Clinical commentary

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A multimodal diagnostic approach for lateralised rhythmic delta activity in the ictal-interictal continuum*

Maddalena Spalletti [1], Francesca Pescini [2], Davide Gadda [3], Benedetta Piccardi [2], Maenia Scarpino [1,4], Riccardo Carrai [1,4], Cristina Boccardi [1], Antonello Grippo [1,4], Aldo Amantini [1,4]

[1] SOD Neurofisopatologia, Dipartimento Neuromuscoloscheletrico e Organi di Senso, AOU Careggi,
[2] SOD Stroke Unit, Dipartimento DEA, AOU Careggi,
[3] SOD Neuroradiologia, Dipartimento dei Servizi, AOU Careggi,
[4] IRCCS Fondazione Don Carlo Gnocchi, Florence, Italy

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ABSTRACT – The ictal-interictal continuum represents a diagnostic challenge even for expert neurrophysiologists, often requiring an additional multimodal diagnostic workup to understand its clinical significance. Lateralised rhythmic delta activity (LRDA) is an ictal-interictal continuum pattern that has only recently been investigated and recognised as potentially ictogenic or sometimes even ictal.

We describe a patient who presented with acute-onset aphasia, initially suspected of having a stroke; advanced brain imaging with CT-perfusion showed features suggesting regional left temporo-parietal hyperperfusion and an EEG revealed LRDA with fluctuations and intermixed sharp waves in the same areas. Treatment with lacosamide caused both clinical and EEG improvement after a few hours, supporting the hypothesis that the EEG pattern represented an ictal/interictal phenomenon.

In the literature, a correlation between metabolic/perfusion imaging and ictal-interictal continuum patterns is described regarding lateralised periodic discharges but less studied for LRDA.

In this case, we adopted a multimodal approach, integrating advanced imaging, EEG, clinical features, and response to therapy, to consider the overall clinical presentation as focal NCSE.

Key words: lateralised rhythmic delta activity (LRDA), ictal-interictal continuum, perfusion imaging, stroke-mimics, non-convulsive status epilepticus

Correspondence:
Maddalena Spalletti
SOD Neurofisiopatologia,
Azienda Ospedaliero-Universitaria Careggi,
Largo Brambilla 3, 50134,
Florence, Italy
<maddalena@spalletti.it>

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A brief description of this case was presented as a poster at the annual congress of the Italian Society of Clinical Neurophysiology (Rome, 29th-31st May 2019).

Continuous electroencephalography has helped to identify not only nonconvulsive seizures and nonconvulsive status epilepticus (NCSE), but also patterns of discharges with epileptiform features and periodicity which do not meet the criteria for seizures. These patterns lie within the ictal-interictal continuum (IIC) and understanding their clinical implications may be complex.

Among these EEG patterns, there is evidence that lateralised periodic discharges (LPDs) in critically ill patients are related to a high risk of subsequent seizures and at times they can even represent an ictal phenomenon (García-Morales *et al*., 2002; Sivaraju and Gilmore, 2016; Rodriguez Ruiz *et al*., 2017; Kapinos *et al*., 2018). More recently, lateralised rhythmic delta activity (LRDA) has been reported to have a similar clinical significance as LPDs, reflecting a high risk of acute seizures, especially nonconvulsive seizures (Gaspard *et al*., 2013; Rodriguez Ruiz *et al*., 2017; Kapinos *et al*., 2018). These periodic and rhythmic patterns are a diagnostic and therapeutic challenge since the degree to which they can be considered epileptiform, ictogenic, epileptogenic and sometimes even ictal remains unclear (Kapinos *et al*., 2018).

EEG monitoring (continuous or repeated recordings) is crucial for the diagnosis of these patterns, but many authors suggest a multimodal stepwise approach including not only EEG (with a focus on dynamic changes of frequency and morphology), but also a pharmacological trial with antiepileptic drugs (AEDs) with integration of neuroimaging and metabolic data (Claassen, 2009; Sivaraju and Gilmore, 2016; Kapinos *et al*., 2018). Since ictal and post-ictal states are a frequent cause of stroke mimics, advanced neuroimaging such as computed tomography-perfusion (CTP) can be useful in distinguishing seizures from a stroke (Hauf *et al*., 2009; Lie *et al*., 2011; Van Cauwenberge *et al*., 2018; González-Cuevas *et al*., 2019; Manganotti *et al*., 2019).

