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

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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...
generalized cerebral atrophy, cavernous angioma, and presence of the MRI, 1 computed tomography) were documented in all but one patient tal or fronto-temporal region. Findings on the brain imaging scans (6 remaining three had seizures localized to the right parieto-temporal, fron-
tation of the cardiac arrest was 15.1 ± 4.1 s. Five patients presented there were 3 males (36%) and 5 females (64%) (Table 1). The mean du-
treatment of cardiac arrhythmias was specified for 7 out of 8 patients with ictal asystole and syncope of whom 4 received pacemaker place-
ment after the diagnosis. Of the remaining three, one patient was not treated for asystole, and two additional patients (one with normal base-
line EKG and one with a prior history of sick sinus syndrome) received a pacemaker prior to diagnostic EEG.

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 recurrent on 5–6 occasions 1–2 weeks apart. The events were pre-
eced 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 approxi-
mately 30 min after each event. The patient was not aware of any trig-
gers 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-sei-
zure 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 electrogrographic sei-
zure confirmation, documentation of semiology, or description of sei-
zure 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 pa-
tients) or experiencing prodromal sensations (16 patients). Eight pa-
tients had recurrent isolated loss of consciousness and falls prior to the admission for continuous EEG [11–17]. The ictal semiology of iso-
lated ictal asystole-syncope was reproduced in 4 patients during the re-
cording of seizures in the EMU [11,13,14]. 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 du-
ration of the cardiac arrest was 15.1 ± 4.1 s. Five patients presented with seizures emanating from the left temporal region, while the re-
mainning three had seizures localized to the right parieto-temporal, fron-
tal 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 ipsilat-
eral to ictal onset [12–14].

The ictal heart rhythm was documented during video EEG monitor-
ing in all 8 patients and was characterized by progressive bradycardia leading to transient asystole that lasted for 5–30 s (Table 1). The brady-
cardia 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 place-
ment after the diagnosis. Of the remaining three, one patient was not treated for asystole, and two additional patients (one with normal base-
line 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 refer-
ral to an EMU in all patients was consistent with isolated ictal syncope and absent epileptic aura or other prodromal clinical symptoms [11–17]. Patients’ postictal symptoms included variable confusion,
weakness, chest pain, decreased responsiveness, nausea or vomiting, di-
aphoresis, and visual disturbances [11–17]. Three patients had been re-
ceiving 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 recog-
nized a decade ago following a report of sudden falls in three patients with drug-resistant epilepsy at the time of presurgical evaluation in-
cluding 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 moni-
toring [12–14] and 4 patients who demonstrated other semiological signs consistent with temporal lobe seizures [11–17]. The average dura-
tion 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 re-
ferral 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 re-
gion to the adjacent insula where a cardioinhibitory effect could be elic-
ted [9]. Interestingly, an experimental stimulation of the left insular cortex in patients with temporal epilepsy resulted in bradycardia inde-
pendent of seizures, while the stimulation of the right insular cortex in-
duced 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
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].
the sudden loss of postural tone during seizures was 6.
other hand, the reported duration of arrested cardiac activity prior to
approximately 4 s after onset of loss of consciousness and has distinct semi-
seizure [28]. Myoclonus, observed in convulsive syncope, develops ap-
Importantly, the prodromal diaphoresis and palpitations as well as posi-
tional component of syncope were predictive for the etiology other than seizure [28]. Myoclonus, observed in convulsive syncope, develops ap-
proximately 4 s after onset of loss of consciousness and has distinct semi-
ology that consists of both multifocal and generalized or other bilateral
proxies [31,32]. The underlying pathophysiology of these events is vagal-
distressing or emotional stimuli and are characterized by syncope, pallor,
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 sei-
zures, the onset of atonia and syncope in the middle of the seizure sug-
posed distinct pathophysiological mechanisms underlying ictal syn-
Table 1
| Age | Sex | EEG | EKG | Seizure localization | Seizure to bradycardia, sec | Seizure to atonia, sec | Duration of atonia, sec | Baseline | Brain imaging | Treatments in relation to seizure diagnosis | Ref |
|-----|-----|-----|-----|----------------------|-----------------------------|------------------------|-----------------------|----------|--------------|--------------------------------------|-----|
| 55  | M   | L   | AT  | Not avail            | 4                           | 67                     | Normal                | Normal   | None          | Anti-seizure drugs started prior       | [7] |
| 44  | M   | L   | T   | 40                  | 10                          | 9                      | Not avail             | Sick sinus| None          | Anti-seizure drugs started after       | [13]|
| 65  | F   | L   | MT  | 5                   | 29                          | 9                      | Mild cerebral atrophy | Normal   | VPA          |                                        | [9] |
| 64  | F   | L   | MT  | 12                  | 9                           | 28                     | Mild cerebral atrophy | Normal   | LEV           |                                        | [9] |
| 14  | F   | L   | T   | Not avail           | 5                           | Not avail             | Normal                | Ommaya reservoir catheter tip in MT lobe | None    | None          | LEV                                   | [8] |
| 18  | F   | R   | PT  | Not avail           | 16                          | Not avail             | Normal                | RT caver nous angioma | None    | None          | VPA                                   | [10]|
| 65  | F   | R   | F   | 5                   | 30                          | Not avail             | Normal                | Normal   | Not avail     |                                        | [11]|
| 32  | M   | R   | FT  | Not avail           | 18.5                        | 31                     | Normal                | Normal   | None          | Anti-seizure medication when identifi ed | [12]|

Importantly, the prodromal diaphoresis and palpitations as well as posi-
tional component of syncope were predictive for the etiology other than seizure [28]. Myoclonus, observed in convulsive syncope, develops ap-
proximately 4 s after onset of loss of consciousness and has distinct semi-
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mechanisms. While atonia can manifest at the start of temporal lobe sei-
zures, the onset of atonia and syncope in the middle of the seizure sug-
posed distinct pathophysiological mechanisms underlying ictal syn-
cicnod their connections to the brain [35].

6. Conclusion

Ictal asystole with isolated syncope is a rare phenomenon with re-
current 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 combi-
nation 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 re-
view” has not been published in whole or in part elsewhere. The manu-
script 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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