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Peri-ictal diffusion abnormalities of the thalamus in partial status epilepticus

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SUMMARY

Purpose—To identify and describe thalamic dysfunction in patients with temporal as well as extratemporal status epilepticus (SE), and to also analyze the specific clinical, radiological and EEG characteristics of patients with acute thalamic involvement.

Methods—We retrospectively identified patients who presented with clinical and electrographic evidence of partial SE and had thalamic abnormalities on diffusion-weighted imaging (DWI) within five days of documentation of lateralized epileptiform discharges (Group 1). The spatial and temporal characteristics of the periodic lateralized epileptiform discharges (PLEDs) and the recorded electrographic seizures were analyzed and correlated with MRI-DWI hyperintense lesions. The findings of Group 1 patients were compared with those of patients with partial SE without thalamic abnormalities on DWI (Group 2).

Results—The two groups were similar with regard to clinical presentation and morphology of epileptiform discharges. Group 1 patients had thalamic hyperintense lesions on DWI that appeared in the region of the pulvinar nucleus, ipsilateral to the epileptiform activity. Statistically significant relationship was noted between the presence of thalamic lesions and ipsilateral cortical laminar involvement ($p=0.039$) as well as seizure origin in the posterior quadrants ($p=0.038$). A trend towards PLEDs originating in the posterior quadrants was also noted ($p=0.077$).

Discussion—Thalamic DWI hyperintense lesions may be observed after prolonged partial SE and are likely the result of excessive activity in thalamic nuclei having reciprocal connections with the involved cortex. The thalamus likely participates in the evolution and propagation of partial seizures in status epilepticus.

Keywords

Thalamus; Status epilepticus; DWI; Diffusion

INTRODUCTION

The thalamus has been found to participate in the pathogenesis of generalized epilepsy (GE). Studies using fMRI-EEG correlation techniques (Hamandi et al., 2006) (Laufs et al., 2006) demonstrated activation of the thalamus in patients with idiopathic and symptomatic GE,

even during interictal spike-wave activity. Magnetic resonance spectroscopy (MRS) and quantitative volumetric data (Betting et al., 2006, Bernasconi et al., 2003, Helms et al., 2006) support the presence of thalamic dysfunction in patients with chronic GE, regardless of whether it is controlled or not. These data support the hypothesis that there are abnormalities of the thalamocortical circuits that underlie the development of generalized epileptic discharges.

The role of the thalamus in localization-related epilepsy has only recently started to receive attention. Thalamocortical synchrony has been identified in patients with temporal lobe epilepsy by intracerebral EEG recordings (Guye et al., 2006). Ictal thalamic involvement in patients with partial epilepsy has been described with fMRI techniques, particularly in the presence of secondary bilateral synchrony (Aghakhani et al., 2006). Acute and chronic thalamic dysfunction has been previously demonstrated in temporal lobe epilepsy (TLE) by diffusion-weighted MR imaging (DWI-MRI) (Szabo et al., 2005) (Kimiwada et al., 2006). Again, thalamic atrophy, suggestive of chronic thalamic dysfunction has been shown in patients with TLE, particularly in the presence of mesial temporal sclerosis (Mueller et al., 2006) although this was not evident in extratemporal epilepsy (Natsume et al., 2003, Gartner et al., 2004).

With regard to specific thalamic nuclei, the medial pulvinar nucleus has been found to harbor ictal activity in patients with TLE (Rosenberg et al., 2006, Guye et al., 2006), particularly when there was propagation outside the onset zone. Indirect imaging evidence of pulvinar involvement in patients with complex partial status epilepticus has also been described (Szabo et al., 2005) although data from larger patient series is lacking. Additionally, decreased glucose metabolism in the mediodorsal nucleus and increased glucose metabolism in the lateral thalamus has been described in patients with TLE (Juhasz et al., 1999). Similar involvement of the thalamus in partial epilepsy has been described in animal studies (Bertram and Scott, 2000, Cassidy and Gale, 1998).

The issue of thalamic activation and/or subsequent dysfunction in patients with partial epilepsy may have significant clinical implications. Asymmetry of thalamic metabolism has been associated with a poorer outcome after temporal lobectomy (Newberg et al., 2000). Moreover, deep brain stimulation of specific thalamic regions holds promise for improved seizure control (Andrade et al., 2006) although the optimal localization is unclear and even minute changes in electrode location can have profound effects on cortical responses (Zumsteg et al., 2006).

