Serial $^{18}$F-fluoro-2-deoxy-D-glucose Positron Emission Tomography and Magnetic Resonance Imaging of Paraneoplastic Limbic Encephalitis

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Objectives: To review and expand the existing literature of magnetic resonance imaging (MRI) and positron emission tomography (PET) of paraneoplastic limbic encephalitis (PLE).

Methods: We performed serial MRI and $^{18}$F-fluoro-2-deoxy-D-glucose (FDG)–PET in a patient with anti-Ma2–positive PLE. In addition, we reviewed the relevant literature by conducting a search in the MEDLINE database.

Results: We found a total of 7 published patient studies of possible or probable PLE containing both MRI and PET data. In 1 of these reports, the diagnosis of PLE can be regarded as proven. The results of the previous studies are controversial. Epileptic activity and inflammation are assumed to be underlying mechanisms of increased FDG uptake. In our study, we found a focal tracer accumulation in the left medial temporal lobe, which increased during the first 9 months of follow-up and corresponded with an increase of serum anti-Ma2 antibody titers. The MRI findings showed a hyperintense signal change in the left medial temporal lobe without contrast enhancement, which remained unchanged over time.

Conclusions: The results of functional and structural imaging in PLE may differ substantially. Results of FDG-PET can demonstrate focal hypermetabolism over a long time, which may indicate therapeutic potential. A prospective study with more patients will be needed to clarify the relevance of PET as a possible outcome measure in PLE. Future studies should include scalp or semi-invasive electroencephalographic recordings during PET acquisition.

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P ARANEOPLASTIC LIMBIC ENCEPHALITIS (PLE) is a rare neurological disorder. The clinical hallmarks of PLE are memory dysfunction, epilepsy, and psychiatric abnormalities. A variety of tumors has been reported, but in about 70% of cases, PLE occurs in association with small cell lung carcinomas (SCLCs) and testicular germ cell tumors. Paraneoplastic antineuronal antibodies—most often anti-Hu and anti-Ma2—are present in about 60% of cases. Because contrast-enhanced computed tomographic findings are often normal, the neuroradiological diagnosis of PLE has to be based on magnetic resonance imaging (MRI). Findings are hyperintense signals on fluid-attenuated inversion recovery and T2-weighted images in the medial temporal lobe(s), frequently without enhancement after contrast administration. However, a normal MRI finding does not exclude PLE. The existing literature of positron emission tomography (PET) in PLE is scarce. By conducting a search in the MEDLINE database, we found a total of 7 case reports in which PET was performed. We report the serial MRI and PET data of a patient with anti-Ma2–positive PLE and provide a review of the literature.

REPORT OF A CASE

The clinical history has been reported in detail elsewhere. In summary, the patient experienced obsessive-compulsive symptoms, epileptic seizures, a profound memory disorder, and daily chronic headache. All signs and symptoms had developed during a 19-month period. The underlying malignancy was a differentiated teratoma and a seminoma in situ with metastasis of the teratoma into the lung. Anti-Ma2 antibodies were detected in the serum and cerebrospinal fluid of the patient.

MRI AND PET

Magnetic resonance imaging and PET were performed 5 times in close temporal relationship between November 2001 and
January 2003 (Table 1). Written informed consent was obtained from the patient.

Magnetic resonance imaging was performed on a 3-T whole-body system (Medspec 3T/100; Bruker Optics, Ettlingen, Germany). The imaging protocol consisted of the following 4 scans of the same geometry, after anterior commissure–posterior commissure orientation (20 sections; axial and coronal plane; section thickness, 2 mm; section gap, 2.5 mm): (1) 2-dimensional T1-weighted reduced-power multisection modified driven-equilibrium Fourier-transformed images \( (\text{repetition time } [\text{TR}], 1.3 \text{ seconds}; \text{echo time } [\text{TE}], 10 \text{ milliseconds}) \); (2) 2-dimensional T2-weighted fast spin echo scans \( (\text{TR}, 8.5 \text{ seconds}; \text{TE}, 21.7 \text{ milliseconds}) \); (3) 3-dimensional T1-weighted modified driven-equilibrium Fourier-transformed images; and (4) 2-dimensional T1-weighted modified driven-equilibrium Fourier-transformed images after gadolinium–diethylenetriamine pentaacetic acid (DTPA) administration \( (0.2 \text{ mL/kg}) \).

