Clinical commentary

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Ictal atrial fibrillation during focal seizures: a case report and literature review

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ABSTRACT – Cardiac arrhythmias are a common but often overlooked symptom that occur during or after epileptic seizures. The characterization of seizure-related heart rhythm disorders could shed light on the functional organization of the so-called "central autonomic network" and possibly on the pathophysiology of sudden death of epilepsy patients (SUDEP). Indeed, epileptic discharges may affect the heart through the involvement of cortical regions selectively driving autonomic functions. Ictal atrial fibrillation is an exceedingly rare phenomenon, usually associated with generalized tonic-clonic seizures. Here, we report a case of paroxysmal atrial fibrillation as a core presenting feature of a focal non-motor seizure in a 68-year-old man, at first misdiagnosed and treated for a typical cardiogenic arrhythmia. A brief literature review is included.

Key words: atrial fibrillation, epileptic seizure, central autonomic network, epilepsy, SUDEP

Epileptic seizures are known to induce multiple forms of autonomic imbalance. Indeed, while overt and impressive vegetative changes commonly occur during generalized tonic-clonic seizures (GTCSs), more subtle, but still significant, autonomic alterations may appear in focal seizures as well (Moseley *et al*., 2013). Seizure-related cardiorespiratory changes have received major attention because of their potential role in sudden unexpected death in epilepsy patients (SUDEP) (Devinsky *et al*., 2016).

As far as seizure-related cardiac arrhythmias are concerned, ictal sinus tachycardia is frequently observed, and is usually a benign condition. Conversely, a potentially harmful complication such as ictal bradycardia and the most threatening ictal asystole are rarely documented and could require a pacemaker implant (Sevcencu and Struijk, 2010). The occurrence of atrial fibrillation (AF) in association with epileptic seizures has been described in a few cases so far, usually as a post-ictal phenomenon

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detected in relation to GTCSs (Tigaran and Dam, 1998; Nei *et al.*, 2000; Nei *et al.*, 2004; Herskovitz and Schiller, 2012; Panduranga *et al.*, 2012; Surges *et al.*, 2012; Vedovello *et al.*, 2012; Jeppesen *et al.*, 2014; Singh *et al.*, 2014; Sanchez-Borque *et al.*, 2015; Sanchez-Larsen *et al.*, 2017; Singh Dangol and Hoffman, 2017) (*table 1*).
Here, we report the case of a patient with late-onset temporal lobe epilepsy of unknown aetiology, presenting with paroxysmal AF as a core clinical feature of his focal non-motor seizures.

Case study

A 62-year-old man sought medical attention because of the onset of recurrent, short-lasting episodes of palpitations and dyspnoea, associated with dizziness and a strange feeling of "mental confusion". His past medical history included type II diabetes, mild hypertension, and nodular thyroid disease. General physical and neurological examination were unremarkable. Routine blood tests were within normal limits, except for high levels of glycosylated haemoglobin (HbA1c=8,4%), a marker of uncontrolled diabetes. The patient was referred to a cardiology consultant, who prescribed transthoracic echocardiography, chest X-ray, and 12-lead EKG, which were unremarkable (sinus rhythm with no signs of atrial enlargement). However, a following ECG Holter recording documented an episode of AF with high ventricular rate, which the patient described in his diary as usual "palpitations". He was started on sotalol (80 mg twice daily) for rhythm control, and oral anticoagulant therapy (dabigatran, 110 mg twice daily). Despite medication, during the following six months, the patient continued to present with several episodes with the same features, but a slight impairment of awareness was noticed. He was then referred to our outpatient clinic, where he underwent a thorough clinical examination (including neuropsychological tests), brain MRI, and epiaortic vessel ultrasonography, which resulted negative. Considering the difficult interpretation of the patient's symptoms, although standard EEG recording did not show any pathological findings, two 24-hour ambulatory EEGs (SystemPlus by Micromed, Treviso, Italy) were eventually performed. During the monitoring, on one occasion, he reported in his diary an episode of "palpitations and mental confusion"; the corresponding ECG tracing documented the occurrence of a paroxysmal atrial fibrillation, and, surprisingly, an ictal activity involving the left temporal region was detected at the same time. Four prolonged video-EEG recordings (Natus NeuroWorks EEG, Xltek, Ontario, Canada) were performed, and two electroclinical seizures, lasting about 60 seconds, were recorded (*figure 1*). Clinically, these were observed as an abrupt onset

