

Emergency multimodal computed tomography for the diagnosis of stroke mimic--epileptic seizure

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Abstract

Background and Objectives: Stroke mimics are medical conditions producing stroke-like symptoms but eventually get diagnosed as non-stroke diseases. Epileptic seizure is a common type of stroke mimic. The purpose of this study is to investigate the application of emergency multimodal computed tomography (CT) in the diagnosis of epileptic seizure. **Methods:** We retrospectively reviewed the case group of patients with suspected stroke in the emergency stroke care service of the First Affiliated Hospital of Suzhou University from September 2017 to October 2019. We included those who underwent multimodal CT, including non-contrasted cranial CT, CT perfusion with CT angiography, and were ultimately diagnosed as epileptic seizures. Ten patients with acute anterior circulation ischemic stroke were assigned as controls. **Results:** A total of five cases met the inclusion criteria. Multimodal CT was completed within 2.25 to 3.50h from symptom onset. On CT perfusion, hyperperfusion was shown in four cases and slightly increased perfusion in one case with epileptic seizures. Cerebral blood flow and cerebral blood volume were significantly increased, while time to peak and mean transit time decreased in the regions of interest of the epileptic hemisphere when compared to either the non-affected hemisphere or the ischemic area in the control group ($P < 0.05$). The abnormal perfusion areas did not follow vascular territory supply and CT angiography did not show vessel occlusion in the case group. **Conclusion:** Emergency multimodal CT could be used effectively to differentiate epileptic seizure from stroke.

Keywords: Multimodal CT, epileptic seizure, stroke mimics, differential diagnosis

INTRODUCTION

Stroke mimics clinically present with stroke-like symptoms but are eventually diagnosed as non-stroke diseases.¹⁻³ About 30% of patients diagnosed with ischemic stroke in the emergency room are eventually found to have stroke mimics.⁴ Stroke mimics include epileptic seizure, somatoform disorder, migraine, intracranial tumors, hypoglycemia, heatstroke, syncope and so on. These different etiologies make the diagnosis of acute stroke in the emergency room much more challenging.^{3,5,6} Due to the difficulty in rapid identification of stroke mimics, up to 15% of stroke mimics are inappropriately treated with thrombolysis.⁷ If treated mistakenly by thrombolytic therapy in stroke mimicking diseases, extra hazards would be imposed on

these patients.⁷⁻⁹ Magnetic resonance image (MRI) or multimodal CT examinations were found to be superior to single CT scan in differentiating stroke mimics.⁹ Multimodal CT includes non-contrasted CT scan, CT perfusion (CTP) and CT angiography (CTA).¹⁰

Epileptic seizure is one of the most common type of stroke mimics.⁶ However, in the emergency room, electroencephalogram (EEG) and MRI may not be readily available in daily practice. Thus, a rapid and effective method is needed to differentiate epileptic seizure from stroke. CTP may be a fast, readily available, and useful tool to diagnose an epileptic seizure presenting with acute-onset neurological signs.^{11,12} Previous studies, however, yielded contradictory findings with CTP showing hyperperfusion, hypoperfusion or normal perfusion in seizure-induced events.¹²⁻¹⁵

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The diagnostic value of CTP for postictal stroke mimics has been uncertain.¹⁶ Rather than relying on CTP alone, multimodal CT could be better to quickly identify stroke mimics, especially epileptic seizures.¹⁰

This study reported five cases presenting with stroke-like episodes, which were eventually found to be epileptic in nature. The aim was to investigate the usefulness of emergency multimodal CT in differentiating between acute ischemic stroke and epileptic seizure.

METHODS

This retrospective analysis reviewed patients from September 2017 to October 2019 in the emergency stroke care service of the First Affiliated Hospital of Soochow University, China. The inclusion criteria for the case group were as follows: i) Patients with stroke-like symptoms in the emergency room; ii) Completed multimodal CT investigations of non-contrasted CT, CTP, and CTA; iii) No occlusion of responsible vessels in CTA; iv) Full remission of neurological deficits within hours and; v) Patients with a final diagnosis of epileptic seizure. Exclusion criteria: i) A patient who has been diagnosed with epileptic seizures and had no indications for CTP and CTA; ii) Other metabolic diseases or toxic encephalopathy were diagnosed or; iii) The quality of CTP and CTA images were poor and could not be further analyzed. The control group were those diagnosed with an acute ischemic stroke of the anterior circulation (case to control group sample ratio 1: 2). This study was performed with the local institutional review board approval. The informed consent of all the patients was obtained for this publication.

