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CT perfusion and EEG patterns in patients with acute isolated aphasia in seizure-related stroke mimics

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ABSTRACT

Purpose: Isolated speech impairment is one of the most challenging clinical manifestations of stroke mimic (SM). We aimed to investigate perfusional and EEG pattern of isolated aphasia to better differentiate between vascular and epileptic etiology in emergency settings.

Method: We retrospectively analyzed 481 cases with acute focal neurological symptoms admitted to our Stroke Unit. The patients showing isolated aphasia and confirmed ischemic infarction or SM with seizure etiology on follow-up were included for subsequent analysis of clinical, neuroimaging, and EEG data. We investigated differences in CT Perfusion maps between ROI in the anatomical area compatible with clinical presentation, contralateral ROI and EEG in order to evaluate perfusion and brain oscillatory activity abnormalities.

Results: 45 patients presented isolated aphasia as principal neurological symptom: 27 cases due to acute ischemic event, 11 due to seizure SM, while 7 were SM due to other etiologies. Out of 11 SM patients with seizure etiology, significant hyperperfusion on CTP maps (MTT AI% < -10%) and sharp EEG waves were observed in 8 patients, while in 3 patients slight hypoperfusion (MTT AI% < 20%) and slow EEG rhythms were detected. 24 out of 27 ischemic stroke patients presented severe hypoperfusion with MTT AI above the stroke threshold (MTT AI > 45%). All ischemic stroke patients presented slower EEG rhythms.

Conclusions: The main finding of this study is the identification of different clinical and neuroimaging patterns of isolated aphasia with epileptic or ischemic etiology in emergency settings.

1. Introduction

Stroke mimic (SM) is a set of conditions with clinical presentation similar to that of an acute ischemic stroke (AIS), albeit not caused by an ischemic event [1]. From 1%–41% of patients presenting stroke-like symptoms at admission to the Emergency Department are actually SM [2]. The most common SM etiologies are seizure (38%), migraine with aura (37%), and conversion disorder (21%) [3]. Other conditions of SM are metabolic, infectious, neurodegenerative disorder, peripheral neuropathy and syncope [3].

When evaluating the administration of reperfusion therapies in emergency settings, mild or dynamic neurological deficits can pose the dilemma that the patient is experiencing a SM. In clinical practice, this leads to a not suitable false-positive recombinant tissue plasminogen activator (rt-PA) therapy in 6–16% of cases [4] exposing patients to risk of bleedings, while delaying appropriate and necessary treatment.

Among the clinical manifestations of SM presentation, isolated aphasia not accompanied by other focal neurologic signs is one of the most challenging ones for etiopathogenic diagnosis. Indeed, isolated aphasia can be a symptom of stroke, seizure, migraine with aura, functional disorder, metabolic, and degenerative conditions. In most of cases, isolated aphasia is caused by an ischemic event or seizure [3].

Advanced CT neuroimaging is becoming pivotal in decision making to make early diagnosis and offer an appropriate treatment [5–8]. However, the role of CT Perfusion in SM differential diagnosis is still debated [9–12]. In particular, for seizure-related SM, studies reported ictal hyperperfusion and postictal hypoperfusion [9,13–15].

In seizure-related SM, an early execution of EEG may detect

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epileptic discharge, but EEG is rarely used in acute decision making in emergency settings.

However, the differential diagnosis of vascular and epileptic etiologies was not studied in patients with isolated aphasia as the only symptom at the time of presentation. The aim of this study is to investigate CT perfusion and EEG pattern of isolated aphasia to better differentiate between vascular and epileptic etiology and define a protocol for the emergency management of patients with isolated aphasia symptom.

