Presurgical evaluation of pediatric epilepsy patients prior to hemispherotomy: the prognostic value of 18F-FDG PET

Tatjana Traub-Weidinger, MD,1 Philip Weidinger, MD,2 Gundrun Gröppel, MD,2 Georgios Karanikas, MD,1 Wolfgang Wadsak, PhD,1 Gregor Kasprian, MD,1 Christian Dorfer, MD,3 Anastasia Dressler, MD,2 Angelika Muehlebner, MD,2 Marcus Hacker, MD,1 Thomas Czech, MD,3 and Martha Feucht, MD2

Departments of 1Biomedical Imaging and Image-Guided Therapy, 2Pediatrics, and 3Neurosurgery, Medical University of Vienna, Austria

OBJECTIVE The objective of this study was to investigate whether fluorine-18 fluorodeoxyglucose PET (18F-FDG PET) can help to predict seizure outcome after hemispherotomy and therefore may be useful in decision making and patient selection.

METHODS Children and adolescents less than 18 years of age who underwent 18F-FDG PET studies during presurgical evaluation prior to hemispherotomy and had follow-up data of at least 12 months after surgery were included. Seizure outcome was classified according to the recommendations of the International League Against Epilepsy. PET data were reevaluated by two specialists in nuclear medicine blinded to clinical data and to MRI. PET data were also reinterpreted visually by an experienced neuroradiologist blinded to clinical data and PET findings. MRI studies were also reinterpreted visually by an experienced neuroradiologist blinded to clinical data and MRI.

RESULTS Thirty-five patients (17 girls) with a median age of 5 years (range 0.4–17.8 years) were evaluable. Of the 35 patients, 91.4% were seizure free after surgery, including 100% of those with unilateral 18F-FDG-PET hypometabolism compared with only 75% of those with bilateral hypometabolism. With respect to MRI, seizure freedom after surgery was observed in 96.4% of the patients with unilateral lesions compared with only 71.4% in those with bilateral MRI lesions. The best seizure outcomes were noted in patients with unilateral findings in both PET and MRI (100% seizure freedom) whereas only 50% of those with bilateral findings in both imaging techniques were seizure free. Furthermore, 100% of the patients with unilateral PET hypometabolism and bilateral MRI findings were also seizure free, but only 87.5% of those with bilateral PET hypometabolism and unilateral MRI findings.

CONCLUSIONS According to these results, candidate selection for hemispherotomy can be optimized by the use of 18F-FDG PET as part of a multimodal presurgical evaluation program, especially in patients with inconsistent (bilateral) MRI findings.

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KEY WORDS 18F-FDG; PET; hemispherotomy; drug-resistant epilepsy

Hemispherectomy has been confirmed to be a highly effective surgical approach for carefully selected children with drug-resistant epilepsies due to hemispheric pathologies.4,7,11 Starting with functional hemispherectomy introduced by Rasmussen,18 various techniques have been developed with less resective and more disconnective components described as hemispherotomies. Today, hemispherectomies/hemispherotomies make up approximately 16% of all epilepsy surgeries performed in pediatric patients. Almost one-third of these surgical candidates are infants younger than 4 years of age.17 However, both seizure and developmental outcomes after surgery primarily depend on the functional integrity of the contralateral nonoperated hemisphere.

Presurgical evaluation prior to hemispherotomy is often hampered by inconclusive seizure semiology and interictal/ictal electroencephalography (EEG) as well as bilateral MRI findings. Additional diagnostic tools providing reli-
able lateralizing information to facilitate decision making are therefore needed. Fluorine-18 fluorodeoxyglucose positron emission tomography ($^{18}$F-FDG PET) is an established diagnostic tool that helps to delineate the epileptogenic zone and to gain information about the functional state of the “remaining” parts of the brain, especially in the absence of radiographic lesions.$^{12,17,21}$

In patients with temporal lobe epilepsy, the presence of extratemporal hypometabolism, ipsilateral and/or contralateral to the epileptogenic focus, was associated with higher rates of unfavorable seizure outcomes after surgery.$^{1,2,23,26}$ However, data are limited concerning the prognostic value of PET in children evaluated for hemispherotomy.$^{6,18,19}$ Moosa et al. reported that presurgical $^{18}$F-FDG PET identifying or excluding hypometabolic areas in the contralateral remaining hemisphere can provide prognostic information.$^{15}$

The purpose of this study was to investigate the lateralizing value of $^{18}$F-FDG PET compared with MRI in children and adolescents with drug-resistant hemispheric epilepsies. The hypothesis was that PET is a reliable tool to obtain additional information supporting the surgical approach, even in cases with inconclusive or bilateral MRI findings. Therefore, $^{18}$F-FDG PET and MRI data obtained during the presurgical diagnostic process were reevaluated in relation to seizure outcomes after hemispherotomy.