All patients with stroke-like episodes got access to emergency stroke service where a standard stroke care protocol would be carried out. The assessment included a full neurological examination, the Cincinnati Prehospital Stroke Severity Scale (CPSSS)¹⁷, National Institute of Health stroke scale (NIHSS), blood cell counts, serum coagulation, blood glucose, electrolytes, liver and kidney function, myocardial enzyme spectrum, electrocardiogram and non-enhanced brain CT scan. An epileptic seizure was diagnosed directly or indirectly as suggested by Van Cauwenberge *et al.*¹⁶ Status epilepticus was defined as per International League Against Epilepsy: any prolonged seizure (>30 minutes) or seizure frequency with diminished consciousness over 30 minutes.¹⁸ A postictal Todd's phenomenon was defined as a new focal neurologic deficit after

seizure cessation, having complete resolution within 48 hours.¹⁹

CTP images

Dual-source CT (Somatom Definition Flash, Siemens, Germany) was used to scan the basal ganglia and adjacent layers within 10cm. The specific parameters were tube voltage 80kV and tube current 150mAs. A total of 40ml iohexol (350mg/ml) and 60ml normal saline were injected through the cubital vein at a speed of 6.0ml/s. After 8s, a continuous 37s dynamic scan was started and reconstruction was performed at a thickness of 5.0mm. Four hundred images were obtained. The images were post-processed by the workstation (Syug.MMWP) using NeuroVPCT-stroke software package, including cerebral blood flow (CBF), cerebral blood volume (CBV), mean transit time (MTT) and time to peak (TTP). The hemisphere involved in the epileptic seizure was determined by medical history, symptoms (hemiparesis, tonic gaze or head deviation), neurological examination, and CBF/CBV visualized abnormalities in the CTP. Otherwise, an old cortical lesion was considered as a possible seizure focus. The symmetrical area of the contralateral hemisphere counterparts and parameter data were automatically produced.

In each patient, we selected four successive sections of the regions of interest (ROI) of different axial slices and the corresponding contralateral hemisphere regions on CTP. ROI was limited to the cerebral cortex in the case group but involved cortical/subcortical areas in the control group. Cortical encephalomalacia, fissures, and ventricles were excluded. Quantitative analysis of CBF, CBV, TTP, and MTT was conducted. Asymmetry indices (AIs) were calculated for the CBF as following: $AI = [(ROI \text{ pathological} - ROI \text{ healthy}) / (ROI \text{ pathological} + ROI \text{ healthy})] \times 100$.²⁰ Hauf *et al.* proposed a CBF AI value greater than 10 to define hyperperfusion and AI less than -10 to define hypoperfusion.²⁰

CTA images

CT Neurovascular software was used for post-processing at the workstation of Syngo.via system, including multi-planar reconstruction, curved surface reconstruction, maximum intensity projection, and volume reconstruction. The diagnosis of intracranial and extracranial blood vessel abnormalities was performed using conventional imaging angles, including coronal, axial, and sagittal projection images. All CTP

and CTA were reviewed by qualified neuro-radiologists. Qualitative visual analysis and quantitative analysis were performed.

EEG and MRI

The scalp EEG (Nicolet, Madison WI and Cadwell, Kennewick WA, USA) was used with electrodes placement based on the international 10-20 system (16 electrodes). The EEG was performed by a certified EEG technician within 2 to 6 days of the patients' admission. The duration of a standard EEG was 20 min. The EEGs were subsequently read by two EEG specialists. The 3.0T MRI (GE, Fairfield CT, USA) was used for T1WI, T2WI, DWI and MRA examinations. The images were reviewed by qualified radiologists and neurologists.

