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Case Report

Ictal asystole with isolated syncope: A case report and literature review

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ABSTRACT

Ictal syncope is a rare phenomenon that occurs in association with 0.002–0.4% of seizures. In the absence of other symptoms, seizures presenting with syncope may be challenging to diagnose. We report a case of a previously healthy male who developed recurrent episodes of syncope with postictal confusion and was later diagnosed with temporal seizures. The patient was successfully treated with anti-seizure drugs and placement of a cardiac pacemaker. In a systematic review of literature, we summarize the clinical characteristics of patients with ictal asystole and isolated syncope. Seizures should be considered in patients with syncope of uncertain etiology.

1. Introduction

Cardiac arrhythmias have been frequently recognized in association with epileptic seizures [1]. Ictal bradycardia defined as prolongation of R-R interval beyond 2 s is significantly less common than ictal tachycardia [2]. Ictal bradycardia with ensuing disappearance of ventricular complexes for 4 or more seconds (i.e., asystole) may be accompanied by loss of consciousness [2,3]. Transient and rapidly reversible loss of consciousness along with the inability to maintain postural tone constitutes the working definition of syncope [4], the etiology of which encompasses cardiovascular and neurological conditions, in addition to epilepsy.

Seizure-related syncope is uncommon [5]; thus, the familiarity of the practitioners with this syndrome remains insufficiently represented. Sudden drop attacks with loss of awareness were described in patients with long-standing temporal and frontal lobe epilepsy and a history of focal seizures with other more characteristic semiologies [5–7]. Semiological features supporting ictal syncope include behavioral arrest and blank stare preceding the atonia during a seizure [7]. An additional distinguishing feature of syncope caused by a seizure is the presence of an epileptic aura comprised of phantosmia, visual, gustatory or psychic phenomena; none of these symptoms are typically reported in cardiogenic syncope [8,9]. Furthermore, a characteristic feature of ictal syncope is postictal confusion that is distinct from situational disorientation present in some patients recovering from cardiogenic syncope [6,9]. In a few case reports, exceptionally rare presentations of ictal syncope were provided in patients with recurrent unexpected collapse without any other ictal signs; the relevant literature is reviewed herein.

While commonly encountered by health care providers, recurrent episodes of atonia and loss of consciousness without any other associated changes in behavior are unlikely to be attributed to seizures; thus, initiation of the appropriate treatment for seizures may be delayed [9]. The recognition of isolated syncope caused by ictal bradycardia can facilitate timely referral for treatment and may reduce seizure-related injuries [3]. Furthermore, terminating the recurrent seizures in these patients may prevent death as asystole has been proposed to be one of the mechanisms of sudden unexpected death in epilepsy (SUDEP) [10]. Here, we described a patient with focal temporal seizures leading to isolated ictal asystole, and performed systematic review of the literature on syncope as the only manifestation of a seizure. Within the scope of the existing literature, we discuss whether isolated ictal syncope not preceded by other epileptic seizures, and the more typical scenario of delayed ictal atonia preceded by other seizure signs, represent two different clinical entities.

2. Methods

The systematic literature search was performed in the Medline and Embase databases to identify original articles since the beginning of

Abbreviations: SUDEP, sudden unexpected death in epilepsy; EKG, electrocardiogram; MRI, magnetic resonance imaging; EMU, epilepsy monitoring unit; EEG, electroencephalographic; AT, anterior temporal; T, temporal; MT, medial temporal; PT, parietal–temporal; F, frontal; FT, fronto-temporal; LEV, levetiracetam; VPA, valproic acid; OXC, oxcarbazepine.

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archive records (i.e., starting in 1946) related to ictal bradycardia and asystole that manifested as syncope. The keywords "ictal bradycardia and syncope" as well as subject headings for each keyword, if available, were included. Articles written in languages other than English were excluded. In addition, articles lacking the documentation of seizure confirmation with electroencephalographic (EEG) and articles containing the description of seizures without asystole were excluded. The patient demographic characteristics, anti-seizure medications, seizure characteristics, brain imaging findings and relevant abnormalities on the electrocardiogram (EKG) were recorded.