Positron emission tomography of the brain was conducted with a dedicated PET scanner (ECAT EXACT HR+; Siemens, Erlangen, Germany). After the patient fasted for more than 12 hours, dynamic scanning with 17 time frames was started immediately after intravenous injection of 8.6 to 10.8 mCi \((320–400 \text{ MBq})\) of \(^{18}\text{F}-\text{fluoro-2-deoxy-D-glucose} \) and lasted 60 minutes. Time frames from 40 to 60 minutes were summed up for analysis. After anterior commissure–posterior commissure reorientation and coregistration of all PET studies to MRI, individual regions of interest (ROIs) were drawn on selected 5-mm transaxial planes. Regions of interest covered the area of pronounced tracer accumulation in the left medial temporal lobe, the corresponding contralateral region, and the cerebellum. Regional tracer uptake compared with mean cerebellar uptake was calculated as the ratio of the medial temporal lobe to the cerebellum for 2 adjacent temporal PET sections.

In addition, multiple (scalp) electroencephalographic (EEG) recordings were performed (Table 1).

### RESULTS

The T1-weighted MRI findings were unremarkable. The T2-weighted images showed a nonenhancing, small, hyperintense signal alteration in the head of the left hippocampal formation (Figure 1). The size and imaging characteristics of the lesion did not show a change over time (a first 1.5-T MRI examination had been performed in September 2000 by different investigators with identical findings, when the diagnosis was hippocampal sclerosis). Spatially corresponding to the MRI hyperintensity, FDG-PET showed increased tracer uptake in the left medial temporal lobe, which increased from the first to the fourth examination and decreased slightly in the last PET scan (Figure 2). For comparison, respective ROI data of FDG-PET scans of 8 healthy probands are presented as mean and range values, illustrating the marked left-sided increase in tracer uptake in the patient studies (Table 2).

The results of multiple EEG recordings (first performed in June 2001 by different investigators) had been unremarkable or nonspecific until January 2002, when the EEG recording once showed discontinuous sharp slow-wave activity in the left frontotemporal region. On follow-up, there was discontinuous theta-wave activity within the same localization, but no epileptiform discharges.

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**Table 1. Dates and Particular Findings of Sequential MRI, FDG-PET, and EEG Recordings**

<table>
<thead>
<tr>
<th>Examination</th>
<th>Date</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRI</td>
<td>September 4, 2000</td>
<td>“Hippocampal sclerosis” (outward)</td>
</tr>
<tr>
<td></td>
<td>November 20, 2001</td>
<td>Hyperintense signal alteration (approximately 3 × 3 mm) in the head of the left hippocampal formation on T2-weighted images; no contrast enhancement</td>
</tr>
<tr>
<td></td>
<td>December 4, 2001</td>
<td></td>
</tr>
<tr>
<td></td>
<td>February 5, 2002</td>
<td></td>
</tr>
<tr>
<td></td>
<td>June 27, 2002</td>
<td></td>
</tr>
<tr>
<td></td>
<td>September 17, 2002</td>
<td></td>
</tr>
<tr>
<td></td>
<td>January 14, 2003</td>
<td></td>
</tr>
<tr>
<td>FDG-PET</td>
<td>December 3, 2001</td>
<td>Focal increased glucose uptake in the left medial temporal lobe</td>
</tr>
<tr>
<td></td>
<td>March 12, 2002</td>
<td></td>
</tr>
<tr>
<td></td>
<td>June 25, 2002</td>
<td></td>
</tr>
<tr>
<td></td>
<td>September 17, 2002</td>
<td></td>
</tr>
<tr>
<td></td>
<td>January 17, 2003</td>
<td></td>
</tr>
<tr>
<td>EEG</td>
<td>July 6, 2001</td>
<td>Normal (outward)</td>
</tr>
<tr>
<td></td>
<td>November 22, 2001</td>
<td>Intermittent bilateral 7-Hz theta wave</td>
</tr>
<tr>
<td></td>
<td>December 17, 2001</td>
<td></td>
</tr>
<tr>
<td></td>
<td>January 14, 2002</td>
<td></td>
</tr>
<tr>
<td></td>
<td>February 26, 2002</td>
<td>Discontinuous focal 6-Hz theta wave, frontotemporal left</td>
</tr>
<tr>
<td></td>
<td>January 15, 2003</td>
<td>Discontinuous focal 4-Hz theta wave, frontotemporal left</td>
</tr>
</tbody>
</table>