Statistical analysis

Ordinal variables were described as median with interquartile range, and categorical variables were presented as frequencies (percentage). Ordinal variables were analyzed using Mann-Whitney *U* test. Categorical variables were analyzed with Fisher exact test. All statistical analyses were performed in SPSS Statistics 16.0 software (IBM, Armonk, NY USA). A double-sided *P*-value <0.05 was defined as statistically significant.

RESULTS

Patients' characteristics

From September 2017 to October 2019, a total of 1,280 patients were treated in the emergency stroke service of the First Affiliated Hospital of Soochow University. They all completed multimodal CT examinations. Five patients (4 males), aged 60 to 75, met the inclusion criteria. Among them, one patient visited the emergency room twice for similar symptoms. The patients presented with disturbed consciousness and/or hemiparesis. Three patients reported pre-hospital suspected seizures. Three patients had partial or secondary generalized seizures in the emergency room. Two patients acknowledged having a history of epilepsy. Other medical history included: hypertension (n=3), diabetes (n=1), transient ischemic attack (n=1), cerebral infarction (n=2) and brain trauma (n=1). Neurological examination revealed impaired consciousness (n=3), hemiparesis (n=3) and tonic gaze (n=4). CPSSS score was 2-4 points (a score ≥ 2 predicting large vessel occlusion severe stroke).¹⁶ The

NIHSS score ranged from 10 to 21 (NIHSS ≥ 15 predicting severe stroke¹⁶, see Table 1. There was no significant difference in age, gender, CPSSS score, and NIHSS score between the case group and the control group ($P > 0.05$). There were no significant abnormalities in blood cell counts, serum coagulation functions, serum glucose, electrolytes, liver and kidney function, and myocardial enzymes in the case group. Three cases had T wave alteration of electrocardiogram and another two had normal ones. Three (30%) patients from the control group had atrial fibrillation while none in the case group did. Non-contrasted CT scans showed old encephalomalacia lesions in three patients of the case group (located in the left frontal, left temporal, and right parietal lobe, respectively). Cerebral hemorrhage and brain tumors were excluded from the scan. One case was misdiagnosed as acute ischemic stroke and was treated with intravenous thrombolysis before CTP and CTA examinations.

CTP and CTA

CTP and CTA examinations were carried out within 2.25 to 3.50 hours of symptom onset in the case group. The affected hemisphere was determined as previously described (left n=1, right n=4). The cortex was mainly affected, especially the temporal lobe, followed by parietal, frontal and occipital lobes or combined. Four patients showed hyperperfusion, with CBF AI more than 10. Another patient had mildly elevated perfusion (CBF AI 8.99). Quantitative analysis indicated that CBF and CBV of the seizure involved hemisphere were significantly increased, while TTP and MTT significantly decreased when compared to the normal hemisphere (Figure 1, Figure 2, Table 2). The area with CTP abnormalities in all patients with seizures had a cortical distribution pattern and did not follow a vascular territory. The CTA also did not show any severe vascular stenosis or vessel occlusion in the seizure group. There were no obvious tonic-clonic seizures during CT, CTP, and CTA examinations. All patients in the control group had vascular occlusion on CTA. Abnormal CTP confirmed vascular cortical and subcortical patterns (Figure 3) in the control group. CBF and CBV in ROI were significantly reduced, and TTP and MTT significantly prolonged, compared to those of the case group (Table 2, $P < 0.05$).

EEG and MRI

The 20-min standard EEG examination was done 2 to 6 days after the symptom onset for three patients

Table 1: Characteristics of five cases with epileptic seizure and ten acute ischemic stroke as the controls.