**Methods**

**Study Population**

All clinical data used in this study were obtained from a longitudinal observational database of the pediatric epilepsy center at the Medical University of Vienna maintained by a senior neurologist familiar with the patients (M.F.). The database contains the complete medical records of all children and adolescents ≤ 18 years of age who have undergone presurgical evaluation and epilepsy surgery since 1999, including retrospective data on patient demographics, medical history, seizure types, and epilepsy syndromes, as well as prospectively collected data on presurgical evaluation, surgery, histopathology, developmental and seizure outcome, and antiepileptic drug use/withdrawal after surgery.$^{5,8}$ Follow-up data are collected on an inpatient basis 3 and 12 months after surgery and annually thereafter.

Study inclusion criteria were 1) drug-resistant hemispheric epilepsy; 2) hemispherotomy performed at the study center; 3) availability of $^{18}$F-FDG PET studies performed prior to surgery; 4) availability of MRI studies with epilepsy-specific imaging protocols performed prior to surgery; and 5) complete follow-up data of at least 12 months after surgery. This study was approved by the ethics committee of the Medical University of Vienna.

**Presurgical Neuroimaging and Interpretation**

$^{18}$F-FDG PET examinations were performed as part of a standardized presurgical evaluation program at the Division of Nuclear Medicine of the Department of Biomedical Imaging and Image-guided Therapy at the Medical University of Vienna. PET acquisition and reconstruction were performed by a dedicated full-ring GE Advance PET scanner (GE Medical Systems). Spatial resolution of the scanner amounts to 4.0 mm in the axial direction and 3.8 mm in the tangential direction. $^{18}$F-FDG was freshly prepared every day according to a well-established method using the GE FASTLab platform (GE Healthcare).$^{25}$ After injection of $^{18}$F-FDG according to the European Association of Nuclear Medicine recommendations for children, a 3-minute transmission scan for attenuation correction was acquired at the beginning of the scanning procedure.$^{25}$ Data acquisition was started 40–60 minutes after injection of $^{18}$F-FDG and lasted for 15 minutes. Image reconstruction was performed by filtered back projection using a Hanning filter with a cutoff value of 6.2 mm and a 256 × 256 matrix. Transverse slices of 4.25 mm were rescaled along the orbitomeatal line and reformatted in coronal and sagittal directions. PET data were retrieved from the internal database of the Division of Nuclear Medicine, and reevaluated with the Hermes Hybrid Viewer (Hermes Medical Solutions) by two specialists in nuclear medicine (T.T.W. and G. Karanikas), who were blinded to the patient’s clinical data including video-EEG monitoring results and MRI findings. Brain regions were defined as pathological findings in comparison with the corresponding contralateral area by rating the extent of $^{18}$F-FDG hypometabolism. In cases of bilateral decrease of $^{18}$F-FDG uptake, ipsilateral areas with homogeneous patterns of $^{18}$F-FDG detection were used for comparison. Because of the presence of hypometabolism of the cerebellum observed in more than two-thirds of the included patients, this brain region was not used as a reference. The absence of pathological findings was defined as nondecreased $^{18}$F-FDG uptake in bilateral comparison. The PET results were then classified as unilateral (pathological findings limited to 1 hemisphere), bilateral (pathological findings in both hemispheres), or without any pathological findings.

MRI studies were performed at the Division of Neuro- and Musculoskeletal Radiology of the Department of Biomedical Imaging and Image-guided Therapy during presurgical evaluation, using either a 1.5-T (Philips Intera) or a 3.0-T machine (Siemens Trio). The protocols applied included at least anatomical, thin-slice volumetric T1-weighted gradient-recalled echo sequences (1 mm isotropic resolution), coronal T2-weighted sequences (2–4 mm slice thickness), axial FLAIR and inversion recovery sequences (2-mm slice thickness), and high-resolution paracoronal FLAIR and T2-weighted sequences acquired perpendicular to the main axis of the hippocampus (2-mm slice thickness). Data were sent to a picture archiving and communication system (Agfa System) and reinterpreted visually by a board-certified neuroradiologist trained in epilepsy and blinded to the patient’s clinical data and PET (G. Kasprian).