**Abbreviations:** EEG, electroencephalography; FDG-PET, \(^{18}\text{F}-\text{fluoro-2-deoxy-D-glucose} \) positron emission tomography; MRI, magnetic resonance imaging.
An early PET study of a patient with probable PLE was published by Franck et al in 1987. The patient had epilepsy and amnesia. One year after the disease onset and again 9 months later, PET was performed. During this period, the patient was clinically free of seizures, but the EEG showed left temporal epileptic bursts. The PET scan first showed increased tracer uptake in the left temporal region and profoundly decreased activity in the same area on follow-up. No information was given about MRI or antibody reactivity. The patient died 3 weeks after the second PET scan. Autopsy disclosed an SCLC and atrophy of left medial temporal structures. The authors assumed that the focal hyperactivity on the PET scan reflected an active epileptic focus, which led to progressive mitochondrial and neuronal impairment, and thus to the hypoactivity on follow-up.

In 1998, Provenzale et al reported a comparison of MRI and FDG-PET findings in a patient with anti-Hu-positive PLE. Positron emission tomography had been performed 1 week before MRI. The findings were discordant in a sense that FDG-PET showed increased tracer activity in both medial temporal lobes, which was worse on the left side, whereas MRI showed non-enhancing hyperintensities in the amygdala and hippocampi, which were worse on the right side. There was no evidence of seizure activity in the EEG recording. The authors stated that MRI and PET had been performed during the acute stage of the disease and that the discordance may reflect different stages of an inflammatory process coexisting in the 2 temporal lobes.

**Table 2. Relative FDG Uptake in Medial Temporal Lobe Structures in 5 PET Scans**

<table>
<thead>
<tr>
<th>PET Scans</th>
<th>ROI MT/C Ratio</th>
<th>Inferior</th>
<th></th>
<th></th>
<th>Superior</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Right</td>
<td></td>
<td></td>
<td>Left</td>
<td></td>
<td></td>
</tr>
<tr>
<td>December 3, 2001</td>
<td>0.87</td>
<td>0.91</td>
<td></td>
<td></td>
<td>0.89</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>March 12, 2002</td>
<td>0.77</td>
<td>0.93</td>
<td></td>
<td></td>
<td>0.72</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>June 25, 2002</td>
<td>0.88</td>
<td>1.01</td>
<td></td>
<td></td>
<td>0.81</td>
<td>1.13</td>
<td></td>
</tr>
<tr>
<td>September 17, 2002</td>
<td>0.90</td>
<td>1.10</td>
<td></td>
<td></td>
<td>0.80</td>
<td>1.23</td>
<td></td>
</tr>
<tr>
<td>January 17, 2003</td>
<td>0.91</td>
<td>0.93</td>
<td></td>
<td></td>
<td>0.78</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>8 Healthy controls</td>
<td>0.83</td>
<td>0.83</td>
<td>0.82</td>
<td>0.80</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>0.71-0.93</td>
<td>0.75-0.93</td>
<td>0.65-0.97</td>
<td>0.67-0.97</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Range</td>
<td>0.67-0.97</td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

Abbreviations: FDG, 18F-fluoro-2-deoxy-D-glucose; MT/C, medial temporal lobe/cerebellum (reference); PET, positron emission tomography; ROI, region of interest.
lobes. Epilepsy was excluded as a cause of the abnormal PET findings. The authors concluded that PET imaging appears to offer greater specificity for staging of the inflammatory process.