No.	Gender	Age (y)	CPSSS	NIHSS	Multimodal CT(h)	CTP CBF (AI)	CTA vessel occlusion	Diagnosis	EEG	MRI
1A	M	75	3	21	4.4	17.14	N	SE	Y	Y
1B			2	16	2.25	24.73	N	SE	Y	Y
2	M	60	3	18	2.67	28.01	N	SE	N	N
3	M	69	2	10	3.15	8.99	N	Postictal	N	N
4	M	71	3	12	3.50	28.57	N	SE	Y	Y
5	F	69	4	10	2.50	12.91	N	SE	Y	Y
6	M	53	2	11	3.25	-69.60	Y	Stroke	N	Y
7	F	68	3	15	4.55	-52.34	Y	Stroke	N	Y
8	M	73	2	10	2.65	-56.25	Y	Stroke	N	Y
9	M	65	3	17	3.40	-60.15	Y	Stroke	N	Y
10	M	72	4	19	2.50	-49.56	Y	Stroke	N	Y
11	M	71	3	14	2.67	-58.97	Y	Stroke	N	Y
12	M	66	3	12	3.55	-57.03	Y	Stroke	N	Y
13	F	70	2	9	2.15	-54.35	Y	Stroke	N	Y
14	M	67	3	18	1.96	-46.53	Y	Stroke	N	Y
15	M	62	3	15	2.73	-62.37	Y	Stroke	N	Y

Notes: 1A/B, one patient visiting emergency two times. CPSSS: The Cincinnati Prehospital Stroke Severity Scale. NIHSS: National Institute of Health stroke scale. Multimodal CT (h): time (hours) from symptom onset to multimodal CT. CTP: CT perfusion. CBF: cerebral blood flow. AI: Asymmetry indices. CTA: CT angiography. Y: tested; N: not tested. SE: status epilepticus. Stroke: acute ischemic stroke. EEG: electroencephalography.

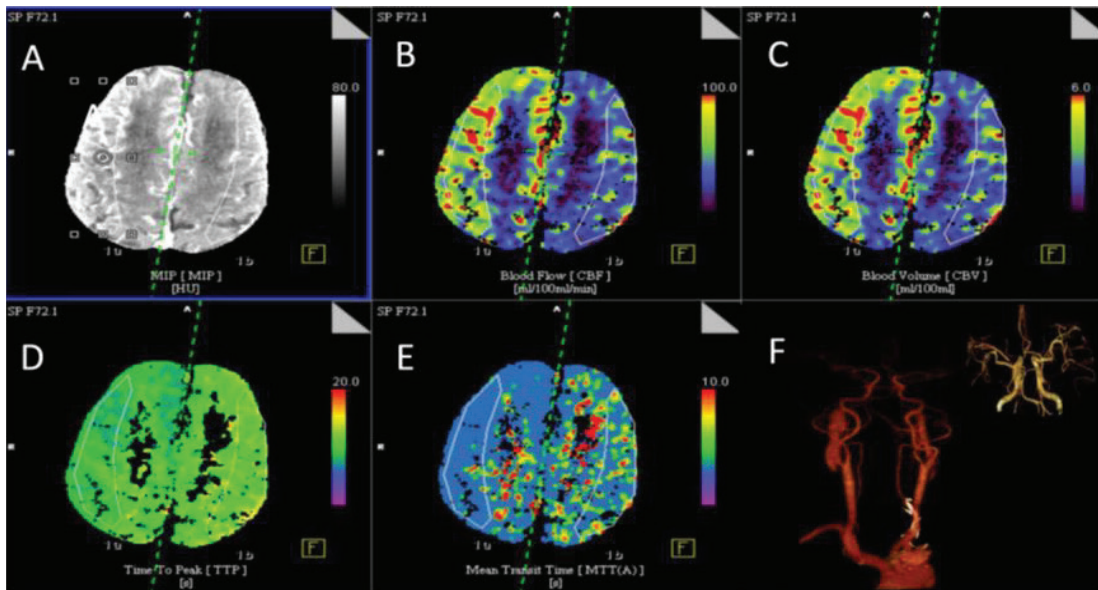


Figure 1. CTP and CTA of the patient No. 2. A: the axial localization; B: CBF, cerebral blood flow; C: CBV, cerebral blood volume; D: TTP, time to peak; E: MTT, mean transit time; F: CTA. The right frontal, parietal and parietal occipital cortices were hyperperfused with a cortical pattern, and CTA showed no stenosis or occlusions of intracranial and extracranial vessels.

in the case group. The interictal EEG showed high amplitude slow waves in the temporal region of the seizure involved hemispheres (Case No. 1A and No. 5). Interictal epileptiform discharges were detected in two patients (Case No. 1B and No. 4) in the hemisphere with hyperperfusion on

CTP (Figure 4). Three patients completed MRI (4 MRI scans) 2 to 3 days after the symptom onset. One case (No. 1B) showed a small DWI abnormal signal on the right hemisphere, which was not consistent with CTP abnormalities and could not explain emergency clinical symptoms.

