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The predictive value of hypometabolism in focal epilepsy: a prospective study in surgical candidates

José Tomás, MD^{1,2}, Francesca Pittau, MD, PhD^{1,3}, Alexander Hammers, MD, PhD^{4,5}, Sandrine Bouvard, PhD⁶, Fabienne Picard, MD^{1,3}, Maria Isabel Vargas, MD^{3,7}, Francisco Sales, MD², Margitta Seeck, MD, PhD^{1,3*}, Valentina Garibotto, MD, PhD^{3,8*}

*these authors contributed equally to this work

1 - EEG and Epilepsy Unit, Neurology Department, University Hospitals of Geneva, Geneva, Switzerland

2 - Neurology Department, Coimbra Hospital and University Centre, Coimbra, Portugal

3 - Faculty of Medicine of Geneva University, Geneva, Switzerland

4 - The Neurodis Foundation, CERMEP Imagerie du Vivant, Lyon, France

5 - King's College London & Guy's and St Thomas' PET Centre, King's College London, Division of Imaging Sciences and Biomedical Engineering, London, UK

6 - Translational and Integrative Group in Epilepsy Research, Lyon Neuroscience Research Center, INSERM - U1028, CNRS - UMR5292, University Claude Bernard Lyon 1, Lyon, France

7 - Neuroradiology Division, Diagnostic Department, University Hospitals of Geneva, Geneva, Switzerland

8 - Nuclear Medicine and Molecular Imaging Division, Diagnostic Department, University Hospitals of Geneva, Geneva, Switzerland

Corresponding author

Valentina Garibotto, MD, PhD

Division of Nuclear Medicine and Molecular Imaging, Geneva University Hospitals

Rue Gabrielle-Perret-Gentil 4

1205 Geneva, Switzerland

valentina.garibotto@hcuge.ch

Phone +41 79 5534459 - Fax +41 22 372 7169

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ABSTRACT

Purpose: FDG-PET is an established tool in presurgical epilepsy evaluation, however, it is most often used selectively in patients with discordant MRI and EEG results. Interpretation is complicated by the presence of multiple or remote hypometabolism, which casts doubt on the true localization of the seizure onset zone (SOZ) and might have a predictive value for surgical outcome. In the current study, we determined the sensitivity and specificity of PET localization prospectively in a consecutive unselected cohort of patients with focal epilepsy undergoing in-depth presurgical evaluation.

Methods: 130 patients between 2006 and 2015 matched our inclusion criteria, of which 86 were operated (72% with favorable surgical outcome, Engel class I). We determined areas of focal hypometabolism using statistical parametric mapping and evaluated concordance with MRI, EEG or intracranial EEG. In the operated patient group, we used postsurgical outcome as gold standard for correctness of localization (minimum follow-up of 12 months).

Results: PET sensitivity and specificity were both 95% in temporal lobe epilepsy (TLE; N=86) and 80% and 95% in extratemporal epilepsy (ETLE; N=44), respectively. Significant extratemporal hypometabolism was observed in 17 TLE cases (20%). Among patients with ETLE (n=44), temporal hypometabolism was observed in eight patients (18%).

Among operated patients (N=86), 26 (30%) had hypometabolism extending beyond the SOZ. The presence of unilobar hypometabolism, included in the resection, was predictive of complete seizure control ($p=0.007$), with an odds ratio of 5.4.

Conclusions: In this group of non-selected patients with focal epilepsy, additional hypometabolic areas can be found in one out of five patients, including cases with “simple” lesional epilepsy, and should prompt further in-depth evaluation of the correlation between EEG-findings, semiology and PET. Hypometabolism confined to the epileptogenic zone as defined by EEG and MRI is associated to favorable post-operative outcome in both TLE and ETLE.

