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Isolated aphasic status epilepticus: CT perfusion, SPECT and EEG reveal neurovascular coupling and support the differential diagnosis

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ABSTRACT

Objective. Among the clinical manifestations of stroke mimics, isolated aphasia is one of the most challenging due to its aetiopathogenic diagnosis. This short communication describes a specific perfusion and brain oscillatory pattern in a challenging case of prolonged isolated aphasia caused by status epilepticus(SE), jointly investigated by computed tomography (CT) perfusion, single-photon emission computerized tomography (SPECT)/CT and EEG qualitative and quantitative analysis.

Methods. We discuss the different patterns of perfusion neuroimaging and EEG between SE and ischaemic stroke or postictal (Todd's)-related isolated aphasia, and propose these differences as a basis to support the differential diagnosis.

Results. The pattern associated with SE was characterized by focal hyperperfusion on CT perfusion maps (the left mean transit time was shorter with >10% asymmetry, and left cerebral blood volume and cerebral blood flow increased or slightly altered, relative to the contralateral side) and SPECT (focal left temporal hyperperfusion), without any early ischaemic signs on non-enhanced CT, while the EEG showed a predominant left hemispheric slow delta power. The aforementioned perfusion pattern contrasts with postictal epileptic Todd's phenomenon, which is characterized by hypoperfusion on CT perfusion (the mean transit time is prolonged and cerebral blood volume and cerebral blood flow are reduced, compared to the contralateral hemisphere) and SPECT (focal hypoperfusion), not restricted to the specific vascular territories.

Significance. CT perfusion patterns may add valuable information to support the differential diagnosis of status epilepticus, rather than acute ischaemic stroke or postictal Todd's phenomenon, in cases with challenging symptoms of prolonged isolated aphasia.

Key words: status epilepticus, stroke mimic, CT perfusion, EEG, SPECT

Stroke mimics (SM) comprise a set of conditions with clinical presentation similar to that of acute ischemic stroke (AIS), albeit not caused by an ischaemic event. Isolated speech impairment is one of the most challenging SM clinical manifestations. Although cerebrovascular events remain the primary cause (that need to be ruled out or, if applicable, treated), patients with temporal or frontal lobe seizures may also present with isolated aphasia in the ictal or postictal phase [1, 2]. In addition, status epilepticus (SE) may manifest similarly to isolated aphasia. Due to the high mortality rates and the potential complications associated with AIS and SE, a prompt diagnosis is essential to provide rapid and adequate treatment.

Against this background, advanced neuroimaging techniques and neurophysiological EEG assessment may provide a clearer picture of the neurovascular coupling [3-5] and support the differential diagnosis in emergency settings [2, 6]. In particular, a recent study identified a perfusion pattern of isolated aphasic epileptic SM assessed using a quantitative approach based on computed tomography perfusion (CTP) maps. A combination of this approach with EEG, clinical and radiological assessment may provide a clearer distinction between vascular and epileptic aetiology [2].

This short communication describes a specific perfusion and brain oscillatory pattern in a challenging case of prolonged isolated aphasia caused by SE, jointly investigated by CTP, single-photon emission computerised tomography (SPECT)/CT and EEG qualitative and quantitative analyses. We discuss the different patterns of perfusion neuroimaging and EEG between SE and ischaemic stroke or postictal (Todd's)-related isolated aphasia, and propose these differences as a basis to support the differential diagnosis.

Clinical presentation, EEG and neuroimaging findings

A 70-year-old, right-handed male with hypertension, cardiac ischaemic disease, atrial fibrillation, chronic liver disease related to HBV infection and a history of alcoholism was admitted to our department for the first time in 2010 with a generalized seizure. An emergency CT scan showed a 2-cm atypical haemorrhagic stroke in the left temporo-occipital area. Malformations or aneurysms were ruled out following further findings. The patient's neurological examination remained normal and unremarkable, and levetiracetam therapy was started. One year later, a few minutes after showing an impairment of verbal expression, he presented with a focal motor seizure involving the right arm with generalization. Two similar seizures followed closely thereafter, causing short-lived postictal right hemiparesis, as well as global aphasia that lasted several days. The dose of levetiracetam was increased to 1 g twice daily.