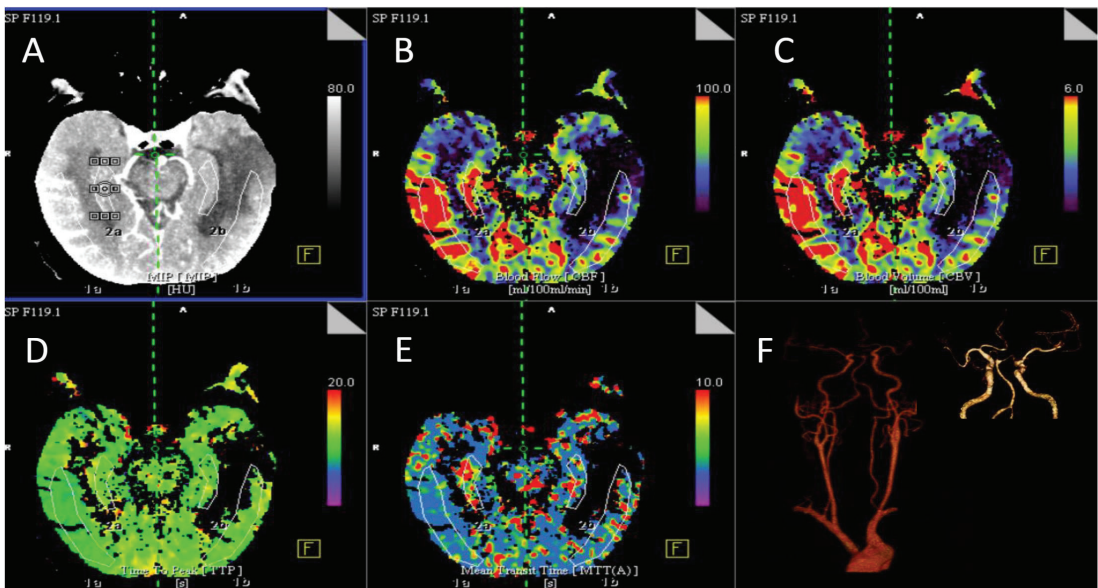


Figure 2. CTP and CTA of the patient No. 4. A: the axial localization; B: CBF, cerebral blood flow; C: CBV, cerebral blood volume; D: TTP, time to peak; E: MTT, mean transit time; F: CTA. The right temporal and occipital lobes were hyperperfused with a cortical pattern. CTA showed no stenosis or occlusions of intracranial and extracranial vessels.

Table 2: CTP in regions of interest compared between seizure hemisphere with contralateral hemisphere or acute ischemic stroke area in the control group

Regions of interest	CTP (median with interquartile range)			
	CBF (ml/100ml/min)	CBV (ml/100ml)	TTP (seconds)	MTT (seconds)
Seizure hemisphere	68.55 (65.06, 85.62)	4:06 (3.66, 4.55)	9.01 (8.62, 11.35)	3.24 (3.15, 3.76)
Contralateral hemisphere	49.29 (40.44, 58.46)	2.84 (2.46, 3.60)	10.62 (9.87, 11.21)	4.15 (3.76, 4.70)
Ischemic stroke	15.43 (9.12, 20.67)	1.95 (0.98, 2.03)	12.83(9.27, 14.56)	5.68 (4.26, 6.79)
P value	<0.01	<0.01	<0.01	<0.01

Notes: CTP: CT perfusion. CBF: cerebral blood flow. CBV: cerebral blood volume. MTT: mean transit time. TTP: time to peak. CBF and CBV significantly increased, while TTP and MTT decreased in the interested areas of the epileptic seizure involved hemisphere compared with the hemisphere counterparts, or acute ischemic stroke area in the control group.

