Original Article

Epileptic activity increases cerebral amino acid transport assessed by [$^{18}$F]-fluoroethyl-L-tyrosine amino acid PET - a potential brain tumor mimic

Running Title

Epileptic activity and $^{18}$F-FET PET

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ABSTRACT

O-(2-[18F]-fluoroethyl)-L-tyrosine positron emission tomography (18F-FET PET) is a well-established method increasingly used for diagnosis, treatment planning and monitoring in gliomas. Epileptic activity, frequently occurring in glioma patients, can influence MRI findings. Whether seizures also affect 18F-FET PET imaging is currently unknown. The aim of this retrospective analysis was to investigate the brain amino acid metabolism during epileptic seizures by 18F-FET PET and to elucidate the pathophysiological background.

Methods. Ten patients with eleven episodes of serial seizures or status epilepticus, who underwent MRI and 18F-FET PET, were studied. The main diagnosis was glioma WHO grade II-IV (n=8), two patients suffered from non-neoplastic diseases. Immunohistochemical assessment of LAT1/LAT2/CD98 amino acid transporters was performed in seizure-affected cortex (n=2) and compared with glioma tissues (n=3).

Results. All patients exhibited increased seizure-associated strict gyral 18F-FET uptake, which was reversible in follow-up studies or negative shortly before and without any histological or clinical signs of tumor recurrence. 18F-FET uptake corresponded to structural MRI changes, compatible with cortical vasogenic and cytotoxic edema, partial contrast enhancement and hyperperfusion. Patients with prolonged postictal symptoms lasting up to eight weeks displayed intensive and widespread (≥ one lobe) cortical 18F-FET uptake. LAT1/LAT2/CD98 was strongly expressed in neurons and endothelium of seizure-affected brains, and less in reactive astrocytosis.

Conclusions. Seizure activity, in particular status epilepticus, increases cerebral amino acid transport with a strict gyral 18F-FET uptake pattern. Such “periictal pseudoprogression” represents a potential pitfall of 18F-FET PET and may mimic brain tumor. Our data also indicate
a seizure-induced upregulation of neuronal, endothelial and less astroglial LAT1/LAT2/CD98 amino acid transporter expression.

**INTRODUCTION**

Positron emission tomography (PET) with the amino acid tracer O-(2-[\(^{18}\text{F}\)-fluoroethyl]-L-tyrosine (\(^{18}\text{F}\)-FET) is increasingly used as an adjunct to magnet resonance tomography (MRI) for brain tumor diagnosis, treatment planning and monitoring (1,2). \(^{18}\text{F}\)-FET uptake is primarily mediated by the system L amino acid transporter subtypes LAT1 and LAT2 (3,4). These transporters are heterodimers consisting of a light (LAT1, LAT2) and a heavy chain (CD98) and function as obligatory stereospecific exchanger (antiporter) of neutral amino acids (3,4).

LAT1/LAT2 are highly expressed in primary brain tumors. The highest levels have been detected in glioma cells and tumor-associated endothelium (5). Consequently, \(^{18}\text{F}\)-FET PET has a high specificity for gliomas mediated by a tracer uptake almost independent of blood-brain barrier (BBB) dysfunction. \(^{18}\text{F}\)-FET uptake by non-neoplastic tissue is considered as a rare phenomenon and has been reported for various inflammatory and vascular brain lesions (1,6-10).

Epileptic seizures are among the most common symptoms of primary brain tumors (11). Focal symptoms after seizures usually disappear within 36 hours (12-14). Prolonged postictal deficits, however, are often similar to symptoms that arise from progressive tumor growth. On the other hand, an increase of seizure frequency may be an early sign of tumor progression (11,15). Therefore, the differentiation of purely seizure-related postictal symptoms from tumor progression is of paramount importance in the clinical management of brain tumor patients.

To complicate this matter, seizure activity, in particular status epilepticus, may result in MRI changes difficult to differentiate from tumor progression (16). For \(^{18}\text{F}\)-FET PET it is still unknown whether and to which extend seizures influence cerebral amino acid metabolism and
18F-FET tracer uptake. Therefore, we retrospectively studied patients with serial epileptic seizures or status epilepticus who underwent MRI and 18F-FET PET imaging with particular focus on spatial distribution pattern and time course of 18F-FET uptake, and elucidated the pathophysiological background by histopathological assessment of amino acid transporter expression in specific cell types involved in epileptogenesis.

MATERIALS AND METHODS

Study design and data collection

We identified eight patients with gliomas WHO grade II-IV and two patients with non-neoplastic diseases from three neurooncology centers (Salzburg, Austria; Regensburg and Freiburg, Germany), who fulfilled the following inclusion criteria: (i) presentation with typical clinical and/or electroencephalographic (EEG) signs of highly frequent seizures (several times per day, serial seizures) or status epilepticus and (ii) multimodal imaging work-up consisting of 18F-FET PET and serial MRI scans.

According to the definitions of the International League Against Epilepsy types of epileptic seizures were classified as simple partial seizure (SPS), complex partial seizure (CPS), tonic-clonic seizure (TCS) and series of epileptic seizures (SES) (17). Status epilepticus (SE) was defined as ≥5 minutes of convulsive seizures or ≥10 minutes of non-convulsive seizures with impairment of consciousness confirmed by EEG criteria (18-20).