3. Case presentation

A 54-year-old male with no known past medical history presented to an epilepsy clinic with recurrent spells of unresponsiveness and loss of muscle tone that developed several months prior to referral and recurred on 5–6 occasions 1–2 weeks apart. The events were preceded by a prodrome of "not feeling well" and were followed by loss of consciousness for 10–30 s. Interestingly, the patient reported "dreaming" during each event; however, he could not describe the content of his dreams or specify whether the dreams were always the same. He experienced nausea, confusion, and speech difficulties for approximately 30 min after each event. The patient was not aware of any triggers and denied any epilepsy risk factors. A typical episode recorded on the mobile phone video revealed the patient sitting reclined with eyes partially closed and his gaze deviated upward. There were no abnormal movements. A previous EEG and brain magnetic resonance imaging (MRI) were normal. The evaluation by a cardiologist was unrevealing, and Holter monitoring was pending at the time of his assessment. The patient was started on valproate which he self-discontinued because it did not prevent further recurrences of the spells. He was subsequently started on levetiracetam and referred to an epilepsy monitoring unit (EMU) for characterization of these events. In the settings of anti-seizure drug withdrawal, patient had five focal seizures emanating from the left temporal region. In association with these events, the patient developed bradycardia with his heart rate decreasing to 20's followed by pauses on the EKG (Fig. 1). The latter progressively increased in duration to 4 s. During one of the events, the patient developed lightheadedness; however, all other seizures were exclusively electrographic. He received a cardiac pacemaker and became seizure-free with a combination of levetiracetam and lacosamide.

4. Results

The proposed strategy for the literature search yielded 46 articles describing 130 patients with confirmed diagnosis of ictal bradycardia or asystole and syncope. Nine patients with absent electrographic seizure confirmation, documentation of semiology, or description of seizure symptoms prior to EMU, respectively were excluded. Twenty-three patients met the inclusion criteria of having seizures with asystole and syncope accompanied by various abnormal movements (7 patients) or experiencing prodromal sensations (16 patients). Eight patients had recurrent isolated loss of consciousness and falls prior to the admission for continuous EEG [11–17]. The ictal semiology of isolated ictal asystole-syncope was reproduced in 4 patients during the recording of seizures in the EMU [13,14]. The median age of patients with isolated ictal asystole and syncope was 49.5 years (range 14–65 years); there were 3 males (36%) and 5 females (64%) (Table 1). The mean duration of the cardiac arrest was 15.1 $\pm$ 4.1 s. Five patients presented with seizures emanating from the left temporal region, while the remaining three had seizures localized to the right parieto-temporal, frontal or fronto-temporal region. Findings on the brain imaging scans (6 MRI, 1 computed tomography) were documented in all but one patient and were normal in 3 patients. The remaining 4 patients demonstrated generalized cerebral atrophy, cavernous angioma, and presence of the catheters' tip from the Ommaya reservoir in the temporal lobe ipsilateral to ictal onset [12–14].

The ictal heart rhythm was documented during video EEG monitoring in all 8 patients and was characterized by progressive bradycardia leading to transietn asystole that lasted for 5–30 s (Table 1). The bradycardia and asystole followed the ictal onset with median latency of 5 and 28 s, respectively (Table 1). The description of interictal EKG was normal in all but one patient who had a sick sinus syndrome [17]. The treatment of cardiac arrhythmias was specified for 7 out of 8 patients with ictal asystole and syncope of whom 4 received pacemaker placement after the diagnosis. Of the remaining three, one patient was not treated for asystole, and two additional patients (one with normal baseline EKG and one with a prior history of sick sinus syndrome) received a pacemaker prior to diagnostic EEG.

As noted above, ictal semiology provided by witnesses before referral to an EMU in all patients was consistent with isolated ictal syncope and absent epileptic auras or other prodromal clinical symptoms [11–17]. Patients' postictal symptoms included variable confusion, weakness, chest pain, decreased responsiveness, nausea or vomiting, diaphoresis, and visual disturbances [11–17]. Three patients had been receiving anti-seizure drugs prior to referral for diagnostic EEG. An additional three patients were placed on anti-seizure drugs after they were diagnosed with epilepsy.

