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PET imaging in extratemporal epilepsy requires consideration of electroclinical findings

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ABSTRACT

Objective: The study aimed to assess the relevance of interictal temporal glucose hypometabolism in patients with extratemporal epilepsy (ETE) by analyzing its association with a seizure semiology suggestive for temporal seizure involvement and the presence of temporal interictal epileptiform discharges (IEDs).
Methods: We retrospectively reviewed the database of our epilepsy monitoring unit for patients with ETE, in whom long-term EEG-video-monitoring and [^{18}F] fluorodeoxyglucose positron emission tomography (FDG-PET) had been performed. The localization of IEDs and the glucose hypometabolism were compared.
Results: Almost half (46%) of the 63 ETE patients had IEDs localized in the temporal lobe. Most patients (87.5%; 7/8) with temporal IEDs and an ipsitemporal hypometabolism showed seizure semiology suggestive of temporal or limbic system involvement in contrast to only 31.0% (9/29, $p = 0.01$) in patients without temporal IEDs nor temporal hypometabolism. Those patients also showed an ictal seizure pattern spread into the ipsitemporal lobe, compared with 75.9% (22/29, n.s.) in patients without temporal IEDs nor temporal hypometabolism. Both, extratemporal (ipsilateral in 82.1%; 23/28 patients) and temporal (ipsilateral in 78.6%; 11/14 patients) hypometabolism significantly ($p < 0.05$) lateralized to the epileptogenic hemisphere.
Conclusion: The common temporal glucose hypometabolism in ETE patients reflects a remote epileptic dysfunction arising from extratemporal epileptogenic zones. Thus, interpretation of interictal FDG-PET results requires consideration of EEG results and seizure semiology to avoid false localization particularly in non-lesional epilepsy.

1. Introduction

It is well established that the interictal [^{18}F] fluorodeoxyglucose positron emission tomography (FDG-PET) has a high localizing significance in temporal lobe epilepsy (TLE) with a sensitivity of 86% (Casse et al., 2002; Gaillard et al., 1995; Knowlton et al., 1997; Rathore et al., 2014; Ryvlin et al., 1998). False PET lateralization seems to occur in only one to 3% of the medically refractory TLE patients (Sperling et al., 1995). However, in extratemporal epilepsy (ETE) only 67% show a hypometabolic area matching the extratemporal seizure onset zone and hypometabolism tends to be more widespread commonly involving temporal regions (Casse et al., 2002; Engel, 1991; Salanova et al., 1993; Swartz et al., 1995; Theodore et al., 1983). Results of resective epilepsy surgery, though, depend on the exact localization of the epileptogenic zone, which is typically based on the results of EEG-video monitoring with structural (high-resolution magnetic resonance imaging, MRI), and functional imaging (PET; single-photon emission computed tomography, SPECT, with MRI coregistration, SISCOM analysis) (Engel, 1999; Widdess-Walsh et al., 2007). Functional imaging techniques

Abbreviations: EEG, electroencephalography; ETE, extratemporal epilepsy; IED, interictal epileptiform discharge; FDG-PET, [^{18}F] fluorodeoxyglucose PET; MRI, magnetic resonance imaging; TLE, temporal lobe epilepsy; SISCOM, substraction ictal SPECT co-registered to MRI.

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such as FDG-PET are particularly important in non-lesional ETE patients.

In TLE patients, there are some hints that frequent interictal epileptiform discharges (IEDs) alter the metabolism of the surrounding tissue (Valentín et al., 2014), but this effect was not yet systematically analyzed for ETE. To better assess its diagnostic relevance, we investigated whether a temporal hypometabolism in interictal FDG-PET examinations is associated with temporal IEDs and seizure semiology characteristic for spread of epileptic activity into temporal regions in ETE.

2. Materials and methods

This study complies with the institutional review board-approved ethical guidelines of the University of Munich and all patients had given written informed consent to the scientific use of their clinically acquired, anonymized data.

2.1. Participants

Patients with ETE were identified from the data base of the epilepsy monitoring unit at the University of Munich. Only ETE patients with available ictal and interictal EEG, as well as FDG-PET data were included in the study. Concerning functional imaging, ictal SPECT had higher priority in our center. Thus, FDG-PET was only performed when the ictal tracer injection could not be performed during EEG-video monitoring.