Abbreviations – FDG – 18F-fluorodeoxyglucose; PET – positron emission tomography; MRI – magnetic resonance imaging; TLE – temporal lobe epilepsy; ETLE – extratemporal lobe epilepsy; EEG – electroencephalogram; SOZ – seizure onset zone; HC – healthy control group; SPM – statistical parametric mapping

INTRODUCTION

Epilepsy is one of the most frequent chronic neurological disorders, with an estimated prevalence in the general population of 6.38 per 1,000 persons [1]. Approximately one-third of the patients are drug-resistant, and in these cases, surgery is the only treatment that offers the possibility of a cure. Localizing the epileptogenic zone in presurgical patients requires a dedicated protocol of electrophysiological, structural and functional examinations, which often includes positron emission tomography (PET) imaging [2]. [^{18}F]fluorodeoxyglucose-PET (FDG-PET) using positron-emitting isotopes is usually performed as an interictal study. FDG-PET contributes to the definition of the functional deficit zone [3] by revealing the area of reduced glucose metabolism. This zone can be larger than the epileptogenic cortex and can extend to remote areas [3, 4]. For example, in patients with a presumed seizure onset zone (SOZ) limited to the mesial temporal lobe due to hippocampal sclerosis, the hypometabolism often involves the whole temporal lobe and extends even beyond [5-7]. Localization of the epileptogenic zone with PET is obtained in up to 90% of patients with temporal lobe epilepsy (TLE) and in up to 60% of patients with extratemporal lobe epilepsy (ETLE) [8].

FDG-PET is particularly useful in TLE without Magnetic Resonance Imaging (MRI) abnormalities: patients with PET hypometabolism concordant with EEG findings benefit from surgery as much as patients with hippocampal sclerosis identified on MRI.[9, 10] In patients with ETLE, FDG-PET has been used as a guide in the search for subtle cortical dysplasia or to inform on the placement of intracranial electrodes [11].

However, FDG-PET can be misleading, as in some patients with ETLE, the hypometabolism is more prominently seen in the temporal lobe [8]. The factors previously reported as being associated with poorer prognosis were both hypometabolism remote from the epileptogenic zone [12] and a less severe hypometabolism of the epileptogenic zone [13]. However, most studies use PET in only selected cases, e.g. with negative MRI; therefore, the presence of remote hypometabolic areas could be due to the complexity of the case or lack of knowledge of EEG on seizure status before or during tracer injection.

The present study has two main aims:

1. To assess the occurrence of a hypometabolism confined to the lobe of the SOZ versus those providing ambiguous results, i.e. extending to other adjacent lobes, seen only in remote structures, or which were incorrectly normal.
2. To evaluate the predictive value of the hypometabolic pattern observed, including a subset of patients treated surgically with follow up for at least 12 months.

Since all our patients received PET as part of the standard presurgical work-up, our series presents a unique opportunity to determine the yield of PET in drug-resistant epilepsy with TLE or ETLE in an unselected patient group.

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MATERIALS AND METHODS

Data collection – subjects

This study was based on a prospectively collected database at a single institution, including a total of 346 consecutive patients attending our epilepsy unit and undergoing PET scan imaging between 2006 and 2015. Informed consent was obtained from all individual participants included in the study and also from legally authorized representatives when minors were concerned. This study was approved by the Geneva Cantonal Ethical Commission, in agreement with the Declaration of Helsinki and its further amendments.

We selected patients matching the following criteria:

- Inclusion criteria: (i) > 6 years of age. Younger children have a more extended diffuse hypometabolism, which could lead to false positive findings; [14, 15] (ii) pharmacoresistant (persistence of seizures after at least two antiepileptic drugs, used at the maximal tolerated doses) and unifocal epilepsy based on the clinical history, semiology and laboratory tests mentioned below; (iii) pre-surgical evaluation consisting of at least MRI, FDG-PET and long-term video-EEG recording; (iv) PET scan acquired with a standardized protocol on a Siemens Biograph PET/CT tomograph (in our hospital since January 2006); (v) patients with no previous brain surgery.
- Exclusion criteria: multilobar lesions visible on MRI, generalized or multifocal epilepsy, post-traumatic epilepsy, and progressive tumor, seizures 24 h before the tracer injection as determined by continuous monitoring before, during and after tracer injection. [16].

A total of 130 patients (86 with TLE, 44 with ETLE) matched our criteria and were included in the present analysis (Fig. 1). 216 patients were excluded for the following reasons: not meeting inclusion criteria (n=48) or having exclusion criteria that could be associated with false positive findings, namely multilobar lesions visible on MRI, including hippocampal sclerosis (HS) in ETLE, generalized or multifocal non-lesional epilepsy, post-traumatic epilepsy, and progressive tumor and seizures within 24 h before the tracer injection (n=109) or having incomplete data (n=59).