Clinical data, laboratory values, EEG, standard MRI, 18F-FET PET and histological records of all patients were analyzed (Table 1). Besides MRI and 18F-FET PET during the course of disease, MR perfusion-weighted imaging (PWI), 99mTc-Hexa-Methyl-Propylen-Aminooxim
(99mTc-HMPAO) SPECT and 18F-2-Fluoro-2-Deoxy-D-Glucose (18F-FDG) PET scans at the time of epileptic disorder were additionally evaluated if available.

The local ethics committee of the University of Regensburg approved this retrospective study (number 14-101-0185) and the requirement to obtain informed consent was waived. The study was conducted according to the standards of the Declaration of Helsinki in its recent revised version of 2013.

**Standard MR imaging**

Standard MR imaging was routinely performed at the local departments of neuroradiology. At the time of seizure disorder and afterwards in the course of disease, all patients received MRI scans using 1.5 T or 3.0 T scanners with standard head coils before and after administration of a gadolinium-based contrast agent. The routine MRI protocol included T1-weighted sequences with and without contrast agent (T1w, T1wCE), T2 and FLAIR sequences, and MR diffusion-weighted imaging (DWI) with calculation of the apparent diffusion coefficient (ADC). In five patients, additional dynamic susceptibility contrast (DSC) PWI was available.

**MR image analysis**

For study evaluation, the cortical changes in standard MRI and, if available, DSC-PWI were retrospectively reviewed by two independent investigators (C.W., M.H.). During this analysis, contrast enhancement in T1wCE sequence (BBB permeability), T2/FLAIR sequences (hyperintensity, vascular edema), DWI/ADC sequences (diffusion restriction, cytotoxic edema) and DSC-PWI (hypo- or hyperperfusion) were graded visually on a three-point scale (no, weak and strong).
**18F-FET PET imaging**

18F-FET PET was routinely performed at the local departments of nuclear medicine according to the German and Austrian guidelines for brain tumor imaging using labeled amino acid analogues (21). All patients fasted for at least 6 hours before PET scanning. Prior to the investigation, a low-dose computer tomography (CT) scan was performed for attenuation correction. PET acquisition was started 20 minutes after intravenous injection of about 250 MBq 18F-FET with a scan duration of at least 20 minutes. The methodological differences between the different neurooncology centers (PET scanner equipment, reconstruction methods, and acquisition specifics) are summarized in supplemental Table 1. All 18F-FET PET scans were conducted between March 2011 and June 2015.

**18F-FET PET image analysis**

18F-FET PET and MR images were co-registered using dedicated software (Vinci V4.40, Max-Planck-Institute for Metabolism Research, Cologne, Germany). The results were reviewed and, if necessary, adapted based on anatomical landmarks. The regions-of-interest (ROI) analysis was based on the summed static 18F-FET PET data. The transaxial slice showing the highest tracer accumulation in the brain lesion was chosen for ROI analysis. The tracer uptake in the unaffected brain was determined by the largest possible ROI placed on the contralateral hemisphere in an area of normal-appearing brain, including white and grey matter and excluding basal ganglia, thalamus and ventricles. 18F-FET uptake was expressed as standardized uptake values (SUV). The ROI of the suspicious lesion was determined using a three-dimensional autocontouring process with a lesion-to-brain ratio (LBR) of ≥1.6 as described previously (22).
Because of the reversibility of seizure-related cortical tracer uptake in follow-up studies and $^{18}$F-FET PET shortly before seizure activity cortical LBR$_{\text{max}}$ was <1.6. In these cases a circular ROI with a diameter of 1.6 cm was centered exactly on the cortex of maximal $^{18}$F-FET uptake observed during seizure activity. Mean and maximum LBRs (LBR$_{\text{mean}}$, LBR$_{\text{max}}$) were calculated by dividing SUV$_{\text{mean}}$ and SUV$_{\text{max}}$ of the $^{18}$F-FET uptake by the mean SUV of the contralateral unaffected hemisphere.

For study evaluation, the cortical changes in $^{18}$F-FET PET were assessed visually by two independent investigators (J.G., M.H.). Cortical $^{18}$F-FET uptake extension was graded as “focal” (extension ≤5 cm), “enlarged” (extension >5 cm, within one lobe), and “widespread” (more than one lobe).

In one patient (case 3), a time-activity curve of SUV$_{\text{mean}}$ in the frontal epileptic brain lesion was generated by measuring a spherical volume-of-interest of 2 ml centered on the maximal $^{18}$F-FET brain lesion uptake and in a reference ROI of unaffected brain (as described above) using the entire dynamic dataset.

**Histological assessment and immunostaining**

Histological specimen were available for study analysis from two patients of the study cohort (Table 2): (i) patient case 3 with oligodendroglioma WHO grade II (no residual tumor) and non-convulsive SE resulting in partial frontal lobe resection of seizure-affected cortex, and (ii) patient case 7 with repeated CPS and TCS leading to first diagnosis of glioblastoma WHO grade IV and resection of seizure-affected cortex and subcortical tumor. Seizure-affected cortex was defined as cortical tissue with seizure-induced changes in MRI and $^{18}$F-FET PET and without tumor cells in histopathological evaluation.
For comparison, three tissue specimens of archival material with astrocytoma WHO grade II, anaplastic astrocytoma WHO grade III and glioblastoma WHO grade IV were evaluated. All specimens were assessed for the protein expression pattern of LAT1, LAT2 and CD98 using formalin fixed and paraffin embedded (FFPE) tissues.

