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Original Contribution

Seizure in code stroke: Stroke mimic and initial manifestation of stroke

Soo Jeong Kim, MD [a], Dong Wook Kim, MD [a,*], Hahn Young Kim, MD [a], Hong Gee Roh, MD [b], Jeong-Jin Park, MD [a]

[a] Department of Neurology, Konkuk University School of Medicine, Seoul, Republic of Korea
[b] Department of Radiology, Konkuk University School of Medicine, Seoul, Republic of Korea

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ABSTRACT

Background: Although seizure is one of the common causes of stroke mimics and can be an initial manifestation of acute stroke, accurate diagnosis of seizure during acute stroke management is frequently difficult. The objective of this study was to analyze the frequency, characteristics and results of neuroimaging including CT perfusion in patients with seizures manifesting initially as stroke-like symptoms.

Methods: We retrospectively reviewed the medical records of patients who were treated with code stroke alarming system. We studied the frequency and characteristics of patients who were finally diagnosed with seizures and further correlated their clinical features with the results of neuroimaging including CT perfusion.

Results: Among the 4673 patients who were treated with code stroke alarming system, seizure was the third most frequent diagnosis (188 patients, 4.0%) among the causes of stroke mimics including 27 patients who manifested seizure as an initial manifestation of acute stroke. CT perfusion showed perfusion changes in more than 25% of them (49 of 188 patients, 26.1%). Thrombolysis was not performed in six patients who presented with seizure as an initial presentation of stroke for delayed diagnosis while one patient underwent thrombolysis for misdiagnosis of seizure.

Conclusions: Seizure is a frequent final diagnosis in acute stroke management. However, careful interpretation of clinical features and results of perfusion imaging is necessary to avoid unnecessary thrombolysis in patients with seizure as a stroke mimic and thrombolysis failure due to delayed diagnosis of seizure as an initial manifestation of stroke.

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1. Introduction

The short time window from symptom onset to initiation of thrombolysis in acute stroke patients only allows quick history taking and neurological examination, often making it difficult to differentiate acute stroke from other disorders that simulate acute stroke, including seizure, metabolic disorders, complicated migraine, and psychiatric problems [1-4]. These heterogeneous disorders, presenting with acute onset focal neurological deficits, which were later found to have nonvascular etiologies, are often termed as stroke mimics, which comprise approximately 20% of patients admitted with suspicion of acute stroke [5,6].

Seizure is one of the most frequent stroke mimics. Compared with other stroke mimics, the diagnosis of seizure may be more complicated, because patients with seizure frequently exhibit altered consciousness and present with transient hemiparesis (kwon as Todd paralysis) [5]. Furthermore, seizure can be an initial presentation of acute stroke and results of the perfusion imaging in acute stroke management protocol may be misleading, because perfusion changes are frequently detected during ictal and post-ictal periods of seizure. However, few studies focused on the frequency and characteristics of seizure during acute stroke management and the pattern of perfusion imaging was rarely investigated [7,8].

The objective of present study was to determine the frequency and characteristics of seizure in patients who initially presented with stroke-like symptoms. We also analyzed the patterns of altered CT perfusion according to the causes of seizure in these patients.

2. Methods

2.1. Patients and acute stroke management protocol

We conducted a retrospective study of patients identified in our prospective stroke registry and epilepsy registry. Between January

* Corresponding author at: Department of Neurology, Konkuk University School of Medicine, 120-1 Neungdong-ro, Gwangjin-gu, Seoul 05030, Republic of Korea.
E-mail address: drdongwkim@kuh.ac.kr (D.W. Kim).

