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Case Report

Ictal asystole as the first presentation of epilepsy: A case report and systematic literature review☆

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ABSTRACT

We report the case of a 69-year-old woman who presented with recurring episodes of mental confusion/dizziness followed by loss of consciousness, intense pallor, and sweating. Cardiologic investigations were unremarkable. The electroencephalogram recorded during one typical episode allowed the demonstration of a right frontotemporal seizure with progressive bradycardia leading to a 9-second asystole. Following levetiracetam treatment up to 2500 mg/day, seizures with ictal asystole (IA) recurred. An MRI compatible pacemaker was then implanted. At 26-month follow-up, the patient has not had further episodes of loss of consciousness. A systematic review (1950–Apr 2014) searching for cases in which IA was an early manifestation of epilepsy led to the observation of 31 cases. The time lag between the first seizures and the correct diagnosis of IA was long (average: 27 months; median: 12 months). Clinical history alone was not sufficient to prompt a correct diagnosis of IA, and only 11 out of 31 cases presented with symptoms suggestive of a seizure disorder. The majority of patients had a frontotemporal epilepsy with a slight prevalence of left-side involvement (19 out of 31).
Ictal bradycardia–asystole is an important condition that should be recognized by epileptologists, neurologists, as well as emergency department physicians. It is important to underscore that IA not only can occur in patients with drug-resistant epilepsy but also may be the first manifestation of the patient's epilepsy.

1. Introduction

Epileptic seizures can influence the heart, and in particular, they frequently generate changes in heart rate (HR) [1]. Sinus ictal tachycardia (IT), defined as an increase in HR higher than the baseline plus one-third [2], is the most frequently found arrhythmia (accounting for 80–100% of all seizures). It has generally no cardiac consequences, and it can anticipate the beginning of the seizure or occur simultaneously with it [3].

A less frequently observed arrhythmia is sinus ictal bradycardia (IB); defined as an R–R interval is greater than 2 s [4]. Ictal bradycardia can be found in <6% of seizures. A severe slowing of the HR leading to asystole is called "ictal bradycardia syndrome". Ictal asystole (IA) is defined as the absence of ventricular complexes for >4 s accompanied by electrographic seizure onset [5]. Ictal asystole is a rare condition that can be found in 0.27–0.4% of patients undergoing video-EEG monitoring [6,7]. The asystole usually follows changes in the scalp-recorded EEG even if, in some cases, cardiac rhythm changes precede an obvious EEG discharge. Ictal asystole always goes along with a diffuse slowing and flattening of the electrical brain activity seen on the EEG that possibly causes the interruption of the ictal activity itself by an anoxic–ischemic mechanism [8,9]. Clinically, the IA corresponds to a loss of consciousness and a loss of muscle tone that sometimes may be accompanied by myoclonic components. This kind of autonomic dysregulation is generally found in focal chronic epilepsies: 80% of IA cases are associated with temporal lobe epilepsy (TLE) [10,11], while the remaining 20% are linked to extra-TLE (mainly frontal lobe epilepsy) [12].

To obtain relevant clinical information on IA when it occurs as an early (or as first) clinical symptom in the patient's epilepsy history, we present a personal experience in a single case and a systematic review (without meta-analysis, narrative) on this topic.

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2. Methods

2.1. Case report

We, hereby, present a case of IA in a patient with new-onset epilepsy observed in our neurology ward.

2.2. Systematic literature search

We conducted a systematic review of the literature available in PubMed (1950–Apr 2014), searching for cases in which ictal asystole was documented (EEG with ECG registration) as an early manifestation in a new-onset epilepsy or in a newly diagnosed epilepsy [13]. We, therefore, included cases in which IA was a clinical symptom that prompted the diagnosis of epilepsy. We also included cases with an already established epilepsy diagnosis whose seizures had not already failed to respond to adequate trials of two tolerated, appropriately chosen antiepileptic drug schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom. As a consequence, we excluded all the cases in which ictal asystole was observed in the context of drug-resistant epilepsy (as defined by the authors themselves).

The search keywords used, according to the MeSH terms, were the following: "Epilepsy AND Asystole OR Ictal Asystole OR Ictal bradycardia syndrome OR Ictal Bradycardia".