Fakhoury et al described 2 patients with probable PLE, in whom they performed MRI and PET. Both patients had generalized and complex partial seizures and memory deficits. In one patient, metastatic breast cancer was finally diagnosed; in the other, metastatic SCLC. There was no information about onconeural antibodies in the first patient. No antibodies were detected in the serum or the cerebrospinal fluid of the latter. The MRI findings were normal in both patients. The EEG recording showed bilateral interictal epileptiform discharges in the first patient, and bitemporal 2- to 3-Hz ictal discharges in the second patient. The FDG-PET scans showed focal areas of increased uptake in the right hippocampal formation in both patients. A repeat PET scan in the second patient, which was performed 6 months after treatment of the SCLC, was unremarkable. There was no information about MRI and EEG at that time. Unlike Provenzale et al, these authors concluded that focal hyperactivity on PET in patients with PLE may be related to subclinical seizures rather than a stage of the underlying (inflammatory) disease process.

Another report describing a patient with probable PLE with MRI and PET data was published by Na et al. The patient presented with memory dysfunction, increased irritability, and anxiety. The EEG recording showed intermittent generalized slowing. The MRI findings showed nonenhancing T2-weighted hyperintense lesions bilaterally in the medial temporal lobes, more marked on the left side. A first FDG-PET scan showed corresponding increased uptake bilaterally. A follow-up PET scan after 6 weeks again showed bilateral medial temporal hypermetabolism, now predominantly on the right side. Concomitant MRI was obviously not performed. Nine months later, an SCLC was diagnosed. Tests for anti-Hu antibodies were negative in the serum and cerebrospinal fluid. The authors assumed that the MRI and PET findings in this patient most likely represented inflammatory changes in the medial temporal lobes, because there was no clinical or EEG evidence of seizures.

Most recently, Kassubeck et al reported results on coregistration of FDG-PET and 3-dimensional MRI in 2 patients with possible or probable PLE. In one patient, a rectal adenocarcinoma was diagnosed; in the other, no malignancy was identified. Test results for antineuronal antibodies were negative in both patients. Both patients had neuropsychological deficits and seizures, and EEG and long-term video-EEG recordings revealed ictal foci. Magnetic resonance imaging showed T2-weighted hyperintense mesiotemporal lesions, and FDG-PET showed a significant asymmetrical focal hypermetabolism in hippocampal areas in both cases bilaterally. Because of the absence of clinical evidence of seizures at the time of PET, the authors concluded that the focal hypermetabolism was caused by inflammatory changes.

In a critical review of the previous reports, it becomes evident that in only one case was there a proven diagnosis of PLE. All of the other patients had clinically possible or probable PLE. However, the definite etiology of the underlying pathologic process may be of crucial relevance with respect to its imaging characteristics on MRI and PET. All reports share more or less pronounced discrepancies between MRI and PET findings. Interpretation of this mismatch is difficult, because not all reports contain sufficient data on the temporal relationships between MRI and PET. However, in cases with lesions of medial temporal structures with other causes (ie, surgery, herpes simplex encephalitis, and ischemic, anoxic, and toxic damage), disturbances of metabolism and blood flow typically extend beyond the morphological defects detected by contrast-enhanced computed tomography or MRI. Of special interest, no contrast enhancement by means of gadolinium-DTPA was found in any of the patients with positive MRI findings. In summary, nearly half of the investigators concluded that the focal hypermetabolism on PET may represent seizure activity, whereas the other half considered the PET-detected abnormalities to be correlates of an underlying inflammatory process.

