



Characteristics of seizure-induced signal changes on MRI in patients with first seizures



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ABSTRACT

Purpose: The aim of this study was to investigate the predictive factors and identify the characteristics of the seizure-induced signal changes on MRI (SCM) in patients with first seizures.

Methods: We conducted a retrospective study of patients with first seizures from March 2010 to August 2014. The inclusion criteria for this study were patients with 1) first seizures, and 2) MRI and EEG performed within 24 h of the first seizures. The definition of SCM was hyper-intensities in the brain not applying to cerebral arterial territories. Multivariate logistic regression was performed with or without SCM as a dependent variable.

Results: Of 431 patients with seizures visiting the ER, 69 patients met the inclusion criteria. Of 69 patients, 11 patients (15.9%) had SCM. Epileptiform discharge on EEG (OR 29.7, 95% CI 1.79–493.37, $p = 0.018$) was an independently significant variable predicting the presence of SCM in patients with first seizures. In addition, the topography of SCM was as follows; i) ipsilateral hippocampus, thalamus and cerebral cortex (5/11), ii) unilateral cortex (4/11), iii) ipsilateral thalamus and cerebral cortex (1/11), iv) bilateral hippocampus (1/11). Moreover, 6 out of 7 patients who underwent both perfusion CT and MRI exhibited unilateral cortical hyperperfusion with ipsilateral thalamic involvement reflecting unrestricted vascular territories.

Conclusion: There is an association between epileptiform discharges and SCM. Additionally, the involvement of the unilateral cortex and ipsilateral thalamus in SCM and its hyperperfusion state could be helpful in differentiating the consequences of epileptic seizures from other pathologies.

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1. Introduction

Approximately 2–5% of the world's population experiences a seizure in their lifetime [1]. The underlying cause may be revealed by brain CT or MRI. However, early peri-ictal imaging often exhibits abnormalities that might be the consequence of seizures, rather than the cause.

With the introduction and increasing use of MRI in patients with seizures, seizure-induced signal changes on MRI (SCM) have been recognized [2,3]. In studies using diffusion-weighted MR images (DWI), transient focal hyper-intensity on DWI and corresponding reduction of the apparent diffusion coefficient (ADC) was shown as a phenomenon in the postictal phase of

epileptic seizures [4]. The pathophysiology of SCM is not clearly understood but these lesions are thought to be associated with increased energy metabolism, hyperperfusion and cell swelling as a consequence of ictal activity [5,6].

The majority of reports that address the SCM were performed in subjects with status epilepticus, regardless of a history of chronic epilepsy. When these patients show Todd's phenomena such as hemiparesis, sensory loss, persistent altered mental status, or aphasia and signal changes on MRI, we might think that those may be associated with seizures. However, if patients with the first and short single seizures develop postictal neurologic deficits and show brain lesions on MRI, these findings may be confused with other diseases, such as cerebral infarction, brain tumor or encephalitis, which makes differential diagnosis difficult. Therefore, to avoid incorrect diagnosis and to prompt subsequent appropriate investigations or treatments in clinical settings, we need to know the characteristics of SCM, especially topography, in patients with first seizures.

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This study aimed to investigate the predictive factors and identify characteristics of SCM in patients with first seizures.

2. Methods

A retrospective review of 431 patients with seizures visiting the emergency room from March 2010 to August 2014 was conducted in a single tertiary hospital. The inclusion criteria for this study were as follows: (1) patients with first seizures regardless of the presence of acute symptomatic seizures, and (2) those who had MRI and EEG performed within 24 h of the first seizures.

We collected the demographic data, such as age and sex, and clinical data, including symptoms, etiology, identified structural lesions on MRI, perfusion CT and EEG. These patients were divided into three groups: patients with first unprovoked seizure, acute symptomatic seizures and remote symptomatic seizures.