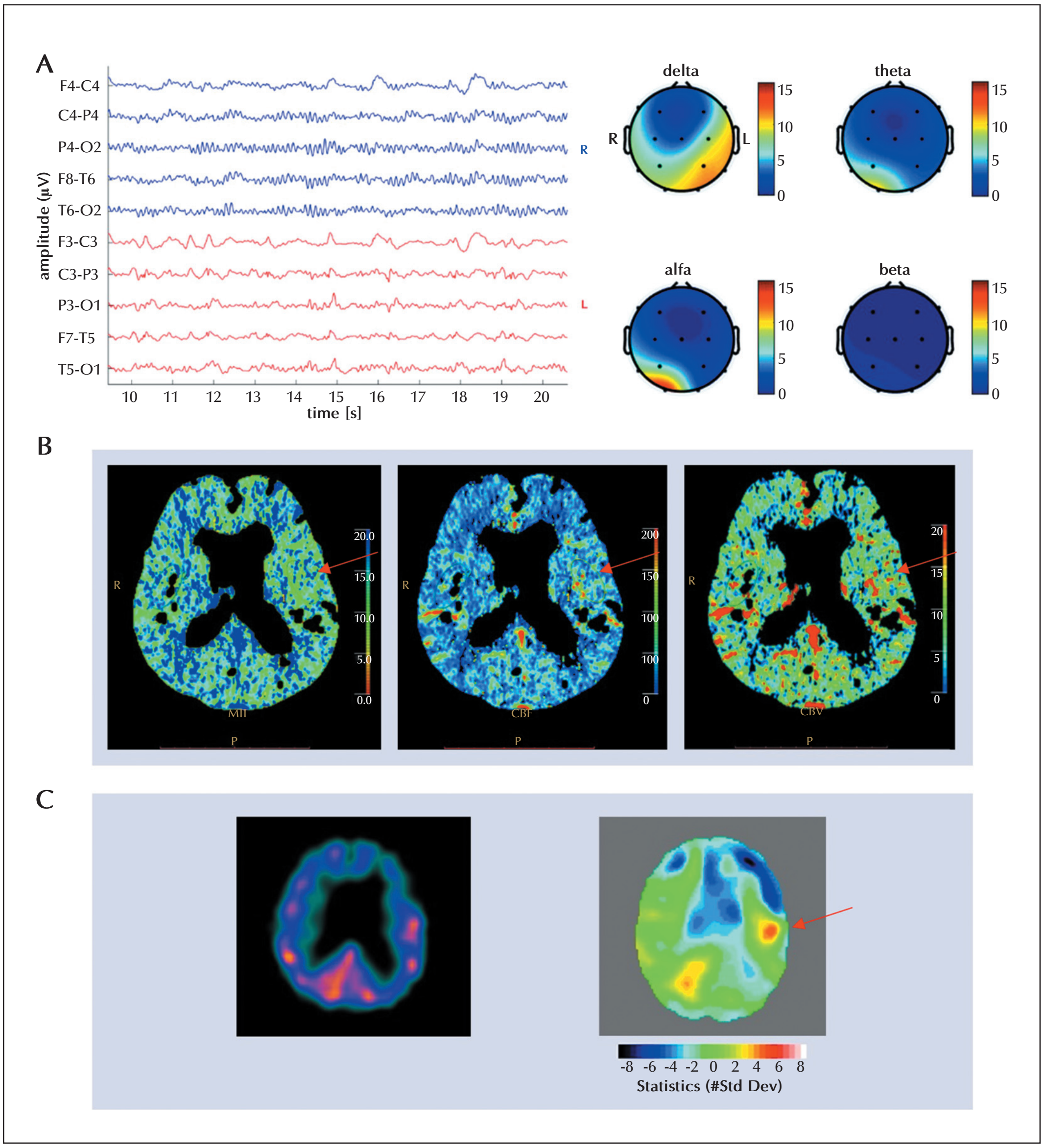
Between 2012 and 2015, six similar seizure clusters followed caused by the patient's poor compliance with the prescribed therapy. In all these episodes, the patient presented with right hemiparesis and aphasia, which resolved within a few days without sequelae.

The EEGs, performed after the above-mentioned seizures and during the aphasic phase, showed generalized background slowing in the theta frequency range along with slow sharp waves at the left hemispheric electrodes. Diagnostic criteria for nonconvulsive status epilepticus (NCSE) were not met.

In 2018, the patient was admitted to the Trieste University Hospital with isolated aphasia, lasting for more than eight hours. After neurological assessment at admission, the patient underwent urgent noncontrast CT, which did not show any new acute lesions or previous areas of hypodensity. EEG recordings showed left hemispheric delta wave predominance without any typical epileptic wave, and SE diagnostic criteria were not fulfilled. The levetiracetam dose was increased to 1 g three times per day. However, the global isolated aphasia persisted for three days.