Our report in comparison with previous studies

To our knowledge, our report is the first one to contain information about serial MRI, FDG-PET, and EEG in a patient with anti-Ma2-associated PLE. In general, this is the second report of cerebral PET in proven PLE. Owing to the serial character of our study, accidental discrepancies or correspondences between the imaging findings themselves and imaging and EEG findings can be neglected. The result of an increasing focal hypermetabolism on PET in the context of stable MRI findings during the course of months is remarkable and has not been reported in PLE. This increase was paralleled by an increase of the Western blot serum anti-Ma2 antibody titers between December 2001 (1:500) and September 2002 (1:16000).

As in all cited reports and most reports of MRI of PLE, we did not find contrast enhancement on MRI. Gadolinium enhancement is a marker of blood-brain barrier disruption and inflammation. As is known from multiple sclerosis, focal inflammatory blood-brain barrier leakage may be preceded by subtle progressive alterations in tissue integrity. However, these lesions are not detected by conventional MRI (“normal-appearing white matter”). It can therefore be hypothesized that PET abnormalities in PLE may be preceded by contrast enhancement, and that hypermetabolism on PET thus reflects different aspects or stages of inflammation than contrast-enhanced MRI. It is noteworthy in this context that a recent report describes diffusion MRI findings in nonparaneoplastic limbic en-
cephalitis. Lesions in the medial temporal lobes, which could be identified on T1- and T2-weighted images, were hyperintense on diffusion MRI, but showed normal apparent diffusion coefficient values, suggesting an absence of cytotoxic edema. Unfortunately, no information was given about contrast-enhanced MRI.

Although it cannot be excluded that focal glucose hypermetabolism in PLE represents subclinical seizure activity, our findings do not support this assumption of previous reports.10,12 There was no clinical evidence of worsening in the patient's epilepsy, and the EEG recording only once had shown epileptiform discharges (Table 1). Thus, one would suspect that the patient was in a subclinical epileptic state every time PET was performed. Moreover, despite few reports of increased regional glucose metabolism during interictal spike activity,21-23 interictal PET findings typically seem to show focal hypometabolism,24-27 even if interictal spikes are recorded.28-30 Unfortunately, because of technical limitations, we were unable to perform EEG recording during the PET procedure.

ETIOLOGY AND SPECIFICITY OF PET FINDINGS

Memory dysfunction usually goes along with severe depression of glucose metabolism in PET.17 The cellular mechanisms underlying increased tracer uptake on PET are unknown. As was assumed in viral encephalitis, it is likely that the tracer accumulates within brain tissue and not within inflammatory macrophages and lymphocytes in areas of T2-weighted signal abnormalities.31 Our observation of stable non–gadolinium-enhancing MRI findings in the presence of increasing focal glucose hypermetabolism supports this hypothesis. Neuropsychiatric sequelae of limbic encephalitis can obviously be related not only to chronic temporal lobe hypometabolism, but to long-lasting hypometabolism as well. However, hypometabolism might be a reliable predictor of long-term outcome and sequelae,17,31 whereas hypermetabolism might indicate therapeutic potential. A limited improvement after nonnontumor therapy could indeed be documented in our patient.15 A distinct advantage of the method may therefore be its potential for staging the disease. The latter would be of great relevance in cases of PLE, in which immunomodulatory therapies can be helpful, and as to date, there is no reliable information regarding the start, length, and frequency of such therapies.3

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Author Contributions: Study concept and design: Scheid and von Cramon. Acquisition of data: Scheid, Lincke,Voltz, and Sabri. Analysis and interpretation of data: Scheid. Drafting of the manuscript: Scheid and Lincke. Critical revision of the manuscript for important intellectual content: Scheid,Voltz,von Cramon, and Sabri. Statistical analysis: Scheid. Administrative, technical, and material support: Scheid, Lincke, Voltz, and Sabri. Study supervision: von Cramon.

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