Adopting a multimodal approach, we investigated a case of acute aphasia that was suspected to be a stroke, showing LRDA on the EEG. This case is described and the clinical (ictal/post-ictal *versus* ischaemic) significance of this peculiar IIC pattern is discussed.

Case study

An 82-year-old male patient was admitted to the emergency room (ER) due to acute-onset of aphasia and confusion that started three hours and 10 minutes earlier. The anamnesis reported a thin traumatic bihemispheric subdural haematoma six months before, which spontaneously reabsorbed within the next few months, without residual neurological deficits.

At the time of presentation, the patient was awake and without any motor deficits, impairment of cranial nerve functioning, or sensory loss; the visual field was bilaterally preserved. Moderate to severe expressive aphasia was present: poor spontaneous speech, partially maintained comprehension, frequent anomias, phonemic paraphasic errors, and neologisms. The National Institutes of Health Stroke Scale score was 5. With a suspicion of acute ischaemic stroke, head CTP and cerebral and neck CT-angiography scans were immediately performed according to the hospital protocol. No new-onset lesions were found on direct CT. The CTP (*figure 1A*) revealed a relative increase in blood volume and flow values in the left cortical temporo-parietal areas, suggesting regional hyperperfusion. CT-angiography showed no occlusions in the main intracranial and cervical arteries.

Considering the multimodal CT results along with the clinical and anamnestic data, an ictal/post-ictal state was hypothesised as the cause of the acute language deficit. Thus, an EEG was performed one hour after the CT. The EEG (*figure 1B, C*) showed a slow alpha rhythm on the right hemisphere and LRDA on the left, with frequent fluctuations and rare intermixed sharp waves. The frequency of this activity was 1-2 Hz with no clear-cut spatio-temporal evolution. Considering the persisting language disturbance, CTP findings, and features of LRDA, antiepileptic therapy with intravenous lacosamide (200 mg + 100 mg bid) was initiated. During the following hours, an initial improvement of the aphasia was observed, even though promazine was administered for psychomotor agitation. Fifteen hours later, in the morning, the patient was drowsy but easily arousable, and speech was fluent and comprehensible although some anomia and paraphasia occasionally still occurred. The EEG was repeated and showed the disappearance of LRDA and clear improvement of left hemispheric slowing (*figure 2A*). In the following days, the aphasia further improved, as did the left hemispheric slowing on EEG. At discharge, no significant aphasia was appreciable and the EEG (*figure 2B*) only showed mild diffuse slowing comparable to what was observed several months before, during the previous hospitalisation.

Discussion

The evaluation of EEG patterns lying within the IIC is a diagnostic and therapeutic challenge which frequently arises in the emergency setting.

In our case, we interpreted an LRDA pattern associated with acute-onset aphasia as an IIC pattern with a clinical significance of focal NCSE. Since the EEG pattern alone was insufficient for the diagnosis, we followed a multimodal approach, integrating EEG features with neuroimaging data and response to AED.

