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How I Treat Patients with EEG Patterns on the Ictal–Interictal Continuum in the Neuro ICU

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Abstract Refractory status epilepticus (RSE) is associated with a high risk of poor outcome and treated by most neurointensivists with continuous intravenous antiepileptic medications (cIV-AEDs). Continuous EEG monitoring has allowed us to unveil a number of epileptiform patterns of less certain significance. These have been labeled ictal to interictal continuum (IIC), many of which are associated with poor outcome. It is unclear to which extent individual patterns are epiphenomena or lead to additional brain injury. The treatment of these patterns is highly controversial and guidelines how to manage them are non existent. In this review of a challenging case, I will discuss a number of approaches to determine the ictal nature of the IIC in an effort to minimize neuronal injury from epileptiform brain activity on the one hand and from the treatment on the other hand. Ultimately it will be most important to replace the dichotomy of ictal versus non-ictal patterns by differentiating between harmful and non-harmful patterns.

Keywords Continuous EEG · Ictal–interictal continuum · Intensive care unit · Non-convulsive seizures · Non-convulsive status epilepticus

Case Report

A 69-year-old African-American woman presented with unresponsiveness to an outside hospital. She had a history of seizures since childhood, hypertension, and had undergone clipping of a right middle cerebral artery aneurysm after subarachnoid hemorrhage 17 years prior with residual right third nerve palsy. On the day of admission she complained of feeling "strange" and became unresponsive within 1 h of symptom onset. In the outside hospital emergency room her blood pressure was 210/11 and her heart rate was 80. She grimaced to pain, was not following commands, and she had a right third cranial nerve palsy and left hemiparesis. She had an NIH Stroke Scale of 21 and was transferred to our institution for possible intra-arterial tPA. On arrival to the Neuro ICU she was noted to have right facial twitching that spread to the contralateral face, left arm, and both legs. CT angiogram revealed no infarct or vessel occlusion. Convulsions stopped after 6 mg of IV lorazepam and she was loaded with 1.5 g of IV fosphenytoin. She remained unresponsive and had withdrawal of the right more than the left extremity. Emergent cEEG revealed frequent electrographic seizures originating from the right temporal region (Fig. 1, panel a). The patient was loaded with IV valproate (30 mg/kg) and the cEEG revealed decreased seizure activity but persistent right-sided PLEDS with superimposed rhythmic slowing. A technetium-99m-HMAPO single photon emission computed tomography (SPECT) scan obtained on hospital day 3 showed increased blood flow in the right temporal lobe (Fig. 2). In response to this, she received a bolus of 1500 mg IV levetiracetam and was started on 1000 mg twice daily of IV levetiracetam (serum levels of valproate 114 μg/ml, phenytoin 14 μg/ml, free phenytoin 3.1 μg/ml). Subsequently, the EEG showed only isolated epileptiform discharges. Lumbar puncture was unremarkable. Her mental status improved slowly and she was discharged to subacute rehabilitation 2 weeks after presentation on phenytoin, valproate, and levetiracetam.

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Due to cognitive deterioration in the rehabilitation facility she was tapered off antiepileptic medications and returned to her neurologic baseline. One month after discharge from our institution she had a flurry of complex partial seizures and was started on phenytoin, valproate, and levetiracetam at an outside hospital. CEEG on arrival at our institution revealed PLEDs at 1–2 Hz frequency from the right hemisphere at times with superimposed delta. The morning after admission EEG showed very frequent epileptiform discharges from the right temporal lobe that evolved in frequency and were followed by right greater than left background slowing. This was interpreted as non-convulsive status epilepticus (NCSE). The seizures were stopped with a midazolam load of 14 mg and drip up to 0.4 mg/kg/h. She had persistent PLEDs with superimposed rhythmic slowing and fast activity (Fig. 1, panel b). MRI revealed an area of restricted diffusion, increased cerebral blood flow (CBF), and cerebral blood volume (CBV), and a slightly decreased mean transit time (MTT) in the right temporo-parietal lobe consistent with hyperemia (Figs. 3, rows a, c; 4, left three columns). The midazolam drip was increased to 1 mg/kg/h and she was bolused with valproate to achieve a level of 83 μg/ml. Six days after admission she was successfully weaned off midazolam without recurrence of seizures. PLEDs persisted for almost 2 weeks (Fig. 1, panel c) then resolved gradually and MRI at this point showed almost complete resolution of the previously noted changes (Figs. 3, rows b, d; 4, right three columns).

