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Ictal asystole in a patient with posterior reversible encephalopathy syndrome (PRES) and seizures

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ABSTRACT – We describe a case of ictal asystole in a patient with posterior reversible encephalopathy syndrome (PRES), which has never been described previously. Ictal asystole is rare and has possible serious medical consequences, including syncope, and may be a potential mechanism for sudden unexpected death in epilepsy (SUDEP). Awareness that PRES may be observed with recurrent ictal asystole may aid in the recognition and treatment of seizures in this condition and the prevention of asystole-associated complications.

Key words: posterior reversible encephalopathy syndrome (PRES), ictal asystole, SUDEP, epilepsy, cardiac arrest

Ictal asystole is a rare phenomenon in which a seizure can cause transient cardiac arrest by affecting central autonomic regulatory centres. It is most commonly seen in temporal or frontal lobe seizures (Tinuper *et al*., 2001). It may lead to syncope and falls and may be related to SUDEP (Shorvon and Tomson, 2011). To our knowledge, there has been only one previously reported case of ictal asystole occurring during a parietal seizure (Serafini *et al*., 2011) and no reported cases of PRES causing ictal asytole. We describe a patient with PRES and ictal asystole during a right parietal seizure.

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Case study

A 75-year-old right-handed woman with a past medical history of chronic kidney disease, diabetes, neuropathy, morbid obesity, hypertension, breast cancer, and depression was admitted after having a witnessed generalized tonic-clonic seizure at home. When she arrived at the emergency department she had another generalized tonic-clonic seizure that lasted for one minute with postictal confusion. She was afebrile. Her blood pressure was 176/98, heart rate was 83 beats per minute (bpm),

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respiratory rate 14 per minute, and oxygen saturation was 95% on room air.

She had no prior history of heart block or bradycardia. Her home medications included carvedilol, furosemide, gabapentin, glipizide, losartan, oxycodone, sertraline, simvastatin, and sitagliptin.

On neurological examination, she had difficulty following commands and was inattentive. Her neurological examination was otherwise normal except for extensor plantar response on the left.

She had a CT scan which showed bilateral parieto-occipital region oedema with mild local mass effect consistent with PRES. Her EKG showed normal sinus rhythm. Her echocardiogram demonstrated left atrial enlargement, normal left ventricular systolic function, and abnormal diastolic function. No brain MRI was performed at this admission.

She was admitted to the Neurological Intensive Care Unit and was started on a clevidipine drip for blood pressure control. She was initially loaded with fosphenytoin, but this was not continued as she had no further clinical seizures during this hospitalization. Her blood pressure and mental status returned to normal and she was discharged to rehabilitation within several days.

A week later, she re-presented to the hospital with encephalopathy, hypotension, and acute chronic kidney disease. Her brain MRI showed confluent signal abnormality in the cerebral white matter predominantly posteriorly, and a new infarct in the right occipital pole (a known complication of PRES). EKG showed first-degree block with PR interval at 220 milliseconds on rhythm strips.

Throughout her admission, her systolic blood pressure remained elevated at 140-160. On Day 8 of hospitalization, she had two episodes of bradycardia, AV block, and asystole for up to nine seconds within five hours of each other. Her heart rate was 30 bpm during the event and her blood pressure after each event went up to 208/95. Her EKG immediately, after one event, showed normal sinus rhythm with PR interval of 196 milliseconds. The staff found her to be unresponsive after both events and she had bleeding from the mouth with one. These episodes were initially attributed to PRES and transient cerebral hypoperfusion related to bradycardia/asystole. However, due to the concern for seizures, she was placed on continuous video-EEG monitoring (VEEG) after the second event.

Four hours later, she had a secondary generalized tonic-clonic seizure, recorded on vEEG-EKG with AV block and sinus arrest, resulting in 20 seconds of asystole, followed by bradycardia for 69 seconds (*figure 1*). The seizure started in the right parietal region (*figure 2*) with rhythmic theta frequencies spreading to the right temporal region, quickly evolving to a secondary generalized tonic-clonic seizure. The staff initiated cardiopulmonary resuscitation with chest compressions. There was return of normal sinus rhythm. The patient was started on sodium valproate and a midazolam infusion for 24 hours and had no further seizures during her hospitalization. Due to complications of acute respiratory distress syndrome, she expired eight days later.

