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Pearls & Oy-sters: Severe Case of Ictal Asystole in Temporal Lobe Epilepsy

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Abstract:

Ictal asystole is a rare condition associated primarily with temporal lobe epilepsy that can cause syncope, falls and head trauma. It is also associated with increased rates of sudden unexplained death in epilepsy (SUDEP). We present a case of a 33-year-old woman with a history of childhood epilepsy who presented with 3 years of recurrent syncope. Video-EEG revealed temporal lobe seizures with ictal asystole. EKG showed stepwise progression of bradycardia, asystole, and tachycardia. MRI showed focal cortical thickening at the right insular cortex with blurring of the grey-white matter interface, consistent with insular focal cortical dysplasia. The patient was transitioned from lacosamide to clobazam due to concern for PR interval prolongation and was referred to cardiology for pacemaker placement. Ictal asystole should be considered as a rare but serious cause of unexplained recurrent syncope, particularly in patients with a history of seizures. Management includes antiepileptic drug regimen optimization, consideration of epilepsy surgery, and referral for cardiac pacing when asystole lasts greater than 6 seconds.

Pearls:

- Ictal asystole is a cause of recurrent unexplained syncope.
- Ictal asystole <6 seconds should be treated with anti-seizure medication optimization and epilepsy surgery, when applicable.
- Ictal asystole >6 seconds should be referred to cardiology for potential permanent pacemaker placement.

Oy-sters:

- The frequency of ictal asystole is likely underestimated as long-term video EEG and associated EKG recording is required to make the diagnosis.
- Arrhythmogenic antiepileptic drugs such as sodium channel blockers may increase risk of arrhythmias (ictal or post-ictal) and/or may prolong recovery.

Case Report:

A 33-year-old woman with a history of childhood epilepsy was admitted to the epilepsy monitoring unit (EMU) for characterization of new-onset recurrent spells. Her seizures started at age 11 and consisted of nocturnal convulsions and staring spells that were well controlled with carbamazepine monotherapy. She was initially thought to have benign epilepsy with centrotemporal spikes (BECTs), also known as benign rolandic epilepsy. She had a normal neurological exam at admission.

Three years prior to EMU admission she began experiencing new episodes characterized by slumping over and/or sudden collapse with occasional stiffening of upper extremities occurring up to once per week. She had no aura or incontinence and no post-event confusion. The episodes were refractory to medication trials including lacosamide, cenobamate, and levetiracetam. Her home regimen at the time of EMU included levetiracetam 1500mg BID, lacosamide 200mg BID, and cenobamate 100mg QD. She had previously been on valproic acid, oxcarbazepine discontinued due to hyponatremia, and carbamazepine discontinued due to hyponatremia and pancytopenia. She had a normal neurological exam.

She had prior EEGs, MRIs, PET scans, and ECGs. An EEG done in Feb 2018 showed single sharp form over the left temporal region. A subsequent EEG in Sep 2021 was read as normal with no seizures or epileptiform discharges. MRIs in January 2018 and December 2021 were both normal, as was her PET in December 2021. Prior EKG in 2019 showed HR 100, PR 140, QRS 90, and QTc 434 with nonspecific T-wave abnormalities in the inferior leads. Similar findings were seen on an EKG from 2021. The patient was admitted to the EMU in March 2022. At that time, video-EEG demonstrated right temporal lobe seizures with ictal asystole (Figure 1). On interictal EEG, there was intermittent paroxysmal fast activity over the right temporal region. Seizures electrographically began with right temporal focal fast activity, which would evolve

bitemporally, followed by a diffuse generalized suppression. In sleep there was no visible clinical change during the seizures, aside from the ictal bradycardia and ictal asystole. In wakefulness, after the ictal onset of her seizure, there were associated heart rate changes. Her clinical symptoms on video correlated with those heart rate changes, such that ictal bradycardia correlated with pallor, ictal asystole correlated clinically with loss of muscle tone and electrographically with diffuse suppression on EEG. After her heart rate resumed, electrographically there was emergence of diffuse delta slowing and clinically, intermittent myoclonic jerks occurred, likely as a result of cerebral reperfusion. She reported no aura. She had a total of 4 seizures during her EMU admission. The patient's baseline EKG showed HR 70, PR 148, QRS 92, QTc 398 and redemonstrated the nonspecific T wave abnormalities. She had no inter-ictal EKG pathology.