Due to thrombocytopenia valproate was stopped and after recurrence of NCSE phenobarbital was started. She remained encephalopathic and while weaning phenobarbital she developed left more than right-sided facial twitching. The EEG demonstrated PLEDs which were at times stimulus induced but did not have a clear association with the facial twitching. A benzodiazepine trial was performed with repeated doses of 1 mg midazolam (total of 4 mg) that led to resolution of facial twitching and PLEDs but otherwise no detectable improvement of the neurologic examination. This was interpreted as an equivocal benzodiazepine trial. Fluorodeoxyglucose positron emission tomography (PET) was obtained while the EEG demonstrated brief bursts of sharp fast activity alternating with 2–8 s of diffuse attenuation. PET revealed decreased

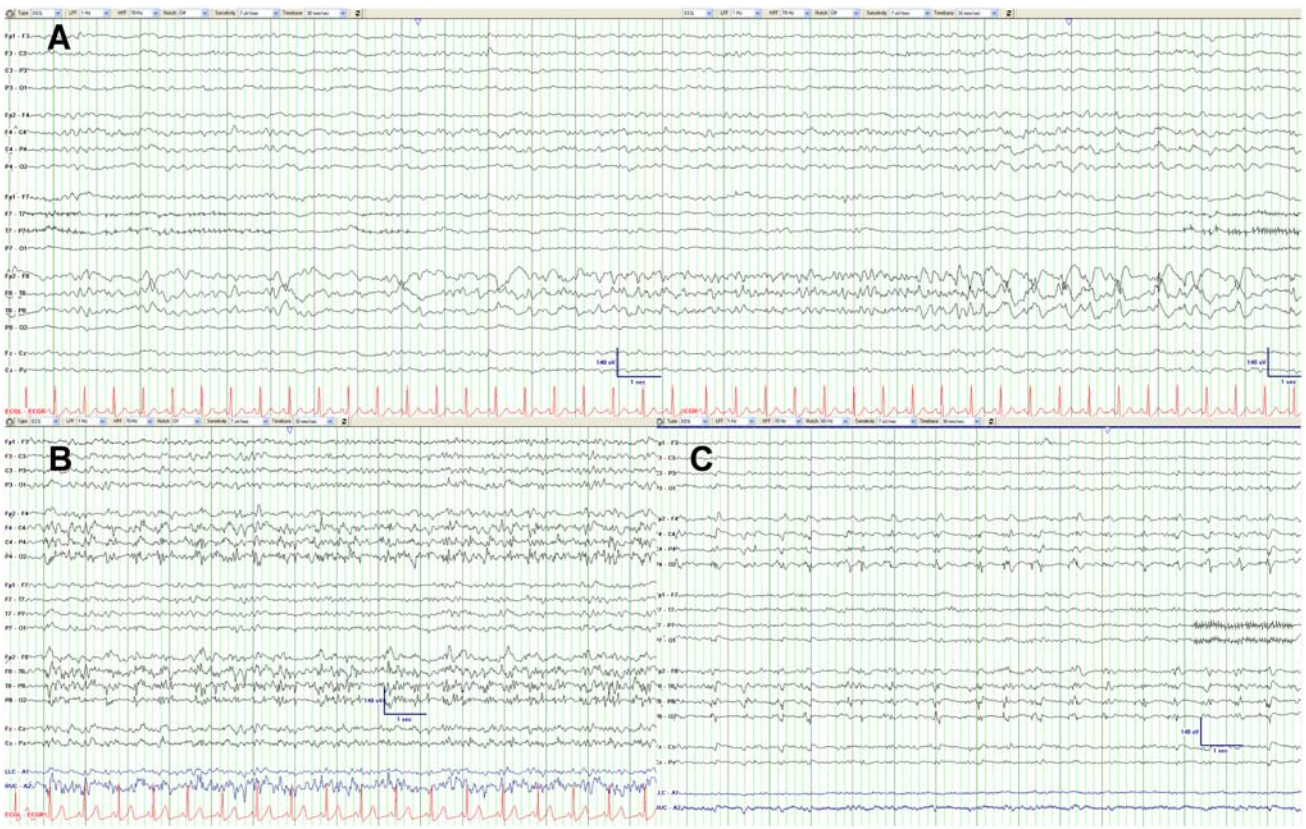

Fig. 1 Continuous EEG recording demonstrating an electrographic seizure from the right temporal region (panel *a*) during the patient's first hospitalization, periodic lateralized epileptiform discharges with superimposed fast activity (PLEDs plus, panel *b*) and PLEDs at 1 Hz from the right temporal lobe (PLEDs proper, panel *c*) during her second hospitalization