Immunohistochemical staining was performed according to standard protocols. Paraffin sections were deparaffinized through an alcohol series and rehydrated. After antigen retrieval for 20 minutes (ethylene diamine tetra-acetic acid [EDTA] buffer, pH 8.5, Sigma-Aldrich) and a blocking step, sections were incubated with the primary antibodies (LAT1/LAT2 for 45 minutes at room temperature, CD98 overnight at 4 °C). The following primary antibodies were used: rabbit-anti SLC7A5 (PA2187, Booster Immunoleader, 1:100), rabbit-anti SLC7A8 (NBP1-70389, Novus Biologicals, 1:1000), rabbit-anti CD98 (bs-6659R, Bioss, 1:100). Immunoreactivity was detected by the EnVisionTM Detection System (#K406511-2, Dako) and 3,3’-diaminobenzidine tetrahydrochloride (DAB, EnVision+, Dako) and afterwards counterstained by hematoxylin. As positive control, FFPE tissue from placenta was used and negative controls were run without the primary antibody. Neuropathological evaluation was carried out by a board-certified neuropathologist (M.J.R.) blinded to clinical and imaging findings. The immunostaining pattern of neurons, astrocytes, microglia, tumor and vascular endothelial cells of tumor bulks and tumor infiltrative zones were analyzed separately.

RESULTS

Study population

In this multicenter study, ten patients with eleven episodes of SES/SE were identified (eight patients with gliomas WHO grade II-IV; two patients with non-neoplastic diseases and
final diagnoses of ischemic stroke and non-convulsive SE caused by septic encephalopathy; Table 1). One patient presented with identical serial focal motor seizures and focal SE followed by prolonged postictal hemiparesis in 2011 and 2014. Because combined MRI and 18F-FET PET was available from both time points, this patient was examined twice (case 1 and 2). 18F-FET PET was performed during or within 7 days after termination of the clinical and/or EEG signs of seizure activity (Table 2). MRI and 18F-FET PET were also obtained out of an epileptic episode. This was during the clinical follow-up after seizure initiation in 5 cases (range, +8 to +12 weeks) and before seizure onset in 2 other cases (-4 and -10 weeks).

**Structural MRI changes during seizure activity**

During SES/SE and prolonged postictal symptoms we observed structural MRI changes including cortical hyperintensity in T2/FLAIR sequences and diffusion-restriction with low ADC values in DWI/ADC (9/11 cases; Table 2; Figs. 1-3; Supplemental Fig. 1), consistent with the presence of cortical vasogenic and cytotoxic edema. In 3/11 cases, additional focal gyral contrast enhancement in T1wCE was noted (Figs. 1 and 2). Cortical perfusion was increased in DSC-PWI in 3/5 available cases with clinical and/or electrophysiological signs of SE or treatment-resistant series of SPS (Figs. 1-3). Patients with high seizure frequency but without SE (2/11 cases) did not exhibit any visible structural brain changes on standard MRI.

**18F-FET uptake during seizure activity**

Seven patients with SES/SE or prolonged postictal symptoms demonstrated increased 18F-FET uptake strictly following the cortical ribbon of seizure-affected brain areas (cases 1-6, 10; Table 2) corresponding to structural MRI changes. 18F-FET PET revealed increased LBR$_{max}$
(range, 1.83 to 4.42; median ± standard deviation [SD], 3.95 ± 1.02) and LBRmean (range, 1.46 to 2.58; median ± SD, 2.27 ± 0.40). 18F-FET tracer uptake occurred in areas with and without contrast enhancement in T1wCE (Figs. 1-3; Supplemental Fig. 1). In contrast, patients with TCS followed by prolonged postictal hemiparesis (case 11; Supplemental Fig. 1D) or high frequent seizures without SE (cases 7-9) exhibited lower LBRmax (range, 1.69 to 1.81; median ± SD, 1.77 ± 0.05) and LBRmean (range, 1.42 to 1.57; median ± SD 1.49 ± 0.08) of more focally enhanced cortical 18F-FET uptake (Supplemental Fig. 1).

In case 3, the time-activity curve of 18F-FET uptake in the frontal epileptic brain lesion was calculated and compared to the unaffected contralateral hemisphere (Fig. 2D). The curve pattern showed a continuously increasing 18F-FET uptake without clear identifiable peak uptake and wash-out kinetics, comparable to that usually observed in low-grade gliomas.

**18F-FET uptake and prolonged postictal symptoms**

Four SES/SE patients showed an increased and widespread cortical 18F-FET uptake spreading into two or three lobes, combined with cortical vasogenic and cytotoxic edema and partial contrast enhancement in MRI (cases 1, 2, 5, 6). This observation was associated with prolonged postictal symptoms lasting 1 to 6 weeks (Table 2).

In contrast, case 4 suffered from clinical stable anaplastic astrocytoma WHO grade III without residual tumor over years and presented with a TCS followed by severe postictal symptoms over 8 weeks (Fig. 3). This condition was associated with distinctly increased cortical 18F-FET uptake over three lobes of the left hemisphere with fronto-temporal accentuation (LBRmax 3.95 and LBRmean 2.08) and slight cortical vascular and cytotoxic edema without contrast enhancement in MRI. Importantly, there was no evidence of status epilepticus in EEG
monitoring, $^{18}$F-FDG PET (regional hypometabolism) and $^{99}$mTc-HMPAO (regional hypoperfusion; not shown in detail), indicating prolonged increased cerebral amino acid metabolism in the postictal period.