A first unprovoked seizure was defined as a seizure occurring in the absence of acute precipitating central nervous system insult, systemic metabolic dysfunction or a history of prior neurologic insult [7]. The definition of acute symptomatic seizure was a seizure that was provoked by a transient factor acting on an otherwise normal brain to temporarily lower the seizure threshold [7]. A remote symptomatic seizure was defined as a seizure caused by an identified cerebral lesion or etiology such as a tumor or chronic cerebrovascular disease [8]. We defined status epilepticus (SE) as 2 or more discrete seizures without the recovery of consciousness or at least 5 min of continuous seizure [9].

Index MR imaging was performed within 24 h of seizure onset using a 3 T system (Achieva; Philips Medical Systems, Best, the Netherlands), and those images included (a) DWI and (b) an axial FLAIR sequence with 5-mm-thick slices. MRI findings were reviewed blindly by two investigators, and structural lesions on MRI were only accepted when there was good agreement between them. The SCM was defined as any signal changes in peri-ictal stages not applying to cerebral arterial territories [10]. Except for the 4 patients who didn't have other brain images, we compared the index MRI with the previous MRI in 3 patients and follow-up MRI in the other 4 patients to make sure SCM was a consequence of seizures. Furthermore, we investigated the characteristics of the cerebral perfusion state of patients with SCM within 24 h of the onset of seizure using dynamic contrast enhanced perfusion CT (Somatom Definition AS+, Siemens Medical Solutions, Forchheim, Germany) with 5-mm slice thickness. Perfusion CT was chosen because of its specific advantages compared to MRI. It is rapid, cost effective and has fewer contraindications. Therefore, it is widely available in the emergency setting. Also, parameters of perfusion

CT can be more easily quantified than MRI counterparts [11]. We evaluated the perfusion study based on perfusion parameter data sets; cerebral blood flow (CBF), cerebral blood volume (CBV), time to peak (TTP), and mean transit time (MTT). For color-coded maps, the image scale was displayed with a rainbow colored bar.

EEG recordings were performed using Comet XL EEG (A Grass Telefactor System with AS40 Amplifier system, AstroNova, Inc., USA) with electrodes attached with electrode paste using the international 10–20 system. The EEG was recorded with 32 channels and lasted at least 30 min. EEG findings were classified as generalized slowing, focal slowing and epileptiform discharges. Epileptiform discharges included interictal epileptiform discharges (IEDs) and ictal discharges. IEDs should meet at paroxysms, an abrupt changes in polarity such as a sharp contour or spike occurring during several milliseconds in a physiologic field [12]. In addition, the IEDs have negative polarity and are followed by a slow wave in the delta range [12]. Ictal discharges represent rhythmic patterns with the evolution of amplitudes, frequency and spatial distributions associated with epileptic seizures with or without clinical manifestations [13].

The institutional review board approved this study. The primary endpoint was the identification of factors associated with SCM in patients with first seizures. For this study, we analyzed all patients with first seizures divided into groups by the presence or absence of SCM. In addition, we studied the characteristics of SCM and the findings of perfusion CT in patients with SCM. Depending on the nature of the variables, differences between the groups were investigated using a Mann–Whitney *U* test, the chi-squared test, or Fisher's exact test. Multivariate logistic regression was performed with or without SCM as a dependent variable. For the multivariate analyses, we dichotomized age as ≥ 44 years old or < 44 years old. All statistical tests were performed using MedCalc (MedCalc Software version 13, Ostend, Belgium). For all calculations, a *p*-value less than 0.05 was considered statistically significant.

3. Results

3.1. Demographic and clinical features between patients with and without SCM

Sixty-nine patients satisfied all of the following selection criteria. Remaining 362 patients were excluded due to previous history of seizures or epilepsy ($N = 282$), unperformed both MRI and EEG within 24 h of seizure onset ($N = 80$). The sample consisted of 31 male and 38 female patients. The median age was 69 years old and ranged from 46 to 92 years old. Of 69 patients, 11 patients

Table 1

A comparison of the demographic and clinical characteristics between patients with and without seizure-induced signal changes on MRI.