Definition of hypometabolism

All PET images were analyzed visually by one expert reader (VG) who was not aware of the supposed localization of the epileptogenic zone based on clinical, EEG and MRI findings. All images were re-analyzed after co-registration of the PET to the patient's individual MRI (on a LEONARDO 3D reconstruction station, Siemens

Healthineers). Statistical parametric mapping (SPM8) was performed by comparing each individual PET image with a reference set of brain PET scans from 38 young healthy controls (38 subjects; 20 males, mean age 35 years, range 18-53) obtained from the CERMEP (Lyon) (© Copyright CERMEP and the authors, 2014. All rights reserved) to identify areas with significantly reduced glucose metabolism, as previously described [17] and detailed in the statistical analysis section below. The PET images of the controls were acquired on a ECAT EXACT HR+ scanner, which has physical properties comparable to those of the Siemens Biograph scanner used for patients [18].

EEG recordings

Conventional long-term video-EEG recording was performed on all patients with standard clinical EEG setups of 31-37 electrodes (10/10 system). The placement of additional inferior longitudinal temporal electrodes was extremely important because of their selectivity to temporal lobe activity. Impedances were kept below 10 k Ω , the sampling rate was 256 Hz and band-pass filters were set to 0.1 and 120 Hz, with a vertex contact as the reference electrode. Patients were recorded 24 h before tracer injection and included in the current analysis if no clinical or subclinical seizures occurred during EEG monitoring, which comprised also the uptake of the tracer.

Magnetic resonance imaging

All patients had MRI scans as part of the pre-surgical evaluation. The scans were acquired with a 3T Trio scanner (Siemens AG, Germany) and were performed according to a standardized epilepsy protocol [19] using a 32-channel brain coil: (a) axial T2-weighted fast spin-echo repetition time (TR) 7520 ms; echo time (TE) 114 ms; voxel size 0.5 x 0.4 x 3 mm (slice thickness); (b) 3D FLAIR (fluid-attenuated inversion recovery) TR 5000; TE 419 ms; inversion time (TI) 1800; isotropic voxel size 0.9 x 0.9 x 0.9 mm); (c) 3D gradient echo T1 or T2, TR 1750 ms; TE 2.29 ms; isotropic voxel size 0.7 x 0.7 x 0.7 mm; (d) diffusion-weighted imaging (DWI) TR 8000 ms; TE 84 ms; 30 directions; (e) and axial arterial spin labelling (ASL) TR 4000 ms; TE 12 ms; voxel size 3.4 x 3.4 x 4 mm (slice thickness). 3D images were analyzed in axial, coronal and sagittal planes. In 101/130 patients, the structural MRI showed a pathological result, indicating an epileptogenic lesion, specifically HS in 45 TLE subjects; the other 29/130 patients had normal MRI findings (12 with a final diagnosis of TLE).

Positron emission tomography acquisition

FDG-PET was performed using 2- ^{18}F fluoro-2-deoxy-d-glucose in all patients in the interictal phase (at least 24 hours after the last seizure). Patients, having fasted at least 6 hours, received an injection of 200 MBq or a weight-adapted dose in children, according to the EANM pediatric card (http://www.eanm.org/content-eanm/uploads/2017/01/EANM_Dosage_Card_040214.pdf) of ^{18}F FDG, while resting in a quiet and dimly lit room. In all patients, the EEG was continuously monitored during the thirty minutes uptake time to exclude subclinical seizures, leading potentially to false negative or positive findings. PET images were acquired on tomographs equipped with lutetium oxyorthosilicate (LSO) crystals, namely the Siemens Biograph Hi-Rez, TruePoint or mCT PET/CT systems, in 3D mode. Scan duration was twenty minutes.

Temporal lobe epilepsy and extratemporal lobe epilepsy

Localization of the epileptogenic zone was based on anatomo-electro-clinical correlations (i.e., correlations between ictal semiology, electro-physiological activity, and structural lesion) [20] by a neurologist (FP) blinded to the results of the PET examination. TLE was defined as having a focus in the mesial temporal lobe and/or temporal pole. The remainder of cases were identified as ETLE, including lateral and posterior temporal, parietal, occipital and frontal lobe epilepsy.

Surgery

All cases were discussed in our weekly interdisciplinary case conference. A total of 86 of the 130 (66%) patients underwent temporal or extratemporal surgical intervention, while 44 were not operated upon for different reasons: epileptic focus in eloquent areas with unclear cost-benefit from a respective surgery (30), severe psychiatric comorbidities interfering with the patient's decision making (10), or refusal of surgery on the part of the patient after considering the risks (4).