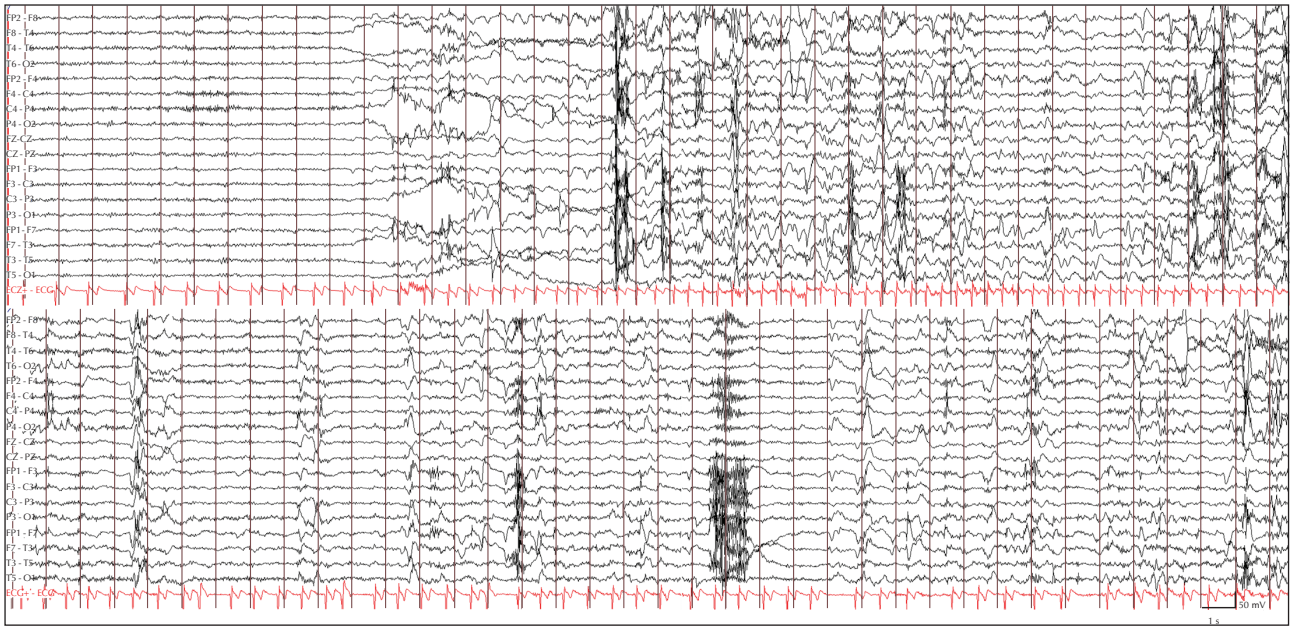

Figure 1. EEG tracing showing an electroclinical seizure arising from the left temporal lobe associated with a cardiac rhythm disorder. At seizure onset, a flattening of the background activity can be observed over the left anterior and middle temporal regions, followed by theta waves and then rhythmic sharp-wave activity, localized in the same regions; the ictal discharge eventually spreads to ipsilateral suprasylvian structures. ECG channel documents a seizure-related change in cardiac activity, consisting of paroxysmal atrial fibrillation, starting five seconds after seizure onset and ending 60 seconds after seizure termination.
Technical details: 21-channel digital EEG recording with time-locked video and single-channel electrocardiography; electrodes were placed according to the 10 to 20 international system; bandpass filters 16 to 30 Hz; sensitivity 10 μV/mm.