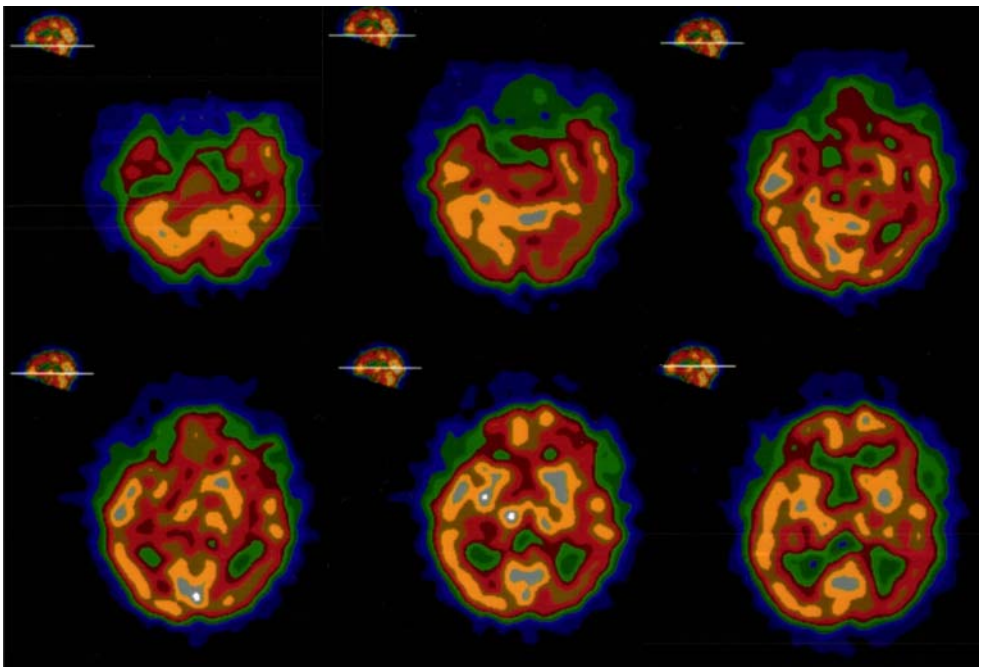

Fig. 2 Technetium-99m-HMAPO single photon emission computed tomography (SPECT) while the EEG demonstrated PLEDS with superimposed rhythmic fast activity (PLEDs plus)

metabolism in the right-temporal lobe most suggestive of an interictal pattern (Fig. 5). Phenobarbital was discontinued and she was discharged to a nursing home 1 month after admission on topiramate, phenytoin, and levetiracetam. We obtained serial neuron specific enolase levels throughout her course (range 2–12 μg/l). The levels did not appear to change with increasing seizure activity. Two months after discharge she is continuing to improve in an active rehabilitation program, she is interactive and able to recognize family members, moves all four extremities, she is mobilized to a chair, and undergoing a ventilator weaning process.

Comments

Management of patients with EEG findings that are epileptiform but that are not clearly ictal is highly controversial with little to no data to support treatment decisions. Much of the underlying pathophysiology still need to be worked out. Nevertheless, neurointensivists that utilize EEG monitoring in the aftermath of convulsive SE and in the acute brain injury setting will frequently encounter this phenomenon. This case illustrates approaches to understand the underlying pathophysiology and raises important issues in the management of epileptiform activity. In the following discussion, I will focus on the highly controversial management of EEG findings that are not clearly interictal but do not meet classic seizure criteria. These patterns have been labeled as the ictal–interictal continuum [IIC, 1].