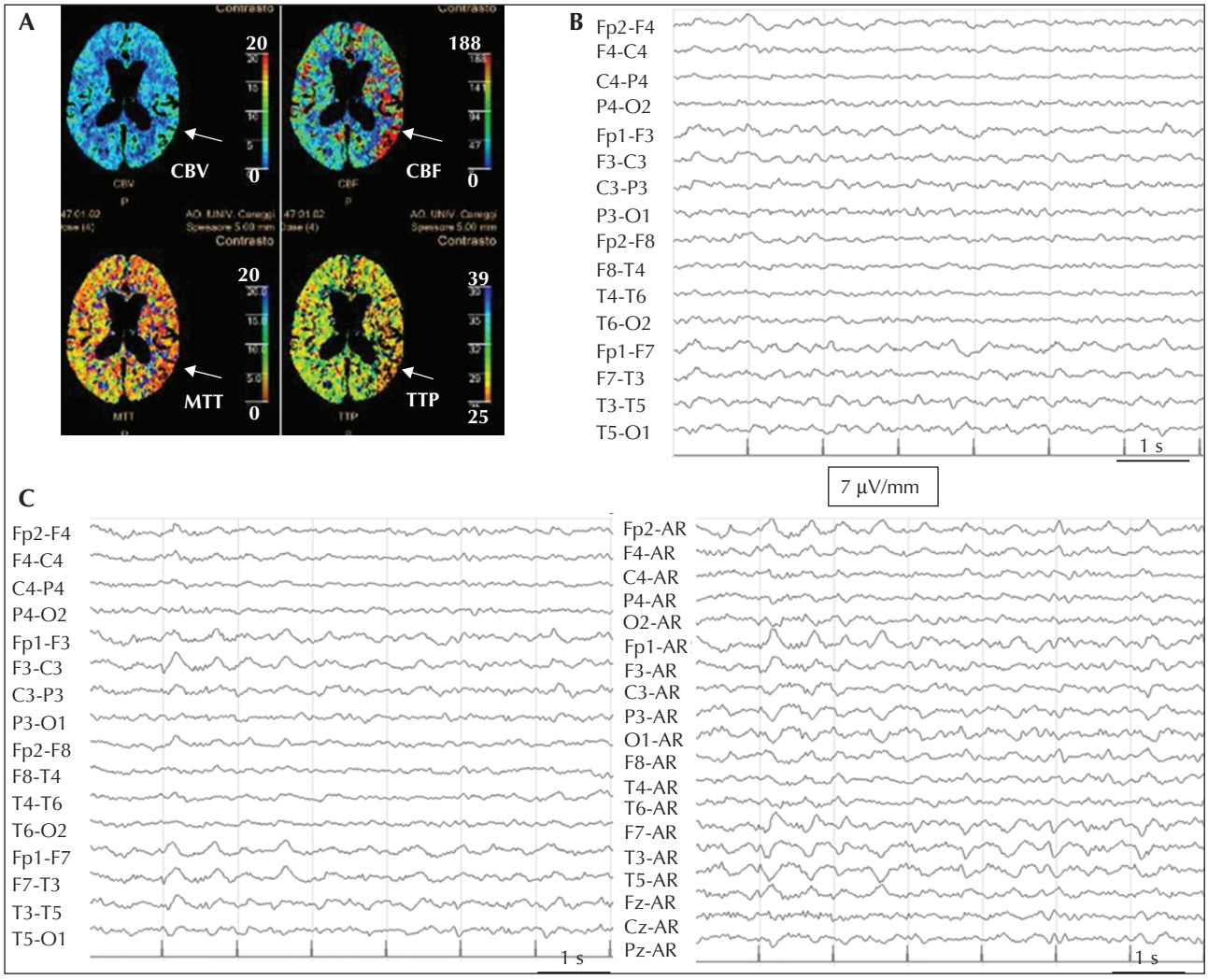

Figure 1. (A) Computed tomography-perfusion on the left temporo-parietal areas (white arrows) showing a relative increase in cerebral blood volume (CBV) and cerebral blood flood (CBF) with minimal values for mean transit time (MTT) and time to peak (TTP), suggesting hyperperfusion. (B ,C) EEG recorded one hour after tCTP (sensitivity: 7 µV/mm). (B) Lateralised rhythmic delta activity (LRDA) on the left hemisphere with a prevalence in the temporal areas. (C) On the same recording, LRDA occasionally showed a sharp aspect (bipolar longitudinal montage [left] and average reference montage [right] of the same trace).