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2008 and August 2017, all consecutive patients visiting emergency department with a sudden onset of focal neurological deficit in a time window of less than 6 h, as indicated for thrombolysis, were included in the present study. In our acute stroke management protocol, a patient with symptoms suggestive of acute stroke was initially evaluated by a resident doctor in emergency medicine and acute stroke management pathway was activated. The patient was automatically notified by short message service to the duty neurology resident, neurology staff, and the neurological intervention team. After rapid neurological evaluation including National Institute of Health Stroke Scale and blood sampling, the patient was transferred to CT room. Emergency multimodal brain CT images were acquired including brain non-enhancement CT, and CT angiography with CT perfusion images (see below). Thrombolysis was performed according to acute stroke management protocol modified from the Korean stroke guideline. Briefly, among patients within 4.5 h of symptom onset (or 3 h before symptom onset before December 2012) with a measurable neurological deficit which failed to improve rapidly and the neurologist still suspected an acute stroke based on the results of neurological evaluation and multimodal CT, intravenous tissue plasminogen activator (t-PA) was administered and additional endovascular treatment was considered. For patients with symptom onset within 4.5–6 h (or 3–6 h before December 2012), endovascular treatment was considered in selected patients. Acute stroke-dedicated MRI protocols including diffusion-weighted imaging (DWI; b = 0–1000 mm^2/s), fluid-attenuated inversion recovery (FLAIR) and gradient echo sequences associated with cerebral tri-dimensional time-of-flight magnetic resonance angiography were usually performed in patients after the administration of intravenous t-PA and during the preparation of endovascular treatment. Scalp EEG was conducted in all patients when seizure was suspected as an etiology of the neurological deficits in 24 h after the arrival of emergency room.

2.2. Multimodal CT protocol

All multimodal CT examinations were performed using a 16-multislice CT scanner (LightSpeed Pro 16, GE healthcare, Milwaukee, WI, USA). The multimodal CT protocol included non-enhancement CT, CT angiography, CT perfusion including cerebral blood flow (CBF), cerebral blood volume (CBV), mean transit time (MTT), CT angiography-source images (SI), and collateral flow evaluation using CT angiography-maximum Intensity Projection (MIP) reconstruction images. The non-enhancement CT was obtained with 5-min contiguous axial section from the skull base to the vertex using imaging parameters of 120 kVp, 300 mA s, 5 mm collimation, and 4 images/rotation. It was followed by CT perfusion scan covering a 20-mm slab in four adjacent 5-mm slices. A 40 s scan was performed beginning 7–10 s after intravenous administration of 40 mL iodinated contrast agent (UltraVist 370, Schering AG, Berlin, Germany, or Iobrix 350, Accuzen, Seoul, Korea) followed by 30 mL saline at a rate of 4 mL/s using a dual-head power injector (Medral, Warrendale, PA, USA) into an antecubital vein. The following parameters were used for CT perfusion: 80 kVp, 200 mA s, 1 rotation/s, and 80 images/section. After waiting for 5 min until the washout of the first contrast agent, 80 mL of the second contrast agent was injected at a rate of 4 mL/s followed by a 60 mL saline flush for CT angiography. Scanning was performed using the parameters of 120 kVp, 267 mA s, 16×0.625 mm collimation, 0.625 mm slice thickness, and 9.37 mm/rotation table speed.

The CT perfusion scan was reconstructed at 5-mm contiguous axial images. Datasets were transferred to an imaging processing workstation (Advantage Workstatin 4.3, GE Healthcare) for post-processing. Perfusion maps for CBF, CBV, and MTT were generated using a semi-automated perfusion analysis software package based on a deconvolution technique (CT perfusion version 4.0, GE healthcare). For CT angiography-MIP images, the axial CT angiography-SI was reformatted into 20-mm thick MIP slabs in the axial and coronal planes with reconstruction increments of 5 mm. The scanning times for non-enhancement CT, CT perfusion, and CT angiography were 30, 50, and 45 s, respectively. The total time of the multimodal CT protocol, including imaging and postprocessing, was about 15 min.

2.3. Statistics

Continuous variables were expressed by the mean ± standard deviation and categorical variables as frequency (%). We compared the clinical characteristics between the two groups using the Student's *t*-test for continuous variables and the $\chi 2$ test for categorical variables.

3. Results

During the study period, we included 4673 patients who were treated with code stroke alarming system. A final diagnosis of stroke was made in 2276 patients, while stroke mimics were found in 2397 patients. Seizure was the third most common diagnosis (188 patients, 4.0%) as a stroke mimic following peripheral vertigo (911 patients, 19.5%) and metabolic disorders (379 patients, 8.1%) (Table 1). No difference in age (69.5 ± 13.8 years vs. 69.9 ± 14.9 years, p = 0.692) and sex (M:F = 965:1311 vs. 75:113, p = 0.539) was detected between patients with acute stroke and seizure. Among the 188 patients who were diagnosed with seizure, the causes of seizure were classified as acute symptomatic in 56 patients (29.8%), remote symptomatic (i.e., associated with previous epileptogenic lesion) in 78 patients (41.5%), and cryptogenic (i.e., neither previous history nor other causes of seizures) in 54 patients (28.7%). In 56 patients with acute symptomatic seizure, acute stroke was the most common cause (27 patients), followed by metabolic disorders such as hypoglycemia and electrical imbalance in 18 patients, CNS or systemic infections in 10 patients, and

Table 1
Final diagnosis of 4673 patients who activated code stroke alarming system in emergency room.