Discussion

Our case illustrates the importance of considering seizures as an aetiology of otherwise unexplained ictal

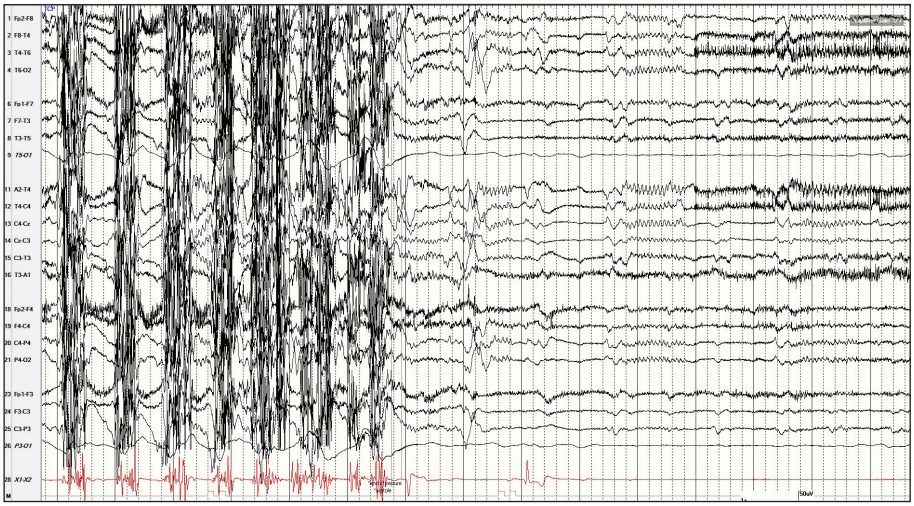

Figure 1. Asystole. At the end of the secondary generalized tonic-clonic seizure (the first six seconds of the page), the EKG shows asystole, which continues for 20 seconds.

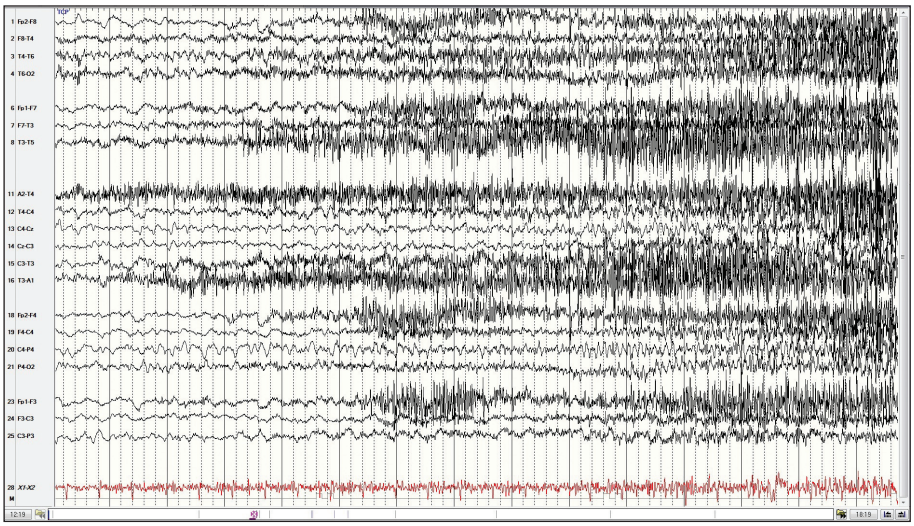

Figure 2. The seizure starts maximally in the right parietal region (P4) with rhythmic theta frequencies. Later, there is ictal spread to the right posterior temporal region (T6).

bradycardia/asystole in neurological disorders. There was a high suspicion of seizures in our case which facilitated early diagnosis and treatment. The anti-epileptic medication effectively prevented further seizures and potentially avoided further cardiac complications.

Prevalence of ictal bradycardia/asystole

Seizures with associated asystole and bradycardia are rare, seen in less than 1% of patients with epilepsy, and most commonly found in temporal or frontal lobe seizures. It is rarely seen in occipital or parietal lobe seizures and has not been described in the setting of PRES (Tinuper *et al*., 2001; Rocamora *et al*., 2003; Britton *et al*., 2006; Schuele *et al*., 2007; Serafini *et al*., 2011; Nei *et al*., 2012; Nguyen-Michel *et al*., 2014).