MRI of Case No. 1A excluded a new ischemic stroke. Cases No. 4 and No. 5 had only old cerebral lesions on MRI with no new lesions.

Diagnosis and prognosis

All patients’ neurological symptoms and signs resolved completely 6 to 33 hours after the onset. These five cases were ultimately diagnosed with focal epilepsy. In the emergency room, three cases had status epilepticus, and two cases had postictal Todd’s phenomenon. The etiological for the epilepsy included brain trauma in one case, post-stroke epilepsy in three cases, and the cause was unknown in another case. All patients were treated with antiepileptic drugs. At follow-up

ranging 2-24 months, three cases had recurrent seizures.

DISCUSSION

A total of five cases (six emergency visits) in this study entered the emergency stroke care service due to acute stroke-like manifestations. Because of the inability to rule out an acute stroke or stroke with acute seizures, multimodal CT examination was performed. A CT and CTA ruled out cerebral hemorrhage and ischemic diseases with large vessel occlusion. When compared to the uninvolved hemispheres, the CBF and CBV of epileptic seizure involved ROI were significantly increased with MTT and TTP being significantly

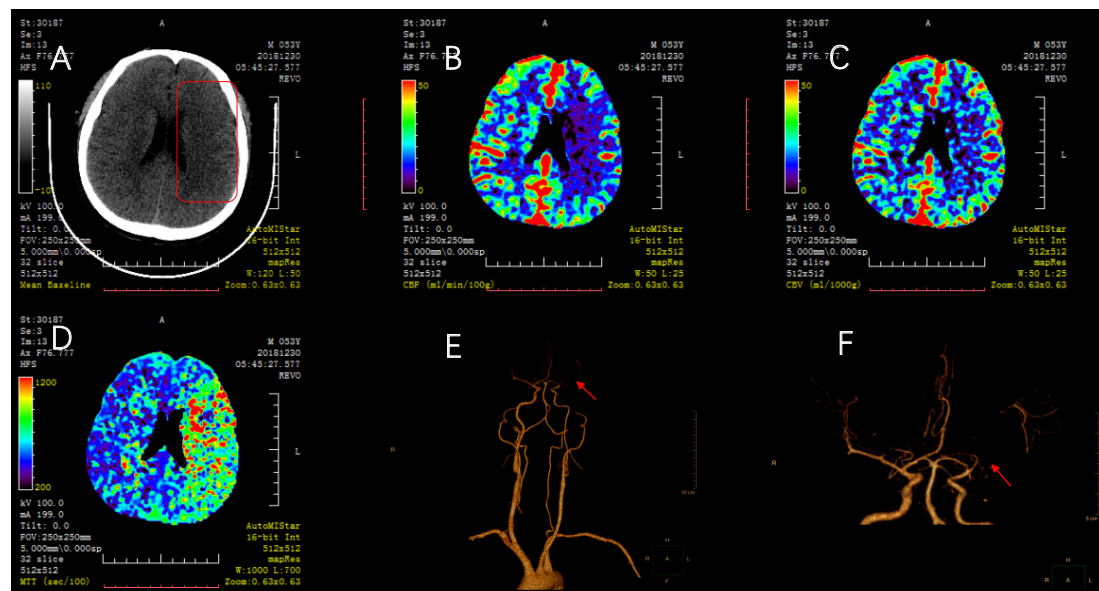


Figure 3. CT, CTP, and CTA of the patient No. 6. A: the axial localization on non-contrasted CT with early signs of acute ischemic stroke (red rectangle); B: CBF, cerebral blood flow; C: CBV, cerebral blood volume; D: MTT, mean transit time. The left middle cerebral artery territory was hypoperfused with cortical and subcortical patterns. E and F: CTA showed the occlusion of left middle cerebral artery (red arrow).