2. Materials and methods

2.1. Study population

We retrospectively analyzed the clinical and neuroimaging data of patients with acute ischemic stroke symptoms admitted to the Stroke Unit of the University Medical Hospital of Trieste (Italy) between January 2017 and January 2018. Inclusion criteria were patients with acute isolated aphasia compatible with ischemic stroke who underwent CT perfusion evaluation within 4.5 h from stroke onset and with confirmed ischemic infarction or SM mimic stroke with seizure etiology on follow-up. We excluded patients with other cerebral pathology or previous brain surgery hemorrhagic stroke, inadequate CT perfusion owing to technical reasons, such as excessive motion artefacts, bolus suboptimal time, and patients who did not undergo CT and EEG follow-up within 24 h.

The following data of included patients were collected: (1) demographic details (age, sex); (2) stroke risk factors (hypertension, diabetes, dyslipidemia, smoke, ischemic cardiopathy, atrial fibrillation); (3) NIHSS score and mRS at admission; (4) IV thrombolysis/thrombectomy administered; (6) symptomatic intracerebral hemorrhage (sICH); (7) localization of ischemic area (side, cerebral vascular territory), (8) stroke subtype classification at discharge classified by Toast [8]; (9) non-enhanced CT (NECT) at admission and at 24 h, CT angiography (CTA), and CTP; (10) EEG.

This study has been approved by the local ethics committee and has been conducted according to the principles of the Declaration of Helsinki. All participants released their informed consent to participate in the study after all procedures had been fully explained.

2.2. CTP acquisition and postprocessing

Multiparametric CT protocol involved a non-enhanced CT, single phase CT angiography and CT perfusion. All CT imaging was performed with 256-slices CT scanner (Brilliance iCT; Philips Medical Systems, Best, Netherlands). CTP acquisition protocol involved injections of intravenous contrast medium and a total scanning time of 60 s. The exposure parameters used were 80 kVp and 150–200 mA s and we performed a three-dimensional axial acquisition on the whole brain volume with a reconstruction of the slices set to 5 mm. CT image processing and analysis were carried out using brain perfusion software (Extended Brilliance Workstation v 3.0, Philips Medical Systems) and Matlab (MathWorks Inc., Natick, MA) with a dedicated code created for this study. Perfusion maps mean transit time (MTT), cerebral blood volume (CBV), and cerebral blood flow (CBF) were obtained from source images using a deconvolution algorithm. Circular ROI was placed in the anatomical area compatible with clinical presentation, while control ROI was automatically positioned symmetrically on the contralateral side. Differences between MTT, CBV, and CBF CT perfusion parameters between ROI placed in the anatomical area compatible with clinical presentation and contralateral ROI were estimated in terms of asymmetry index (AI%), which was calculated for each CTP parameter as follows:

$$AI\% = \frac{CTP_{left} - CTP_{right}}{CTP_{right}} \bullet 100\%$$

2.3. EEG acquisition and analysis

19 channel (10–20 system) 20-min standard clinical surface EEG was acquired within 24 h from symptom onset by using Be Plus PRO amplifier (EB NEURO, Florence, Italy) and Ag/AgCl electrodes. EEG signals were filtered by second order band-pass Butterworth filter with 0.1–30 Hz cut-off frequencies. Brain oscillatory activities were assessed by qualitative visual inspection of EEG tracings by two experienced neurologists (P.M. and P.C.), initially blinded to perfusion results, in order to identify epileptiform patterns and altered EEG rhythms.

2.4. Statistical analysis

We performed all statistical analysis using Matlab (MathWorks Inc., Natick, MA). Kolmogorov-Smirnov test was used to evaluate normal distribution of variables. Variables were presented with mean and standard deviation or median and range depending on the distribution. The $\chi 2$ test and the Wilcoxon rank sum were used. Statistical significance was assumed at P-value < 0.05.

3. Results

During the study period, 481 patients with acute focal neurologic symptoms compatible with ischemic stroke were admitted to our Emergency Department. A final diagnosis of stroke was made in 438 (93%) patients, while SM was found in 34 (7%) patients: 18 with epileptic etiology, 6 with migrainous etiology, 6 functional etiology, and 4 with other etiologies.