**Seizure Outcome Evaluation After Hemispherotomy**

Seizure outcome after hemispherotomy was classified according to the International League Against Epilepsy (ILAE) proposal based on patient and family reporting.$^{22}$ This classification takes into account fluctuations in seizure frequency after surgery. For this study seizure outcome was simplified to seizure freedom versus ongoing seizures.
Because of the small sample size only descriptive analysis was used. Pathological findings and their association with postsurgical outcomes were displayed in absolute and relative frequencies.

Results
Clinical Data and Seizure Frequencies After Hemispherotomy

Fifty-five patients were screened, and 20 were excluded from further analysis because of incomplete MRI and/or PET data. Data from 35 patients (17 girls) with a median age of 5 years at the time of surgery were analyzed. The surgical technique applied in all patients was vertical perithalamic hemispherotomy. All operations were performed by the same neurosurgeon (T. C.) between December 1999 and June 2013.

The underlying pathologies were vascular defects in 18 patients, malformations of cortical development (MCD) in 9, encephalitis including Rasmussen encephalitis in 3, Sturge-Weber syndrome in 3, and tumors in 2 patients (Table 1). The mean follow-up period was 39.43 months (range 12–144 months). Seizure freedom (Wieser Class 1a) after surgery was observed in 32 patients (91.4%). Three patients (8.6%) were not seizure free: Cases 10,
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19, and 24, who showed seizure outcomes of Wieser Class 4.

18F-FDG PET, MRI Findings, and Clinical Outcome After Hemispherotomy

Because normal 18F-FDG distribution patterns in both hemispheres were not found in any of the patients, the study population was divided into two groups with respect to unilateral (Group A, 23/35 patients) or bilateral hypometabolic brain regions (Group B, 12/35 patients). Seizure-freedom after surgery was observed in 100% (23/23) of the patients in Group A and in 75% (9/12) of the children in Group B (Table 2).

MRI showed unilateral findings in 79.9% (28/35) of the children, and 96.4% (27/28) of them were seizure free after hemispherotomy, MRI was bilateral in 20% (7/35) of the patients, and only 71.4% (5/7) of them were seizure free after surgery.

According to the results of both imaging modalities, patients were assigned to 4 groups (Groups AI and AII, and Groups BI and BII). As noted in Table 2, seizure freedom after surgery was achieved in 100% of the patients in Group AII (unilateral PET hypometabolism, bilateral MRI findings) compared with only 87.5% of the patients in Group BI (bilateral PET hypometabolism, unilateral MRI findings).

Discussion

At least 35% of all infants and children with epilepsy are pharmacoresistant.14,24 Many of them suffer from early-onset epileptic encephalopathies due to multilobar/hemispheric pathologies. Hemispheric resection/disconnection has become an increasingly performed and successful treatment option in carefully selected children, and median seizure-free rates of 73.4% (range 40%–94%) have been reported.7 In particular, the vertical approach of hemispherotomy was confirmed by our group to be safe and effective, with seizure-free rates of 92%.4,5

Prerequisites of favorable outcomes after surgery are the precise lateralization of the hemisphere harboring the epileptogenic zone as well as the proven integrity of the remaining contralateral hemisphere. Unfortunately, many of these infants and young children do not show lateralizing seizure semiology and/or interictal/ictal EEG findings. Neuroimaging studies are therefore of paramount importance during the presurgical evaluation process. Structural MRI gives information about the localization and extent of the epileptogenic lesion and may also reveal structural abnormalities in unaffected brain areas.27 However, the significance of contralateral abnormalities in patients evaluated for hemispheric surgery is controversial. Hallbrook et al. reported that contralateral MRI findings, less prominent than those in the ipsilateral hemisphere, do not correlate with seizure outcome and therefore may not be a contraindication in otherwise favorable candidates.8 In contrast, Moosa et al. observed a poorer outcome in children with bilateral MRI abnormalities after hemispherectomy.16

PET-based and SPECT-based techniques have also been investigated with respect to their value for both a

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**TABLE 2. Presurgical PET and MRI findings in relation to seizure outcomes**