Given the relative paucity of clinical data, we decided to investigate further the involvement of the thalamus in partial-onset seizures and, more specifically, in patients with complex partial status epilepticus. We focused on analysis of DWI-MRI images because of the non-invasive nature of the test and the excellent spatial resolution during the acute peri-ictal phase. Our aim was to identify, define the frequency of, and describe thalamic dysfunction in patients in the peri-ictal phase of SE and also to analyze the specific electrographic, radiological, and clinical characteristics of patients with acute thalamic involvement.

METHODS

Patients

We examined the archives of Henry Ford Hospital for the time period between January 2000 and January 2005. Patients were included in the study if they fulfilled the following criteria: a) they were above the age of 18 at the time of presentation, b) they had no history of idiopathic or symptomatic generalized epilepsy, c) they were admitted to the hospital with a clinical diagnosis of status epilepticus (defined as a seizure or series of seizures lasting more

than 30 minutes without interim return of consciousness), d) they had electroencephalographic evidence of ongoing partial status epilepticus or periodic lateralized epileptiform discharges (PLEDs), e) they underwent MR imaging including DWI sequences for clinical purposes within five days of the time of EEG testing, and f) they had evidence of thalamic lesions on DWI that could not be ascribed to a pre-existing pathological process. We identified thus eleven patients (Group 1) and analyzed their clinical, electrographic and radiological data. Additionally, we compared these to a control group of 25 patients (Group 2) that fulfilled all study criteria except for criterion (f), meaning that they did not have thalamic lesions on DWI.

This retrospective study was approved by the Institutional Review Board (IRB) of the Henry Ford Health System. In accordance with the HIPAA privacy rule Section 164.512(i), the IRB determined that the criteria for waiver of patient authorization had been met.

Patient information was obtained through Henry Ford Health System's electronic medical record system (Care PlusR). All patients had received previous medical care in the Henry Ford Health System. Their demographic data, previous medical history (particularly in relation to neurological disease), and details of current hospitalization were reviewed and analyzed. The etiology of the underlying neurological disease was identified when possible. Two patients expired during hospitalization. Follow-up data were available for five of the remaining patients.

EEG analysis

EEG testing was performed either on a Nicolet Voyageur System (from 2000 until July of 2004), or on Nihon-Kohden 9200 EEG Systems (from mid-July of 2004 until January 2005). Twenty-four Ag/AgCl electrodes were placed utilizing 21 standard electrodes of the International 10–20 System of Electrode Placement in addition to 10–10 system electrodes, Oz, T9, and T10.

EEG records were reviewed by the study epileptologist (DB, Director of the EEG Laboratory, HenryFord Hospital), who was blinded to the clinical information, study design, or any relevant details at the time of interpretation. PLEDs were identified, and the following variables were analyzed: a) location, b) presence of a PLEDs-plus pattern (transitional fast rhythmic discharges), and c) duration of each PLED complex.

Seizure and PLED origin were further classified as: 1) *Frontal*: Origin in frontopolar or frontal leads, 2) *Frontotemporal*: Origin between frontal and T₇/T₈ leads, 3) *Mid-temporal*: Origin from T₇₋₈/P₇₋₈ leads only, 4) *Centroparietal*: Origin from central or parietal leads, or 5) *Temporo-occipital*: Origin between P₇/P₈ and occipital leads.

If there were ongoing electrographic partial seizures (status epilepticus), the following variables were also documented: a) localization of onset of the partial seizures, b) morphology of rhythmical activity at the onset of seizures with particular attention to frequency of discharges and the suppression (or not) of the underlying PLED pattern, and c) pattern of seizure spread.

MRI analysis

All MRIs were performed on a 1.5-T General Electric Signa MRI unit with echo-planar capability. The MRI acquisition parameters were as follows: 1) sagittal T1WI: repetition time (TR), 600 milliseconds; echo time (TE), 25–30 milliseconds; field of view (FOV), 23X23 cm; matrix, 192/256; slice thickness, 5 mm; interslice gap of 2.5 mm; 2) axial T2WI: TR, 3500–6000 milliseconds; TE 90–120 milliseconds; FOV 23X23 cm; matrix, 192/256; slice thickness, 5 mm; interslice gap 2.5 mm; and 3) axial DWI: TR, 10 000; TE, 120

milliseconds; b value, 1000 s/mm²; FOV, 23X23 cm; matrix; 128/128; slice thickness, 6 mm; no interslice gap; number of excitations (NEX) 1. Throughout the acquisition of the images, the patients were clinically monitored.

The MRI examinations of patients who fulfilled study criteria (a–e), (36 patients) were retrospectively reviewed by the study neuroradiologist (SCP – Division Head, Neuroradiology), who was blinded to the clinical information as well as the context and purpose of the study, at the time of interpretation. The location of concurrent acute and chronic lesions in different locations was also noted.