The isolated aphasia as principal neurological symptom without any other motor and/or sensory deficit was found in 45 out of the total 481 cases, and were subsequently included in the study for further CTP and EEG analyses. In 27 cases isolated aphasia was due to acute ischemic event, in 11 was due to seizure, while 7 was due to other etiologies.

Demographic and clinical characteristics at baseline, as well as clinical outcomes are summarized in Table 1. No difference in age (median 80 years; range 43–90 vs median 76 years; range 59–87, P-value = 1.0) was detected between patients with acute aphasic stroke and seizure. Male gender, ischemic cardiopathy, atrial fibrillation were

Table 1
Demographic, clinical characteristics and outcomes of ischemic and epileptic patients with isolated aphasia. * - P-value < 0.05.

	Ischemic Aphasia (N 27)	Epileptic Aphasia (N 11)	P value
F	10 (37%)	10 (91%)	0.003*
Median Age (range)	80 (43-90)	76 (59-87)	0.98
Risk Factors			
Hypertension N (%)	15 (55.6%)	7 (63.6%)	0.64
Diabetes N (%)	10 (37.0%)	2 (18.2%)	0.25
Dyslipidemia N (%)	12 (44.4%)	4 (36.4 %)	0.65
BMI ≥ 25 N (%)	7 (25.9%)	3 (27.3%)	0.93
Ischaemic cardiopathy N (%)	8 (29.6%)	0 (0%)	0.04*
Atrial Fibrillation N (%)	12 (44.4%)	0 (0%)	0.007*
Cigarette Smoking N (%)	12 (44.4%)	2 (18.2 %)	0.12
Previous Stroke/TIA N (%)	3 (11.1%)	2 (18.2%)	0.56
History of Epilepsy N (%)	0 (0%)	3 (27.3%)	0.005*
History of alcohol abuse N (%)	3 (11.1%)	1 (9.1 %)	0.85
Antiplatelet/Anticoagulant therapy N (%)	8 (29.6%)	6 (54.5%)	0.15
Median NIHSS baseline (range)	5 (1-9)	6 (2–9)	0.55
Median NIHSS discharge (range)	2 (0–11)	0	0.01*
N Pre-mRS 0–2 (%)	27 (100%)	8 (72.7%)	0.005*
N mRS at discharge 0-2 (%)	19 (70%)	7 (63.6%)	0.68
Mortality N (%)	2 (7.4%)	1 (9.1%)	0.86
Length of hospitalization median (range)	13 (5-35)	11 (3-40)	0.34

Table 2
NCCT, CTA, CTP and EEG findings of epileptic aphasia patients. MTT = Mean Transit Time; CBV = Cerebral Blood Volume; CBF = Cerebral Blood Flow.