	Patients with SCM (n = 11)	Patients without SCM (n = 58)	p-value
Men, n(%)	5(45.5%)	26(44.8%)	1.000‡
Median age, years (range)	69(46–92)	12.5(0–80)	0.0001*
Etiology			
Acute symptomatic seizure	5(45.5%)	16(27.6%)	0.2901‡
First unprovoked seizure	4(36.4%)	33(56.9%)	0.3237‡
Remote symptomatic seizure	2(18.2%)	9(15.5%)	1.0000‡
Status epilepticus	7(63.6%)	6(10.3%)	$P < 0.0001$ †
Electrophysiology			
Epileptiform discharges	8(72.7%)	18(31.0%)	0.0094†
Generalized slowing	9(81.8%)	18(31.0%)	0.0017†
Focal slowing	3(27.3%)	8(13.8%)	0.3642‡

*Mann–Whitney *U* test.

†Chi-square test.

‡Fisher's exact test.

SCM indicates seizure-induced signal changes on MRI.

(15.9%) had SCM. The demographic and clinical features between patients with and without SCM were summarized in Table 1. Acute symptomatic seizures were diagnosed in 5 cases (45.5%, 5/11); the causes of acute symptomatic seizures were interpreted to be either of metabolic or infectious origin, such as renal failure, alcoholic liver cirrhosis, alcohol withdrawal, pneumonia, and viral encephalitis. The other 6 patients (54.5%, 6/11) were classified as having first unprovoked seizures (4/6) or remote symptomatic seizures (2/6). Patients with remote symptomatic seizures developed SCM in locations different from the previous cerebral lesions.

Demographic data, such as sex (men 45.5% vs. 44.8%, $p = 1.000$) and etiology of first seizures (45.5% vs. 27.6%, $p = 0.2901$ for acute symptomatic seizure, 36.4% vs. 56.9%, $p = 0.3237$ for first unprovoked seizure, 18.2% vs. 15.5%, $p = 1.000$ for remote symptomatic seizure), were not significantly different between subgroups, whereas patients with SCM were significantly older [69 years (46–92) vs. 12.5 years (0–80), $p = 0.0001$] and the frequency of SE (63.6% vs. 10.3%, $p < 0.0001$) was significantly higher in patients with SCM. In addition, both epileptiform discharges (72.7% vs. 31.0%, $p = 0.0094$) and generalized slowing (81.8% vs. 31.0%, $p = 0.0017$) on EEG were more frequently found in patients with SCM compared to patients without SCM.

Table 2

Results of multivariate analysis of the variables of the patients with seizure-induced signal changes on MRI.

Independent variable	Adjusted odds ratio	95% CI	p-value
Age (>44 years)	7.82E-011		0.9970
Epileptiform discharges	29.7	1.79–493.37	0.0180
Status epilepticus	0.9	0.07–11.36	0.9297
Generalized slowing	1.6	0.14–17.00	0.7200

Multivariate analysis revealed that the presence of epileptiform discharges on EEG (OR 29.7, 95% CI 1.79–493.37, $p = 0.018$) was the independently significant variable predicting SCM in patients with first seizures (Table 2).

3.2. Topographic characteristics of SCM

Detailed etiology, MRI, perfusion CT and EEG data of patients with SCM are shown in Supplementary Table 1.

We analyzed the topographic characteristics of SCM. Of 11 patients, both DWIs and FLAIR were available in 10 patients and the other 1 patient had the FLAIR image only. Of 11 patients, 3 patients had previous MRI (all 3 patients were normal on MRI) and the other 4 patients underwent follow-up MRI scans. We compared the findings of the previous MRI, index and follow-up MR images. Three patients with previous MRI showed newly developed signal changes after the first seizures. Of the other 4 patients, follow-up MRI scans showed that SCM resolved over a variable period of time (range: 1 day to 1 year 8 months) in 3 patients (Fig. 1).

