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PRACTICAL PEARL

Loss of Vestibular Ocular Reflex in Nonconvulsive Status Epilepticus

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Abstract

Background: Electroencephalogram (EEG) findings of generalized periodic discharges (GPDs) with triphasic morphology were introduced as a metabolic phenomenon, but more recently have been associated with epileptic phenomenon. Resolution of EEG findings along with clinical improvement from treatment is diagnostic. The known causes of reversible, isolated loss of OVR include medication toxicity, lead exposure, and thiamine deficiency, but its association with nonconvulsive status epilepticus (NCSE) has never been published. Medication induced loss of OVR resolves after a 24-hour washout period. We report a case of reversible, isolated loss of vestibular ocular reflex (VOR) associated with epileptic phenomenon.

Methods: This is a case report of a single patient.

Results: A 74-year-old male with a history of complex partial seizures admitted for a pneumonectomy had a postoperative course complicated by two instances of coma, the latter associated with an isolated loss of VOR. EEG revealed GPDs with triphasic morphology initially interpreted as a metabolic phenomenon. The patient's mental status, exam and EEG findings improved after low dose infusion of propofol for tracheostomy, and he was eventually discharged at baseline neurological function. Due to this response, his coma, loss of VOR and EEG were later interpreted as a consequence of NCSE.

Conclusion: The interpretation of GPDs with triphasic wave morphology range from metabolic phenomenon to NCSE. NCSE should be highly considered on the differential for encephalopathy regardless of the circumstances. NCSE may be a potential cause of reversible, isolated loss of the VOR and an AED trial in the appropriate clinical context should be considered. This is the first report of loss of VOR possibly associated with NCSE.

Case Report

A 74-year-old man with history of incomplete tetraplegia secondary to gunshot wound to the spine and complex partial seizures was 2-days status-post-uncomplicated left pneumonectomy for lung cancer when he became acutely comatose. Postoperatively, the patient was awake, oriented, and following commands. On postoperative day (POD) 1, he was noted to be falling asleep easily, although he remained oriented and situationally appropriate. His pain was initially controlled with low-dose gabapentin and an epidural pain catheter with an infusion of bupivacaine and hydrocodone. This catheter was discontinued and naloxone was given without improvement in examination. His gabapentin dose was increased to 600 mg twice a day (BID). During this time, he was continued on his home doses of carbamazepine 400 mg three times daily (TID) and levetiracetam 1500 mg BID for which he had been on for many years. That evening, the patient's mental status declined in the setting of respiratory distress. In the morning, patient was unresponsive to sternal rub. Neurology was consulted, and his examination was noted to be a Glasgow Coma Scale (GCS) of 8 that declined to 4 by the end of evaluation (E2V1M1). There were no additional sedating medications administered

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at the time of this evaluation. There was no observed seizure-like activity. All brainstem reflexes were intact including oculocephalic reflex (OCR). He was febrile, tachycardic, hypotensive, and hypoxic with an oxygen saturation of 86% on 100% oxygen. He was transferred to the neurointensive care unit (NICU) for further management. His laboratories revealed an increase in his white blood cell count from 13.1×10^9/L with 10% band cells to 16.4×10^9/L with 26% band cells. His lactate was 2.5 mmol/L. Carbamazepine level was above normal at 15.0 μg/mL (normal 4.0–12.0 μg/mL), but his prior baseline levels were 11.8–15.3 μg/mL. Blood cultures were sent. Copious amounts of secretions were produced when he was intubated for respiratory failure. Chest X-ray revealed left mid and lower lobe opacities with left apical pneumothorax. Bronchoscopy was subsequently performed, and sputum culture was sent. The patient's chest tube, which was left after his surgery, was placed to suction. The patient was started on broad spectrum antibiotics, intravenous fluids, and vasopressors for sepsis management. He was maintained on dexmedetomidine for sedation to minimized further hypotension, as well as fentanyl for analgesia. Gabapentin was discontinued at this time.