	ASPECT on NECT	CTA vessel occlusion	CT Perfusion alterations	MTT left	MTT right	MTT AI%	CBV left	CBV right	CBV AI%	CBF left	CBF right	CBF AI%	Left Prevalent EEG Pattern
1	10	No	No	7.2 ± 4.1	10.1 ± 4.8	−28 %	6.6 ± 5.2	4.7 ± 3. 0	42 %	71.3 ± 50.7	38.7 ± 21.8	84 %	Sharp Waves
2	10	No	No	6.8 ± 5.3	10.2 ± 6.5	−34 %	2.6 ± 2.4	2.8 ± 2.4	−8 %	43.9 ± 42.9	20.3 ± 18.9	116 %	Sharp Waves
3	10	No	No	9.7 ± 3.4	10.8 ± 3.7	−10%	13.6 ± 6.4	9.9 ± 6.0	37 %	106.2 ± 60.9	63.9 ± 40.8	66 %	Sharp Waves
4	10	No	No	5.8 ± 4.8	7.1 ± 4.7	−18 %	6.3 ± 5.2	6.1 ± 4.9	3 %	97.6 ± 66.9	80.3 ± 64.0	22 %	Sharp Waves
5	10	No	No	12.3 ± 2.5	14.3 ± 2.5	−14 %	8.6 ± 5.8	9.2 ± 7.1	−6 %	46.4 ± 35.5	47.4 ± 44	−2 %	Sharp Waves
6	10	No	No	12.2 ± 4.7	13.5 ± 3.8	−11 %	10.0 ± 5.9	10.8 ± 5.7	−8%	64.3 ± 44.9	56.8 ± 29.9	13 %	Sharp Waves
7	10	No	No	6.2 ± 4.6	8.0 ± 6.5	−23 %	7.7 ± 5. 4	6.6 ± 4.7	17 %	108 ± 58.7	114.7 ± 59.8	−6 %	Sharp Waves
8	10	No	No	15.5 ± 6.8	18.5 ± 6,1	−12 %	2.9 ± 2.1	2.9 ± 3.3	1 %	57.1 ± 54.3	61.1 ± 53.4	−7 %	Sharp Waves
9	10	No	No	12.8 ± 3.8	10.8 ± 3.2	18 %	9.9 ± 5.5	13.5 ± 6.5	−27 %	55.1 ± 34.9	99.4 ± 63.3	−45 %	Slow Waves
10	10	No	No	13.9 ± 3.7	12.5 ± 3.5	11 %	3.5 ± 5	3.8 ± 3	−11 %	18.5 ± 14.4	20.8 ± 13.1	−11 %	Slow Waves
11	10	No	No	13.4 ± 3.9	10.9 ± 3.2	22 %	3.3 ± 2.9	4.9 ± 3.9	−32 %	18.8 ± 12.6	32.3 ± 22.6	−42 %	Slow Waves

more frequent in ischemic aphasia patients compared to seizure-related aphasia patients. Patients with epileptic aphasia presented history of epilepsy and pre-existing mRS > 2 more frequently. Median NIHSS at admission did not differ between ischemic and epileptic group (5, range 1–9, 6 range 2–9, respectively) while NIHSS at discharge was significantly lower in epileptic patients (0) compared to ischemic patients (2, range 0–11). All ischemic and epileptic patients presented an acute onset of aphasia symptoms. 3 out of the 11 epileptic patients were characterized by fluctuating aphasia symptoms. The other 7 epileptic patients and all ischemic patients showed a constant symptom presentation in the first hours from onset. In all epileptic patients, the aphasia symptom disappeared within 24 h, in ischemic patients the symptoms persisted, and in 14 out of 27 ischemic cases aphasia completely recovered at discharge.

Neuroimaging and EEG findings in epileptic patients are reported in Table 2. All epileptic patients presented ASPECT of 10 on NECT, no occlusion on CT angiography, and CT perfusion alteration below ischemic stroke core-penumbra thresholds [16] and not restricted to stroke vascular territories. In particular, epileptic aphasia patients presented mean CBV > 2.0 ml/100 g and MTT AI% < 45%.

Out of 11 aphasia epileptic patients, 8 presented with hyperperfusion pattern on CT perfusion maps and sharp EEG waves (Fig. 1**A**), while 3 patients showed slight hypoperfusion and slow EEG rhythms (Fig. 1**B**). In particular, hyperperfusion patients showed left MTT lower than contralateral MTT with asymmetry > 10%, left CBV and CBF higher or slightly altered compared to contralateral CBV and CBF, respectively. Patients with hypoperfusion pattern showed left MTT higher than contralateral with asymmetry ranging from 11% to 22%, and both lower CBV and CBF.

Median MTT AI% in ischemic aphasia patients was 53% (range 21–99%). Out of 27 ischemic cases, 24 showed left hypoperfusion with MTT AI% above the ischemic stroke penumbra threshold (MTT AI % > 45%), while in other 3 cases the hypoperfusion was moderate (MTT AI% > 20%) but under the threshold. Moreover, six ischemic patients presented CBV values lower than 2.0 ml/100 g, indicating ischemic core later confirmed on 24 h NECT. All ischemic stroke patients presented slower EEG rhythms (Fig. 1**C**).