The IIC includes periodic epileptiform discharges (PEDs) that may be lateralized (i.e., periodic lateralized epileptiform discharges, PLEDs) or generalized (i.e., GPEDs), and may or may not be inducible by alerting stimuli [SIRPIDs, 2]. PEDs are seen in between one-fourth and one-fifth of patients in a number of acute brain injuries or epileptic patients post SE [3] and are independently associated with poor outcome [4–7]. It is unclear why PEDs are associated with poor outcome. One theory is that these patterns are surrogate markers for more severely injured brain (that could not be accounted for by multivariate analyses) and do not by themselves cause further brain injury. Rare cases of benign clinical courses with longstanding chronic PLEDs [8] or bilateral independent PLEDs [9] support this view. The alternative hypothesis is that PEDs and seizures in the acutely injured brain lead to secondary neuronal injury via excessive metabolic demand, excitotoxicity, or other mechanism. Biomarkers of neuronal injury such as neuron specific enolase (NSE), glutamate, glycerol, and the lactate–pyruvate ratio may rise after electrographic seizures [10–15]. Electrographic seizures are associated with increasing mass effect and midline shift in patients with non-traumatic ICH [6, 16]. In animal models [17] of ischemic stroke, electrographic seizures are associated with increased infarct volume and higher mortality. It is possible that some IIC patterns may be more harmful than