5. Discussion

The association of ictal syncope with cardiac arrhythmia was recognized a decade ago following a report of sudden falls in three patients with drug-resistant epilepsy at the time of presurgical evaluation including both video-EEG and cardiac monitoring [18]. Subsequently, large retrospective studies confirmed that ictal asystole occurs in 0.002% - 0.4% of all monitored patients [7,19–21] and when prolonged, may cause syncope [7,21]. In these studies, the constellation of sudden atonia and the corresponding slowing or attenuation of the background EEG rhythm was strongly associated with prolonged cardiac arrest [7, 20,22].

Our search strategy identified a total of 130 patients and yielded 23 patients with ictal asystole and syncope supporting the premise that ictal asystole is rare [7,19–21]. With the focus on isolated ictal syncope, we identified reports involving 8 patients with syncope who failed to demonstrate any typical seizure signs during the habitual spells prior to admission for EEG monitoring. Those included 4 patients who later had confirmed isolated ictal asystole-syncope during video-EEG monitoring [12–14] and 4 patients who demonstrated other semiological signs consistent with temporal lobe seizures [11–17]. The average duration of asystole in the patients identified in the present review was 15 s which was strongly associated with syncope in previous studies [20]. Several patients had prior histories of focal impaired awareness seizures or convulsive seizures [13,14] that likely facilitated more expedited referral for diagnostic EEG monitoring compared to the other patients whose only symptoms were loss of consciousness and falls. Given that cardiac arrest, bradycardia, and syncope may not develop consistently with every seizure, a sufficient number of seizures has to be recorded in patients with characteristic symptoms [19]. Thus, the diagnosis of ictal asystole remains challenging even in the monitored environment.

In the present review, all patients with isolated ictal syncope and asystole were diagnosed with temporal lobe epilepsy. These findings are in support of the current hypothesis that induction of asystole could be due to the propagation of ictal activity from the temporal region to the adjacent insula where a cardioinhibitory effect could be elicited [9]. Interestingly, an experimental stimulation of the left insular cortex in patients with temporal epilepsy resulted in bradycardia independent of seizures, while the stimulation of the right insular cortex induced tachycardia [23]. In the presented case and literature review, 5 out of 8 patients with ictal syncope and asystole had seizures lateralized to the left hemisphere; however, it is unclear whether these seizures