Given the EEG focal fast activity, there was a high suspicion for focal cortical dysplasia (FCD). As prior MRI 3T seizure protocol studies were normal and a 7T MRI was not available within the state, a 3T MRI with fast grey matter acquisition T1 inversion recovery (FGATIR) sequence was obtained. MRI with FGATIR sequence showed focal cortical thickening at the right insular cortex with blurring of the grey-white matter interface, consistent with FCD (Figure 2). The patient was transitioned from lacosamide to clobazam due to concern for PR interval prolongation, which may delay recovery. She had a pacemaker placed and is currently undergoing evaluation for epilepsy surgery with an upcoming stereo EEG.

Discussion:

Ictal asystole is a rare event that occurs primarily in temporal lobe epilepsy. It is estimated to occur between 0.27 to 0.4% of epilepsy patients undergoing monitoring.¹ Ictal asystole is defined as epileptogenic activity accompanied by a cessation of ventricular complexes for >4 seconds.² There is no clearly established underlying pathophysiology related to the heart or conduction system. Ictal asystole is thought to be due to activation of brain regions that influence cardiac function through efferent neural pathways causing a “vagal storm” that induces ictal asystole and ictal bradycardia.³ Cardiac dysfunction subsequently causes decreased cerebral perfusion, resulting in seizure termination and syncope. This hypothesis is based on the time delay between seizure onset and onset of asystole.^{3,4} A recent review of 103 cases of ictal asystole showed that asystole began on average 30 seconds after seizure onset and lasted for 20 seconds.⁵ This phenomena has a higher prevalence in seizures with temporal lobe onset, as in this patient.³

Ictal asystole is most often associated with areas of the brain related to autonomic function, including the temporal lobe, insular cortex and amygdala. While it was previously thought that ictal asystole was primarily related to the left hemisphere, both hemispheres have been found to contribute.³

The American Heart Association maintains that first-line treatment should be anti-seizure medication optimization as well as epilepsy surgery for appropriate candidates. Cardiac pacing is reserved for cases in which anticonvulsant drug optimization has not prevented asystole episodes >6 seconds in length.^{3, 6} Pauses greater than 6 seconds have been shown to contribute to syncope/loss of consciousness (LOC). Thus, pacing for asystole <6 seconds may not reduce risk of falls and syncopal injury. The second rationale behind the 6-second limit is that neuronal cells are thought to have a 6-9 second energy reserve.^{3, 6}

Additional factors to consider when determining if a patient is a candidate for pacemaker placement include the lifelong need for pacemaker management and replacement. Drawbacks to pacing include the thought that asystole may contribute to seizure cessation through the resultant transient cerebral ischemia, and thus eliminating asystole may paradoxically prolong the seizure duration.³

Permanent pacemaker implantation is recommended when epilepsy surgery is not an option and when AED regimen optimization has failed.⁶ However, in all cases of ictal asystole, if the asystole is severe and unremitting pacemaker implantation should be considered.

FCDs are estimated to have a prevalence between 5-25% in focal epilepsy and are known to cause refractory epilepsy.⁷ There are several treatment modalities for FCDs, including surgical resection, stereotactic minimally invasive thermal ablation, subpial transection, or electrical stimulation implants.⁸ Treatment is tailored based on the FCD classification, location, and patient factors.

Frequency of sudden unexplained death in epilepsy (SUDEP) ranges from 0.4-9 deaths per 1000 patient years.³ The most important risk factors include uncontrolled seizures, particularly generalized tonic-clonic seizures.³ There are conflicting opinions regarding the relationship between ictal bradycardia / asystole and SUDEP. Some authors claim insufficient evidence exists to claim a relationship,³ while other studies have shown that specifically post-ictal arrhythmias - rather than ictal arrhythmias - may have a higher risk of developing SUDEP.^{5, 9}

In this case, the clinical history, EEG, telemetry, and imaging findings were concordant with an insular focal cortical dysplasia as cause of this patient's presentation. The addition of the FGATIR to a traditional 3T MRI Seizure Protocol was instrumental in uncovering a lesional etiology for her previously non-lesional medically refractory epilepsy. Given the insula's deep location, interictal or ictal activity may be seen over the temporal leads on scalp EEG, so for this reason, the seizure's electrographic onset was referred to as temporal.¹⁰ However, based on her imaging that was suggestive of an insular focal cortical dysplasia, the insula is the likely true onset point of this patient's seizure. Medical optimization, pacemaker placement and epilepsy surgery evaluation are all recommended management options for ictal asystole.