In detail, SCMs were identified on both DWI and FLAIR. The topographic patterns of peri-ictal signal changes were as follows: i) the ipsilateral hippocampus, thalamus and cerebral cortex in 5 patients, ii) the ipsilateral thalamus and cerebral cortex in 1 patient, iii) the unilateral cortex only in 4 patients, and iv) the bilateral hippocampus in 1 patient, respectively (Fig. 2). Of 69 patients, epileptiform discharges on EEG were shown in 26 patients (37.7%). Seven of 11 patients were concordant with the laterality of EEG abnormalities.

Of 11 patients with SCM, 7 patients were also analyzed with perfusion CT. Of 7 patients with perfusion CT, 6 patients showed SCM on the ipsilateral thalamus and cortex and the other 1 patient revealed SCM on the cortex only. Six out of 7 patients with perfusion CT showed unilateral cortical hyperperfusion with

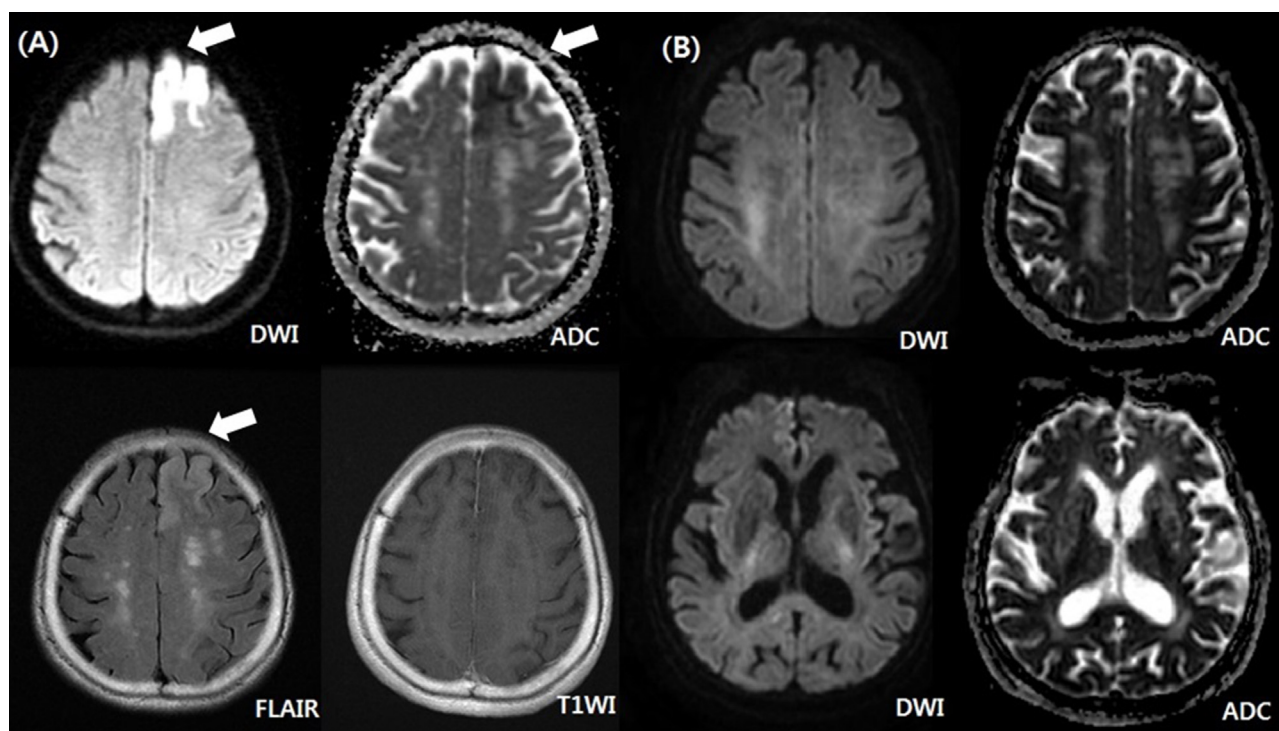


Fig. 1. A case of reversible SCM.