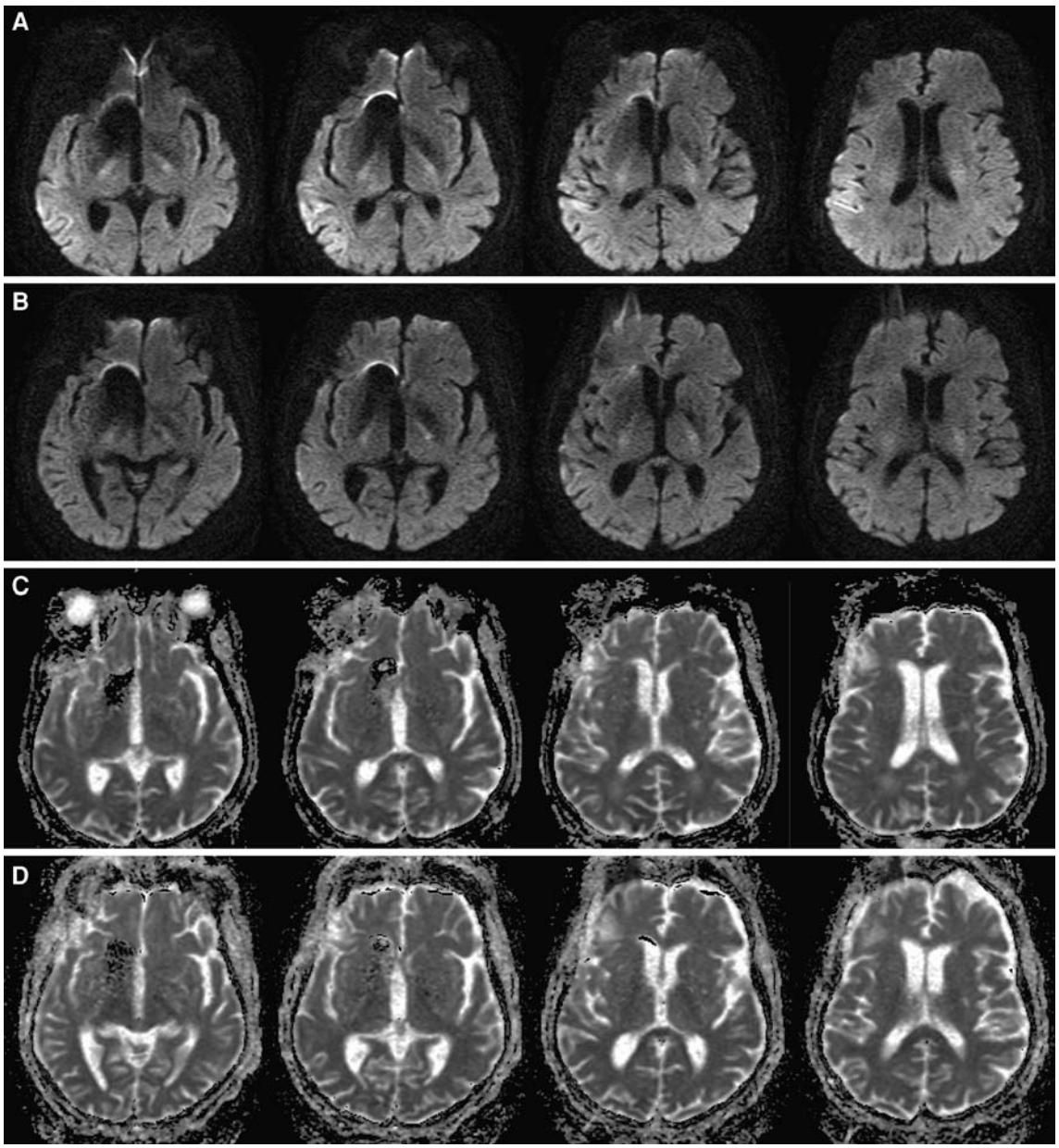

Fig. 3 DWI images (row *a*) during PLEDs with superimposed rhythmic slowing and fast activity (PLEDs plus, see Fig. 1, panel *b*) and after revealed an area of restricted diffusion in the right temporo-parietal lobe with minimal impressive ADC changes (row *c*). After increasing doses of the midazolam drip and valproate less ictal PLEDs persisted (PLEDs proper, see Fig. 1, panel *c*) and MRI at this point showed almost complete resolution of the previously noted changes (panels *b*, *d*)

others, with some just being epiphenomena of acute brain injury [1]. A large number of powerful treatments for ictal EEG activity exist but some of the most powerful ones carry substantial risks, such as hypotension, immunosuppression, respiratory compromise, and prolonged immobilization. The challenge for the clinician lies in weighing the risk that a given EEG pattern is harmful against the risk of aggressive therapy. However, it is worth noting that even if the seizures and PLEDs were not brain damaging, they seem to produce brain dysfunction. This dysfunction may lead to prolonged hospital stay and in itself, may be worth treating to lessen the morbidity and ICU length of stay.

Practically I use three strategies to support treatment decisions for patients in the IIC: (1) compare the EEG signature of the IIC to seizures, (2) characterize physiologic measurements of the IIC to compare them to those seen during seizures (i.e., changes in cerebral blood flow), and (3) quantify ongoing neuronal injury in the presence of the IIC (i.e., measurements of NSE or glycerol on microdialysis; which currently are primarily investigational).

