. [10]. A three-dimensional isotropic Gaussian kernel with 8 mm FWHM was used for smoothing all spatially normalized images. To remove the effect of global metabolism, we used global normalization with a proportional scaling method [11].