Performance of PET as a test

The epileptogenic zone was defined on the concordance of clinical information (semiology), EEG and MRI findings. Intracranial EEG was performed in 29 patients (22% of the total sample; X operated) and was considered for the present analysis. Out of the 29 patients with intracranial EEG, 14 were implanted with depth electrodes only, two were implanted with subdural electrodes only, and 12 were implanted with both depth and subdural electrodes. Twenty had bilateral explorations, while the explorations were limited to one hemisphere in nine patients.

Using standardized PET analysis with SPM, as described above, the degree of concordance of the PET results with the presumed SOZ was described as follows:

- Concordant (C): if the hypometabolism is concordant and confined to the lobe of the presumed SOZ;
- Concordant Plus (C+): if the hypometabolism extends from the epileptogenic zone to adjacent lobes;
- Multifocal (M): if multiple clusters of hypometabolism in non-adjacent lobes exist;
- Remote (R): if the hypometabolism is located outside the presumed SOZ lobe;
- Normal (N): no significant hypometabolism, either at the presumed SOZ or at elsewhere.

Examples for the different categories TLE and ETLE patients are shown in Fig. 2.

Analyses were performed by dichotomizing between category C and the remaining categories.

Seizure outcome after epilepsy surgery

All 86 operated patients were seen postoperatively by the neurosurgeon and neurologist or neuropsychiatrist. The mean follow-up period was 30.5 $\pm$ 22.9 months (range 12-108 months). Seizure outcomes were classified according to the classification proposed by Engel: Class I: free of disabling seizures (specifically including patients who were seizure free after surgery –Ia–, with nondisabling simple partial seizures only since surgery –Ib–, with some disabling seizures after surgery, but free of disabling seizures for at least 2 years –Ic–, and patients with generalized convulsions with anti-epileptic drug discontinuation only –Id–); Class II: rare disabling seizures ("almost seizure-free"), i.e., seizure decrease of > 90%; Class III: worthwhile improvement (seizure decrease of 50-90%); Class IV: no worthwhile improvement (< 50% decrease). In the present study, patients free of disabling seizures (Engel class I) were compared to all other patients (Engel class II-IV). [21]

Statistical analysis

PET images were processed using Statistical Parametric Mapping (Wellcome Department of Cognitive Neurology, London, UK, version 8 – SPM8). After normalization to the CERMEP FDG-PET template (© Copyright CERMEP and the authors, 2014. All rights reserved), with an isotropic voxel size of 2 mm and smoothing (8 mm), individual patients were compared to controls in a 2-sample t test using proportional scaling to global activity and age as covariate. The resulting statistical parametric map was thresholded at $p < 0.01$ (uncorrected), and a minimum cluster extent of 40 voxels was considered, taking into account only true hypometabolic clusters, i.e., abnormalities with cortical locations and concordant with subsequent visual analysis of fused PET/MRI data [17].

Hypometabolic clusters were described quantitatively by their size (number of voxels above the threshold) and severity (highest Z score in the cluster).

We also correlated cluster size and severity of hypometabolism with different clinical variables using Spearman's correlation.

A logistic regression analysis was used to predict the presence of a favorable (Engel class I) outcome, including the type of epilepsy (TLE and ETLE) and the type of hypometabolism (C vs. others) as variables in the analysis.

We also tested the benefits of gender, age at onset, age at PET and lesional epilepsy as predictors.

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RESULTS

The main characteristics and the demographic data of the 130 patients (66 female) are displayed in Table 1. The mean age of the patient group was 27.4 ± 13.5 years (range 6-60), the mean duration of epilepsy was 15.0 ± 11.5 years (range 0-53), and the age of onset was 12.8 ± 10.5 years (range 0-46).

Among lesional epilepsy, the lesions consisted in hippocampal sclerosis (45 cases), cortical dysplasia (34, of which 25 operated, including 15 FCD type II, 3 FCD type I, 3 cases with cortical dysplasia not otherwise specified and 4 with mild malformations of cortical development), non-progressive tumors (14, of which 10 operated including 6 dysembryoplastic neuroepithelial tumor, 2 oligodendrogliomas WHO grade II and 2 gangliogliomas WHO grade I), polymicrogyria (1), hemimegalencephaly (1), post-traumatic (2), vascular lesions (3) and post-infectious lesions (1).