Nonconvulsive seizures contributing to the patient's change in mental status were high on the initial differential for his encephalopathy given his reported history of epilepsy. A prolonged electroencephalography (EEG) for 24 h revealed a background of 5–6 Hertz (Hz) and occasional periodic generalized periodic discharges (GPDs) at a rate of 1 per second with triphasic morphology as per American Clinical Neurophysiology Society's Standardized Critical Care Unit EEG Terminology, version 2012 [1] (Fig. 1a). His EEG was interpreted as generalized brain dysfunction without concern for seizures, consistent with a metabolic encephalopathy. While the GPDs were considered to be on the ictal–interictal continuum, the risk that they represented seizures was considered low. Because of the low risk for seizures, the EEG monitoring was discontinued. His medication list was re-evaluated for potential causes of medication toxicity. No medications seemed overtly sedating; however, due to his poor mental status, his levetiracetam was reduced from 1500 mg to 1000 mg twice a day. He was continued on his home carbamazepine dose. Subsequent workup for his encephalopathy was unremarkable, including lumbar puncture studies, liver function tests, thyroid function tests, ammonia, head computed tomography (CT), CT angiogram of the head and neck, urinalysis, blood cultures, and vitamin levels of B12 and folate. He was supplemented with high-dose thiamine. A magnetic resonance imaging (MRI) of his brain was unable to be performed due to a spinal cord stimulator. The sputum culture grew Escherichia coli, and the presumed etiology of his cognitive decline was septic shock from aspiration pneumonia. On POD 4, the patient's sedation was weaned off and he awoke in distress due to pain. Given ventilator dyssynchrony due to the patient's discomfort and risk of further injury to his compromised lungs, he was quickly resumed on dexmedetomidine infusion and fentanyl boluses as needed. His awake examination was abbreviated due to the situation. On gross assessment, the patient's GCS prior to resumption of sedation was 9T (E2V1TM6). Presumably, the patient's agitation indicated an improvement from his initial comatose state that was likely due to sepsis. Given satisfactory extensive workup performed for his encephalopathy, the patient was transferred back to the cardiothoracic intensive care unit (CT-ICU), with neurology assistance as a consult service. Prior to transfer, an examination was performed while sedated that documented in tact brainstem reflexes, including OCR, although his GCS was 5T, which was attributed to the sedation.

Upon initial reevaluation of patient in the CT-ICU, patient had been off sedation and analgesia for 24 h and his GCS was 7T (E2V1TM4). On examination, he would grimace and open eyes to pain inconsistently. Notably, the patient had a new isolated loss of his OCR. This was confirmed with absent response to oculovestibular reflex (OVR) testing. It was verified with the NICU that the patient had intact OCR prior to transfer. The NICU also reported a history of the patient having delayed awakening from general anesthesia for a procedure, although the source of this knowledge was not clear. At this time, his temperature was 37.4 °C, heart rate 110, and white blood cell count 12×10^9/L. With this new examination finding, there was initial concern for a new structural insult such as anoxic brain injury due to septic shock, but repeat head CT was unchanged. Given that the patient could not obtain MRI and that head CT is a suboptimal study to evaluate brainstem insults, we did not feel a structural lesion could be ruled out and still considered this a potential explanation for his loss of vestibular ocular reflex (VOR). He was clinically monitored at this time. Our research regarding loss of OVR did not provide much guidance, as other than a structural lesion, medication and heavy metal toxicity and thiamine deficiency were the only reported causes of this isolated examination finding [2–5]. Moreover, in the instances of medication toxicity, OCR and OVR recovered after a 24-h washout period for which our patient had passed [3]. There was no literature to suggest that seizures could present with such an isolated examination finding. Septic encephalopathy and delayed awakening from sedation were our main concerns, and we recommended holding sedation, further treatment of his infection, and clinical