**Reversibility of metabolic and structural cortical changes**

Follow-up MRI and $^{18}$F-FET PET scans from five patients were available after seizures termination (range, 2 to 12 weeks). Despite antiepileptic treatment, patients with widespread and extensive cortical $^{18}$F-FET uptake showed only a slow recovery of structural and metabolic cortical changes within 4 to 12 weeks (Table 2; Fig. 1D; Figs. 3B-C). The figure 4A-C shows the time course of $^{18}$F-FET uptake decrease. $^{18}$F-FET PET scans were performed 4 days ($LBR_{\text{max}}$ 3.95, $LBR_{\text{mean}}$ 2.08), 11 days ($LBR_{\text{max}}$ 2.34, $LBR_{\text{mean}}$ 1.45) and 12 weeks (no tracer uptake) after seizure onset.

**Histopathological evaluation and immunostaining**

Since the results of MRI and $^{18}$F-FET PET findings suggested tumor recurrence or progression, three patients underwent stereotactic biopsy or microsurgical resection of the putative lesions (cases 1, 3, 6; Table 2). In those cases, standard neuropathological evaluation of seizure-affected brain yielded cortical brain edema with reactive astrocytosis and microglia activation without any evidence of tumor cells.

Based on the known transport mechanisms of $^{18}$F-FET, additional immunohistochemical analysis of LAT1, LAT2 and CD98 protein expression was performed using FFPE tissue specimens derived from partial frontal lobe resection of seizure-affected brain tissue in MRI and $^{18}$F-FET PET (case 3; Fig. 2 and Figs. 4A-B) and tumor resection of a newly diagnosed
glioblastoma WHO grade IV including histological tumor-free cortex and subcortical tumor tissue (case 7). For comparison, three tissue samples from archival material with astrocytoma WHO grade II, anaplastic astrocytoma WHO grade III and glioblastoma WHO grade IV were additionally evaluated (Figs. 4C-F).

In seizure-affected cortex, LAT1/LAT2/CD98 amino acid transporter showed a strong and extended expression in neurons and brain endothelium (Figs. 4A-B), and was also detected in reactive astrocytes, especially when located adjacent to brain capillaries (Fig. 4B). Overall, LAT1/LAT2/CD98 staining in neurons and vascular endothelial cells was much more frequently observed than in reactive astrocytosis. Within the glioma infiltration zone, cortical neurons also revealed a pronounced expression of LAT1/LAT2/CD98, in particular when neurons and glioma cells interacted directly (“tumor cells as satellites of neurons”, Fig. 4C). Additionally, interspersed LAT1/LAT2/CD98 positive reactive astrocytes were observed (Fig. 4D). As expected, glioma and tumor-associated endothelial cells strongly expressed LAT1/LAT2/CD98 (Figs. 4E-F).

**DISCUSSION**

For the first time, we report a substantial increase of cortical amino acid transport assessed by \(^{18}\text{F}-\text{FET}\) PET during and after serial seizures or status epilepticus in patients with gliomas and non-neoplastic brain lesions. Elevated \(^{18}\text{F}-\text{FET}\) tracer uptake appears to be associated with cortical vasogenic and cytotoxic edema, hyperperfusion and contrast enhancement in MRI. \(^{18}\text{F}-\text{FET}\) uptake was clearly not caused by tumor progression or relapse in the subgroup of glioma patients, as proven by multimodal long-term follow-up MR/PET imaging and histological
confirmation in three patients. Therefore, our observation represents a so far unknown limitation of $^{18}$F-FET PET in brain tumor diagnosis resembling “periictal pseudoprogression”.

$^{18}$F-FET uptake values in SES/SE patients were similar to those observed in high-grade gliomas ($\text{LBR}_{\text{max}}$ median ± SD, SES/SE vs. HGG, 3.95 ± 1.02 vs. 2.04 ± 0.72) (1). In contrast, patients with frequent seizures but without SES/SE presented with lower and more focally pronounced cortical $^{18}$F-FET uptake, comparable with values seen in low-grade gliomas ($\text{LBR}_{\text{max}}$ median ± SD, seizures vs. LGG, 1.77 ± 0.05 vs. 1.52 ± 0.70) (1). In addition, the time-activity curve pattern of $^{18}$F-FET uptake corresponded to that described for low-grade gliomas (23). Based on these results, it appears that $^{18}$F-FET tracer uptake values, and possibly dynamic $^{18}$F-FET PET imaging, are not capable of distinguishing between seizure-induced alterations and tumor progression. In contrast, typical findings for seizure-induced $^{18}$F-FET tracer uptake were the strict gyral uptake pattern and the reversibility in follow-up-studies. Although methodological differences between the neurooncology centers exist (Supplemental Table 1), quantification of tracer uptake should in principle lead to similar results. In any case, it can be assumed that the methodological differences are less relevant for intra-individual courses.