Localizing value of PET

In TLE patients, including operated and non-operated patients, both the sensitivity and specificity of interictal PET were 95%. For ETLE patients, the sensitivity was 80%, and the specificity was 95%. Table 2 shows the distribution of metabolic patterns among TLE (with and without HS) and ETLE patients. Hypometabolism only at remote sites (metabolic pattern R) was found in only one patient with TLE and ETLE each (1.5%; one lesional left temporal epilepsy with right frontal hypometabolism only, one case with non-lesional right frontal epilepsy but bilateral temporal hypometabolism), i.e., this constellation is rarely observed. Entirely normal PET, i.e., without any hypometabolism, was found in 3/86 (3%) of TLE and 8/44 (18%) of ETLE patients ($p=0.007$) and in 5/101 (5%) of patients with lesional and 6/29 (21%) of patients with non-lesional epilepsy ($p=0.015$).

There were no significant differences in the distribution of “metabolic patterns”, namely C, C+, M, R and N, between ETLE and TLE, nor between TLE patients with and without HS ($p=0.08$ and $p=0.31$).

The analysis of the different hypometabolic regions in TLE patients showed that five patients had extratemporal hypometabolism in more than one area ($n=22$ hypometabolic foci in total). These were noted in frontal, insular, parietal/temporal posterior and occipital cortex. Overall, remote hypometabolism was more frequent in the frontal lobe (12/22; 55%) and ipsilateral to the side of the temporal focus (18/22 - 82%; an example is provided in Fig. 2). Among patients with HS, we observed additional hypometabolism outside the SOZ lobe in 14 out of 45 patients with HS, most commonly consisting in contralateral temporal hypometabolism (7 subjects).

In ETLE, additional temporal hypometabolism was observed in 8/44 of the patients (18%), 5/8 (62%) ipsilateral and 3/8 (38%) bilateral. Temporal hypometabolism was associated with frontal epilepsy in three cases (one bilateral), with parietal epilepsy in two cases (one bilateral), and occipital epilepsy in three cases (one bilateral, Fig. 2).

No differences in age of onset, age at evaluation and duration were found between C patients and the other hypometabolism categories in the TLE and ETLE groups. There was no significant difference between TLE and ETLE groups regarding the cluster size of the hypometabolism corresponding to SOZ versus those which showed hypometabolism beyond SOZ ($p=0.245$).

Predictive value of PET in operated patients

A total of 86 patients were operated (62 with TLE, 24 with ETLE), allowing to determine the predictive value on postoperative outcome. The patient numbers who post-surgically achieved freedom from disabling seizures were 53/62 (85%) among operated TLE patients and 19/24 (79%) among operated ETLE patients ($p=0.477$).

When considering only operated patients, the hypometabolic patterns among TLE patients were distributed as follows: 43 C (69%), 7 C+ (11%), 11 M (18%) and 1 R (2%). Extratemporal hypometabolic areas (16) were most frequently observed in the ipsilateral frontal lobe (7, 44%).

Among ETLE, there were 16 C (67%), 1 C+ (4%), 5 M (21%) and 2 N (8%). The extra-SOZ hypometabolic sites (8) were most frequently seen in the ipsilateral temporal anterior region (5; 62%). There were no significant differences between the frequency of fully concordant or other hypometabolism between the TLE and ETLE groups.

The presence of unifocal hypometabolism limited to the epileptogenic zone (C) had a favorable predictive value compared to the remaining groups ($p=0.007$), with a high odds ratio of 5.4 (95% confidence interval – CI - 1.6 – 18.3), i.e. 6.2 for TLE and 4.2 for ETLE when analyzing both groups separately. The distribution of metabolic patterns and post-operative outcome is summarized in Table 3. The odds ratio estimate was unchanged (5.4; 95% CI 1.5-19.3) when including gender, age at onset, age at PET and lesional vs. non-lesional epilepsy in the model.

DISCUSSION

The results of our prospective study show, in a large consecutive cohort, two main findings: a) hypometabolism beyond the presumed SOZ is not rare and occurs with a similar frequency in both TLE and ETLE surgical candidates, b) hypometabolism outside the SOZ contains a significant predictive value regarding surgical outcome.

Localizing value of PET abnormalities

In the literature, localizing information ranged from 60 to 90% in the patients with TLE and from 30 to 60% in the patients with ETLE [8, 22-29]. Additional areas of hypometabolism are frequently reported and seen in 10-43 % of the subjects. However, these studies applied PET in selected patient groups, so the true frequency of additional hypometabolic foci and non-concordant findings were not known.