2.2. Video-EEG-monitoring

All patients underwent a standardized presurgical evaluation between 1996 and 2014, including continuous long-term EEG-video-monitoring with closely spaced surface electrodes using the international 10-20 system of electrode placement and additional 10-10 electrodes according to the guidelines of the American Electroencephalographic Society. In case a temporal lobe pathology was expected, additional sphenoidal electrodes were used. EEG was recorded with 32-64 channel EEG machines (Vanguard, Cleveland/Ohio, USA; XLTEK, London/Ontario, Canada) with a sampling rate of 200–256 Hz and 12–16 bit A-D conversion. Syndrome classification and localization of the extratemporal epileptogenic zone was defined by consensus of two German EEG board certified epileptologists, based on available clinical, EEG, MRI and nuclear medicine data (SPECT with SISCOM analysis, FDG-PET). In nine non-lesional epilepsy patients syndrome classification was based on the result of invasive EEG-monitoring. The EEG data were classified into ictal and interictal discharges according to a system described in detail elsewhere (Lüders and Noachtar, 2000; Noachtar and Rémi, 2016). Interictal activity was defined temporal if the maximum amplitude of epileptiform discharges was recorded in electrodes SP1/2, FT7/8, FT9/10, T7/8, TP7/8 and/or P7/8 and appearing in a temporal independent manner (>100 ms) from IEDs in extratemporal areas. The FDG-PET result was compared to the long-term interictal EEG recorded during EEG-video-monitoring instead to the simultaneously recorded EEG, because the latter is usually artifact obscured and reflects only a short period (30 min) of the interictal activity. Simultaneously recorded EEG was used to detect subclinical seizure patterns. A temporal IED spike frequency >10/min during PET-EEG was excluded, as frequent spiking could elevate regional glucose utilization and mask a possible temporal glucose hypometabolism.

2.3. FDG-PET

Interictal [^{18}F] fluorodeoxyglucose PET (FDG-PET) was performed using a Siemens ECAT EXACT HR scanner (Siemens, Erlangen, Germany). The scanner acquires 63 contiguous transaxial planes, simultaneously covering 15.5 cm of axial field of view. The transaxial and axial resolutions (full width at half maximum) of the PET system were 4.6 mm and 4.0 mm, respectively, at the center and 4.8 mm and 5.4 mm, respectively, at a radial offset of 10 cm. All subjects were scanned in a fasting state following a standardized protocol. Continuous EEG recording was performed during the whole PET examination to ensure interictal state at the time of tracer injection and to exclude subclinical seizure activity during tracer uptake. FDG (124 ± 29 MBq) was injected intravenously as a bolus while patients lay supine with their eyes closed in dimmed ambient light without any artificial stimulation. Data acquisition started with a transmission scan obtained with a rotating [^{68}GE] point source, used for subsequent attenuation correction. The emission recording started 30 min after injection and consisted of a series of three 10-min frames (128×128 matrix, 3D acquisition), which were later combined to a single frame to comprise the entire 30-min acquisition.

Images were reconstructed by filtered backprojection using a Hann filter with a cutoff Nyquist frequency of 0.5 and corrected for scatter and attenuation. The images were realigned and stereotactically normalized into the standard anatomical space of Talairach and Tournoux by means of linear and nonlinear transformation. Datasets were then blurred with a three-dimensional Gaussian filter in order to increase the signal-to-noise ratio. Furthermore z-score maps were calculated using Neurostat (Minoshima et al., 1995).

The observers were blinded to the medical history. Visual analysis of the PET data, coregistered and superimposed on the individual MRI, was performed by two board certified nuclear medicine physicians using standard axial, sagittal and coronal views in order to exclude other causes of hypometabolism, e.g. due to resection or ischemia. Then the z-score maps were analyzed in the temporal as well as extratemporal brain regions, where a threshold of two standard deviations was defined as pathological, compared with normal control subjects (Drzezga et al., 1999; Ferrie et al., 1997). Thereby, standardized 3D stereotactic surface projections (SSPs) of z score images were generated after pixelwise comparison of the individual dataset with a normal database. For this study the results of the software-based evaluation were used.

2.4. Statistical analysis

Data were expressed as means ± standard deviation or medians. Fisher's exact test was used for categorical testing. A p-value < 0.05 was considered significant. All statistical analyses were performed using Microsoft Office Excel 2007 version 12.0 for Mac (Microsoft Office Corporation, Redmond, Washington).

3. Results

In total, 63 patients (31 females, 32 males; 30.11 ± 12.21 years of age at monitoring) with ETE were included in the study (Fig. 1). Mean disease duration was 14.70 ± 12.02 years. One patient has undergone a left parieto-occipital tumor resection before monitoring and two had prior biopsy. Sixty patients did not have prior brain surgery. All patients underwent long-term EEG-video-monitoring (6.98 ± 3.93 days) with surface EEG recording. Additional sphenoidal electrodes were used in 50 (79.4%) patients. Median latency between FDG-PET and EEG-video-monitoring was 37 days.

IEDs were recorded in 84.1% (53/63) of all ETE patients. Almost half (29 patients, 46%) of the 63 ETE patients had IEDs localized in the temporal lobe. In ten of those patients (10/29; 15.9%), the IEDs were localized exclusively in the temporal regions with bitemporal IEDs in 6/10 patients.