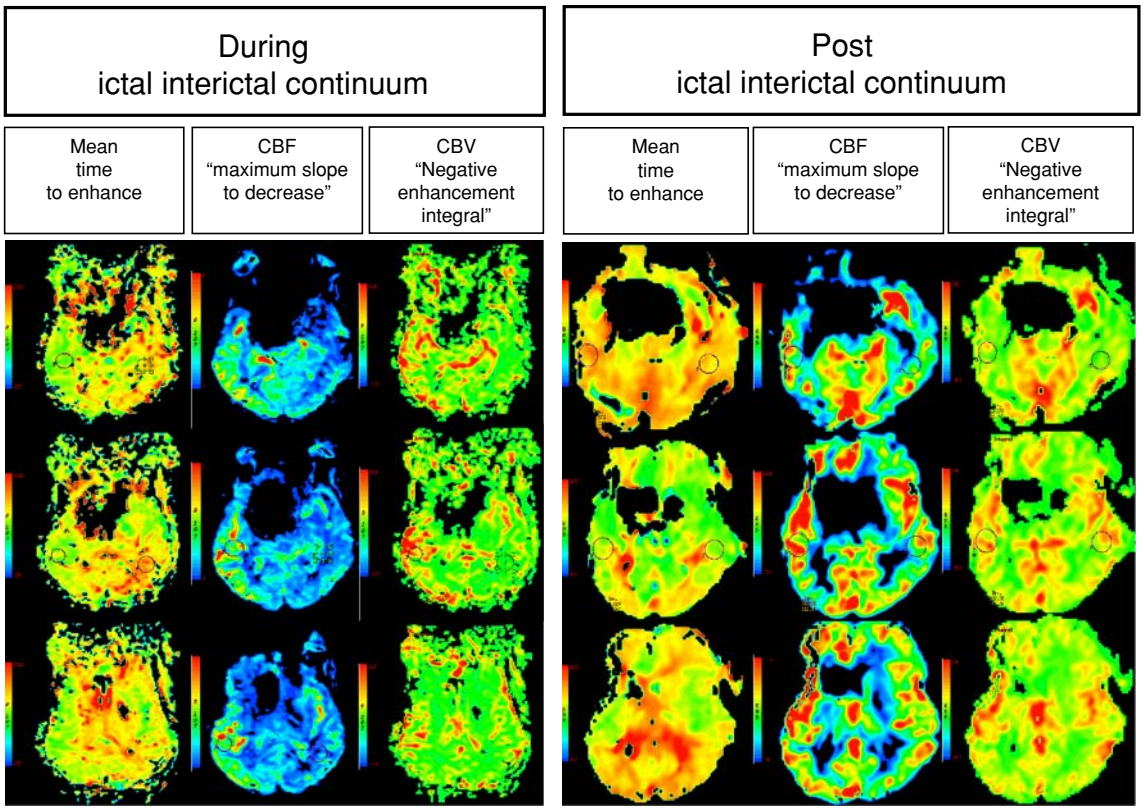

Fig. 4 Dynamic susceptibility contrast-MRI revealing increased cerebral blood flow (CBF) and cerebral blood volume (CBV), and decreased mean transit time (MTT) in the right temporo-parietal lobe (same time points as Fig. 3)

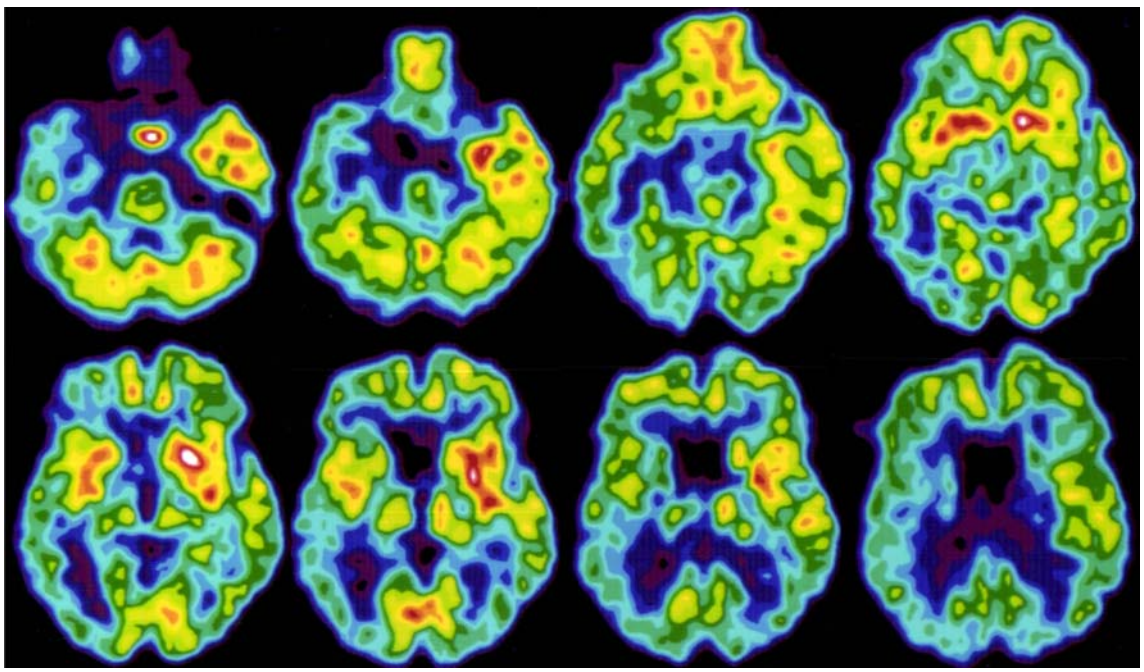

Fig. 5 Fluorodeoxyglucose positron emission tomography (PET) revealed decreased metabolism in the right-temporal lobe at a time of PLEDs proper associated with facial twitching

Strategy 1

An attempt has been made to subclassify EEG patterns of the IIC into those that are more ("PLEDS plus") and those that are less frequently associated with electrographic seizures during the hospital course ["PLEDs proper"; 18]. In this study, PLEDs were classified as "PLEDs plus" if a low amplitude rhythmic discharge was seen in addition to PLEDs. Patients that have this EEG finding frequently cycle between seizures and PLEDs, while patients that only have "PLEDs proper" have a much lower seizure frequency [18]. The current patient was a good example of this since she had convulsive and electrographic seizures, IIC, including PLEDs plus, and PLEDs proper at different points in time. Taking into account that EEG findings in many of these patients change constantly, classification of the patterns is achieved with only moderate interrater reliability [19, 20]. Due to the lack of large studies demonstrating that one pattern is clearly more harmful than others, ancillary testing is often sought.