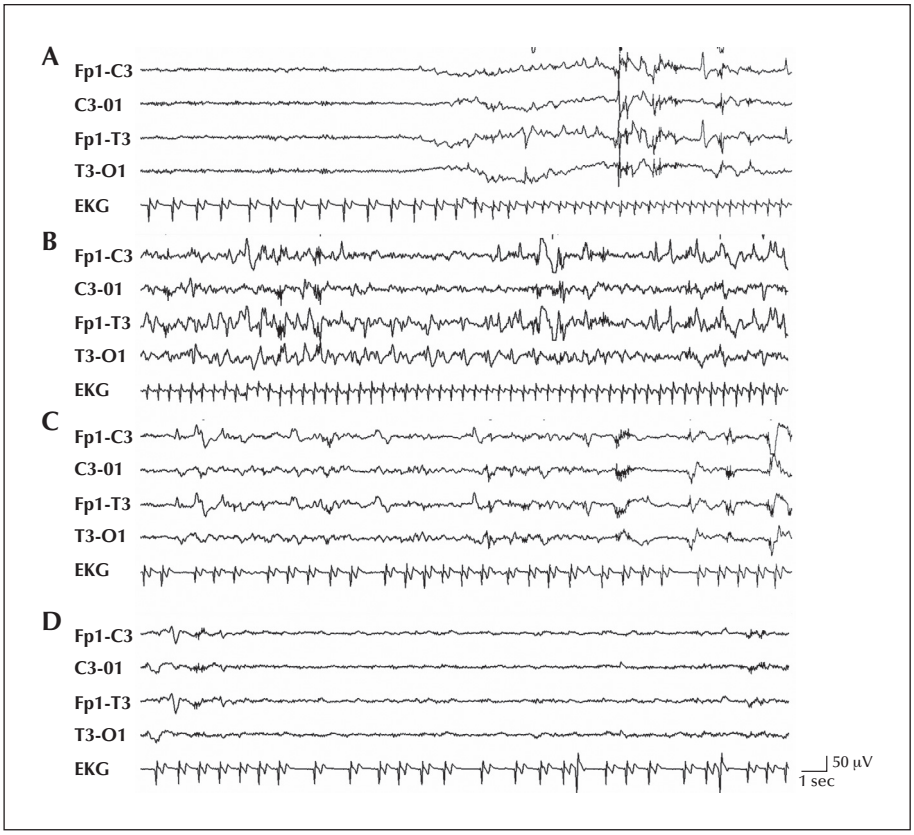

Figure 2. EEG samples emphasizing the ictal pattern and the related ECG changes during seizure evolution on the left temporal regions (A) EEG onset, (B) seconds 25-45, (C) seconds 50-70, (D) post-ictal phase.

of hyperventilation, grimacing, and simple oral and gestural automatisms, followed by dysphasia and mild impairment of awareness. The ictal EEG tracing showed an epileptiform activity spreading over the ipsilateral supra-sylvian regions, located over the left temporal derivations. The co-registered one-lead ECG documented the onset of atrial fibrillation (with ventricular rate of approximately 150 beats/minute), starting abruptly a few seconds after the beginning of the other clinical manifestations, approximately five seconds after the appearance of the ictal EEG changes, and interrupting at around one minute after seizure termination (*figure 2*). The same EEG pattern was observed in both recorded seizures. When seizures ended, the patient was finally able to recall experiencing palpitations, breathing difficulties, and goose bumps, with "mental confusion. . .I couldn't find the words". He was started on antiepileptic medication (levetiracetam at first and due to inefficacy, switched to carbamazepine at 400 mg bid) with complete resolution of his symptoms. No paroxysmal AF was documented during follow-up ECG Holter recording, performed 6, 12 and 24 months after diagnosis. Anti-arrhythmic therapy was then discontinued without any symptom relapse. Anti-coagulant therapy was discontinued after a one-year seizure-free period.

Discussion

Atrial fibrillation during an epileptic seizure is an exceedingly rare phenomenon. In the literature, cases of peri-ictal (post-ictal or not specified) atrial fibrillation are few and often ill-documented. Indeed, only 19 cases of peri-ictal AF have been published so far, all occurring in relation to GTCSs, except for one patient who presented with cardiac arrhythmia associated with a focal seizure arising from the left temporal lobe (*table 1*). To our knowledge, our paper describes the second ever reported case of atrial fibrillation related to a focal seizure, and is the only documented report with available ictal EEG and ECG tracings. Our patient's electroclinical features, *i.e.* ictal manifestations along with EEG evidence of a concurrent paroxysmal discharge arising from the left temporal derivations and promptly spreading to perisylvian regions, support the hypothesis of a seizure which selectively involves the left temporo-insular structures.

Table 1. Peri and post-ictal atrial fibrillation reported in current literature.