Index diffusion MRI (figure A) showed high signal intensity (SI) on with low SI on ADC map in the anterior and medial cortex of the left frontal lobe of unusual vascular territory. And there were Flair signal changes in same lesion on DWI but no lesions on T1 weighted image (T1WI). 5 months later, previous lesion disappeared in follow up MRI (figure B).

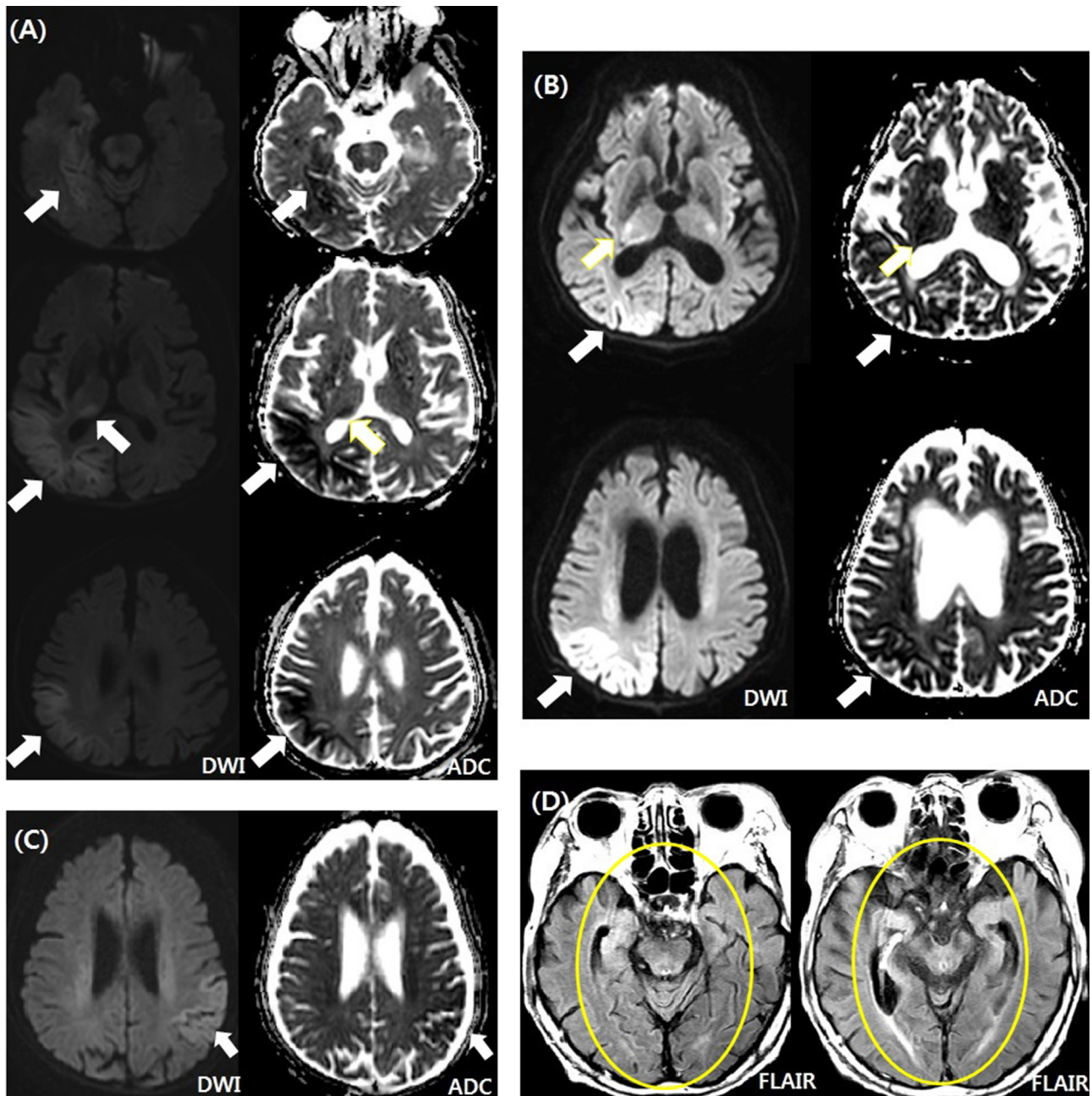


Fig. 2. Topography of SCM.