Strategy 2

I frequently use benzodiazepine trials to determine if an electroclinical scenario behaves like a seizure. Sequential small doses of intravenous benzodiazepines are administered under constant clinical and EEG monitoring [21]. Resolution of the potentially ictal EEG pattern and either an improvement in the clinical state or the appearance of previously absent normal EEG patterns (i.e., posterior-dominant rhythm) suggest an ictal phenomenon. As seen in my patient, this test is more often than not equivocal, often demonstrating resolution of the EEG pattern but no clear clinical improvement.

Imaging studies may be used to show that questionable EEG patterns result in similar blood flow and metabolic changes that are well described for epilepsy patients with seizures but have rarely been reported for IIC patterns post SE or in the acute brain injury setting. Imaging options include SPECT (Fig. 2), CT perfusion, dynamic susceptibility contrast MR imaging (Fig. 4), arterial spin labeling, and PET scanning (Fig. 5). In my patient, SPECT showed an area of increased blood flow (Fig. 2) similar to patterns seen on ictal SPECT scans. This supported my decision to add levetiracetam to her antiepileptic treatment and subsequently her EEG improved and she improved neurologically. It has been shown that focal hyerperfusion on SPECT can disappear with the resolution of PLEDs [22, 23]. Increased perfusion with restricted diffusion on MR imaging using dynamic susceptibility contrast (DSC) has been described in patients with complex partial SE [24]. My patient had a slightly decreased mean transit time and increased CBV and CBF in the right hemisphere at a time of PLEDs plus from this region (Fig. 4, left three columns). This resembles the few reports of MR perfusion in human SE usually performed in the post-ictal phase [24, 25] but imaging findings of the IIC are not well studied. In experimental SE hyperperfusion can be seen on DSC MR imaging within 3 min of SE onset that is followed by hours of hypoperfusion [26]. Interestingly, these authors reported that the pattern of recovery was predictive of outcome. After increasing midazolam and valproate she had almost complete resolution of these abnormalities (Fig. 4, right three columns).

Local cerebral glucose metabolism changes on PET scanning are well described in patients with seizures. Similarly, in PLEDs, PET scanning may show hypermetabolism during and hypometabolism after resolution of PLEDs [27]. Late in the course of my patient's illness, we found decreased glucose metabolism in the right-temporal lobe on PET (Fig. 5) while her EEG demonstrated PLEDs proper and facial twitching. The EEG and imaging study supported the decision to treat less aggressively and tolerate the EEG findings.

Interpretation of these studies is tricky since very little is known about blood flow changes of IIC patterns particularly after convulsive SE or in the setting of acute brain injury. My patient's remote brain injury probably makes her more similar to epilepsy patients but many of the patients with IIC findings will have severe acute brain insults such as massive subarachnoid hemorrhage. In the acute brain injury setting, repeated functional imaging studies should be studied to compare blood flow patterns before and after treatment and determine if blood flow patterns are due to the "ictal" EEG findings and not secondary to the dynamic changes that may be caused by the underlying disorder. It is conceivable that in the acute brain injury setting increased blood flow from a brain region generating PEDs reflects a "healthier" response than decreased blood flow. The lack of blood flow elevations in this setting may indeed relate to a higher risk of injury since the brain is not getting desperately needed extra oxygen and glucose. These phenomena need to be studied systematically before treatment recommendations can be based on them. Blood flow and metabolism changes are secondary phenomena that may be used to corroborate a clinical impression but the main question remains if and to what extent do epileptiform patterns result in additional brain damage. This question is the focus of Strategy 3.