Concerning the clinical significance of LRDA, although this pattern has long been considered more "benign" than LPD, in the last few years, some authors described a clear association between LRDA and seizure, similar to that observed with LPDs (Gaspard *et al*., 2013; Rodriguez Ruiz *et al*., 2017), which are known to be associated with a high risk of seizure and are sometimes ictal themselves (García-Morales *et al*., 2002; Sivaraju and Gilmore, 2016; Rodriguez Ruiz *et al*., 2017; Kapinos *et al*., 2018). In the context of IIC, metabolic and perfusion studies with positron emission tomography (PET), single-photon emission computed tomography (SPECT), or CTP showing hypermetabolism/hyperperfusion further supported the ictal significance of some periodic/rhythmic EEG patterns (Assal *et al*., 2001; Claassen, 2009; Struck *et al*., 2016).

When the diagnostic criteria for NCSE (Leitinger *et al*., 2015) are incompletely or equivocally fulfilled, EEG alone is not sufficient for the diagnosis of an ictal pattern. Recent expert opinions suggest that clinical features, fine analysis of EEG discharges, adjunctive data from neuroimaging, and a pharmacological trial are needed (Rodríguez *et al*., 2016; Sivaraju and Gilmore, 2016; Kapinos *et al*., 2018).

In our patient, the LRDA pattern did not fulfil the primary criteria (A:1-3) for NCSE (Leitinger *et al*., 2015), but only the secondary criterion A:4 (rhythmic activity > 0.5 Hz with fluctuations). Therefore, the ictal significance was uncertain and correlation with other findings was

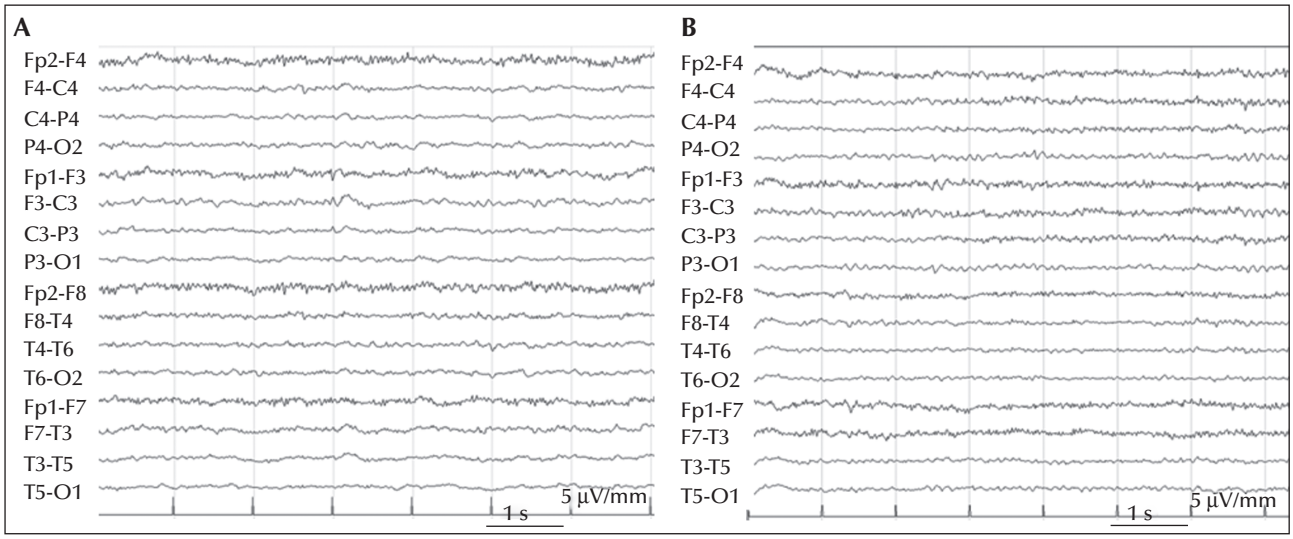

Figure 2. (A) EEG performed 15 hours after the introduction of antiepileptic treatment showing the disappearance of left lateralised rhythmic delta activity (LRDA) and persistence of mild left hemispheric slowing (asymmetry of the posterior rhythm and some intermittent delta waves). (B) EEG at discharge showing no significant visible asymmetry, but only mild diffuse slowing which was already observed months before.