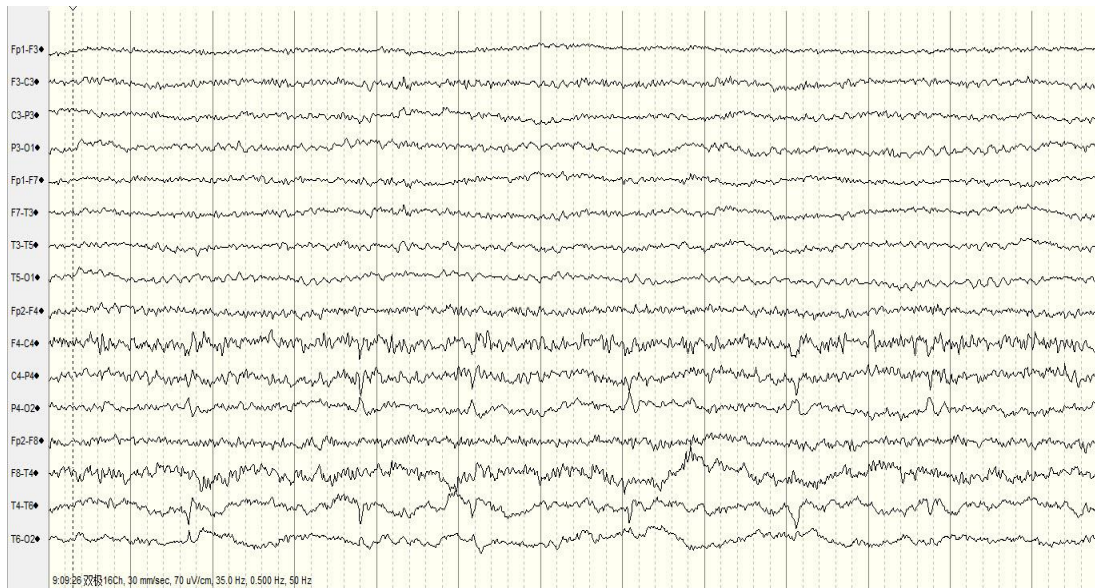


Figure 4. From Patient No. 4, interictal EEG (16-electrodes, bipolar montage) showed frequent epileptiform discharges on the right posterior head (the right parietal P4 and right posterior temporal T6 showed phase reversal), two days after admission. These epileptiform discharges were located in the area of CTP hyperperfusion (see Figure 2).

decreased. The abnormal area of CTP was also only seen in cortical distribution. This pattern was different from the vascular CTP patterns seen in acute strokes. They were ultimately diagnosed as stroke mimics, i.e. epileptic seizures (status epilepticus $n=3$, postictal state $n=2$). Therefore, emergency multimodal CT examinations may help to quickly distinguish epileptic seizure from acute ischemic stroke.

Multimodal CT is the most important investigation for emergency ischemic stroke evaluation.^{21,22} The CTP abnormalities of our ischemic stroke cases were consistent with vascular territories. The CBF and CBV were also significantly decreased, while MTT and TTP significantly prolonged. CTP could be used for evaluation in deciding for intravenous thrombolysis and endovascular treatment. Stroke mimics are challenging in the clinical practice of acute stroke care. Misdiagnosis of stroke mimics could lead to incorrect treatment and adverse consequences for patients.⁷ This would lead to wasted emergency medical resources and increased patient healthcare costs. This study found that one of five cases with epilepsy was misdiagnosed as acute ischemic stroke and was treated with intravenous thrombolysis.

Epilepsy accounts for a large proportion of stroke mimics.^{3,5,6} The diagnosis of epileptic seizure in this study was based on patients' history, complete resolution of the symptoms,

multimodal CT, EEG, and brain MRI findings. A careful anamnesis, clinical manifestations, multimodal CT and MRI images, or blood tests excluded other types of stroke mimics.¹² EEG is critical for the diagnosis of epilepsy but is not readily available in the emergency room setting. This leads to the importance of multimodal CT to help the diagnosis of epileptic seizures presenting as a stroke mimic.¹³