Structural changes of the brain cortex in MRI are the most stereotypic imaging features suggesting seizure activity or status epilepticus (16). On this account, the combination of a strict gyral, and mostly extended, $^{18}$F-FET uptake associated with cortical MRI changes and high seizure activity, status epilepticus, or unusually prolonged postictal symptoms, should raise the suspicion of “periictal pseudoprogression”. In order to avoid overtreatment, this phenomenon must be considered in the interpretation of $^{18}$F-FET PET images and clinical decision making, especially in patients suffering from cerebral glioma and symptomatic epilepsy.
In general, transient postictal deficits are reversible within 36 hours (12-14). In our study population, however, prolonged postictal symptoms were observed for up to 8 weeks after seizure termination and were associated with structural and metabolic cortical changes of more than one lobe in MRI and $^{18}$F-FET PET. In all patients with follow-up investigations, increased gyral $^{18}$F-FET uptake, cortical edema, contrast enhancement and hyperperfusion normalized in parallel with clinical symptoms and EEG findings. Therefore, if clinically justified, a close clinical, MRI and $^{18}$F-FET PET follow-up for at least 8 weeks should be considered in these patients before therapeutic decisions, in particular invasive procedures, are undertaken.

Our findings also provide new insights into the pathophysiological changes in seizure-associated cortical amino acid metabolism. Previous studies have shown that $^{18}$F-FET does not participate in specific metabolic pathways and is transported predominantly via the system L amino acid transporters LAT1 and LAT2 (3,4). In normal cerebral cortex, LAT1 protein is only moderately expressed and LAT2 protein is absent (24). In contrast, immunohistochemical analysis of tissue specimen derived from seizure-affected cortex revealed a strong expression of LAT1/LAT2/CD98 in neurons and brain endothelium, indicating a seizure-induced upregulation of LAT1/LAT2 transporter mediating cortical $^{18}$F-FET tracer uptake.

Interestingly, also neurons in the infiltration zone of glial tumors strongly expressed LAT1/LAT2/CD98, in particular when directly interacting with tumor cells as “satellites” (Fig. 4C). This observation supports the hypothesis of a link between LAT1/LAT2/CD98 expression and epileptogenesis, since in glial brain tumors epileptogenic activity arises in the cortex adjacent to the tumor, while the tumor itself is considered electrically inert with regard to seizure initiation (25). Structural and metabolic changes in the peritumoral tissue may lead to cortical
cell alterations with imbalance between excitatory and inhibitory neurotransmitter, especially high intra- and peritumoral glutamate levels (25-27).

Reactive astrocytosis has been shown to be associated with increased \(^{18}\)F-FET uptake in various non-neoplastic brain lesions (e.g., inflammatory and demyelinating lesions, brain ischemia and hemorrhage, brain abscesses and radiation necrosis), representing another potential “pitfalls” in \(^{18}\)F-FET PET (1,6-10). In the presented group of patients, however, there were no clinical or radiological signs that would have been consistent with one of these differential diagnoses. Furthermore, the presented lesions showed a strict gyral pattern, which is untypical for the lesions mentioned above and suggests a connection with an epileptogenic genesis. This notion is further supported by the fact that in specimen of seizure-affected cortex LAT1/LAT2/CD98 was stronger expressed in neurons and brain endothelium than in reactive astrocytes, indicating a predominant neuronal \(^{18}\)F-FET uptake during seizure activity.

Other aspects that need to be discussed concerns the relationship of seizure-mediated increased \(^{18}\)F-FET uptake, regional blood flow and blood-brain-barrier disruption. Numerous PET and SPECT studies using various tracers have shown that the cerebral blood flow is increased in the ictal and decreased in the interictal state (28). In the present report, enhanced cortical \(^{18}\)F-FET uptake was observed in brain areas with increased (Figs. 1-3) and decreased regional perfusion as well as increased (Supplemental Fig. 1) and decreased (Fig. 3) glucose metabolism. Similarly, previous studies have shown high \(^{18}\)F-FET uptake in gliomas with low cerebral blood flow or blood volume (29,30). Therefore, it is unlikely that increased \(^{18}\)F-FET uptake during seizure activity is caused by hyperperfusion to a major extent.

Along with gyral hyperperfusion most SES/SE patients developed a mixture of vasogenic and cytotoxic edema, and partly contrast enhancement in MRI, indicating enhanced permeability
and/or disruption of the BBB. BBB dysfunction is one of the earliest pathophysiological features of status epilepticus mediated by several mechanisms, including glutamate receptor activation of endothelial cells, rapidly activated brain inflammation, and seizure-associated angiogenesis (31,32).

Although a correlation between $^{18}$F-FET uptake and contrast enhancement in brain tumors has been reported (1), there are many examples of brain lesions with BBB disruption and contrast enhancement (e.g. radionecrosis, abscesses) that are clearly negative on $^{18}$F-FET PET. This observation excludes that $^{18}$F-FET uptake is significantly influenced by BBB disruption. Therefore, it is most likely that the observed phenomenon of increased $^{18}$F-FET uptake in epileptogenic brain areas is due to a process which mediates an upregulation of LAT1/LAT2/CD98 expression in neurons and the brain endothelium.