References:

1. Ravat SH, Bhatti AA, Shah MV, Muzumdar DP, Ravat SH. Ictal asystole: A rare cardiac manifestation of temporal lobe epilepsy, treated with epilepsy surgery. *Ann Indian Acad Neurol.* 2017;20(1):55-57. doi:10.4103/0972-2327.199916
2. Moseley, B.D., Ghearing, G.R., Munger, T.M. and Britton, J.W. (2011), The treatment of ictal asystole with cardiac pacing. *Epilepsia*, 52: e16-e19. <https://doi.org/10.1111/j.1528-1167.2010.02972.x>
3. Benditt DG, van Dijk G, Thijs RD. Ictal asystole: life-threatening vagal storm or a benign seizure self-termination mechanism? *Circ Arrhythm Electrophysiol.* 2015 Feb;8(1):11-4. doi: 10.1161/CIRCEP.114.002546. PMID: 25691552.
4. Catenox H, Mauguière F, Guénot M, Isnard J, Ryvlin P. Recording the insula during ictal asystole. *Int J Cardiol.* 2013 Oct 30;169(2):e28-30. doi: 10.1016/j.ijcard.2013.08.100. Epub 2013 Sep 8. PMID: 24063929.
5. van der Lende M, Surges R, Sander JW, Thijs RD. Cardiac arrhythmias during or after epileptic seizures. *J Neurol Neurosurg Psychiatry.* 2016 Jan;87(1):69-74. doi: 10.1136/jnnp-2015-310559. Epub 2015 Jun 2. PMID: 26038597; PMCID: PMC4717443.
6. Bestawros M, Darbar D, Arain A, et al. Ictal asystole and ictal syncope: insights into clinical management. *Circ Arrhythm Electrophysiol.* 2015;8(1):159-164. doi:10.1161/CIRCEP.114.001667
7. Bast T, Ramantani G, Seitz A, Rating D. Focal cortical dysplasia: prevalence, clinical presentation and epilepsy in children and adults. *Acta Neurol Scand.* 2006 Feb;113(2):72-81. doi: 10.1111/j.1600-0404.2005.00555.x. PMID: 16411966.
8. Guerrini R, Duchowny M, Jayakar P, Krsek P, Kahane P, Tassi L, Melani F, Polster T, Andre VM, Cepeda C, Krueger DA, Cross JH, Spreafico R, Cosottini M, Gotman J, Chassoux F, Ryvlin P, Bartolomei F, Bernasconi A, Stefan H, Miller I, Devaux B, Najm I, Giordano F, Vonck K, Barba C, Blumcke I. Diagnostic methods and treatment options for focal cortical dysplasia. *Epilepsia.* 2015 Nov;56(11):1669-86. doi: 10.1111/epi.13200. Epub 2015 Oct 5. PMID: 26434565.
9. Ryvlin P, Nashef L, Lhatoo SD, Bateman LM, Bird J, Bleasel A, Boon P, Crespel A, Dworetzky BA, Høgenhaven H, Lerche H, Maillard L, Malter MP, Marchal C, Murthy JM, Nitsche M, Patarraia E, Rabben T, Rheims S, Sadzot B, Schulze-Bonhage A, Seyal M, So EL, Spitz M, Szucs A, Tan M, Tao JX, Tomson T. Incidence and mechanisms of cardiorespiratory arrests in epilepsy monitoring units (MORTEMUS): a retrospective study. *Lancet Neurol.* 2013 Oct;12(10):966-77. doi: 10.1016/S1474-4422(13)70214-X. Epub 2013 Sep 4. PMID: 24012372.
10. Levy A, Yen Tran TP, Boucher O, Bouthillier A, Nguyen DK. Operculo-Insular Epilepsy: Scalp and Intracranial Electroencephalographic Findings. *J Clin Neurophysiol.* 2017 Sep;34(5):438-447. doi: 10.1097/WNP.0000000000000391. PMID: 28520631.

Figure Legends:

Figure 1: Representative EEG during EMU stay. Sensitivity 7 uV/mm, low-frequency filter 1 Hz, high-frequency filter 70 Hz, bipolar montage.

A. Demonstrates a brief ictal rhythmic discharge (BIRD) consisting of paroxysmal fast activity in the right temporal region (blue arrow) and an example of a right temporal sharp over T4 (red arrow).

B. Right temporal seizure onset with sentinel spike at T4>F8>F7. Clinically, patient is sleeping. Eyes open 3 seconds after sentinel spike but continues to rest in bed. Onset of ictal asystole on EKG.