In this study, five patients had consciousness disturbances and tonic gaze or hemiparesis when assessed by neurologists. They were clinically diagnosed with status epilepticus and early postictal state of epilepsy at that time. Unfortunately, we did not have EEG evidence for them. Emergency CTP examinations played an important role in the differential diagnosis. CBF and CBV were significantly increased, accompanied by a decrease in MTT and TTP. A prospective study reported more focal or unilateral increased perfusion of CTP in patients with status epilepticus though EEG and CTP were not performed simultaneously.²³ Payabvash *et al.* found that in CTP done within 3 hours after seizures, 14 out of 18 patients had CTP hyperperfusion with the temporal lobe being most commonly involved.¹⁵ Case reports and small sample reports indicated that seizures^{11,24}, status epilepticus^{25,26}, and non-convulsive status epilepticus²⁰ were associated with increased cerebral perfusion by CTP examination while

MTT or TTP was reported to be decreased in some studies.^{11,15,20,26} In our study, 4 cases showed hyperperfusion, with CBF AI more than 10 and another had a mild elevation of CBF (AI 8.99).

Other studies have reached conflicting conclusions. Hyperperfusion or hypoperfusion of CTP in patients with epilepsy may be closely related to the state of seizures. CTP examination after epileptic seizures shows hypoperfusion of the affected brain area.^{13,27} With more prolonged post-ictal periods, cerebral perfusion returns to the base level of an interictal seizure stage.²² The decrease in perfusion may be related to the interictal low metabolism in the epileptic zone in between seizures. This low metabolism is confirmed by interictal single-photon emission computerized tomography (SPECT) and positron emission tomography CT (PET-CT).^{22,28,29} The increased SPECT perfusion is seen during the ictal phase, and then temporarily decreased within a few minutes after seizures.^{16,25} In some studies, patients with epilepsy had different CTP manifestations, namely hyperperfusion, hypoperfusion, or normal perfusion.^{10,14} Van Cauwenberge *et al.* described the CTP changes in 133 patients with seizures (67 patients with Todd's paralysis and 27 ictal patients). Early CTP showed that 64% of Todd's paralysis patients had normal perfusion, 21% had hypoperfusion, and 14% had hyperperfusion.¹⁶ Ictal patients, on the other hand, were more likely to have hyperperfusion of CTP, with a sensitivity of 38% and a specificity of 86%.¹⁶ These studies support the association between different seizure states with CTP abnormalities and the CTP results should be interpreted carefully. The absence of vessel occlusion, especially in the setting of normal or reduced hemispheric cerebral perfusion should alert the clinician that the patient may be having a stroke mimic.

Our cases underwent interictal EEG 2 to 6 days after the onset of the disease. The abnormalities were located on the side with hyperperfusion on CTP. Our findings were consistent with the EEG findings done within 7 days of symptom onset in another study.¹⁵ Only one study had EEG performed within 2 hours after CT scan.²⁰ EEG findings may vary depending on the time the EEG was done from onset of symptoms. Epileptic discharges were recorded for early EEG within 2 hours²⁰, focal or diffuse abnormalities for those within 12 hours¹², and ictal or interictal activities for those within 1–3 days.^{13,14} There has been only a case report on emergency bedside EEG examination where continuous periodic unilateral epileptiform discharges were found, and

the patient was diagnosed as status epilepticus.²⁶ EEG abnormalities (within 5 days) were reported to be consistent with clinical symptoms and CTP abnormalities in one study.¹⁰ It could be implied that EEG is helpful for the diagnosis of epilepsy. Conversely, multimodal CT could be used when EEG is not available in the emergency room, for the differential diagnosis of epileptic seizures.

The limitations of this study were the small sample size, coupled with the retrospective and observational nature of the study design. It was difficult to separate the ictal phase from the postictal phase of seizures just on clinical grounds. Some cases had not completed EEG and MRI examinations. In the future, prospective, case-control studies with simultaneous EEG and CTP would be expected to clarify the characteristics of CTP in seizures.

In conclusion, emergency multimodal CT could rapidly and effectively assist in the diagnosis of epileptic seizure mimicking an acute stroke.

DISCLOSURE

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Conflicts of Interest: None.

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