Statistical analysis

Patients with and without thalamic DWI lesions were compared using Fisher's exact tests for the categorical variables. A two sample t-test was done to compare the mean ages for the two groups of patients. Wilcoxon two sample t-tests were done to compare the patient groups for length of hospitalization, time from onset of seizures to MRI, and all three modified Rankin scores (mRS).

Specific information regarding the PLEDs and seizure foci from the patients with and without thalamic DWI lesions were compared using Rao-Scott chi-square tests (Rao and Scott, 1981). This method adjusts for multiple foci within the same patient.

RESULTS

Thirty six patients with documented clinical and/or electrographic partial status epilepticus underwent peri-ictal MR imaging. Eleven (31%) of them had acute thalamic lesions on DWI. The clinical information, MRI data, and EEG data of those 11 patients are described in Tables 1 and 2. Data of the 25 patients of Group 2 are presented in summary only and are compared to those of Group 1 in Tables 3 and 4. All patients were able to tolerate MRI testing within five days from their initial EEG evaluation. The mean time interval from onset of status epilepticus to the initial MRI study was 3 days and 12 hours. Three patients had follow-up MR imaging, all of them within four months from the initial study.

Ten out of eleven patients in Group 1 were admitted to the hospital after presenting to the emergency room and receiving acute treatment there. Patient 11 had undergone orthotopic liver transplantation and developed status epilepticus in the immediate post-operative period. Eight patients developed recurrent complex partial seizures at the onset of the SE. The remaining three patients had partial-onset seizures with secondary generalization.

All patients had received appropriate treatment with IV benzodiazepines and a first-line IV antiepileptic medication by the time the EEG was performed. Eight (72%) of eleven patients did not respond to this initial treatment. They were considered to have refractory SE and were treated with anesthetic doses of IV barbiturates to a PLED or eventual burst-suppression pattern.

No statistical differences between the two groups were identified, with regard to basic demographic data, past medical history, clinical presentation, refractoriness of SE, or etiology of seizures.

Nine out of 10 seizure foci in Group 1 patients were in the posterior regions of the brain (mid-temporal, centroparietal or temporo-occipital) (Table 2). PLED patterns (without temporal or topographic electrographic evolution) were identified in 9/11 patients in Group 1. PLEDs (as was the case for the seizures) also appeared to originate from the posterior regions of the brain. Patient 1 had PLEDs arising from a right frontopolar region. Patient 8

had bilateral independent PLEDs (BIPLEDs) arising from three independent foci (right frontal and bilateral mid-temporal areas), but only the temporal foci produced evolving seizure activity. Patient 10 had right temporal PLEDs which evolved into seizure activity as well as an additional independent focus of seizures in the right centroparietal area, which, when activated, failed to suppress the right temporal PLEDs.

Comparison between the two groups showed that there was a significant relationship between thalamic lesions and posterior origin of epileptiform discharges. A stronger association was noted with seizures, rather than with PLEDs (Table 4). However, no particular posterior region was significantly associated with the presence of thalamic DWI lesions. The PLED and seizure foci in patients of both groups are schematically depicted in Figure 2.

The locations of maximum PLED activity and of electrographic seizure onset were compared in six Group 1 patients (the remaining five patients had PLEDs or continuous seizures only). Interestingly, those did not necessarily correlate. Patients 4 and 10 had seizures arising from a more posterior region compared to the PLEDs, while the seizures of patient 5 had a relatively more anterior origin. In patients 8 and 9, both PLEDs and seizures came from the same regions. Patients 10 (separate focus) and 11 had seizures that were generated from regions that were non adjacent to the PLEDs. Patients 6 and 7 had almost continuous seizures, and no underlying PLED pattern could be seen.

With regard to the mode of evolution of the electrographic activity, we noted spread within contiguous areas of the same hemisphere in patients 4, 5, 6, 7 and 10. Patient 7 was the only one (of the 11) with documented secondary bilateral synchrony. Patient 8 had seizures arising from both temporal areas, whereby the seizures consistently arose in the right temporal derivations and propagated to the left. Only seizures that spread in close proximity to the regions generating PLEDs effectively suppressed the PLED activity. The latter would re-appear after seizure cessation.

Most PLEDs in Group 1 patients had monophasic morphology and duration of 200–500 msec. Average periodicity was 55.5 complexes per 60 seconds (range 30–108/60). Most patients had monophasic PLEDs patterns, although biphasic and poly-spike discharges were also encountered. Three out of 11 PLEDs foci generated PLEDs-plus patterns. No morphological characteristic of the epileptiform discharges (duration of PLEDs complex, PLEDs-plus morphology, discharge frequency at seizure onset) was found to be significantly different between the two Groups.