Strategy 3

Theoretically, treatment intensity may be determined by quantifying neuronal injury associated with specific EEG patterns and determining the potential benefit of therapies by studying these parameters over time. The techniques discussed below are not meant as recommendations but

intended to conceptualize approaches that may warrant further investigation. Biomarkers of injury may include imaging studies (i.e., ADC quantification, MR spectroscopy), serum markers (i.e., neuron specific enolase or glial fibrilary acidic protein; [28], or microdialysis endpoints (i.e., lactate–pyruvate ratio or glycerol). Long term follow-up studies may quantify neuronal loss by volumetric measurements of the whole brain or specific areas of the brain (i.e., hippocampus). These approaches can be confounded by co-existing acute brain injury but may be helpful when seizures occur in the setting of epilepsy or remote brain injury. Restricted diffusion was seen on DWI without impressive ADC changes at a time when my patient had IIC patterns on EEG. Both, imaging and EEG findings resolved during the clinical course (Fig. 3). The degree of ADC decrease has been found to correlate with neuronal cell loss in animal studies [29] and restricted diffusion has been seen in the hippocampal formation, cortex, and the posterior thalamus after SE [24, 30, 31] in humans. So far no studies investigated diffusion abnormalities of the IIC. Therefore, a degree of uncertainty in interpreting imaging findings of the IIC persists but like other ancillary testing these are used to illustrate pathophysiolgical similarities to better understand the entity of SE. The DWI changes in my patient resolved with treatment intensification and after resolution of IIC patterns but her ADC findings were underwhelming.

In rats, serum NSE correlates with the amount of histologic injury following lithium–pilocarpine-induced SE [32]. Human studies suggest that serum NSE may be elevated in the setting of neuronal injury including during NCSE [12–15]. We obtained serial NSE levels during our patient's second hospitalization but this was not done in a systematic fashion and levels did not correlate well with ictal EEG activity. Serial assessment of the metabolic effects of epileptic phenomena may also be achieved by analyzing microdialysis fluid. GABA, a major inhibitor of neuronal excitation, measured in microdialysate has been found to be increased during seizures in animals [33] and human complex partial seizures [34]. In traumatic brain injury spikes of glutamate reflecting exitotoxicity, [35], glycerol reflecting membrane breakdown, [10], and lactate–pyruvate ratio [11] have been reported. Microdialysis measurements in general and LPR elevation in particular can reflect a state of energy crisis in the brain. The high temporal resolution of invasive brain monitoring techniques such as microdialysis, cerebral blood flow monitors, and brain tissue oxygen tension measurements may make these attractive to understand pathophysiological processes underlying questionable epileptiform activity in the setting of a study. Disadvantages of these techniques include that they are invasive and may be less accurate if the probe location is distant from a focal epileptic phenomenon. Depth EEG monitoring may also at times be helpful in clarifying questionable surface EEG findings [36]. Our patient did not undergo multimodality monitoring and MR spectroscopy was technically limited.

Continuous EEG monitoring has become widely used in Neuro critical care but the science underlying the interpretation of the observed EEG findings is in its infancy. Small carefully designed studies need to be conducted to better understand the pathophysiology that is associated with epileptic phenomena after convulsive SE and acute brain injury. Based on a better understanding of the pathophysiology we will then have to run large multicenter studies focusing on harmful and treatable EEG findings. In the future we may be able to individualize our therapy based on physiologically driven decision making in a given patient with a given EEG pattern. In the meantime neurointensivists need to be vigilant and make use of ancillary testing to decide on the treatment aggressiveness on a case-by-case basis.

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Author Biography

Jan Claassen: was born in Wuppertal, Germany. He received his MD from the University of Hamburg in 1998 and trained in Critical Care Neurology at the same institution. He received a PhD in clinical neurophysiology from the University of Hamburg studying recovery of somatosensory-evoked potentials in patients with severe traumatic brain injury. He trained as a Postdoctoral Research Fellow in Critical Care Neurology and Epilepsy and Clinical Neurophysiology at Columbia University, New York, under the mentorship of Stephan A. Mayer and Lawrence J. Hirsch. At the same institution, he completed Neurology Residency and Clinical Fellowship in Critical Care Neurology. He is currently an Assistant Professor of Clinical Neurology and Neurosurgery at Columbia University. He is recipient of the Founders Award from the American Academy of Neurology in 2007. He is the author of many original articles, review papers, and book chapters.

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