Clinical, radiological, and pathophysiological features of PRES and prognosis

PRES is a clinico-radiological diagnosis in which there is breakdown of the blood brain barrier caused by abrupt changes of blood pressure or cytokines causing endothelial damage, which causes brain oedema. The typical neurological symptoms of PRES include encephalopathy (50-80%), seizure (60-75%), headache (50%), visual disturbance (35%), focal neurological deficit (10-15%), and status epilepticus (5-15%). Precipitating causes include renal failure, hypertension, cytotoxic drugs, autoimmune disorders, and eclampsia. Brain MRI in PRES usually reveals asymmetric vasogenic oedema in the bilateral parietal-occipital, frontal, and temporal regions, and the basal ganglia, brainstem or cerebellum may also be involved. Although PRES usually has a good prognosis with full recovery within 2-8 days, not all patients recover completely. Mortality can be as high as 3-6%. Persistent neurological sequelae are seen in 10-20% of patients. PRES can recur in 5-10% of patients. Both ischaemic and haemorrhagic strokes can be seen in 25% of patients and are associated with worse outcomes (Fugate and Rabinstein, 2015).

The risk of epilepsy has been reported to occur in less than 1% of patients with PRES (Datar *et al*., 2015). In contrast, seizures are very common in PRES (Fugate and Rabinstein, 2015). Short-term treatment with antiepileptic medications is recommended for several weeks up to three months. It is rare that a patient will require long-term therapy due to a low risk of developing epilepsy in PRES (Datar *et al*., 2015).

Proposed mechanisms of ictal bradycardia/asystole

Human studies stimulating the insula suggest that parasympathetic functions responsible for bradycardia/asystole are localized in the left hemisphere (Oppenheimer *et al*., 1992). As most ictal bradycardias are seen in temporal lobe seizures, one proposed mechanism is ictal activation of parasympathetic networks or a disruption of sympathetic networks. Many case studies have shown that the left hemisphere side of seizure onset does not always correlate with ictal bradycardia (Schuele *et al*., 2008). Contralateral seizure spread to the left insular cortex or temporal lobe and generalized seizure activity may cause bradycardia and asystole. Another proposed mechanism is that the

ictal asystole is caused by an excessive reflex of vagal tone triggered by the tachycardia during the seizure (Schuele *et al*., 2008).

Clinical significance of ictal bradycardia/asystole

In most cases, ictal asystole may be a benign condition which is self-limiting and does not require treatment (Schuele *et al*., 2008). If the ictal aystole is associated with syncope, this may lead to falls and other trauma (Strzelczyk *et al*., 2008). Postictal asystole may also be a potential mechanism for SUDEP, a major cause of death in epilepsy (Shorvon and Tomson, 2011). The pathophysiology remains unknown, but the MORTEMUS study revealed several common features in 25 monitored cases of SUDEP or near-SUDEP patients. They all (except one) had a nocturnal generalized tonic-clonic seizure, followed by postictal cardiorespiratory dysfunction characterized by central apnoea and bradycardia, leading to asystole and subsequent death in 1/3 of patients (Ryvlin *et al*., 2013).

Treatment options for ictal bradycardia/asystole

Seizure control with antiepileptic medications is attempted first for the treatment of ictal bradycardia/asystole. If this is not possible, or if the asystole is prolonged (greater than 20 or 30 seconds), then a pacemaker should be considered. Alternatively, in the acute period, transvenous pacing may be used for several days to weeks, especially in patients with PRES as they infrequently develop epilepsy. Pacemaker implementation has shown to improve outcomes and prevent injuries in patients with epilepsy (Strzelczyk *et al*., 2008, Moseley *et al*., 2011). It is unknown how often ictal asystole recurs and at what frequency. One study in which six patients with epilepsy were investigated suggests that it does not commonly reoccur. These patients had a pacemaker implanted for five years and none had recurrent asystole (Schuele *et al*., 2008). One caveat in interpreting this study is that rare epochs of pacing, such as those only during seizures, may not be detectable during routine pacemaker interrogation.

Conclusion

Seizures should be suspected and investigated in patients with neurological disorders and otherwise unexplained asystole/bradycardia. *De novo* asystole can be related to seizures, and different foci can trigger asystole, as seen in our patient. There may be several clues, such as a tongue laceration, urinary incontinence or syncope, that increases the degree of suspicion for seizure. Seizures are very common in PRES, whereas asystole has never been described. If a patient has both seizures and asystole, then simultaneous video-EEG-EKG may be helpful in confirming a correlation between the two problems. It is important to recognize that ictal asystole can be seen in PRES and early recognition may help prevent asystole-associated complications, including death and/or SUDEP. □

Disclosures.
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TEST YOURSELF

(1) What is the risk of epilepsy in patients with PRES?

(2) Name a common feature seen in patients with SUDEP?

(3) In which types of seizures (localization) has ictal asystole been more commonly described?

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".