With regard to the MRI findings, abnormal thalamic signal intensities appeared to involve preferentially the region of the pulvinar nucleus in all patients (Figure 1). In patient 11, hyperintensity of the entire parenchyma of the left thalamus was evident, while in a follow-up MRI 3 days later, abnormal signal appeared in the pulvinar region, as in the other patients (Figure 1, pt 11a–b). Other extrathalamic acute lesions, that did not respect vascular territories, were noted. DWI hyperintensities of the cortical strip gray matter were noted in patients 2, 3, 4, 5, 6 and 11. All of them involved the temporal, parietal and occipital cortices and, in patient 2 only, the insular cortex. Abnormal DWI signal intensities of the mesial temporal lobes were seen in patients 2, 4, 5 and 11. In almost all patients, both thalamic and extra-thalamic signal abnormalities were ipsilateral to the PLED or seizure foci. Patient 5 had PLEDs and seizures arising from the right but had bilateral thalamic lesions (as well as bilateral primary intracranial pathology). Patient 8 had seizures from both hemispheres and bilateral thalamic lesions. In contrast to the above, among the 4 patients of Group 2 with cortical laminar involvement, 2 had anterior lesions, 1 had posterior, and 1 had diffuse hemispheric cortical lesions bilaterally but more prominently in the right posterior quadrant.

The majority of patients of both Groups had refractory SE that resulted in prolonged hospitalization. The modified Rankin score (mRS) was estimated from hospital and outpatient records for both patient Groups, when available. The presence of DWI thalamic lesions was not significantly associated with differences in length of hospitalization or subsequent short- and long-term disability (Table 3).

With regard to follow-up imaging, patient 2 had a follow-up MRI 2 months later. Persistent cortical and thalamic T2 abnormalities with hemorrhagic conversion were noted. Patient 5 also had persistent thalamic T2 abnormalities on follow up MRI 90 days later. However, the possible presence of posterior cortical lesions was obscured by progression of a venous sinus thrombosis. There were no persistent T2-weighted imaging lesions in patient 1 on follow up scan 90 days later.

DISCUSSION

Our study confirms that in patients with partial status epilepticus, ipsilateral focal thalamic hyperintense lesions are seen on DWI, reflecting acute thalamic dysfunction. In addition, it offers insight into the functional connectivity and seizure propagation in partial status epilepticus based on a detailed analysis of electrographic and imaging variables of the studied patients.

The study focused on the imaging and electrographic characteristics of patients with recent clinical SE. However, we acknowledged that by the time of EEG, clinical status had often ceased and abnormal electrographic activity consisted mostly of PLEDs, focal slowing, or generalized slowing. We decided to include only patients that had ongoing seizure activity or post-status PLEDs because those two patterns may localize to a specific cortical area and allow for meaningful MRI-EEG correlations. Focal slowing while lateralized to one hemisphere does not necessarily indicate focal cortical dysfunction locally. Interictal spikes could be another localizing pattern if strictly unilateral and unifocal. Unfortunately, our EEG data were limited to one or two post-SE studies and did not allow for this distinction.

We also elected to study only patients with a maximum interval of 5 days between the EEG and MRI examinations, following the ischemic stroke paradigm (Ahlhelm et al., 2002), wherein the apparent diffusion coefficient (ADC) values start declining after the onset of ischemia and reach a minimum after about 24–48 hours and thereafter increase to become similar to that of normal contralateral tissue (pseudo-normalize) after 7–14 days. We arbitrarily chose a slightly shorter interval, so that we could study acute DWI thalamic lesions before their anticipated pseudo-normalization. There are no pertinent studies describing the time course of the ADC value change in SE-related thalamic lesions.

We identified thalamic lesions on DWI in 31% of patients with partial SE, a frequency that is considerably lower than that in a previously published case series (Szabo et al., 2005), in which 9 of 10 patients with complex partial SE had similar thalamic lesions. This is likely related to the retrospective nature of our study, as well as to the inclusion only of patients who were stable enough to undergo MRI scans for clinical purposes. It is possible that patients with more prolonged SE, who were unable to undergo MRI scans in the prespecified timeframe, would have had a higher than here-stated frequency of thalamic lesions on DWI.

The vast majority (9 of 11) patients in this study had no prior history of seizures, and in the remaining two there was no evidence of uncontrolled or frequent seizures before the onset of status epilepticus. None of the patients had mesial temporal sclerosis. The above characteristics are in accordance with a previous systematic review (Claassen et al., 2002),

in which the majority of patients with refractory partial SE did not have a prior history of epilepsy.