C. Termination of the seizure with ongoing ictal asystole.

D. Termination of the ictal asystole after 32 seconds. Post-ictal slowing seen on EEG after termination of the seizure.

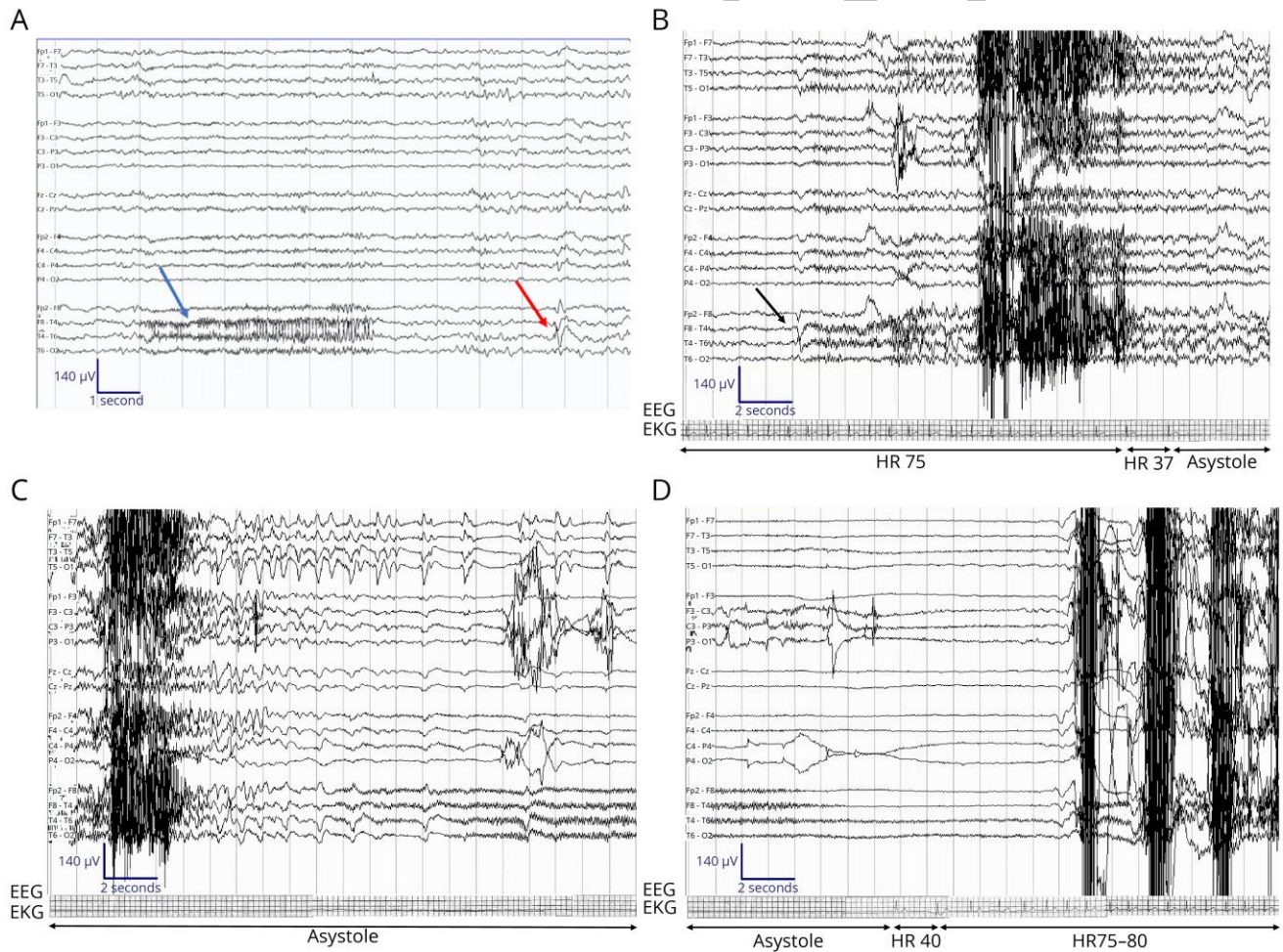
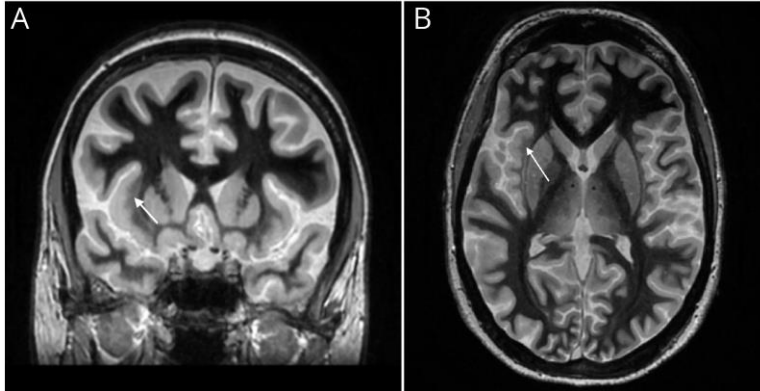


Figure 2: MRI FGATIR sequence consistent with focal cortical dysplasia

Coronal (A) and axial (B) view of focal cortical thickening at the right insular cortex-external capsule margin with blurring of the gray-white matter interface.



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