<table>
<thead>
<tr>
<th>Combined PET &amp; MRI*</th>
<th>Seizure Free (%)</th>
<th>Not Seizure Free (%)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group AI</td>
<td>100</td>
<td>0</td>
<td>20</td>
</tr>
<tr>
<td>Group AII</td>
<td>100</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Group BI</td>
<td>87.5</td>
<td>12.5</td>
<td>8</td>
</tr>
<tr>
<td>Group BII</td>
<td>50</td>
<td>50</td>
<td>4</td>
</tr>
<tr>
<td>Total</td>
<td>91.4</td>
<td>8.6</td>
<td>35</td>
</tr>
</tbody>
</table>

* Group AI = unilateral PET hypometabolism, unilateral MRI findings; Group AII = unilateral PET hypometabolism, bilateral MRI findings; Group BI = bilateral PET hypometabolism, unilateral MRI findings; Group BII = bilateral PET hypometabolism, bilateral MRI findings. All unilateral abnormalities on PET and MRI were ipsilateral to the operated hemisphere.
FIG. 1. Case 4. Imaging results from a girl who suffered a perinatal stroke, showing unilateral results in PET as well MRI prior to hemispherotomy. Seizure freedom was observed after surgery over a follow-up period of 48 months. The axial T2-weighted MRI sequence (left) revealed a large parenchymal defect in the territory of the right middle cerebral artery. In the axial 18F-FDG PET view (right), a large tracer defect corresponding to the parenchymal defect of the right hemisphere is present. Figure is available in color online only.

FIG. 2. Case 11. Imaging results from a boy who suffered a perinatal stroke of the right hemisphere as well as polymicrogyria showing bilateral results on MRI, but unilateral results on PET prior to hemispherotomy. Seizure freedom was observed after surgery over a follow-up period of 12 months. The axial T2-weighted sequence (left) shows a large parenchymal defect in the territory of the right middle cerebral artery, occipital-lateral thinned cortex, and reduced gray/white matter differentiation, but also polymicrogyria of the right frontal and right occipitomesial cortex, as well as of the occipitomesial cortex of the left hemisphere. The 18F-FDG PET axial view (right) presents reduced tracer uptake within the large ischemic defect of the right hemisphere, but not in the regions of polymicrogyria of both hemispheres. Figure is available in color online only.

**Limitations of the Study**

The results of 18F-FDG PET have to be interpreted with caution, especially in infants and children, because brain glucose metabolism underlies developmental changes during the first years of life. This also explains why our PET data were analyzed only visually due to the lack of standardized normal 18F-FDG brain controls for semiquantitative assessment in infants and children.

The small sample size of this study and the nonhomogeneity with respect to etiology allowed only descriptive data analysis. The retrospective, cross-sectional nature of this study implies a bias in the selection of our cohort. In addition, outcomes of different pathologies are known to be different (MCD vs ischemic lesions) and thus also may have biased the results. Furthermore, the main parameters we wanted to correlate with surgical outcome—presurgical 18F-FDG PET and MRI findings—were already a factor in the presurgical evaluation process, which shaped our cohort.

However, all PET and MRI examinations were performed in a standardized fashion and reevaluated by specialists blinded to the patients’ clinical data. Disconnection of the hemispheres is a highly effective but also complex procedure in the treatment of pharmacoresistant epilepsy. Trained and experienced surgeons are needed for excellent outcome. Our small group of patients was operated on by the same neurosurgeon using the vertical perithalamic surgical approach. Nevertheless, to our best knowledge, there is no other study that reported a similar prediction of seizure recurrence by bilateral 18F-FDG PET findings or that analyzed presurgical 18F-FDG PET in a comparable study design. Nevertheless, our results require confirmation by prospective controlled studies.

**Conclusions**

Infants and children with pharmacoresistant epilepsies should undergo a comprehensive examination including EEG, seizure semiology, and presurgical imaging with MRI and 18F-FDG PET, assessed by an interdisciplinary team prior to hemispherotomy. Functional imaging by 18F-FDG PET appears to have both decision-making and predictive value, especially in situations in which clinical information and MRI may not sufficiently support the treatment decision.

**References**


**Disclosures**

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

**Author Contributions**

Conception and design: Feucht, Traub-Weidinger. Acquisition of data: Weidinger, Gröppel. Analysis and interpretation of data: Feucht, Traub-Weidinger, Karanikas, Kasprian. Drafting the article: Feucht, Traub-Weidinger. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Feucht. Statistical analysis: Traub-Weidinger, Wadak, Dressler, Mühlbauer. Study supervision: Feucht.

**Correspondence**

Martha Feucht, Department of Paediatrics, Medical University of Vienna, Währinger Gürtel 18-20A-1090 Wien, Austria. email: martha.feucht@meduniwien.ac.at.