Final diagnosis	Number of patients (%)
Stroke	2276 (48.7%)
Peripheral vertigo	911 (19.5%)
Metabolic disorders (drug, alcohol, hyperglycemia etc.)	379 (8.1%)
Seizure (including 27 patients as an initial manifestation of stroke)	188 (4.0%)
Psychogenic	122 (2.6%)
Syncope	121 (2.6%)
Peripheral nerve diseases	118 (2.5%)
General weakness	104 (2.2%)
Transient global amnesia	97 (2.1%)
Incomplete work-up	79 (1.7%)
Headache	76 (1.6%)
CNS infection	58 (1.2%)
Movement disorders	55 (1.2%)
Brain tumors	19 (0.4%)
Ocular diseases	17 (0.4%)
Delirium	12 (0.3%)
Trauma	11 (0.2%)
Spinal cord diseases	9 (0.2%)
Neurodegenerative diseases	6 (0.1%)
Heart diseases	6 (0.1%)
Peripheral vascular diseases	3 (0.1%)
Musculoskeletal diseases	2 (0.0%)
Allergy	2 (0.0%)
Neurobechet disease	1 (0.0%)
Myasthenia gravis	1 (0.0%)
Total	4673 (100%)

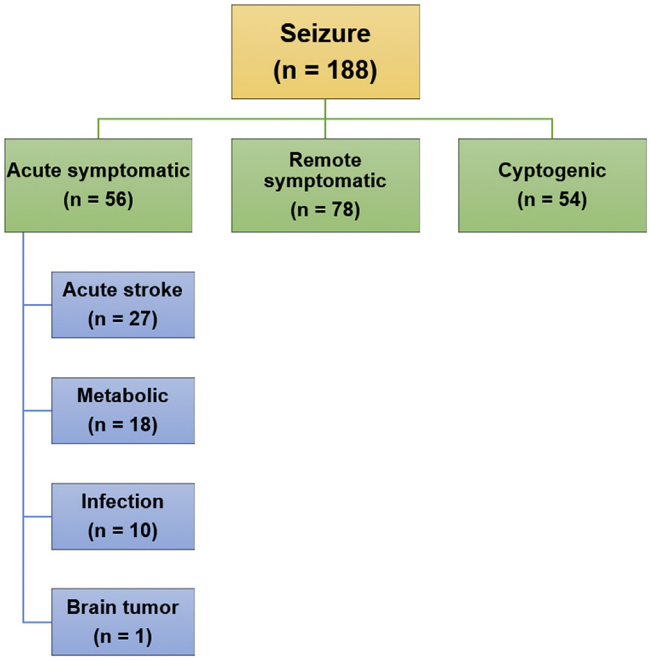

Fig. 1. The etiologies of seizure in patients presenting with stroke-like symptoms.

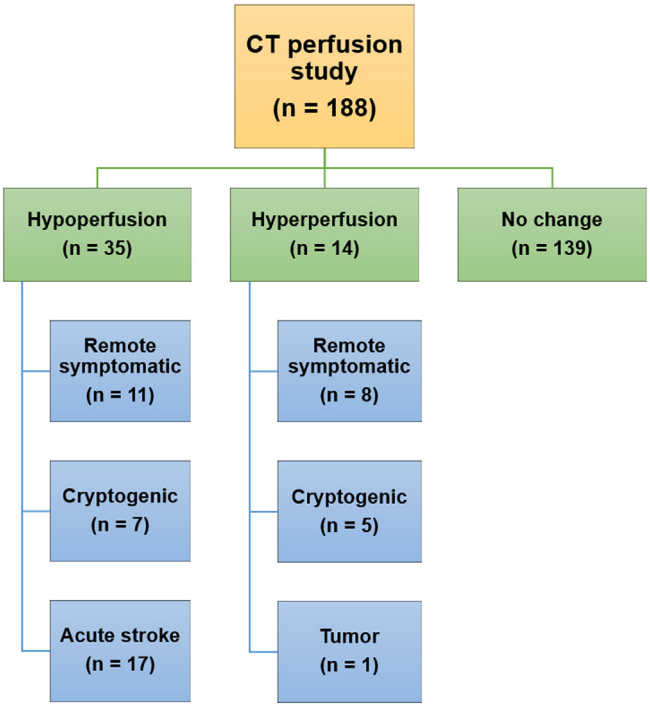

Fig. 2. The incidence and pattern of changes in CT perfusion according to seizure etiology.