In order to evaluate for SE or a postictal epileptic phenomenon, we decided to perform an advanced neuroimaging work-up, including CTP and SPECT/CT, in addition to the EEG with frequency map analysis.

EEG signals (19 channel, 10–20 system) were acquired prior to CTP and SPECT/CT on the same day. EEG qualitative analysis showed left hemispheric slow wave predominance with rare homolateral sharp waves. Power spectral density (PSD) was estimated for each channel with Welch's periodogram method during offline analysis with MATLAB® (The MathWorks Inc., Natick, MA). Subsequently, the topographic representation of power for each power band was calculated and plotted (*figure 1A*). CTP imaging was performed according to the protocol and processing described in a previous study, as were the perfusion maps [7]. ^{99m}Tc-HMPAO SPECT/CT imaging was performed immediately after the CTP scan using a hybrid SPECT/CT system (Symbia Intevo 2; Siemens Healthineers, Erlangen, Germany). The SPECT/CT datasets were reconstructed using iterative reconstruction supplied by the vendor (Flash 3D OSEM). Subsequent image processing and quantitative statistical analyses (Z-score), compared on a voxel-by-voxel basis versus healthy controls, was performed using the Syngo-Scenium brain analysis software package (Siemens Healthineers, Erlangen, Germany) and MATLAB® (The MathWorks Inc., Natick, MA), as described in a previous study [8]. Z-score was calculated as intensity difference, expressed as the number of standard deviations (SD) from the mean observed in healthy controls, *i. e.* Z-score = (voxel value − control mean)/control SD. According to the analysis, a predominant delta (δ) spectral power band was observed in the posterior left hemisphere, with an asymmetry index of δ left/δ right=1.43. This location corresponds to the regional



■ **Figure 1.** (A) EEG analysis: EEG bipolar recordings (left) and EEG power maps for each spectral band; delta, theta, alpha and beta (right). (B) CTP maps: MTT, CBF and CBV (from left to right). (C) SPECT/CT analysis: SPECT/CT reconstructed uptake values; (left) and Z-score map (right).

blood flow alterations observed on both CTP and SPECT/CT scans. In our patient, slightly shortened mean transit time (MTT) and slightly increased cerebral blood flow (CBF) and cerebral blood volume (CBV) values were detected on CTP in the left temporal area compared to the contralateral side, suggesting left-side hyperperfusion (*figure 1B*). The focal hyperperfusion was more pronounced on SPECT. In particular, the SPECT uptake also showed significant left temporal hyperperfusion, with a zeta score of Z_L=4.7 SD (contralateral Z_R = -0.6 SD) (*figure 1C*).

Such evidence of left hyperperfusion led to the diagnosis of aphasic SE, and an antiepileptic treatment with lacosamide was quickly administered, showing progressive improvement and ultimate resolution of aphasia. Moreover, after establishing home nurse assistance in order to guarantee patient compliance, no other seizures occurred.

Discussion

Isolated aphasia not accompanied by other focal neurological signs proves to be a challenging aetiopathogenic differential diagnosis, possibly due to stroke, seizure, migraine with aura, functional disorder, and metabolic conditions.

Recently, we have described the importance of CTP in emergency settings to discriminate vascular from epileptic isolated aphasia [2]. The present communication highlights the contribution of CTP/SPECT/EEG in the differential diagnosis of isolated aphasia between SE and postictal epileptic Todd's phenomenon. In particular, we observed a SE pattern characterized by focal hyperperfusion on CTP maps (shortened left MTT with asymmetry ≥10% -asymmetry index ≥10% was considered significant [2,6,9]- and left CBV and CBF increased or slightly altered, compared to the contralateral side) and SPECT (focal left temporal hyperperfusion), without any early ischaemic sign on non-enhanced CT, while EEG showed predominant left hemispheric slow delta power. The aforementioned perfusion pattern contrasts with postictal epileptic Todd's phenomenon, which was characterized by hypoperfusion on CTP (MTT prolonged and CBV and CBF reduced, compared to the contralateral hemisphere)/SPECT (focal hypoperfusion) that was not restricted to the specific vascular territories [2]. In an acute setting, differentiating postictal negative symptoms from SE is mandatory in order to allow appropriate and prompt treatment with antiepileptic drugs.