The initial search identified 829 citations. After data analysis and extraction, we identified 29 reports of suspected ictal asystole in new-onset/newly diagnosed epilepsy, but eight articles were finally excluded because they lacked a clear EEG/ECG coregistration of the phenomenon (see flowchart, Fig. 1).

The primary outcomes of the review were to evaluate the time lag between the first episode of loss of consciousness and the diagnosis of ictal asystole and to define the ictal clinical symptoms associated with or preceding loss of consciousness. We also evaluated the following: lobar involvement, etiology, hemispheric lateralization of the seizure, and therapy (AEDs chosen and pacemaker implantation).

3. Case presentation

A 69-year-old woman came to the emergency department for recurring episodes over the previous month characterized by mental confusion, light-headedness, and dizziness followed by loss of consciousness, with intense pallor and sweating. Recovery was quite rapid (20–40 s), and no postictal aphasia or other deficits were reported. Interictal neurological examination was normal.

In her past medical history, the relevant elements were as follows: a thyroid papillary tumor treated with thyroidectomy (16 years before), a catamenial migraine (since her youth), a meningioma of the left cavernous sinus treated with surgery (11 years before) followed by gamma-knife radiosurgery (5 years before), and a right frontal meningioma treated with gamma-knife radiosurgery (the year before).

The carotid sinus massage and the tilt-table test were both negative for vasovagal syncope and orthostatic hypotension. The cardiologic investigations performed (transthoracic echocardiography and Holter ECG) were also unremarkable.

Even if the semiology of the events was not suggestive of seizures/epilepsy, this possibility was considered (multiple meningiomas). Indeed, a prolonged EEG monitoring allowed the recording of one typical episode demonstrating a right frontotemporal epileptic seizure with progressive bradycardia leading to a 9-second asystole (Fig. 2A). The brain MRI confirmed the presence of multiple meningiomas together with postactinic gliosis of the right temporal lobe (Fig. 2B).

Since there were no modifications from the previous MRI, a neurosurgical intervention to remove the right frontotemporal meningioma was not considered a priority, also taking into account the previous neurosurgical history of the patient and the presence of postradiotherapy white matter changes in the right temporal lobe that could have had, per se, a role in the ictogenesis of the patient's seizures. An appropriate antiepileptic drug (AED) therapy was then started with levetiracetam progressively titrated to 1500 mg/day. The patient remained seizure-free for a month, after which, a seizure with IA and falls recurred. Firstly, the AED therapy was increased to 2500 mg/day; however, since the patient presented with two IA events in the following month, she was readmitted to the hospital, and a dual-chamber MRI-compatible pacemaker was implanted.