required. The CTP showed a hyperperfusion pattern in left temporo-parietal areas co-localised with LRDA visible on the EEG. Regional hyperperfusion on CTP in small retrospective case series (Hauf *et al*., 2009) and case reports (Lie *et al*., 2011) to identify seizure-related stroke mimics and a large retrospective study has demonstrated specificity in distinguishing ictal stroke mimics from ischaemic stroke (Van Cauwenberge *et al*., 2018). The same study pointed out that post-ictal states are less frequently associated with hyperperfusion on CTP. Another recent retrospective study, including a patient with isolated aphasia of ischaemic or epileptic origin, found hyperperfusion on CTP in 73% of the patients with epileptic aphasia and in none of those with ischaemic aphasia (Manganotti *et al*., 2019). Therefore, in our patient, the finding of hyperperfusion on CTP added weight to the suspicion that fluctuating LRDA with sharp features represented an IIC activity rather than ischaemic or post-ictal slowing. In addition, according to criterion A:4 (Leitinger *et al*., 2015), to support the diagnosis of NCSE, we performed an AED trial choosing lacosamide over benzodiazepines to avoid a sedating effect, which would have hindered the clinical evaluation. The effectiveness of lacosamide is usually less rapid relative to benzodiazepines, therefore its efficacy could not be evaluated in the 10-minute window specified by the NCSE criteria (Leitinger *et al*., 2015), and we observed progressive clinical improvement a few hours after starting lacosamide. Delayed improvement is acknowledged as being common in NCSE cases, especially in critically ill or elderly patients, and is accepted in practical diagnostic algorithms for IIC (Rodríguez *et al*., 2016; Sivaraju and Gilmore, 2016). Therefore, we interpreted the clinical and EEG improvement as a confirmation of an aphasic status, rather than stroke presentation.

In most studies in which EEG and CTP were integrated as part of the investigation for seizure-related stroke mimics, EEG was not performed at an early stage. Van Cauwenberge *et al*. (2018) performed EEGs days after CTP, whereas Lie *et al*. (2011) did not specify the time between CTP and EEG. In the already-mentioned study by Manganotti *et al*. (2019), EEG was performed within 24 hours. Only one retrospective (Hauf *et al*., 2009) and one prospective study (González-Cuevas *et al*., 2019) performed EEGs in the emergency setting at a short time following CTP, allowing a better correlation between CTP and EEG findings. Hauf *et al*. found regional hyperperfusion in eight out of nine NCSE patients, although this was never observed in the post-ictal group. González-Cuevas *et al*. reported good sensitivity (78.95%) and specificity (90%) in distinguishing SE from control patients with post-ictal or SE mimics. In the latter study, the EEG shown for Patient 9 (left parietal LRDA and evolving fronto-rolandic sharp waves) is similar to that in our case, although in our patient, there was not a clear-cut spatio-temporal evolution but only fluctuating sharp LRDA. However, since we performed a routine 30-minute EEG recording, we cannot exclude that a clearer evolving pattern could have been captured on a more prolonged recording.

In conclusion, in a patient with a stroke-like presentation and LRDA, the integration of clinical (modality

of onset, response to AED), EEG and CTP data led us to interpret the overall clinical presentation as focal NCSE. A multimodal approach tailored to each patient is recommended by many authors when dealing with IIC (Rodríguez *et al*., 2016; Sivaraju and Gilmore, 2016; Kapinos *et al*., 2018). □

Supplementary data.
Summary didactic slides are available on the www.epilepticdisorders.com website.

Disclosures.
None of the authors have any conflict of interest to declare.

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TEST YOURSELF

(1) In a patient with focal neurological deficits and CT-perfusion showing regional hyperperfusion, which condition is most probable?

(2) According to recent studies in critically ill patients, lateralised rhythmic delta activity (LRDA) is associated with what aspect of epileptic seizures?

(3) Regarding NCSE primary diagnostic criteria, when the significance of an ictal EEG pattern is uncertain, what diagnostic approach is recommended?

Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com, under the section "The EpiCentre".