Nº	Reference	Sex/ Age	Epilepsy syndrome/ seizure type	Seizure related to AF	Interictal/ ictal EEG	Ictal ECG	AF duration/ remission	MRI	Treatment	Cardiological comorbidities
1	Surges *et al.*, 2012	M/23	Focal epilepsy	GTCS	Normal/NA	Post-ictal AF	25 h/self-limiting	Junctional micro-calcifications > left P lobe	LEV-LTG	None
2		M/25	Focal symptomatic	GTCS	NA/NA	Post-ictal AF	3 h/self-limiting	DNT mTL left	LTG-LEV-LCM	NA
3	Sanchez-Borque *et al.*, 2015	F/44	Focal epilepsy/ FSIA; FTBTCS	FTBTCS	NA/PGES	Post-ictal AF	NA/electric cardioversion	NA	NA	WPW
4	Singh *et al.*, 2014	M/18	NA/new-onset UTCS	UTCS	Negative/NA	Post-ictal AF	NA/electric cardioversion	L frontal FCD type 1	None	Marijuana abuse
5	Panduranga *et al.*, 2012	F/10	New-onset UTCS	UTCS	NA/NA	Post-ictal AF	NA/amiodarone e.v.	NA/NA	None	WPW
6	Herskovitz and Schiller, 2012	M/52	New-onset UTCS	UTCS	GSSW/NA	Post-ictal Aflu	4 days/self-limiting	Normal	None	Brief VT after stress test
7		M/41	IGE; GTCS	GTCS	GSW/NA	Post-ictal AF	2 h/self-limiting	Normal	VPA	LBBB after stress test
8		M/37	Focal symptomatic/ FS; FTBTCS	UTCS	NA/NA	Post-ictal AF	3-4 h/calcium channel blocker	R temporal encepha-lomalacia	CBZ	Hypertension, hyperlipidaemia
9		M/24	IGE/GTCS	GTCS	Normal/NA	Post-ictal AF	1-2 h/self-limiting	Normal	None	None
10		M/21	New-onset UTCS	UTCS	Normal/NA	Post-ictal AF	1-2 h/self-limiting	Normal	None	None
11	Vedovello *et al.*, 2012	M/45	IGE/GTCS	GCTS	Bilateral irregular SW/NA	Post-ictal AF	1-2 h/self-limiting or propaphenone	Normal	None	None

Table 1. Peri and post-ictal atrial fibrillation reported in current literature (*Continued*).

Nº	Reference	Sex/ Age	Epilepsy syndrome/ seizure type	Seizure related to AF	Interictal/ ictal EEG	Ictal ECG	AF duration/ remission	MRI	Treatment	Cardiological comorbidities
12	Nei *et al.*, 2000	-	NA	GTCS	NA	Post-ictal APD; AF	NA	NA	NA	None
13	Nei *et al.*, 2004	-/22	IGE/GCTS; absences	GTCS	GSW/GSW	Post-ictal rrRBBB, AF, Aflu	110 sec/NA (death: SUDEP)	Normal	NA	None
14		-/34	Focal epilepsy/ FSIA; GTCS	FSIA	Normal/ ED Temporal L	Ictal AF	55 sec/NA (death: SUDEP)	Cerebellar hypoplasia	NA	None
15	Sanchez-Larsen *et al.*, 2017	M/32	GGE (Phelan-McDermid syndrome)/GTCS	GTCS	Multifocal (F bilat. SW, F-T PS)/PGES	Post-ictal AF-Aflu	4 min 40 sec/self-limiting	Normal	VPA-ZNS	None
16	Singh Dangol and Hoffman, 2017	M/33	NA/FS; FTBTCS	GTCS	NA	Post-ictal AF	2 h/diltiazem self-limiting	NA	LCS-CBZ	None
17	Tigaran and Dam, 1998	F/74/	NA	GTCS	NA	NA	2 h/self-limiting	NA	NA	NA
18		M/47	NA	GTCS	NA	NA	IV digoxin and verapamil	NA	NA	NA
19	Jeppesen *et al.*, 2014	M/25	Focal symptomatic	GTCS	ED F-T L/PGES	Tachycardia-PVCs-Bradycardia-Asystole, AF, VT/VF	28 sec/CPR/ SUDEP	L temporal FCD	None	Short QTc

NA: not available; M: male; F: female; WPW: Wolff-Parkinson-White syndrome; LBBB: left bundle brunch block; FS: focal sensory, FTBTCS: focal to bilateral tonic clonic seizure; FSIA: focal seizure with impaired awareness; FCD: focal cortical dysplasia; UTCS: unknown-onset tonic-clonic seizure; IGE: idiopathic generalized epilepsy; GGE: genetic generalized epilepsy; P: parietal; DNT: dysembryoplastic neuroepithelial tumour; mTL: mesio temporal lobe; F: frontal; T: temporal; R: right; L: left; GSSW: generalized spike-slow wave; GSW: generalized spike-wave; SW: spike and wave, PS: polyspikes; PGES: post-ictal generalized electroencephalographic suppression; ED: epileptic discharge; CPR: cardiopulmonary resuscitation; PVCs: premature ventricular complexes; SUDEP: sudden unexpected death in epilepsy patients; LEV: levetiracetam; LTG: lamotrigine; LCM: lacosamide; VPA: valproic acid; CBZ: carbamazepine; ZNS: zonisamide; AF: atrial fibrillation; Aflu: atrial flutter; APD: atrial premature depolarizations; rrRBBB: rate-related right bundle branch block; sec: seconds. VT: ventricular tachycardia.