Topography of SCM was as follows; 1) ipsilateral hippocampus, thalamus and cerebral cortex (figure A), 2) ipsilateral thalamus and cerebral cortex (figure B), 3) unilateral cerebral cortex (figure C), 4) bilateral hippocampus (figure D).

ipsilateral thalamic involvement, not restricted to the arterial distribution of middle cerebral artery and posterior cerebral artery. Rapid perfusion of the ipsilateral thalamus and cortex was demonstrated by increased CBF, CBV and decreased TTP, MTT (Fig. 3).

4. Discussion

Several reports have described the peri-ictal MRI changes in patients with status epilepticus and single seizures, regardless of a history of chronic epilepsy. Most of the studies investigated patients with SE. Studies of patients with SE showed that MR imaging findings included increased signal intensity on T2-weighted images and DWI, gyral swelling, and gyral contrast enhancement [14–16]. Moreover, the topography of the SCM of

complex partial SE (CPSE) was discussed in the following study. Szabo et al. studied 10 patients with a previous history of TLE and acute symptomatic seizures developing CPSE. All patients showed regional hyperintensity on DWI and a reduction of the ADC in the hippocampal formation and the pulvinar region of the thalamus (6/10), the pulvinar and cortical regions (2/10), the hippocampal formation, the pulvinar and the cortex (1/10), and the hippocampal formation (1/10). They said subtle but obvious signs of hyperperfusion were shown in perfusion MRI, which were confirmed by additional SPECT studies in 2 patients [4]. Chatzikonstantinou et al. reported the most common localization of DWI abnormalities associated with ictal activity in SE was the hippocampus and the pulvinar. They found that combined DWI and EEG analysis provided clues to seizure localization and propagation [16]. Milligan et al. studied the frequency and patterns of MRI