Additionally, none of the patients had evidence of a disorder (vascular, neoplastic, inflammatory, or other) primarily involving the thalamic areas. These data indicate that a prior history of epilepsy, whether poorly controlled or not, is not necessary to produce evidence of thalamic dysfunction during the course of partial status epilepticus. Therefore, thalamic dysfunction is purely a consequence of the current SE event and not of pre-existing epilepsy-related dysfunction.

The nature of the here-observed acute DWI abnormalities is not entirely clear. In ischemic stroke, the ADC decline is directly correlated with focal cerebral hypoperfusion and reversible or irreversible tissue injury(Heiss, 2000). In contrast, epileptic activity is associated with focal hypermetabolism. In prolonged seizures, uncoupling between metabolism and cortical regional cerebral blood flow (rCBF) has been demonstrated and may result in relative tissue hypoxia, anaerobic glycolysis, Na^+/K^+ pump failure, and cytotoxic edema (Szabo et al., 2005, Calistri et al., 2003). Hyperperfusion of the thalamus has been demonstrated by ictal single photon emission computed tomography (SPECT) in patients with temporal lobe epilepsy and ictal dystonic posturing (Joo et al., 2004). Activation or dysfunction of the thalamus (an anatomically remote site) in patients with prolonged partial seizures could be related to seizure facilitation and propagation via corticothalamic pathways (Rosenberg et al., 2006) or part of a physiologic process that results in termination of the ictal event. Alternatively, remote seizures could induce thalamic dysfunction through a mechanism of diaschisis (Lee et al., 2002). Further studies are required to clarify this issue.

Very few patients with thalamic abnormalities during or shortly after partial SE have been previously reported(Tatum et al., 2004, Szabo et al., 2005). Of course this does not preclude thalamic ictal involvement on a sub-imaging level. It is possible that only prolonged seizures can promote excessive thalamic activation or dysfunction with a focal energy deficit that manifests as ADC decrease. Previous studies have failed to show thalamic diffusion changes interictally, even in patients with intractable epilepsy(Diehl et al., 2005). Similarly, no thalamic lesions have been demonstrated after single short seizures (Diehl et al., 2001), and thalamic ictal activity is less likely in seizures that did not evolve past their onset zone (Rosenberg et al., 2006). On the contrary, prolonged pediatric febrile seizures have been associated with ipsilateral thalamic (and hippocampal) diffusion abnormalities (Natsume et al., 2007).

Moreover, three patients were noted to have thalamic lesions after an episode of clinical SE although the concurrent EEG only demonstrated PLEDs. It is possible that the DWI changes were related to the preceding SE that was terminated before electrographic documentation. Alternatively, PLEDs themselves could trigger remote thalamic activation. It has been previously shown that PLEDs themselves are associated with increased cortical rCBF(Assal et al., 2001).

The most significant finding of the study was the multi-faceted relationship between the thalamus and the posterior brain quadrants. Thalamic lesions were significantly associated with DWI laminar lesions in the temporal, parietal and occipital cortices as well as PLEDs and seizure origin in the posterior quadrants. Only the ipsilateral (to the epileptiform activity) pulvinar, relative to other thalamic nuclei, was noted to have discrete DWI lesions after SE. This is in agreement with previously reported imaging studies (Szabo et al., 2005). The pulvinar is an associative thalamic nucleus whose function and connectivity is incompletely understood. It has been postulated that cortico-pulvino-cortical connections

coordinate but do not duplicate direct cortico-cortical circuits. Moreover, functional connections of the pulvinar with the cortex do not respect the traditional neuroanatomical boundaries of pulvinar subnuclei (Shipp, 2003). The role of the thalamus and the pulvinar, in particular, in the production of widespread synchronized neuronal epileptiform discharges in patients with partial epilepsy is still open to query. It is clear that the pulvinar in the normal brain connects mainly to the striate cortex (Shipp, 2003), as well as the extra-striate visual and sensory multi-modal association areas (Yeterian and Pandya, 1997). This correlates well with the fact that in all of our patients with electrographic status, pulvinar lesions were associated with evolving seizures arising from the posterior quadrants of the brain and only from the dorsolateral surfaces. No isolated mid-sagittal seizure origin was identified.