Indeed, a recent comprehensive review of seizure-related cardiac arrhythmias showed a consistent predominance of temporal lobe-onset seizures (91%) (van der Lende *et al*., 2016). Moreover, in both our case and another with focal seizure-related AF (in a patient who later died from SUDEP), ictal discharges arising from the left hemisphere were documented. Although speculation is limited by the rarity of the phenomenon, such intriguing findings might suggest a possible major role of the left insula in the genesis of ictal AF.

In contrast to focal seizures, in AF related to GTCSs, the widespread cortical and subcortical activation and/or deactivation do not allow a localizing hypothesis to be formulated. Furthermore, in this type of seizure, dramatic metabolic imbalances (such as hypoxemia and acidosis) and the severe cardiovascular stress could easily facilitate the occurrence of cardiac dysfunctions, especially in patients with additional risk factors.

From a speculative point of view, cardiac arrhythmia presenting exclusively during a focal non-motor seizure is of interest as a possible expression of the ictal involvement of the so-called "central autonomic network" (CAN); the complex ensemble of brain structures (including mesial temporal cortex, insula, amygdaloid nuclei, hypothalamus, anterior cingulated, and ventromedial prefrontal cortex) subserving vegetative functions (Palma and Benarroch, 2014). The contribution of the CAN to cardiovascular control in humans has not been fully defined yet, especially regarding lateralization and the function of the insula (Oppenheimer and Cechetto, 2016). Interestingly, CAN dysfunctions (particularly those involving its subcortical components) have been proposed among the mechanisms responsible for SUDEP, of which the pathophysiology is still unclear. Indeed, several factors have been considered as possible determinants, including post-ictal generalized EEG suppression (PGES), ictal/postictal apnoea, and malignant tachy/brady-arrhythmias. A centrally mediated neurovegetative breakdown is likely to play a crucial role (Ryvlin *et al*., 2013; Vilella *et al*., 2019). For instance, in their excellent paper, Jeppesen *et al*. described in detail a case of SUDEP occurring in a patient hospitalized in an epilepsy unit for pre-surgical evaluation. As clearly demonstrated through continuous EEG/ECG monitoring, a complex cardiac dysrhythmia (including atrial fibrillation) developed after a cluster of GTCS, with dramatic consequences. Moreover, the patient was shown to have a vagal overdrive preceding his final seizure, as suggested by changes in heart rate variability. Interestingly, a focal cortical dysplasia in the left temporal lobe was found during the post-mortem study. This case illustrates the complexity of heart-brain interactions during seizures in which not only "central" factors but also "peripheral" ones may predispose to peri-ictal rhythmic changes; in particular, in this patient, a short QT interval was documented which possibly contributed to SUDEP (Jeppesen *et al*., 2014). Among predisposing factors, GTCS-related cardiac microlesions and fibrosis should not be underestimated since they might lead to abnormal ventricular conduction as reported by an autopsy study of SUDEP cases (Natelson *et al*., 1998; Chyou *et al*., 2016).

In conclusion, our report provides a well-documented case of ictal AF related to a focal seizure; a phenomenon rarely described among peri-ictal cardiac rhythm disorders. This observation highlights once again the intriguing issue of heart-brain interactions in neurological diseases, and the clinical implications of the ictal involvement of the CAN. A better knowledge of the neural network underlying autonomic control as well as the cardiac effects of certain types of seizures/epilepsies could shed light on the pathogenesis of cardiac dysfunctions and may also contribute to risk stratification in people with epilepsy. □

Disclosures.

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

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TEST YOURSELF

(1) From a pathophysiological point of view, the knowledge of ictal cardiac arrhythmia is crucial to speculate about:
A. Cardiac autonomic innervation
B. Functional organization of the central autonomic network
C. Vagal nerve distribution

(2) Which one of the following structures is more likely to be involved in autonomic cardiovascular control?
A. Temporo-insular regions
B. Occipital lobe
C. Primary sensory motor areas

(3) What treatment should be considered for neurogenic atrial fibrillation?
A. Antiepileptic and anticoagulant
B. Antiepileptic and anti-arrhythmic
C. Antiepileptic, anti-arrhythmic and anticoagulant

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".