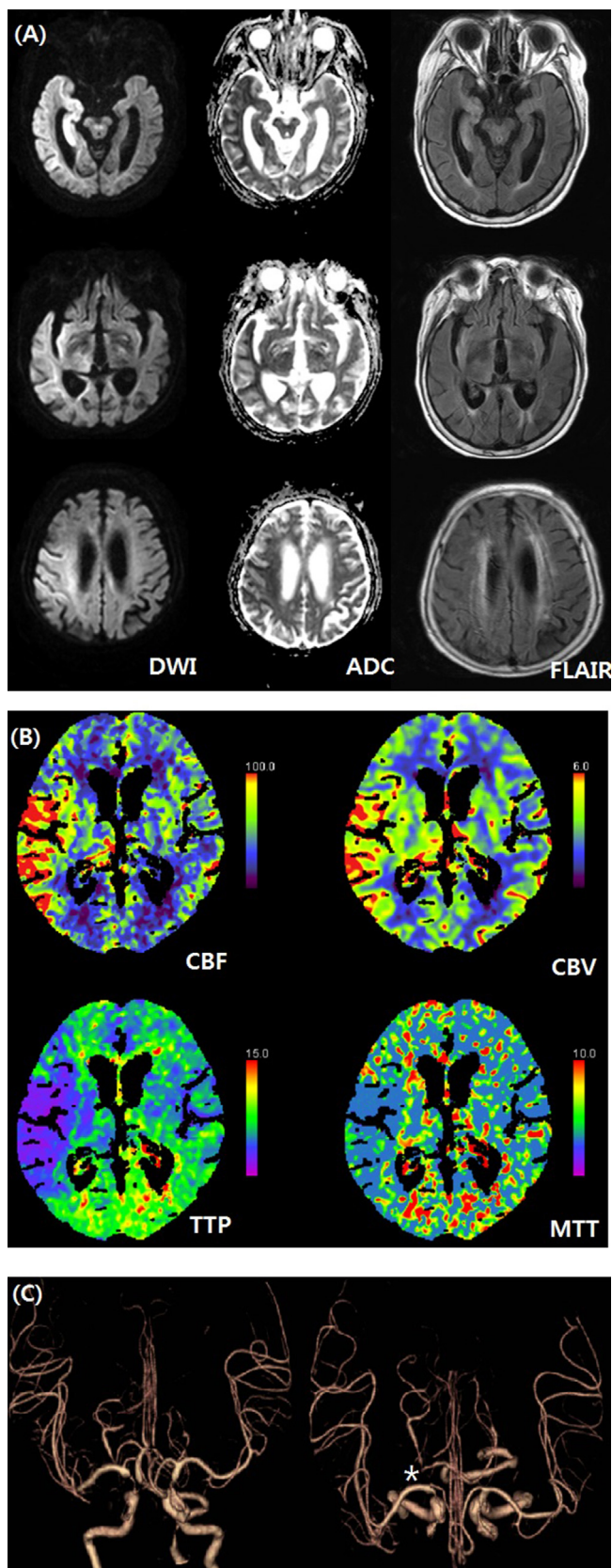


Fig. 3. Illustrative case of topography of SCM involving the unilateral cortex and ipsilateral thalamus and its hyperperfusion state. DWI showed regional cytotoxic edema in the right frontotemporal lobe, right hippocampus, and right thalamus (figure A). And perfusion CT revealed cerebral hyperperfusion state (increased cerebral blood flow [CBF], cerebral blood volume [CBV] and decreased time to peak [TTP], mean transit time [MTT]) in the right

abnormalities due to SE. Ten (11.6%) of 86 patients had MRI abnormalities likely due to seizures. Four had focally increased signals on T2 and DWI in the hippocampus ipsilateral to the seizure focus. Five had a gyral distribution of restricted diffusion and increased signaling on T2 weighted images [17]. Conversely, Hufnagel et al. studied ADC changes during serial postictal DWI after single seizures. These researchers selected 9 patients with temporal lobe epilepsy, temporal and extratemporal lobe epilepsy, and extratemporal lobe epilepsy. ADC changes were shown as decreases in the epileptogenic zone, generalized ADC changes, no major changes and widespread bilateral increases [18].

However, there have been no studies of SCM on patients with only first seizures. Therefore, unlike previous peri-ictal imaging studies, we studied SCM on patients with first seizures presenting as SE as well as single short seizures. Our results showed that MRI signal changes were associated with epileptiform discharges. Moreover, the specific topography of SCM and the hyperperfusion state, especially involving the ipsilateral thalamus and cortex, could be helpful for the differential diagnosis of other pathologies, including cerebral infarction.

Like other previous studies, SCMs were localized to the EEG abnormalities especially in 7 patients with IEDs. This result supported peri-ictal signal changes on MRI could be useful in seizure localization. Seizure-related MRI changes induced by epileptiform discharges have been supported by previous reported studies.

In experimental animals with kainate-induced SE, a decrease in ADC values by 7–30% was reported during a period 5–24 h postictally [19]. These changes could be explained by cytotoxic edema in the early stages of seizure activity with swelling of astrocytes and dendrites in the affected brain 2–24 h after the systemic injection of kainate [19,20]. Ictal depolarizations may lead to the massive influx of sodium and calcium ions and potassium efflux, which results in a transient breakdown of the Na⁺/K⁺-ATPase and subsequent cytotoxic edema [19,21]. The excessive release of excitatory amino acids, such as glutamate and increased membrane ion permeability, may also contribute to the subsequent progression to vasogenic edema with swelling of the extracellular space [22–24]. During seizure activity, the metabolic rate in the affected region is increased, resulting in enhanced blood flow to maintain normal but insufficient oxygenation. Therefore, unmatched metabolic needs and blood flow leads to anaerobic glycolysis, releasing lactate and aggravating cytotoxic edema. In the study using MR spectroscopy, acute changes in tissue metabolism during SE or shortly after acute symptomatic seizures were assessed. Increased DWI signals, decreased ADC and the presence of lactate, decreased N-acetylaspartate were demonstrated on MR spectroscopy to represent anaerobic glycolysis and neuronal dysfunction [25–27].