It is particularly intriguing that patient 11, in the immediate peri-ictal phase, (only 12 hours after SE onset) had a subtle hyperintensity of the entire ipsilateral thalamus, while, 3 days later, the lesion was confined to the region of the pulvinar nucleus (as in the vast majority of the patients in our and similar studies). This could imply that there is more widespread thalamic activation in the early phases of SE, while pulvinar activation could be related to late and/or inhibitory processes. A patient with PLEDs and a similar involvement of the entire thalamus has recently been described, but no further clinical data are provided (Kalamangalam et al., 2007). In this reference, it is presumed that a thalamic lesion can independently cause “subcortical” PLEDs. As noted above, the significant radiological and electrographic relationships between the thalamus and posterior cortex, (fragments of which are appreciated in each individual patient) support the role of corticothalamic networks in PLED generation.

The presence of thalamic lesions is not simply a non-specific indicator of prolonged seizure activity. The time from onset of status to MRI-DWI imaging was very similar in patients with and without thalamic lesions. However, we were not able to calculate the total duration of clinical or electrographic status in each individual patient. Prolonged duration of status could potentially be related to the appearance of peri-ictal MRI-DWI lesions. We hypothesize that prolonged seizures are necessary but not sufficient for the induction of thalamic lesions unless the epileptiform discharges arise in the posterior regions of the brain.

As noted in previous publications (Szabo et al., 2005), mesial temporal lobe acute diffusion abnormalities were also evident. These might co-exist with thalamic lesions, but the association was not statistically significant. Moreover, the laterality of these lesions was particularly intriguing. Although the posterior cortical strip was radiologically affected only in half of the patients, the abnormality was always ipsilateral to the affected thalamus. In contrast, we found that the mesial temporal lobes could be affected bilaterally with unilateral thalamic involvement or unilaterally with bilateral thalamic involvement. This could also imply, however, that the corticothalamic interaction in prolonged seizures is more direct and pathophysiologically relevant, whereas hippocampal activation requires direct propagation of recurrent, prolonged seizures. Correspondingly, previous studies have demonstrated thalamic atrophy only ipsilateral to the seizure focus in patient with temporal lobe epilepsy (Natsume et al., 2003), whereas bilateral limbic system diffusion abnormalities have been described in patients with unilateral mesial temporal sclerosis (Concha et al., 2005). It is interesting that our patient with bilateral mesial temporal lesions on DWI had seizures arising from an extra-temporal focus.

Additional collateral findings were evident from the analysis of the electrographic findings. We were able to localize the PLEDs and the intermittent, evolving seizures. In four patients, these arose from adjacent but distinct areas suggesting that there was a PLEDs-producing area of neuronal irritation that could consistently trigger electrographic seizures in a nearby area but was intrinsically unable to initiate one. Moreover, we noted that PLEDs were

effectively suppressed by seizures with a nearby onset zone but not by remote ones. This implies that although PLEDs frequently coexist with and may even trigger seizures, they do not necessarily form a functional continuum. We are not aware of any similar published observations.

Two out of 3 patients who underwent follow-up imaging had persistent hyperintense lesions of the pulvinar on T2-weighted imaging several months after the acute event. This likely indicates permanent thalamic dysfunction in these patients. The role of this permanent dysfunction in the recurrence of seizure activity and final clinical outcome is unclear. Interestingly, in a similar paradigm, peri-ictal diffusion abnormalities of the hippocampus have been noted to precede the development of hippocampal sclerosis in children with SE and no prior history of epilepsy (Farina et al., 2004).

This study is unavoidably limited by its retrospective nature and the small number of patients. The clinical reality also indicates that many patients who present to the emergency department with clinical SE do not have lateralized epileptiform discharges by the time the EEG is done and that most patients with SE are not able to tolerate an MRI in the immediate post-ictal phase, factors which will render the completion of a large prospective study difficult. Moreover, it was not possible to calculate ADC maps for most of the patients because of limited DWI data. We only included patients without a significant corresponding T2 lesion, in order to avoid the confounding effect of “T2 shine-through” phenomenon.

Despite its limitations, our study provides further evidence that in partial SE, acute thalamic and secondarily extrathalamic lesions are often seen. These are likely the consequence of the prolonged seizures and not due to poorly controlled epilepsy, and they correlate with specific electrographic and radiological abnormalities. We believe that this study provides an intuitive paradigm for the non-invasive, in vivo evaluation of the pathologic substrates and electrical correlates of partial epilepsy. A large prospective study could further delineate the correlations between specific electrographic findings and imaging abnormalities and shed more light on the role of the thalamus in partial epilepsy, information that may facilitate the development of targeted interventional or pharmacological treatments.

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The authors have reported no conflicts of interest. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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Figure 1.