Enhanced amino acid uptake during seizure activity has also been discussed in a few case reports using $^{11}$C-methionine ($^{11}$C-MET) (33-35), which is also transported via LAT1/LAT2 (36). Moreover, increased amino acid uptake in epileptic foci was reported for PET using $\alpha$-[11C]methyl-L-tryptophan ($^{11}$C-AMT) (37,38), which measures the serotonin synthesis rate. It was speculated that its increased uptake in epileptogenic tubers reflects changes in the kynurenine pathway. Since L-tryptophan is also a substrate of LAT1/LAT2 (39), it is tempting to hypothesis that increased $^{11}$C-AMT uptake in epileptogenic foci has also been influenced by increased LAT1/LAT2 transport as observed in the present study for $^{18}$F-FET.

**CONCLUSION**

Seizure-induced increase of cerebral amino acid transport seems to be primarily mediated by neuronal, endothelial and to a lesser extent astroglial LAT1/LAT2/CD98 expression. A strict
gyral $^{18}$F-FET uptake in combination with cortical MRI changes, high seizure activity and unusually prolonged postictal focal symptoms, should raise the suspicion of “periictal pseudoprogression”. In order to avoid overtreatment, this phenomenon has to be taken into account in the interpretation of $^{18}$F-FET PET images and a close clinical and MRI/$^{18}$F-FET PET reevaluation for at least 8 weeks should be considered.

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POTENTIAL CONFLICTS OF INTEREST

The authors have no conflicts of interest related to this work and confirm the originality of this study. All authors have seen and agree with the contents of the manuscript. The Journal of Nuclear Medicine requirements for authorship have been met. Parts of the study were presented at the 2014 Scientific Meeting of the Society for Neurooncology (SNO) as poster.

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Abbreviations

$^{11}$C-AMT  $\alpha$-$[^{11}$C$]$methyl-L-tryptophan

$^{11}$C-MET  $[^{11}$C$]$-methionine

$^{18}$F-FDG  $[^{18}$F$]$-2-Fluoro-2-Deoxy-D-Glucose

$^{18}$F-FET  O-(2-$[^{18}$F$]$-fluorethyl)-L-tyrosine

$^{99m}$Tc-HMPAO  $[^{99m}$Tc$]$-Hexa-Methyl-Propylen-Aminooxim

ADC  apparent diffusion coefficient

CD98  4F2hc/CD98, heavy subunit of LAT transporter

CPS  complex partial seizure

DWI  diffusion-weighted imaging

FFPE  formalin fixed and paraffin embedded tissue

FLAIR  fluid attenuated inversion recovery

LAT1/2  L-type amino acid transporter, light subunit of LAT transporter

LBR  lesion-to-brain ratio

PWI  perfusion-weighted imaging

SD  standard deviation

SE  status epilepticus

SES  series of epileptic seizures

SPS  simple partial seizure

SUV  standardized uptake values

T1w  T1-weighted sequence

T1wCE  contrast enhanced T1-weighted sequence

TCS  tonic-clonic seizure
TTP  
time-to-peak
REFERENCES


Figure 1.

Figure 1. Structural and metabolic changes in MRI and $^{18}$F-FET PET in focal status epilepticus. Case 1 represents a 64-year old female with clinically stable right frontal anaplastic astrocytoma WHO III without residual tumor. In 2011, she developed a series of treatment-refractory motor SPS and a focal SE of the left arm and leg, followed by a severe and prolonged postictal left hemiparesis for 4 weeks. (A-C) MRI and $^{18}$F-FET PET was performed simultaneously with motor SPS and revealed a distinct increased and extended cortical $^{18}$F-FET uptake right temporo-parieto-occipital ($LBR_{\text{max}}$ 4.18, $LBR_{\text{mean}}$ 2.58) associated with cortical vasogenic (T2/FLAIR hyperintensity) and cytotoxic (diffusion-restriction in DWI + low ADC values) edema, contrast enhancement (T1wCE, BBB leakage) and hyperperfusion (PWI-PBP, baseline at peak map). $^{18}$F-FET uptake was observed independently from BBB disruption in cortex with (*) and without (+) contrast enhancement in T1wCE. (D) Nine weeks after seizure onset and antiepileptic treatment, structural and metabolic MRI and $^{18}$F-FET PET signal
alterations completely resolved, except for slight cortical atrophy in T1 and T2/FLAIR. In 2014, the same patient again developed a treatment-resistant series of motoric SPS with prolonged postictal hemiparesis for 4 weeks with similar morphological and metabolic changes in MRI/$^{18}$F-FET PET ($LBR_{\text{max}}$ 4.02, $LBR_{\text{mean}}$ 2.50) (not shown).
Figure 2. Widespread $^{18}$F-FET uptake, vasogenic and cytotoxic edema, contrast enhancement and hyperperfusion with strict gyral pattern during non-convulsive status epilepticus. Case 3 demonstrates a 66-year old female with clinically stable right frontal oligodendroglioma WHO II without residual tumor. In 2014, the patient presented with repeated CPS followed by treatment-resistant non-convulsive SE. (A) $^{18}$F-FET PET revealed a distinct elevated cortical $^{18}$F-FET uptake of the right hemisphere with frontal and parietal accentuation ($\text{LBR}_{\text{max}}$ 4.42, $\text{LBR}_{\text{mean}}$ 2.45), corresponding to cortical contrast enhancement in T1wCE, marked gyral vasogenic (T2/FLAIR, cortical swelling) and cytotoxic (DWI/ADC) edema and (B) cortical hyperperfusion in DSC-PWI (CBF, cerebral blood flow; CBV, cerebral blood volume; MTT, mean transit time; TTP, time to peak). (C) Clinical deterioration in combination with MRI and $^{18}$F-FET PET imaging was interpreted as tumor recurrence. Therefore, the patient underwent subtotal frontal lobe resection without any histological evidence of tumor progression. (D)
Additional $^{18}$F-FET kinetic analysis of the right frontal lesion and normal contralateral brain demonstrated a SUV$_{\text{mean}}$ time-activity-course curve pattern with continuously increasing $^{18}$F-FET uptake without wash-out.
Figure 3. Cortical amino acid metabolism in $^{18}$F-FET PET in the course of a prolonged postictal episode. Case 4 demonstrates a 44-year old male with clinically stable anaplastic astrocytoma WHO III without any residual tumor over years who presented with TCS followed by severe and prolonged postictal symptoms (global aphasia, right-sided hemiplegia and hemineglect) over 8 weeks. (A) MRI (day 1) and $^{18}$F-FET PET (day 4) showed a distinct increased and extended cortical $^{18}$F-FET uptake of the left brain hemisphere ($LBR_{\text{max}}$ 3.95, $LBR_{\text{mean}}$ 2.08) with frontal and temporal accentuation, corresponding to slight cortical vasogenic and cytotoxic edema (T2/FLAIR, DWI/ADC) without contrast enhancement (T1wCE). EEG monitoring, $^{18}$F-FDG PET (glucose hypometabolism, red arrows) and $^{99m}$Tc-HMPAO SPECT (hypoperfusion, only written report available), however, revealed no evidence of status epilepticus. (B) $^{18}$F-FET PET 11 days after symptom onset and 7 days after first $^{18}$F-FET PET a slight regression of cortical $^{18}$F-FET uptake ($LBR_{\text{max}}$ 2.34, $LBR_{\text{mean}}$ 1.45) was observed. (C) The
patient slowly recovered within 8 weeks after seizure onset. $^{18}$F-FET PET and MRI 12 weeks after symptom onset demonstrated complete recovery of cortical $^{18}$F-FET uptake and brain edema, only residual cortical atrophy in T1 and T2/FLAIR sequences remained.
Figure 4