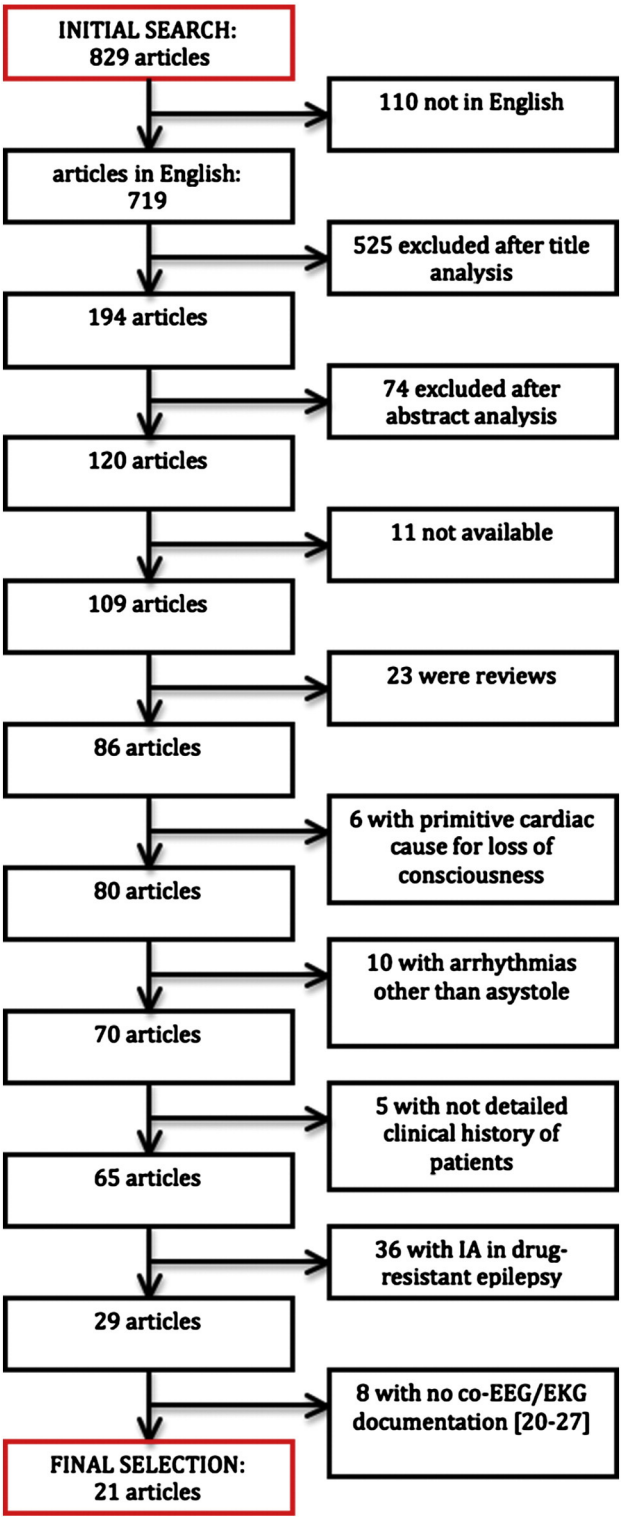

Fig. 1. Flowchart illustrating the literature review process.