brain tumor in another patient (Fig. 1). In 27 patients manifesting acute symptomatic seizure due to acute stroke, 14 patients met the current criteria for intravenous or endovascular thrombolysis; however, only 3 of them were actually treated with thrombolysis because of delayed diagnosis of acute stroke (6 patients) and failure to provide informed consent or considered as contraindications for thrombolysis (5 patients). Intravenous t-PA was administered to a single patient who presented as a stroke mimic but was finally diagnosed as seizure. However, the patient did not report any adverse event related to thrombolysis (see the illustrative case).

CT perfusion showed perfusion changes in more than 25% of patients with seizure (49 of 188 patients, 26.1%). Thirty-five patients (18.6%) exhibited focal hypoperfusion with prolonged MTT and decreased CBV and CBF, and 14 patients (7.4%) manifested focal hyperperfusion with shortened MTT and increased CBV and CBF. CT angiography demonstrated no large vascular pathology underlying the perfusion changes in any of these patients, and the perfusion abnormalities were not localized to traditional vascular territories. Among the 27 patients diagnosed with symptomatic seizures due to acute stroke, CT perfusion showed focal hypoperfusion in 17 patients and no change in 10 patients (Fig. 2).

An illustrative case was a 57-year-old female who was found with altered consciousness and arrived at the hospital after 2 h of previous normal time. Neurological examination revealed stupor, and markedly decreased response to painful stimuli on the left extremities. No other clinical clues suggested a diagnosis of seizure, such as abnormal deviation of head or eye, or abnormal limb movement. The patient's family denied the presence of personal or familial history of seizure, and the patient had no previous medical history associated with seizure such as head trauma or CNS infection. In the emergency multi-modal CT protocol, brain non-enhancement CT and CT angiography showed no abnormality, whereas CT perfusion showed markedly increased perfusion involving the right temporal area. Intravenous t-PA was administered considering the possibility of luxury hyerperfusion after spontaneous re-canalization. The acute stroke-dedicated MRI revealed no abnormality on the area of hyperperfusion, whereas high signal intensity was detected in the right pulvinar area of thalamus on the DWI and FLAIR MRI. Scalp EEG showed persistent sharp waves with a frequency of 1 Hz in the right temporo-occipital area (Fig. 3). The patient did not manifest any adverse event related to thrombolysis and recovered completely with antiepileptic drug treatment. The high signal intensity on the DWI and FLAIR images disappeared with follow-up MRI performed 2 weeks after admission.

4. Discussion

In our study, more than half of all patients who were treated with code stroke alarming were finally diagnosed with other non-vascular etiologies. Seizure was the third common cause of stroke mimics following peripheral vertigo and metabolic disorders. Although the reported incidence and the etiology of stroke mimics varied between the studies, seizure was always one of the most important causes of stroke mimics, accounting for approximately 2% of patients with a final diagnosis treated for suspicion of acute stroke [1,5]. The accurate diagnosis of seizure during acute stroke management may be more challenging due to the frequent focal neurological deficits and perfusion changes observed in neuroimaging. The occasional co-incidence of stroke and seizure complicates the diagnosis, since stroke is the leading cause of adult-onset epilepsy and post-stroke seizure occurs more frequently during the hyper-acute period of stroke and may even represent the initial manifestation of acute stroke [9-11].