Another interesting point in our study is the topographic involvement of the ipsilateral thalamus and cortex. Of 11 patients with SCM, SCM was located in the hippocampus, thalamus and cortices in 5 cases. Including one patient with SCM in the thalamus and cortex but not the hippocampus, 6 patients with SCM in the ipsilateral thalamus and cortex and hyperperfusion in same regions were observed. This might be the point of discriminating between seizure and cerebral infarction when the patients without a past history of epilepsy show paralysis. The hippocampus is known as the seizure-vulnerable structure in the brain [28]. And it is considered that there is an epileptic network defined as

middle cerebral artery (MCA) territory and right thalamus (figure B). Cerebral CT angiography demonstrated increased vascularity of right MCA compared to the left MCA. Considering posterior cerebral artery was not fetal type (asterisk), increased perfusion to thalamus was not associated to increased flow through the ICA (figure C).

functionally and anatomically connected cortical and subcortical brain structures in which activity in any part affects activity in all the others [29]. Epileptic network is involved in ictal activity and disrupted in patients with mesial temporal lobe epilepsy [30]. Hypothetically, there are extensive neuronal connections between the hippocampus and the thalamus, referred to as functional connectivity [31]. The thalamus has widespread connections to the cortex, including the temporal, parietal, and insular cortices [32]. Across patients, we found that the network connectivity is structured. This study using MRI and Perfusion CTs suggested propagation of discharges coming from the primary active focus in the epileptic network. In other words, this might explain the neuronal excitability of the hippocampus, and the thalamus can affect many of the cortical regions related to seizure generation. Blood supply would increase in those territories, which was demonstrated on perfusion CT scans in our cases.

In addition, the topologic distribution on SCM showed an effect of cortical areas in all cases. Because during ictal activity, the cortex has maximal neuronal activity, the extracellular space shrinks because of water flux into cells [33]. At the same time, with the decrease in cortical diffusion, the extracellular space expands in areas remote from the neuronal activity, resulting in an increase in diffusion in the subcortical white matter [33,34].

The reversal of restricted diffusion is rare but is observed more often in seizures than in other etiologies [35,36]. In our 3 cases, the diffusion images were reversible and the ADC returned to normal, indicating that cell death is not an unavoidable sequelae.

This study has limitations. First, this is a retrospective study conducted at a single hospital which was one of the largest hospitals in our city and the possibility of selection bias exists. Our patients comprised a group with more critical patients who were vulnerable to develop seizures including acute symptomatic seizures. And more than half patients who developed SCM had status epilepticus. We think that these might lead to relatively high percentage of presence of SCM when compared to the previous studies. Second, non-convulsive status epilepticus (NCSE) could be missed from limited duration of EEG monitoring. When reviewing the chart retrospectively, 4 patients had just single seizures among patients with SCM. However, we could not completely rule out NCSE clinically, because 30-min EEG was performed, not continuous quantitative EEG monitoring. Third, the sample size was relatively small, particularly in terms of the number of patients with SCM, and previous and follow-up MR imaging was performed for only a limited number of patients. Finally, definitive comparison was limited because the demographic, clinical features and time interval of brain imaging were variable among the patients.

In conclusion, using detailed retrospective clinical, MRI and EEG studies, we demonstrated that epileptiform activities were associated with SCM in patients with first seizures. And the involvement of the unilateral cortex and ipsilateral thalamus in SCM and its hyperperfusion state could be helpful in differentiating the consequences of epileptic seizures from other pathologies, including cerebral infarction. When considering these results, we need to be cautious of the differential diagnosis of the pathologies of MRI lesions in patients who developed first seizures, including SE and single seizures.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.seizure.2017.04.005>.

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