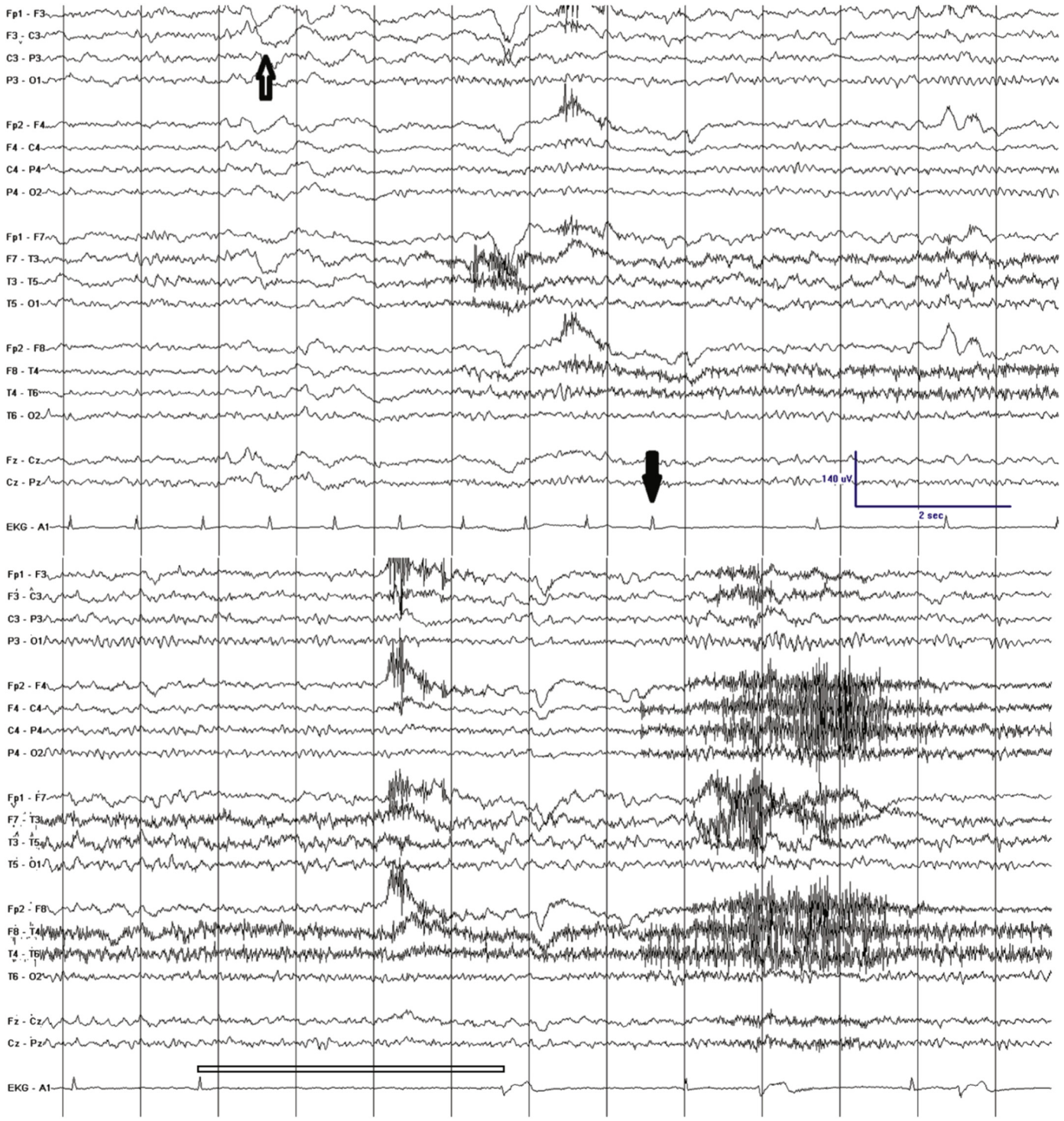

Fig. 1. Representative tracing of a focal seizure with onset in the left fronto-temporal region (open arrow) followed by bradycardia (solid arrow) with subsequent brief asystole (open square) and complaints of lightheadedness.

ultimately propagated to the insula. Importantly, the ictal onset in all patients presented herein preceded the changes in the heart rate.

Another theory of the pathophysiology of ictal bradycardia suggests that epileptic activity affects the heart rate through an increase in vagal tone [24,25]. It has been postulated that the vagus nerve located in the autonomic reflex centers of the brainstem may be stimulated by the spread of seizures [25]. Such ictal autonomic dysfunction was proposed to independently cause cerebral hypoperfusion in addition to bradycardia [25]. In light of this theory, the treatment of ictal asystole with a cardiac pacemaker was proposed to reduce the mortality from SUDEP [3,26]; however, the direct evidence of causative link between bradycardia and SUDEP is currently lacking. Interestingly, in the present review, 68% of all patients with confirmed ictal bradycardia received a pacemaker even when their interictal EKG was normal.

Seizures are found to be an etiological factor in approximately 7% of patients with syncope [27]. Prospectively sought historical criteria that distinguish syncope with other etiology from seizure included signs of déjà vu, tongue laceration, limb jerking, and postictal confusion [28].

Table 1
Demographic and clinical characteristics of patients with ictal asystole accompanied by isolated syncope. AT, anterior temporal; T, temporal; MT, medial temporal; PT, parietal–temporal; F, frontal; FT, fronto-temporal; LEV, levetiracetam; VPA, valproic acid; OXC, oxcarbazepine.