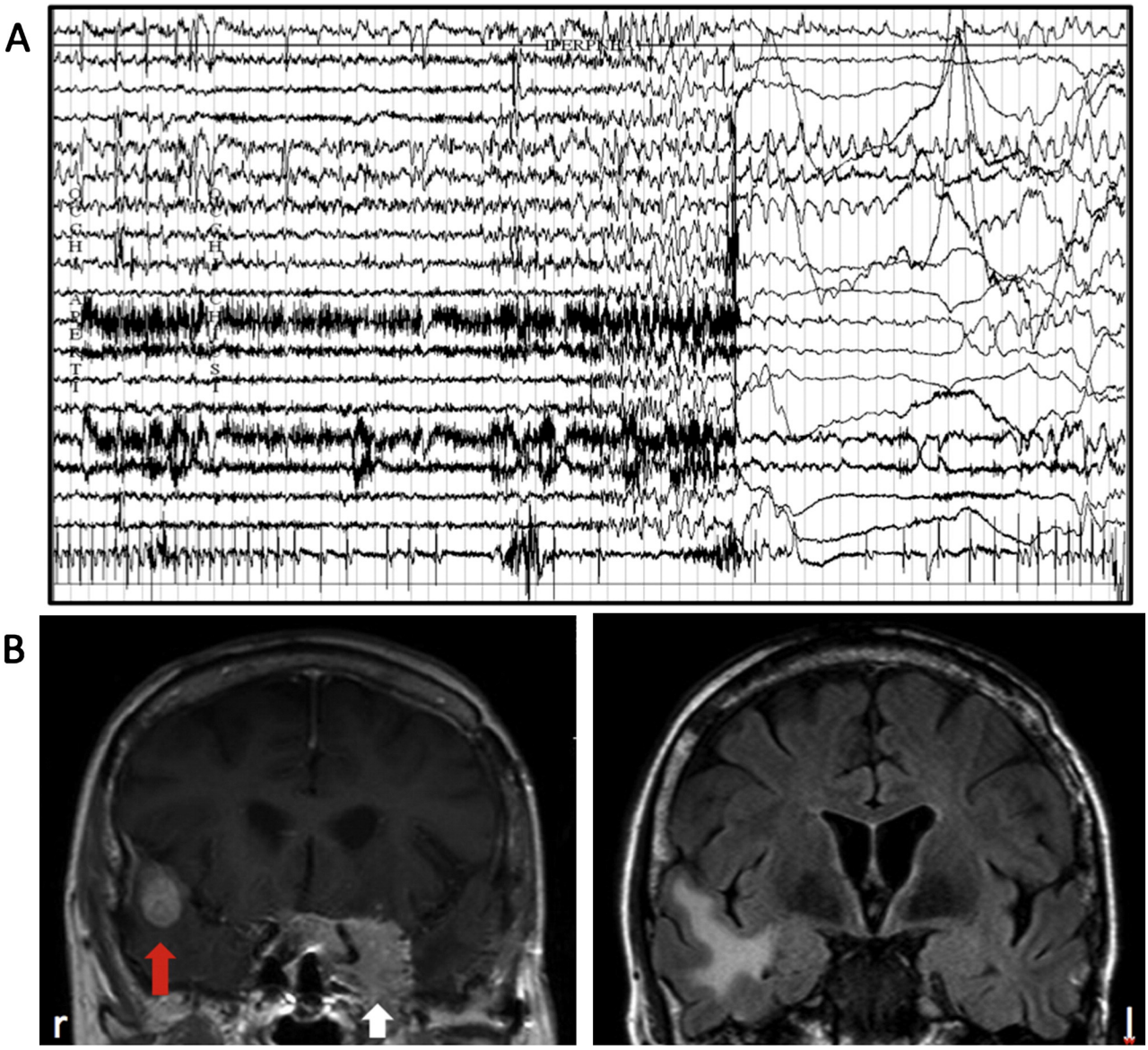

Fig. 2. A. During hyperventilation, rhythmic theta activity and spikes started from the right frontotemporal regions. The ECG trace showed a baseline HR of approximately 80 bpm. 27 s after the beginning of the seizure, the HR dropped; after 47 s, an asystole lasting for 9 s appeared, then the baseline cardiac rhythm returned. During the asystole, the EEG showed hypersynchronous slowing and amplitude increasing of the background electrical activity. Then the brain electrical activity flattened, and the patient presented with loss of consciousness. B. Coronal IR sequence (left panel) with gadolinium showing a meningioma of the left cavernous sinus (white arrow) and a meningioma of the right frontotemporal convexity (red arrow). Coronal FLAIR image (right panel) showing postactinic white matter hyperintensity of the right temporal lobe.

At 26-month follow-up, the patient has had no further episodes of loss of consciousness, and no arrhythmia was recorded by the pacemaker.

4. Discussion

The relations between seizures and the heart are very complex. The pathogenesis of these events is not completely and clearly understood. These arrhythmic events could easily occur in patients without any cardiac alterations. The mainstream theory is that the seizures may lead to the involvement and the stimulation of a circuit comprising the insula, the cingulate cortex, the amygdala, and the hypothalamus. This circuit regulates the cardiac functions through the connections to the brainstem and the spinal cord nuclei [14]. The ictal bradycardia syndrome could be found in patients with a long-lasting history of epilepsy, in particular of refractory epilepsy caused by a continuing impairment of the neurocardiac regulatory system as a result of repeated seizures and, maybe, AED treatment. The impairment of the neurocardiac regulatory system is well demonstrated by the lower heart rate variability (HRV) in patients with TLE [15]. This can make patients more susceptible also to fibrillation and tachyarrhythmias [16–18]. In these cases, IA should be particularly suspected if the usual semiology of seizures occur together with syncopal episodes [19–21]. On the contrary, the presented case demonstrates clearly that IA can be the only and the first ictal manifestation of new-onset epilepsy, and for this reason, it could be easily overlooked.

4.1. Treatment choices in the presented case

As there are no guidelines to address the management of ictal arrhythmias, we focused on the decision-making process of implanting a pacemaker [22]. Even if these events are generally benign and self-limited, it is theorized that they could contribute to SUDEP, although a link of the IA with SUDEP is still missing [23]. When an IA is detected,

Table 1
Reviewed studies.