In our study of non-selected patients, we observed temporal hypometabolism in 18% of ETLE subjects and extratemporal hypometabolism, mostly in the ipsilateral frontal lobe, in 20% of TLE patients [30-32]. This is at the lower end of the frequency of non-localizing findings previously reported, ranging from 20% to 67% [8, 30]. Apart from the selection criteria, the studies differed in analysis tools and patient populations (e.g. number of children or ETLE patients). We like to stress that in contrast to the present observation, many previous studies did not offer EEG monitoring before and during cerebral tracer absorption [15, 24, 27], thus the presence of subclinical seizures is unknown and could have added to the variability of findings.

The occurrence of additional and remote abnormalities in focal epilepsy represents a diagnostic dilemma, which occurs in 1 out of 5 patients approximately. This calls for meticulous comparison of the site of PET abnormality with the semiology, structural anomalies, ictal, interictal EEG findings. It is of note that even in “simple” lesional focal epilepsy, 5/130, i.e. 4%, have an entirely normal PET.

The precise relationship between SOZ and PET hypometabolism was studied in patients with intracranial electrodes and suggests a complex association. Two studies in pediatric patients undergoing subdural EEG monitoring showed that the ictal onset electrodes were located over the most hypometabolic area as well as over adjacent regions within 2 to 3 cm. However, a large proportion of hypometabolic regions had no early seizure involvement [33, 34]. A previous study in cavernous angioma suggested deafferentation as a possible mechanism [35].

Predictive value of remote metabolic abnormalities on surgical outcome

Our number of patients without seizures post-operatively compares favorably with the numbers in the literature [36, 37].

In our series, the pattern of hypometabolism carried predictive information with respect to surgical outcome, in agreement with the majority of the studies available in the literature, which are summarized in Table 4. Overall, the majority of studies in TLE concordantly showed that PET patterns carry a predictive information, with a more severe hypometabolism in the SOZ and the absence of extra-SOZ hypometabolism associated with a better prognosis [13, 25, 30, 38-43]. In ETLE the results are instead discordant, with four studies showing a significant predictive value for a positive PET [12, 26, 44, 45] and two studies failing to show such a predictive value [46, 47].

In our data we found that hypometabolism confined to the lobe of the SOZ (C), assessed with a combined visual and semiquantitative approach, was a significant predictor of seizure-free postoperative outcome in both TLE and ETLE. Importantly, in our series, gender, age at onset, age at PET and the presence of a lesion at MRI had no additional predictive value.

Possible explanations for a worse outcome if remote and non-concordant hypometabolism are present, could relate to diffuse seizure spreading or incorrect presurgical localization of the resected region. Fast propagation to other areas, as determined by EEG, usually indicates a more pathological and widespread network, with lower chances to benefit from surgery. This might be due to the type of pre-existing epilepsy or a consequence of long-standing epilepsy. Additional areas of hypometabolism then might reflect these constitutional or acquired conditions. We are not aware of prospective studies using follow-up PETs in patients with chronic epilepsy to distinguish between these two conditions. Alternatively, the additional or remote hypometabolism represents the true focus, despite its smaller size, and harbors subtle structural anomalies. Independent of the underlying pathophysiological mechanism, our results suggest that incongruent findings between the PET localization and SOZ as determined by EEG and semiology should be considered as “red flags”. They call for further investigations, if there is no epileptogenic MRI-lesion with concordant semiology, including electric source localization, ictal SPECT or intracranial EEG.

Non-FDG PET tracers as predictors of surgical outcome

Besides FDG-PET, other tracers have been tested, mainly in research settings, in the presurgical evaluation of epilepsy, targeting other pathophysiologic and neurotransmission pathways, for example GABA-ergic, glutamatergic, serotonergic and dopaminergic neurotransmission or neuroinflammation, as recently reviewed [48, 49]. Only a minority of studies, however, tested specifically the predictive value of these tracers for surgical outcome, mainly in TLE. An association was found between worse post-operative outcome and periventricular white matter increase of [11C]flumazenil-PET binding, a GABA-A targeting radioligand, in patients with TLE and hippocampal sclerosis, possibly due to the presence of an increased concentration of heterotopic neurons [50, 51]. The probability of being seizure-free in TLE has also been associated with reduced serotonin 1A receptor density, as measured with 18F-FCWAY, and reduced metabotropic glutamate receptor type 5 density, as measured with 11C-ABP688 [52, 53]. A study with 11C-alpha-methyl-tryptophan, a tracer of serotonin synthesis which helps identifying epileptogenic tubers in patients with tuberous sclerosis, showed that the resection of tubers with a higher uptake was a good predictor of surgical outcome [52, 54]. Finally, one study investigated the expression of P-glycoprotein, which can be associated with drug-resistant epilepsy, by the tracer [11C]verapamil: an optimal post-surgical outcome was associated with higher Pgp function before surgery and larger Pgp reduction postoperatively [55].