We have previously described the importance of CTP in emergency settings to discriminate between vascular and epileptic aetiology in patients with language disturbances [2]. CTP is also extremely important in the emergency setting for acute management of stroke [5, 7], in particular, to identify patients who are most likely to benefit from the reperfusion treatment with unknown onset and wake-up stroke [7]. The NIHSS score was strongly correlated with hypoperfused CTP volumes, in particular, in anterior circulation stroke. In acute stroke, the hypoperfused side was related to delta wave EEG power [5]. Recent studies also showed that alpha and delta power alterations are correlated with total hypoperfused volume, ischaemic core volume and neurological deficit at admission [10], and they are good predictors of post-thrombolysis morphological and functional outcome [11]. The functional imaging of CTP can add important information regarding seizure- and migraine-related stroke mimics [2, 6]. Continuous EEG and perfusion magnetic resonance imaging (MRI), if available, would also be useful in such cases to support differential diagnosis.

Brain perfusion abnormalities were observed in epileptic patients, showing hyperperfusion during seizures and hypoperfusion in interictal periods over the epileptogenic areas. MRI- or CTP-based perfusion analysis can support differential diagnosis in emergency settings, allowing rapid treatment of SE [12]. Using arterial spin labelling MRI, perfusion imaging changes were recently detected in interictal patients

▼ **Table 1.** Key elements distinguishing acute ischaemic stroke from status epilepticus and post-ictal Todd's phenomenon based on comparison of neurological examination, EEG, multiparametric CT and SPECT data.

	Acute ischaemic Stroke	Focal status epilepticus	Post-ictal Todd's phenomenon
History of previous stereotypical episodes	No	Yes	Yes
NECT	ASPECT≤10	ASPECT=10	ASPECT=10
CTA vessel occlusion	Yes	No	No
CT perfusion abnormalities: restricted in dependent vascular territories	Yes	No	No
MTT	↑↑	↓	↑
CBF	↓↓	↑	↓
CBV	↑→ (penumbra) ↓↓ (core)	↑	↓
SPECT abnormalities in affected hemisphere	Focal hypoperfusion	Focal hyperperfusion	Focal hypoperfusion
EEG findings in affected hemisphere	Focal slow waves	Sharp waves (rare focal slow waves)	Focal slow waves +/- sharp waves

NECT: non-enhanced CT; CTA: angiography; CTP: CT perfusion; MTT: mean transit time; CBF: cerebral blood flow; CBV: cerebral blood volume.

and seizures [3, 4]. Storti *et al*. observed hyperperfusion using an EEG/fMRI method during an ictal epileptic event in a post-lesional epilepsy patient [13]. Arterial spin labelling may be advantageous as neither contrast agent nor ionizing radiation exposure are required, while CT-based perfusion imaging is more available and less-time consuming in emergency settings. Furthermore, a transient increase in blood flow in response to enhanced metabolism of the involved cortical areas has been widely recognized and documented based on SPECT during epileptic seizures [14-17] and perfusion MRI [18, 19], while decreased blood flow has been described in the postictal phase [20, 21]. Hyperperfusion in ischaemic stroke [22] and during the interictal phase in epilepsy [23] have already been described. However, these patterns are relatively rare and do not allow ictal phenomena and ischemic stroke to be differentiated based on CTP.

Distinguishing between SE and postictal (Todd's) phenomenon may be a challenging task, especially in patients presenting with aphasic symptoms. When patients show isolated aphasia and are otherwise normal based on CT, clinicians are faced with two key issues: 1) whether an ischaemic stroke can be ruled out; and 2) whether the observed aphasia is linked to an ictal or postictal phenomenon. In this regard, CTP scans may provide a readily available and relatively inexpensive answer to both, as it is already widely implemented for the differential diagnosis of acute focal neurological symptoms (*table 1*). Thus, we suggest its application in cases of suspected epileptic aphasia without an EEG with clear ictal characteristics, as well as in subacute cases, in order to differentiate between ictal and postictal manifestations. ■

Key points

- Isolated aphasia is one of the most challenging clinical manifestations of stroke mimics.
- CTP/SPECT/EEG can aid in the differential diagnosis of isolated aphasia between SE and Todd's phenomenon.
- The SE pattern on CTP/SPECT may be characterized by focal hyperperfusion.
- We suggest that CTP should be performed in cases of suspected epileptic aphasia if the EEG study does not show clear ictal characteristics.

Compliance with ethical standards.

All procedures performed in the study were approved by the CEUR FVG Ethical Committee in accordance with the ethical standards of the Institutional Research Committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Informed consent was obtained.

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