DWI thalamic lesions of the 11 patients are shown. Associated cortical strip and hippocampal hyperintensities can also be seen. Patient 11 presented initially with a faint DWI hyperintensity involving almost all the thalamic nuclei (11a). A few days later a brighter, better defined hyperintensity appeared in the region of the pulvinar nucleus (11b), similar to the other patients

Figure 2.
Schematic representation of origin of PLEDs (red dots) and seizures (blue dots) in patients of Groups 1 and 2.

Table 1

Demographic and clinicopathological characteristics of Group 1 patients. (BZD=benzodiazepines, IV=intravenous, AED=antiepileptic drugs, MTL=mesial temporal lobe, F=frontal cortex, T=temporal cortex, O=occipital cortex, I=insular cortex, BL=bilateral, R=right, L=left, ESLED=end stage liver disease, MCA=middle cerebral artery)

Patient	Age/sex	Clinical presentation	History of epilepsy	Control with BZD and first-line IV AED	Refractory SE	Previous medical history	MRI findings	DWI abnormality
1	66/M	Complex partial seizures	No	Yes	No	Non-small cell lung cancer	Right occipital and right sub-insular metastases	R thalamus
2	45/M	Complex partial seizures	No	Yes	No	Nasopharyngeal Ca	No mass lesions or abnormal enhancement	L thalamus, L MTL, L T-P-O-I
3	83/F	Partial onset-Generalized convulsions.	No	Yes	No	No significant history.	No mass lesions or abnormal enhancement	R thalamus, R T-P-O
4	45/M	Partial onset-Generalized convulsions.	Yes	No	Yes	Chronic alcohol use. Epilepsy	Chronic ischemic changes Cerebral-cerebellar atrophy.	L thalamus, L MTL, L T-P-O
5	52/F	Complex partial seizures	No	No	Yes	Meningioma of tentorium.	Thrombosis of superior sagittal sinus, lateral sinuses	BL thalami, BL MTL, BL T-P-O
6	74/M	Complex partial seizures	No	No	Yes	No significant history	No mass lesions or abnormal enhancement	L thalamus, L T-P-O
7	80/F	Complex partial seizures	No	No	Yes	Breast cancer	No mass lesions or abnormal enhancement	R thalamus
8	40/F	Complex partial seizures	No	No	Yes	No significant history.	BL anterior temporal encephalomalacia	BL thalami
9	76/M	Complex partial seizures	Yes	No	Yes	Dementia	Acute L occipital infarct with hemorrhagic transformation	L thalamus
10	62/F	Complex partial seizures	No	No	Yes	Stroke	Chronic infarct R MCA territory	R thalamus

Patient	Age/sex	Clinical presentation	History of epilepsy	Control with BZD and first-line IV AED	Refractory SE	Previous medical history	MRI findings	DWI abnormality
11	60/M	Partial onset-Generalized convulsions.	No	No	Yes	ESLD s/p liver transplantation	No mass lesions or abnormal enhancement	L thalamus, BL MTL, L T-P-O

Electrographic characteristics of the Group 1 patients are shown. The PLEDs are characterized by their location, duration and presence (or not) of a PLEDs-plus pattern. Evolving seizures are characterized by location, morphology, presence of PLED suppression, and pattern of spread

Table 2

Patient	PLEDS origin	Duration	PLEDS-plus	Seizure origin	Morphology at onset	Spread of seizures
1	Fp2	150–300	NO	N/A	N/A	N/A
2	P7=O1	100–200	YES	N/A	N/A	N/A
3	Pz=P4	50–150	NO	N/A	N/A	N/A
4	P7	100–200	NO	P7=O1	7–9 Hz with PLED suppression	P3
5	O2=P8	300–500	YES	F8=T8	2–4 Hz with PLED suppression	F4
6	Continuous seizures	Continuous seizures	Continuous seizures	T7	10–11 Hz	Posterior spread
7	Continuous seizures	Continuous seizures	Continuous seizures	C4=P4	15–20 Hz	BL synchrony Posterior spread
8	F4	20–50	NO	N/A	N/A	N/A
	T7	50–100	NO	T7	10–12 Hz with PLED suppression	T7 propagating from P8
	P8	50–100	NO	T8=P8	8–10 Hz with PLED suppression	No
9	T7	200	YES	T7	6–8Hz with PLED suppression	None
10	T8	50–100	NO	T8=P8	6–8 Hz with PLED suppression	Anterior spread
				C4=P4	30 Hz. Occasional PLED suppression	Posterior spread
11	Fz=F3	300–400	NO	P7=O1	8–10 Hz. No PLED suppression	No

Table 3
Patient specific information

Comparison of the two groups with regard to demographics, medical history, clinical presentation, refractoriness of status, presence of extra-thalamic MRI lesions, length of hospitalization and subsequent functional disability. (mRS=Modified Rankin Score)