CONCLUSION

Extratemporal hypometabolism in TLE and temporal hypometabolism in ETLE occurred in about 18-20% of the cases, i.e. 1 in 5 patients, and were more frequently observed in the same hemisphere (82% for ipsilateral extratemporal hypometabolism in TLE; 73% for ipsilateral temporal hypometabolism in ETLE). These abnormalities are not only diagnostically challenging but also have negative predictive meaning in TLE and ETLE, as they are associated with a greater risk of post-surgical disabling seizures. Our prospective study confirms previous retrospective observations in TLE and ETLE suggesting that careful analysis of the metabolic pattern, also beyond the presumed SOZ, has predictive value, even in “simple” lesional cases.

AUTHOR CONTRIBUTIONS

JT, MS and VG contributed to the concept and study design. MS and F Picard were responsible for the patient management. JT, F. Pittau, F. Picard, MIV, MS and VG contributed to the data acquisition and analysis. JT and VG drafted the manuscript, tables and figures. F. Pittau, AH, SB, F. Picard, MIV, FS and MS contributed to the critical revision of the manuscript. All authors approved the final version.

POTENTIAL CONFLICTS OF INTERESTS

None of the authors has any conflict of interest to disclose.

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Figure legends

Fig. 1

Flow diagram of patient enrolment.

Fig. 2

Individual examples of metabolic patterns identified in temporal lobe epilepsy (TLE) and extratemporal lobe epilepsy (ETLE) study participants (colour bars indicate T values, individual maps are thresholded at $p < 0.01$, $k > 40$). The figure reports the presumed SOZ localization and the surgical outcome for operated patients.

	Concordant (C)	Concordant plus (C+)	Multifocal (M)	Remote (R)
TLE
SOZ	R TLE without HS	R TLE without HS	R TLE with HS	R TLE with HS
Outcome	Ia	IIB	IIa	Ia
ETLE
SOZ	L occipital	R frontal	R occipital	R frontal
Outcome	Ia	IIB	Not operated	Not operated

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Table 1. Demographic data of healthy controls (HC) and patients with temporal (TLE) and extratemporal lobe epilepsy (ETLE). ETLE patients were classified as frontal (n=28), parietal (n=7), occipital (n=3), multilobar (n=4) and others with remaining extratemporal focus (n=2).

	HC (n=38)	TLE (n=86)	ETLE (n=44)	TLE vs. ETLE (p)
Female, n (%)	18 (47%)	45 (52%)	21 (48%)	0.712
Age at evaluation, mean±sd (years)	35.2 ± 10.2	29.1±12.8	25.2±14.5	0.06
Age of onset, mean±sd (years)	-	14.6±10.4	9.3±9.7	0.001
Lesional*, n (%)	-	74 (86%)	27 (61%)	0.001
Underwent presurgical invasive evaluation, n (%)	-	22 (26%)	8 (18%)	0.387
Underwent surgery with curative intent, n (%)	-	62 (72%)	24 (55%)	0.045
Post-surgical outcome, Engel Class, n (I/II-IV)	-	53 (85%) / 9 (15%)	19 (79%) / 5 (21%)	0.522
Follow-up duration, mean±sd (months)	-	32±24.4	26.4±18.6	0.351

Abbreviations: HC, healthy controls; TLE, temporal lobe epilepsy; ETLE, extratemporal lobe epilepsy; *HS was present in 45 TLE, and in none of the ETLE, as the presence of HS in ETLE was considered an exclusion criterion, as specified in the Methods.

Table 2. Metabolic patterns in TLE and ETLE patients.