Changes in cerebral blood perfusion following seizure have been well documented with ictal SPECT during the presurgical evaluation of epilepsy patients [12]. Seizure onset increases cerebral perfusion in regions of epileptogenesis and early propagation [7,13] and cerebral perfusion rapidly, and transiently, decreased following seizure termination [14]. Although CT perfusion is a widely used imaging technique for detection of regional differences in blood flow in acute stroke treatment, little is known about the frequency and patterns of perfusion changes in patients with seizure mimicking a stroke. A small case series showed CT

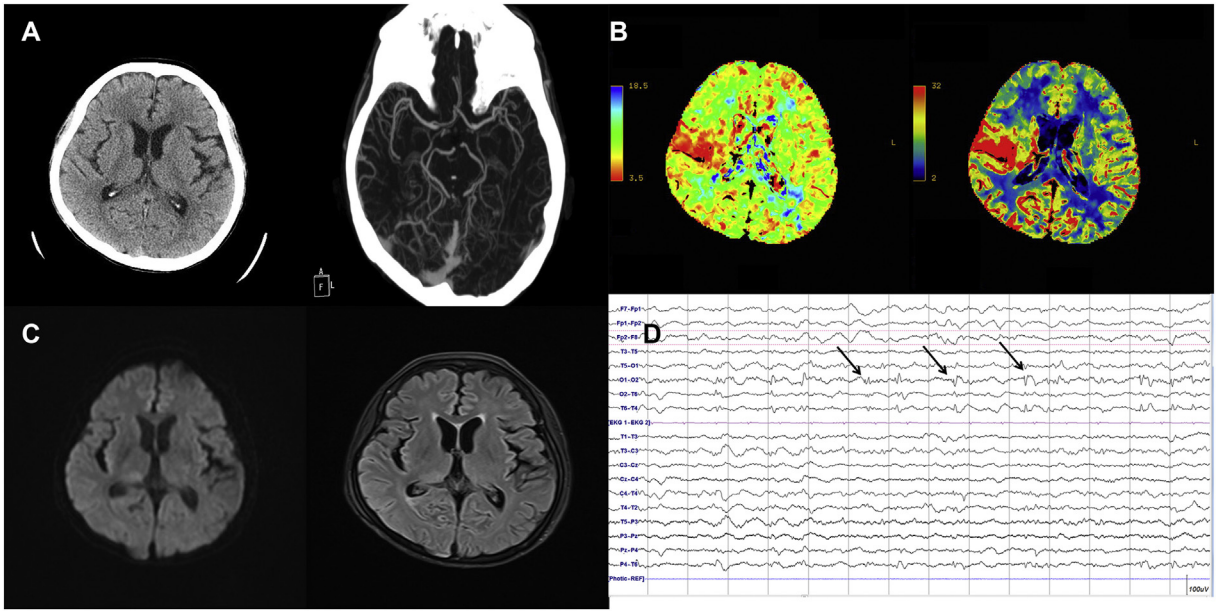

Fig. 3. Initial multi-modal CT evaluation of an illustrative case shows no abnormality in the initial non-contrast CT and CT angiography (A). However, CT perfusion showed markedly increased perfusion in the right temporal area (B). High signal intensity was observed in the right pulvinar area of thalamus in the DWI and FLAIR MRI (C). Scalp EEG showed persistent 1-Hz sharp waves (arrows) in the right temporo-occipital area (D).

hyperperfusion in patients with status epilepticus and post-ictal hypoperfusion was documented in patients with post-ictal paralysis [15,16]. One study analyzed patterns of perfusion change in patients with seizure mimicking a stroke, and found that the most frequent perfusion abnormality involved focal post-ictal hypoperfusion in distribution that did not respect traditional vascular territories and tended to spare the basal ganglia [7]. Another study reported that focal hyperperfusion was the most common finding in post-ictal patients with persistent neurological deficits [8]. We observed that more than 25% of patients with seizure had altered CT perfusion. Two-thirds of them had focal hypoperfusion while the others had focal hyperperfusion. Focal hypoperfusion without concurrent DWI change is frequently detected in patients with seizure during post-ictal periods. However, this finding usually indicates the presence of ischemic penumbra in patients with acute stroke, which is an ideal candidate for thrombolysis. Focal hyperperfusion may also be found in patients with thrombolysis candidates because luxury hyperperfusion may follow spontaneous recanalization of major cerebral blood vessels, which is a marker of favorable outcome of thrombolysis treatment [17-19]. Therefore, careful interpretation of results of perfusion imaging and clinical correlations are required to accurately differentiate acute stroke and seizure mimicking a stroke.