LAT1  LAT2  CD98

Seizure-affected tissue

A. Neurons

B. Reactive astrocytes

Glioma infiltration zone

C. Neurons

D. Reactive astrocytes

Tumor tissue

E. AA WHO II

F. GBM WHO IV
Figure 4. LAT1, LAT2 and CD98 protein expression pattern in seizure-affected and glioma tissue. LAT1, LAT2 and CD98 protein expression pattern in seizure-affected and tumor tissue. 

(A) LAT1, LAT2 and CD98 showed strong and widespread expression in neurons of seizure-affected cortex obtained from a patient with non-convulsive status epilepticus and subtotal frontal lobe resection (case 3; Fig. 2; blue arrow = neuron; red arrow = vessel). (B) LAT1, LAT2 and CD98 were also detected in brain endothelial cells and reactive astrocytes (astrocyte-endothelium interaction as part of the blood-brain barrier; red arrow = vessel, black arrow = reactive astrocyte). Overall, LAT1, LAT2 and CD98 expression from neurons was more frequent than that from reactive astrocytes as reactive astrogliosis was only focally represented. (C) Within the infiltration zone of an astrocytoma WHO grade II cortical neurons revealed a pronounced staining of LAT1/LAT2/CD98, in particular when glioma cells directly interact with neurons (“tumor cells as satellites of neurons”; blue arrow = neuron, open black arrow = satellitosis by tumor cells). (D) In addition, sporadic LAT1/LAT2/CD98 positive reactive astrocytes were observed within the tumor infiltration zone. In comparison, tumor cells and tumor endothelium of (E) anaplastic astrocytoma WHO grade III and (F) glioblastoma WHO grade IV were also strongly positive for LAT1, LAT2 and CD98 expression.
<table>
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<tr>
<th>Case</th>
<th>Center</th>
<th>Age (y)</th>
<th>Sex</th>
<th>Diagnosis</th>
<th>Tumor localization</th>
<th>Treatment</th>
<th>Disease status</th>
<th>Seizure disorder before</th>
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<td>1+2*</td>
<td>F</td>
<td>64</td>
<td>f</td>
<td>AA (1989)</td>
<td>right frontal</td>
<td>SU, RA, CT 1989</td>
<td>SD, no residual tumor yes (motor SPS, TCS)</td>
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<tr>
<td>3</td>
<td>R</td>
<td>66</td>
<td>f</td>
<td>O (1985)</td>
<td>right frontal</td>
<td>SU, RA, PCV 1985</td>
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<td>54</td>
<td>m</td>
<td>A (2014)</td>
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<td>SU, TMZ 2014</td>
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<td>7</td>
<td>R</td>
<td>51</td>
<td>m</td>
<td>GBM (2013)</td>
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<td>SU 2013</td>
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<td>R</td>
<td>76</td>
<td>f</td>
<td>Non-convulsive SE caused by septic encephalopathy (06/2013)</td>
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<td>no recovery yes (non-convulsive SE 04/2013)</td>
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<td>S</td>
<td>66</td>
<td>f</td>
<td>Embolic cerebral ischemia (2011)</td>
<td>Anticonvulsive treatment</td>
<td>seizure free after 1 day no</td>
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**Table 1. Patient characteristics at the time of seizure diagnosis**