4. Discussion

The main finding of this study is the identification of a perfusion pattern of isolated aphasia epileptic SM assessed by quantitative approach in CT perfusion maps that - combined with EEG, clinical and radiological assessment - may better differentiate between vascular and epileptic etiology in the emergency setting. The novelty of this study points at the efficacy and remarkable performance of CT perfusion to detect the perfusion abnormalities in focal epileptic seizures in the emergency setting. In particular, isolated aphasia epileptic SM patients presented in 73% of cases with a hyperperfusion pattern and sharp EEG waves, while in other 27% slow EEG rhytms and a slight hypoperfusion (< 20% AI% MTT) below ischemic stroke threshold were found. Conversely, in most of ischemic stroke patients a significant severe focal hypoperfusion with MTT AI% above the ischemic stroke penumbra threshold (MTT mAI% > 45%) and slower EEG rhythms were detected. Our study highlights the importance of detecting early red flags to improve suspicion for ischemic or epileptic etiology of an isolated aphasia in order to administer appropriate therapy, especially when other focal neurologic deficits are not present. Table 3 summarizes the key clinical, neuroradiological, and EEG findings which may support the isolated aphasia differential diagnosis of seizure related SM from ischemic stroke in cases of isolated aphasia.

Cerebrovascular risk factors as male gender, ischemic cardiopathy and atrial fibrillation had a higher prevalence in ischemic stroke aphasia compared to seizure SM. As expected, history of epilepsy and premorbidity mRS > 2 were more present in epileptic SM patients. Indeed, the mimic genesis is more likely in patients without vascular