Ref.	Age (years)	Sex	Baseline EKG	Duration before diagnosis	Lobe	MRI/etiology	Side	Asystole duration	AED before diagnosis	AED after diagnosis	Pacemaker implantation
Fincham R.W. et al. [27]	68	M	UNK	Some w	O	Posttraumatic	R	33	–	PHT	Yes
Reeves A.L. et al. [28]	60	M	Run of SVT	3 y	T	Normal	R	6	–	CBZ	No
Fuhr and Leppert [4]	69	M	Normal	First episode	FT	Not performed	R	5	UNK	UNK	UNK
Rugg-Gunn et al. [7]	34	M	Normal	1 y	Bil	Normal	Bil	25–30	PHT, CBZ	PHT, CBZ	Yes
Dubois-Teklali F. et al. [29]	2	M	Normal	9 m	T	Normal	L	20	–	VPA, OXCBZ	Yes
Carinci V. et al. [30]	78	M	UNK	2 d	FT	Previous clipping of intracranial aneurysm	L	10	–	–	Yes
Ghearing G. et al. [31]	72	F	Normal	3 y	T	Normal	L	4	–	UNK	UNK
Bae E.K. et al. [32]	61	F	2nd degree AV block	7 m	T	Normal	L	UNK	–	LEV	Yes
Dinan A. et al. [33]	59	M	Normal	4 d	T	Ischemic changes in insular region	L	4	–	LEV	Yes
Enkiri S. et al. [34]	38	M	Normal	Some d	F	Normal	L	22.5; 8.5; 24.5	–	OXCBZ	No
Schuele S.U. et al. [35]	14	F	Normal	<1 y	T	Normal	L	33	LEV	LEV	Yes
	13	F	Normal	1 y	Vertex	Normal	–	5	LEV	LEV	Yes
Kouakam C. et al. [36]	37	F	Normal	4 y	T	Normal	L	30	–	VGB, CBZ	No
	77	F	1st degree AV block	5 y	T	Posttraumatic	R	10	–	CBZ	No
	47	F	Normal	2 y	T	Normal	R	30	–	VGB	Yes
	54	F	Normal	8 y	T	Normal	L	15	–	OXCBZ, CLB	No
	52	M	Normal	1 y	T	Normal	L	30	–	CBZ	No
	21	F	Normal	2 y	T	Normal	L	27	–	CBZ, TPM	Yes
	29	F	Normal	18 y	T	Normal	L	12	–	LTG	No
	83	F	Normal	3 y	T	Normal	R	20	–	OXCBZ	No
	34	F	Normal	m	T	HS	L	40	–	CBZ, LEV	No
Novy J. et al. [37]	46	M	Normal	5 y	T	Normal	L	7	–	VPA	Yes
Lanz A. et al. [38]	41	M	Normal	1 y	T	Normal	R	25	CBZ, PRI	CBZ	Yes
	63	F	Left bundle brunch block	14 m	FT	DNET	L	34	TPM	–	Yes
Lee et al. [39]	41	F	Normal	Some w	T	Anti-NMDAR encephalitis	L	15	–	Steroids, TPM, LEV	Yes
Marynissen T. et al. [40]	48	M	Atrial fibrillation	2 y	T	Normal	UNK	15	–	YES (Not spec)	Yes
Millichap J.J. et al. [41]	15	F	Normal	1 m	T	Anti-NMDAR encephalitis	L	22	–	IVG, PHT, LEV, PB, Steroids	Yes
Strzelczyk A. et al. [42]	66	F	Normal	5 y	T	Normal	R	21	–	VPA	Yes
Kang D.Y. et al. [43]	54	M	UNK	2 y	T	Normal	L	40	CBZ	CBZ	Yes
Wittekind S.G. et al. [25]	32	M	Normal	16 m	FT	Normal	R	18.5	–	LEV	Yes
Heerey et al. [44]	24	F	Normal	1 y	T	Normal	L	30	LEV, LCS	LEV, LCS	Yes
Present study	69	F	Normal	Some m	T	Meningiomas and gliosis	R	9	–	LEV	Yes

F, female; M, male; d, days; m, months; y, years; T, temporal; FT, frontotemporal; L, left; R, right; Bil, bilateral; SVT, supraventricular tachycardia; HS, hippocampal sclerosis; CBZ, carbamazepine; CLB, clobazam; GBP, gabapentin; LEV, levetiracetam; LCS, lacosamide; LTG, lamotrigine; OXCBZ, oxcarbazepine; PHT, phenytoin; PRI, primidone; TPM, topiramate; VGB, vigabatrin; VPA, valproic acid; IVG, intravenous globulin; UNK, unknown.