*Abbreviations:* (m) male, (f) female; (F) Freiburg - Germany, (R) Regensburg – Germany, (S) Salzburg – Austria; (ID) initial diagnosis; (A) astrocytoma WHO II, (OA) oligoastrocytoma WHO II, (O) oligodendroglioma WHO II, (AA) anaplastic astrocytoma
WHO III, (AO) anaplastic oligodendroglioma WHO III, (AOA) anaplastic oligoastrocytoma WHO III; (GBM) glioblastoma WHO IV
(s, secondary); (SU) surgery, (RA) radiotherapy, (TMZ) temozolomide, (BCNU) carmustine, (CCNU) lomustine, (PC) procarbazine +
CCNU, (BEV) bevacizumab; (SD) stable disease, (PD) progressive disease
(*) The patient presented with the same clinical symptoms and EEG findings according to status epilepticus in 2011 and 2014. At both
time points combined MRI and $^{18}$F-FET PET imaging was available.
<table>
<thead>
<tr>
<th>Case</th>
<th>Diagnosis</th>
<th>EEG Findings</th>
<th>Hemisphere</th>
<th>Lobe(s)</th>
<th>T1wCE</th>
<th>T2/FLAIR</th>
<th>DWI/ADC</th>
<th>LBR&lt;sub&gt;max&lt;/sub&gt;</th>
<th>LBR&lt;sub&gt;mean&lt;/sub&gt;</th>
<th>MLV</th>
<th>Upptake Extension</th>
<th>Epi-PET Duration</th>
<th>Biopsy/Surgery</th>
<th>Symptom Duration</th>
<th>18F-FET PET Pre-investigation</th>
<th>18F-FET PET Follow up</th>
<th>18F-FET Reversibility</th>
<th>LBR&lt;sub&gt;max&lt;/sub&gt;</th>
<th>LBR&lt;sub&gt;mean&lt;/sub&gt;</th>
<th>MLV</th>
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<td>SA</td>
<td>R, P, T, O</td>
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<td>++</td>
<td>++</td>
<td>4.18</td>
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<td>++</td>
<td>++</td>
<td>++</td>
<td>4.02</td>
<td>2.50</td>
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<td>++</td>
<td>++</td>
<td>4.42</td>
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<td>+++ 6d</td>
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<td>2.47</td>
<td>1.68</td>
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<td>+++ 5d</td>
<td>-</td>
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<td>Daily (5-10) motor SPS followed by focal motor SE</td>
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<td>++</td>
<td>++</td>
<td>++</td>
<td>2.63</td>
<td>1.71</td>
<td>26</td>
<td>++ 7d</td>
<td>-</td>
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<td>Repeated motor SPS, secondarily TCS followed by focal acoustic SE</td>
<td>ED, SA</td>
<td>R, F, P</td>
<td>-</td>
<td>+</td>
<td>++</td>
<td>na</td>
<td>1.83</td>
<td>1.46</td>
<td>19</td>
<td>++ 5d</td>
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<td>1.42</td>
<td>23</td>
<td>+ 3d</td>
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<td>na</td>
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<td>8</td>
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Table 2. Overview on seizure activity, EEG findings, MRI and 18F-FET PET imaging and disease course of the study population

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<td>1.75</td>
<td>1.57</td>
<td>16</td>
<td>+ sim</td>
<td>SU\textsuperscript{TU}</td>
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<td>1.23</td>
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**Abbreviations:** (SE) status epilepticus, (SA) slow activity, (ED) epileptic discharges; (nr) not recovered; (na) not assessed or available, (LBR) lesion-to-brain ratio, (MLV) metabolic lesion volume [ml]

**Footnotes:** (*) Evaluation of structural and metabolic cortical changes in MRI and 18F-FET PET, (+) Tumor localization [(L) left, (R) right and (F) frontal, (P) parietal, (T) temporal, (O) occipital]; (†) Visual assessment of cortical MRI changes [(-) no, (+) weak, (+++) strong]; (‡) Visual assessment of cortical 18F-FET uptake extension [(+) focal (one lobe and ≤ 5 cm), (++) enlarged (one lobe and > 5 cm), (+++) widespread (more than one lobe)]; (§) Time period between seizure onset or last EEG finding and 18F-FET PET in (d) days or (sim) simultaneous; (‖) Surgery due to tumor progression, (SU\textsuperscript{EPI}/BI\textsuperscript{EPI}) surgery/biopsy due to false positive tumor diagnosis in MRI/PET, (-) no surgery/biopsy; (**) The patient presented with identical clinical symptoms and EEG findings in 2011 and 2014 and was evaluated twice;
Epileptic activity increases cerebral amino acid transport assessed by $^{18}$F-fluoroethyl-L-tyrosine amino acid PET - a potential brain tumor mimic

Markus Hutterer, Yvonne Ebner, Markus J Rimenschnieder, Antje Willuweit, Mark McCoy, Barbara Egger, Michael Schröder, Christina Wendl, Dirk Hellwig, Jirka Grosse, Karin Menhart, Martin Proescholdt, Brita Fritsch, Horst Urbach, Günther Stockhammer, Ulrich Roelcke, Norbert Galldiks, Philipp Meyer, Karl-Josef Langen, Peter Hau and Eugen Trinka

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