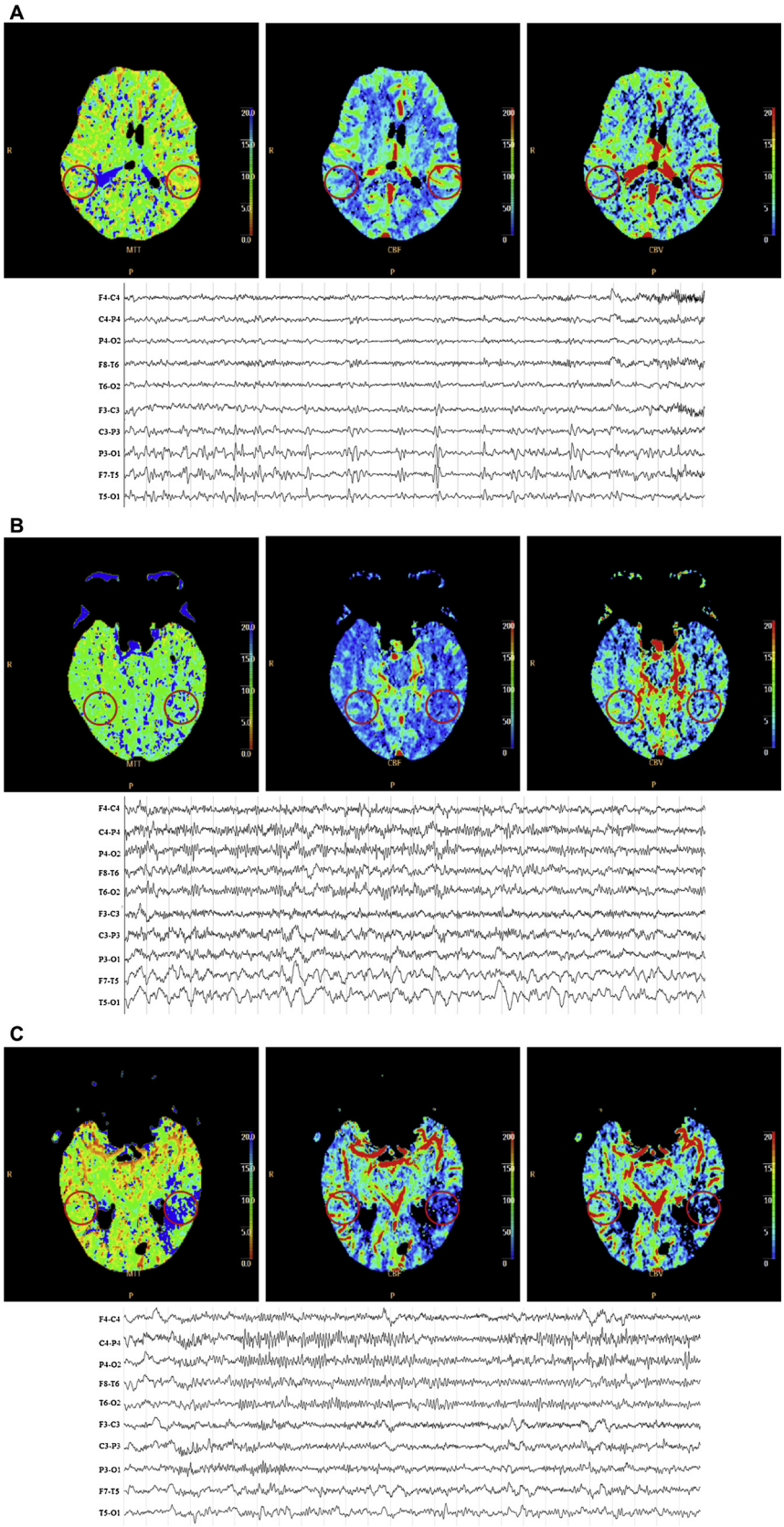

Fig. 1. CTP (from left to right MTT, CBF, and CBV maps) and EEG tracings (below). **(A)** Acute epileptic aphasia with ASPECT 10 on NECT, negative CTA and focal increase of perfusion assessed on CTP maps congruent with epileptic foci characterized by left fronto-parietal sharp waves; **(B)** Acute epileptic aphasia with ASPECT 10 on NECT, negative CTA and focal decrease of perfusion not restricted to a specific vascular territory and lateralized delta waves on EEG; **(C)** Acute Ischemic aphasia with ASPECT of 9 on NECT, occlusion of a distal branch of middle cerebral artery and focal increase of MTT in temporal lobe with a region of CBV below the core threshold and EEG characterized by left predominant delta waves.

risk factors [2,17], while patients with vascular risk as atrial fibrillation had increased odds of stroke [18]. These clinical features should be complementary to brain imaging and other instrumental assessment. Other clinical features as evolution, duration, and recovery of aphasia symptoms were different in the two groups, but as these features are not available in the early stage, they cannot contribute to therapy decision making in hyper-acute phase.

Negative NECT and CT angiography without vessel occlusion or

Table 3
Key finding to distinguish ischemic isolated aphasia from seizure epileptic etiology.

	Ischemic Aphasia	Seizure related hypoperfusion Aphasia	Seizure related hyperperfusion Aphasia
Sex	M	F	F
Ischemic Cardiopathy	Yes	No	No
Atrial Fibrillation	Yes	No	No
History of epilepsy	No	Yes	Yes
Pre mRS	≤2	> 2	> 2
NECT	ASPECT ≤ 10	ASPECT = 10	ASPECT = 10
CTA vessel occlusion	Yes	No	No
CT Perfusion abnormalities restricted in dependent vascular territories	Yes	No	No
EEG findings in dominant hemisphere	Focal slow waves	Focal slow waves	Focal sharp waves
MTT	↑↑	↑	↓
CBF	↓↓	↓	↑→
CBV	↑→ (penumbra) ↓↓ (core)	↓	↑→

relevant stenosis were observed in all epileptic SM patients. As far as ischemic stroke etiology is concerned, in some cases we observed early ischemic changes in NECT with ASPECT < 10 and a intra/extra cranial vessel occlusion. Furthermore, most of the ischemic patients (89%) presented a severe left focal hypoperfusion on CTP restricted in dependent vascular territories. Stroke presenting with aphasia are most often due to ischemic lesion in left middle cerebral artery territory. Blood flow decrease in these areas is far more likely associated with co-existing motor, sensory and visual deficits [19].