We included 27 patients who were diagnosed with seizure as an initial manifestation of acute stroke. Actually, these patients did not meet the definition of stroke mimic, and could be candidates for thrombolysis when they presented at the hospital within the appropriate time window. However, we found that more than half of them failed to undergo thrombolysis due to delayed diagnosis and were considered as contraindication for thrombolysis. Traditionally, a clinical suspicion of seizure at onset of stroke syndrome was considered a contraindication to treatment stroke patients with intravenous t-PA based on the rationale that a focal neurological deficit in this setting was more likely due to post-ictal Todd paralysis rather than acute stroke [20]. Therefore, the initial guideline of thrombolysis listed seizure at the onset of stroke as a contraindication to intravenous t-PA, whereas the 2013 guidelines list seizure at onset with post-ictal residual neurological impairments as a relative exclusion criterion [21]. The most recent guideline, however, has deleted any reference to seizure from the warnings and contraindications, and recommended that thrombolysis was reasonable for patients with seizure at the time of onset of acute stroke if evidence suggested residual impairments secondary to stroke and not a postictal phenomenon [3]. Our study suggests that in practice, acute stroke patients who present as seizure may have a lower chance of thrombolysis. It may be related to the long duration of the study, since seizure has long been considered as a contraindication of thrombolysis until the 2013 guideline. Nonetheless, our study shows that seizure as an initial manifestation of acute stroke is not a rare condition and the possibility of concurrent stroke should be considered in patients who presented with seizure. Differentiation of an ischemic stroke from post-ictal Todd paralysis based on clinical examination and non-enhancement CT may be difficult and additional neuroimaging studies including DWI, CT or MR angiography, and perfusion images with EEG may facilitate the identification of ischemic tissue and the corresponding arterial occlusion within the time window for thrombolysis [19,22]. Our representative case illustrates the utility of combined DWI and CT or MR angiography in acute ischemia in the setting of concurrent seizure. The lack of arterial occlusion may facilitate the differential diagnosis, and changes in the DWI or MRI T2 weighted/FLAIR images in specific areas, where are not corresponding to arterial territories but frequently involved in prolonged seizures such as hippocampus and thalamic pulvinar, may also be helpful in the differential diagnosis [23].

Although there is widespread consensus regarding the utility of t-PA in acute ischemic stroke, there is still a concern about administration of intravenous t-PA to patients who present with clinical features suggestive of acute ischemic stroke but have alternative diagnosis. Acute ischemic stroke triggers neurologic deficits that generally occur in other disorders, which are not amenable to t-PA treatment and may increase the risk of hemorrhage [24]. In the absence of additional imaging, it is estimated from studies that 3% to 14% of patients treated with intravenous t-PA for assumed acute cerebral ischemia may have a stroke mimic [24]. Notably, the risk of spontaneous intracranial hemorrhage after thrombolysis

of stroke mimics is exceedingly low; however, the concern due to thrombolysis therapy in patients with seizure may be higher because of disruption of blood-brain barrier in patients with prolonged seizure, which may increase the risk of intravenous thrombolysis [25].

Our study has several important clinical implications in critical emergency medicine. First, our study suggests that seizure is one of the common causes mimicking stroke and careful treatment is necessary for patients with seizure who present with stroke-like symptoms because seizure can simulate clinical features and neuroimaging findings of acute stroke. Second, seizure as an initial manifestation of acute stroke is not rare and could be candidates for thrombolysis when they presented at the hospital within the appropriate time window. Finally, careful interpretation of neuroimaging can be helpful in differentiation of acute stroke and seizure in emergency setting. MRI abnormality in specific areas, where frequently involved in prolonged seizures such as hippocampus and thalamic pulvinar, may also be helpful in the differential diagnosis.

We acknowledge several limitations in our study. First, this study included a small number of patients in a single tertiary center. Therefore, we cannot generalize our results to a general population. Second, with the long duration of the inclusion period, the probability of collection bias cannot be excluded. It is also possible that the improved technique affected the diagnostic sensitivity of neuroimaging in acute stroke management. The differences in the criteria for the activation of acute stroke management protocol by the resident doctors in an emergency room also lead to possible of selection bias. Failure to measure EEG in all patients diagnosed with acute stroke and EEG within 24 h in patients with seizure was also a limitation. Additional studies with a prospective design and complete consideration of clinical features is needed to corroborate our findings.

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