	C	C+	M	R	N
TLE	55 (64%)	11 (13%)	16 (19%)	1 (1%)	3 (3%)
TLE <i>with HS, n=45</i>	31 (69%)	5 (11%)	8 (18%)	1 (2%)	0
TLE without <i>HS, n= 41</i>	24 (59%)	6 (15%)	8 (20%)	0	3 (7%)
ETLE, n=44	23 (52%)	5 (11%)	7 (16%)	1 (2%)	8 (18%)

Abbreviations: TLE, temporal lobe epilepsy; ETLE, extratemporal lobe epilepsy; SOZ, seizure onset zone; C, concordant; C+, concordant plus; M, multifocal; R, remote; N, normal; HS, hippocampal sclerosis.

Table 3. Predictive value of PET pattern in operated patients

	Engel Class I Number (TLE/ETLE)	Engel Class II-IV Number (TLE/ETLE)
Hypometabolism confined to the SOZ (C)	54 (40/14)	5 (3/2)
Hypometabolism outside the SOZ or negative (C+, M, R, N)	18 (13/5)	9 (6/3)

Abbreviations: TLE, temporal lobe epilepsy; ETLE, extratemporal lobe epilepsy; SOZ, seizure onset zone; C, concordant; C+, concordant plus; M, multifocal; R, remote; N, normal.

Table 4. Main research papers evaluating the predictive value of FDG PET for the surgical outcome

	Study	Number of operated patientstype of epilepsy	Outcome evaluated	Analysis	Main result
TLE	Guedj et al. 2015 [13]	30 operated TLE	Engel class > 2 years (I-II vs. III-IV)	SPM	Better outcome in more severe hypometabolism
	Salanova et al., 2001 [25]	69 TLE operated	Engel class > 2 years, class I vs higher	Visual (2 readers)	More frequent hypometabolism (vs. normal scan in patient with better outcome)
	Wong et al., 2010 [30]	64 mTLE	Engel > 2 years	Visual + SPM (temporal/contiguous/remote)	Remote negative prognostic impact
	Radtke et al., 1993 [38]	30 TLE	Seizure free > 2 years	Visual	Presence of hypometabolism associated with a positive outcome
	Knowlton et al., 1997 [39]	25 unilateral TLE	Engel class (I-II vs higher > 1.5 years)	Visual	HS and hypometabolism of 3 or more temporal subregions associated with good outcome
	Dupont et al., 2000 [40]	30 MTLE	Engel > 2 years	Region-based analysis in temporal and frontal regions	Better outcome in stronger asymmetry
	Struck et al., 2011 [41]	34 TLE	ILAE class > 6 months Class I vs higher	Visual	FDG unilateral temporal only predictor (as compared with MRI and EEG of outcome)
	Higo et al., 2016 [42]	40 mTLE	Engel at 1 and 2 years (I-II vs III-IV)	Visual and 3D-SSP	Better outcome in more asymmetric temporo-mesial metabolism. None with extratemporal hypometabolism
	Choi et al., 2003 [43]	47 mTLE	Engel > 5 years	Visual (agreement of 2 readers)	Negative outcome for extratemporal hypometabolism
ETLE	Wong et al., 2012 [12]	68 neocortical epilepsy	Engel > 2 years	SPM: concordant vs remote	Remote negative prognostic impact
	Lee et al., 2005 [26]	89 neocortical epilepsy	Engel class > 2 years	Visual + SPM	PET concordant in 44% of the cases. Localizing/concordant PET more frequently associated with a Engel I outcome
	Kim et al., 2017 [44]	109 nonlesional neocortical epilepsy	Engel > 10 years (class I vs II-IV)	Visual + SPM	Localizing FDG PET associated with better outcome
	Desarnaud et al., 2018 [45]	103 focal cortical	Engel > 2 years	Visual (fusion with MRI)	Higher Engel I and Ia in PET positive cases,

		dysplasia type 2			with OR lower than MRI
	Kim et al., 2004 [46]	26 parietal lobe epilepsy	Engel class > 1 year	SPM (considering only the most severe abnormality)	No difference in positivity rate between seizure free and non-seizure free
	Kogias et al., 2017 [47]	26 3T MRI neg patients (10 TLE/16 ETLE)	Engel class > 1 year	Visual (two readers)	Lateralizing PET was correlated with better outcome in TLE, not in ETLE

Abbreviations: TLE, temporal lobe epilepsy; ETLE, extratemporal lobe epilepsy; OR, odds ratio; SPM, statistical parametric mapping; HS, hippocampal sclerosis.

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