Our key result is the frequent observation of two different seizure-related CT perfusion patterns: we observed hyperperfusion pattern in patients, and a slight hypoperfusion in 3 patients. Both observed seizure related perfusion patterns can be clearly distinguished from ischemic perfusion alterations, especially considering MTT asymmetry parameter.

In particular, hyperperfusion seizure patients showed a left MTT lower than contralateral with asymmetry > 10%, a left CBV and CBF higher or slightly altered than contralateral.

Seizure patients with hypoperfusion pattern demonstrated a left MTT higher than contralateral with asymmetry ranging from 11% to 22%, and both lower CBV and CBF. In these patients, the slight decrease in CBV was a further difference compared to the ischaemic penumbra patients. In patients with ischaemic penumbra, focal brain perfusion is reduced, while autoregulation phenomena is maintained and involvement of collateral vessels leads to increased CBV.

Conversely, in seizure related hypoperfusion patients there is a focal reduced metabolism, no vessel occlusion and the tissue does not require collateral blood flow.

Perfusion alterations in epileptic brains are a well-known phenomenon described in human studies, mainly using SPECT [20–22] and ASL MRI [23–27], as well as in experimental animal models [22,28,29]. In particular, these studies showed that the different CBF levels detected during interictal/ictal/postictal phases show not only a variation of cerebral blood flow but also the underlying damage to the blood-brain barrier due to inflammatory processes in the epileptogenic focus. Neuroimaging in experimental epilepsy provides unique information about anatomic, functional, and metabolic alterations linked to epileptogenesis. Recently, several in vivo biomarkers for epileptogenesis have been investigated for characterizing neuronal loss, inflammation, blood-brain barrier alterations, changes in neurotransmitter density, neurovascular coupling, cerebral blood flow and volume, network connectivity, and metabolic activity in the brain [28,29]. ASL MRI is a sensitive method to detect structural and functional changes in the brain, especially to identify region-specific neuronal damage patterns in epilepsy characterized by hyperperfusion during focal seizures [30] and by focal hypoperfusion in interictal phase [24,31]. Similar results are obtained in ^{18}F-FDG-PET studies which generally showed areas of interictal hypometabolism and ictal hypermetabolisim in patients with temporal and frontal lobe epilepsy [32,33]. We confirmed the possibility of observing the epileptical focus with a hyperperfusional pattern during the ictal phase and a hypoperfusional pattern of the postictal phase. Yet, the novelty of our study is the possibility to detect these changes in hemodynamic perfusion in epileptic focus in the hyper acute event during the epileptic attack using CT perfusion, which is highly applicable in emergency settings. A considerable agreement was found between the perfusion alterations and EEG predominant rhythms. Most of seizure patients were characterized by focal sharp EEG pattern, while all ischemic stroke patients by slow lateralized slow waves. The main limit of this study is the small sample size. EEG is not easy to perform in emergency settings, however new technologies with wireless amplifiers and pre-cable cuffs may overcome this problem and allow the EEG assessment during the hyper acute assessment phase.

5. Conclusions

This study showed that advanced multimodal Computed Tomography including CT perfusion may add important information in the emergency setting differential diagnosis between ischemic stroke and seizure mimic in patients with isolated aphasia. The main finding is the identification of a perfusion pattern in the seizure related aphasia patients which were in substantial agreement with the clinical factors and brain oscillatory EEG alterations. The combination of Clinical, Advanced Neuroimaging, and EEG assessment may be valuable in the emergency management of patients with isolated aphasia symptom and lead to a significant clinical impact.

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