Age	Sex	EEG		EKG				Brain imaging	Treatments in relation to seizure diagnosis			Ref
		Seizure lateralization	Seizure localization	Seizure to bradycardia, sec	Seizure to asystole, sec	Duration of asystole, sec	Baseline		Anti-seizure drugs started prior	Anti-seizure drugs started after	Pacemaker placed	
55	M	L	AT	Not avail	4	67	Normal	Normal	None	LEV	Prior	[7]
44	M	L	T	40	10	Not avail.	Sick sinus	Normal	None	None	Prior	[13]
65	F	L	MT	5	29	9	Normal	Mild cerebral atrophy	LEV	None	After	[9]
64	F	L	MT	12	9	28	Normal	Mild cerebral atrophy	LEV VPA	None	After	[9]
14	F	L	T	Not avail.	5	Not avail	Normal	Ommaya reservoir catheter tip in MT lobe	None	None	None	[8]
18	F	R	PT	Not avail.	16	Not avail	Normal	RT cavernous angioma	OXC	LEV	After	[10]
65	F	R	F	5	30	Not avail	Not avail.	Not avail.	None	Not avail.	Not avail.	[11]
32	M	R	FT	Not avail.	18.5	31	Normal	Normal	None	LEV	After	[12]

Importantly, the prodromal diaphoresis and palpitations as well as positional component of syncope were predictive for the etiology other than seizure [28]. Myoclonus, observed in convulsive syncope, develops approximately 4 s after onset of loss of consciousness and has distinct semiology that consists of both multifocal and generalized or other bilateral synchronous muscle activity [29]. The latter has no ictal electrographic correlates and is thought to be related to the preservation of reticular formation activity in the settings of decreased oxygen supply and cortical hypoxia [29,30]. Reflex hypoxic seizures, predominantly affecting children, are paroxysmal nonepileptic events that occur in the settings of distressing or emotional stimuli and are characterized by syncope, pallor, generalized stiffening and brief clonic movements affecting the extremities [31,32]. The underlying pathophysiology of these events is vagal-induced transient cardiac asystole leading to transient cerebral hypoperfusion, and therefore anti-seizure medication is not indicated [31].

Ictal atonia with loss of consciousness observed in focal seizures can either precede or follow the loss of consciousness and may be misdiagnosed as syncope [33]. In previous large retrospective studies on the ictal bradycardia-asystole syndrome, the average latency from seizure onset to muscle atonia and syncope was 35–42 s [7,20]. On the other hand, the reported duration of arrested cardiac activity prior to the sudden loss of postural tone during seizures was 6–8 s [7]**.** While the former is proposed to be induced by ictal activation of the primary and supplementary motor area or corticoreticular pathways [33], the latter is thought to be precipitated by cerebral hypoxia among other mechanisms. While atonia can manifest at the start of temporal lobe seizures, the onset of atonia and syncope in the middle of the seizure suggests ictal asystole [34]. Despite these semiological differences and proposed distinct pathophysiological mechanisms underlying ictal syncope and ictal atonia, the direct evidence on whether these conditions represent two different ictal phenomena is currently lacking.

A cardiac pacemaker should be considered in patients with ictal asystole and falls regardless of the duration of asystole given that placement of such device was previously demonstrated to reduce morbidity [35,36]. Specifically, placement of a pacemaker decreased the incidence of seizure-related falls nearly 600-fold in the years following the treatment [35]. In addition, the risk of fractures and motor vehicle accidents related to seizures was also mitigated with cardiac pacing. Placement of a pacemaker in ictal asystole was also proposed in cases with persistent failure of medication therapy for seizures [37]. The seizure burden in these patients has been noticeably reduced possibly due to the direct influence of cardiac pacing on cardiovagal afferents and their connections to the brain [35].

6. Conclusion

Ictal asystole with isolated syncope is a rare phenomenon with recurrent events that may be the first or the only symptom of epilepsy. In the appropriate clinical context, evaluation of patients presenting with syncope should include monitoring for focal seizures. Placement of cardiac pacemaker in these patients should be considered in combination with anti-seizure medication when identified.

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Conflict of interest

The authors declare no conflict of interests.

Ethical statement

Our article submitted to Epilepsy and Behavior Case Reports entitled "Ictal asystole with isolated syncope: a case report and literature review" has not been published in whole or in part elsewhere. The manuscript is not currently being considered for publication in another journal. All authors have been personally involved in substantive work leading to the manuscript.

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