to avoid ictal traumatic falls and to reduce the correlated morbidity, a pacemaker is often implanted [5,24]. However, the benefit of cardiac pacing in patients with IA has not been confirmed. In a clinical series of patients with IA, the benefits of the pacemaker implantation during long-term follow-up were not clear since the recurrence rate of IA was lower than expected, and, therefore, there was no need for the pacemaker activation [2]. Since, in our case, the patient did not have refractory epilepsy (it was a new epilepsy diagnosis), we first tried to achieve seizure control (preventing asystole too) with an effective medical therapy. Indeed, it has been suggested that if one achieves, medically or surgically, seizure freedom, there is no risk of further asystole, so the pacemaker's implantation could be avoided [25]. Contrarily, if seizure freedom could not be achieved and there is persistence of IA, a pacemaker implantation shall be taken into account, as it was in our patient [26].

4.2. Literature review

There are relatively few reported cases of ictal asystole in the context of a new-onset/newly diagnosed epilepsy. Twenty-one articles in 31 patients (18 females) were fully analyzed [4,7,25,27–44] (see Table 1). The asystole was self-limiting in every case and lasted 20 s on average (ranging from 4 to 40 s).

Notably, the time between the first presentation of epilepsy and the diagnosis of ictal asystole was, on average, 27 months (median: 12 months), ranging from 1 day to 18 years.

Interestingly, subjective symptomatology suggestive of a focal seizure preceding loss of consciousness was reported in only seven out of 31 cases: visual illusion [27], hallucinations [36], jamais vu [43], fear [37], psychic aura [35], and epigastric auras [28,42]. Ictal motor behaviors suggestive of a seizure disorder (tonic and clonic contractions and automatisms) were described in four patients [31,34–36]. Finally, postictal confusion or focal neurological deficit was described in seven cases [4,25,29,30,36,40,43]. Overall, in the majority of cases, as in the described patient, seizure-related auras or ictal seizure-related semiology was lacking: blurred vision, dizziness, nausea, and light-headedness were the most commonly reported symptoms.

The average age at presentation was 46 years (ranging from 2 to 83 years, median: 47 years). In five cases, interictal alterations of the basal ECG were described, and this could be identified as a further risk factor. The majority of patients had a frontotemporal epilepsy with a slight prevalence of left side involvement (19 out of 31 cases), supporting the idea that there is not a strict side effect [45,46], even if previous findings suggested a “lateralization hypothesis” where the right-sided seizures would result in tachycardia and the left-sided seizures in bradycardia [47–50]. Interestingly, in two patients, the IA was observed in the context of an anti-NMDA receptor encephalitis [39,41], a condition that involves a more generalized autonomic dysregulation.

The majority of patients had no AED therapy at the time of ictal asystole diagnosis (24/31). In the majority of cases (21 patients out of 31), a pacemaker was implanted. Antiepileptic drug therapy was begun after the diagnosis of IA in all but two patients. Interestingly, only four out of 31 patients had sodium channel blocker drugs before diagnosis. Therefore, a major causal mechanism of these drugs in inducing IA can be ruled out in this context.

We would like to highlight the importance of ECG–EEG monitoring in diagnosing the real cause of a recurrent unexplained loss of consciousness [21]. In fact, the time elapsed between first seizures and IA diagnosis was, on average, more than two years. This delay in correct diagnosis can potentially expose the patient to risks of traumatic falls and, theoretically, to sudden unexplained death in epilepsy (SUDEP) [51–55]. Notably, the absence in the clinical patient's history of symptoms or signs suggesting the diagnosis of a seizure disorder is insufficient to exclude IA. Indeed, only a minority of patients with IA presented with signs/symptoms suggestive of seizures/epilepsy. Therefore, an EEG with ECG monitoring is mandatory in these cases.

5. Conclusions

Ictal asystole is an important condition that should be recognized by epileptologists, neurologists, as well as emergency department physicians as the nonrecognition of this entity leads to a misdiagnosis (syncope) with consequences that can be dangerous for the patient. In particular, it is important to know that IA not only can occur in patients with a diagnosis of epilepsy already known but also may be the first manifestation of the patient's epilepsy.

Disclosure of conflicts of interest

None of the authors has any conflict of interest to disclose. No financial or material support was received by any of the authors in conducting this research or in preparing this manuscript. We also confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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