Variable		Thalamic DWI lesions (N= 11)	No thalamic DWI lesions (N= 25)	p-value
Age		62.1 ± 15.1	61.4 ± 17.7	0.911
Sex	F	5 (45%)	12 (48%)	1.000
	M	6 (55%)	13 (52%)	
History of epilepsy	No	9 (82%)	14 (56%)	0.259
	Yes	2 (18%)	11 (44%)	
Presentation	Simple and complex partial seizures	8 (73%)	14 (56%)	0.467
	Partial and secondarily generalized	3 (27%)	11 (44%)	
Control	Benzodiazepines and IV AED	3 (27%)	8 (32%)	1.000
	Refractory	8 (73%)	17 (68%)	
Extra-thalamic MRI lesions	Cortical laminar involvement	6 (55%)	4 (16%)	0.039
	Mesial temporal involvement	4 (36%)	5 (20%)	0.408
	Neither	1 (9%)	16 (64%)	0.003
Etiology	Pre-existing cryptogenic partial epilepsy	2 (18%)	3 (12%)	0.390
	Ischemia	2 (18%)	3 (12%)	
	Hemorrhage	0 (0%)	2 (8%)	
	Malignancy	1 (9%)	9 (36%)	
	Infection	0 (0%)	1 (4%)	
	Global hypoxia	0 (0%)	1 (4%)	
	Unknown	6 (55%)	6 (24%)	
Days of hospitalization	Mean ± S.D. Median (Range)	27.5 ± 43.9 14 (6, 157)	22.9 ± 28.8 14 (3,135)	0.946
Estimated pre- morbid mRS	Mean ± S.D. Median (Range)	2.7 ± 1.2 3 (0,4)	2.1 ± 1.6 2 (0,5)	0.275
Estimated mRS upon discharge	Mean ± S.D. Median (Range)	4.6 ± 0.9 5 (3,6)	4.2 ± 1.2 4 (2,6)	0.428
Estimated mRS in 3 Months	Mean ± S.D. Median (Range)	4.7 ± 1.3 5 (3,6)	4.2 ± 1.9 4.5 (1,6)	0.734
Clinical onset/MRI hours	Mean ± S.D. Median (Range)	84.0 ± 72.8 54 (12,240)	89.4 ± 58.7 70 (19,206)	0.425

Table 4

Foci specific information

Variable	Response	Thalamic DWI lesions	No thalamic DWI lesions	p-value
PLEDs region¹	Centroparietal	3 (27%)	1 (6%)	0.237
	Frontal	3 (27%)	7 (41%)	
	Frontotemporal	0 (0%)	3 (18%)	
	Mid-temporal	3 (27%)	3 (18%)	
	Temporooccipital	2 (18%)	3 (18%)	
PLEDs quadrant	Anterior ³	3 (27%)	10 (59%)	0.077
	Posterior ⁴	8/11 (72%)	17 (41%)	
Seizure region of origin²	Centroparietal	2 (20%)	2 (10%)	0.191
	Frontal	0 (0%)	7 (35%)	
	Frontotemporal	1 (10%)	3 (15%)	
	Mid-temporal	5 (50%)	5 (25%)	
	Temporooccipital	2 (20%)	3 (15%)	
Seizure quadrant	Anterior ³	1 (10%)	10 (50%)	0.038
	Posterior ⁴	9 (90%)	10 (50%)	
PLEDS-plus¹	NO	8 (73%)	12 (71%)	0.909
	YES	3 (27%)	5 (29%)	
Discharge frequency at seizure onset²	Theta	2 (20%)	6 (30%)	0.572
	Alpha	5 (50%)	5 (25%)	
	Beta	2 (20%)	5 (25%)	
	Delta	1 (10%)	4 (20%)	
Discharge frequency at seizure onset²	Beta + Alpha	7 (50%)	10 (38%)	0.439
	Delta + Theta	7 (50%)	16 (62%)	
Duration of each PLED complex¹	<500 msec	11 (100%)	14 (82%)	0.529
	>500 msec	0 (0%)	3 (18%)	
Duration of each PLED complex¹	<300 msec	9 (82%)	11 (65%)	0.345
	>300 msec	2 (18%)	6 (35%)	

¹ 11 PLEDs foci for thalamic DWI lesions and 17 PLEDs foci for non-thalamic DWI lesions.

² 10 seizure foci for thalamic DWI lesions and 20 seizure foci for non-thalamic DWI lesions.

³ Anterior quadrant= Origin from frontal or frontotemporal leads

⁴ Posterior quadrant= Origin from mid-temporal, temporo-occipital or centroparietal leads.