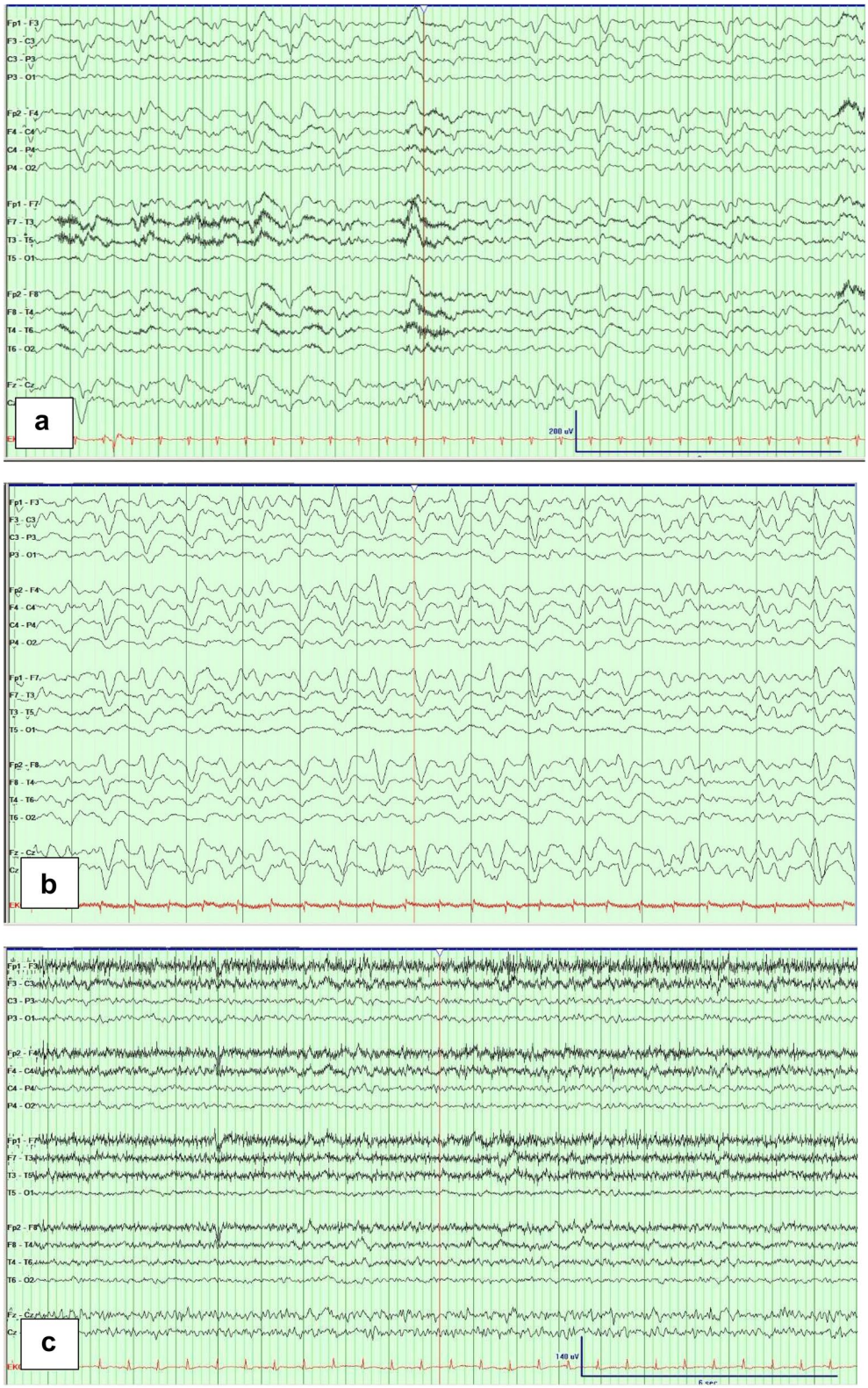

Fig. 1 **a** Occasional generalized periodic discharges with triphasic morphology at 1 Hz. **b** Runs of frontally predominant generalized periodic discharges with triphasic morphology at 1–2 Hz. **c** Generalized periodic discharges resolved

monitoring at this time. During this time, he was continued on levetiracetam 1000 mg BID and carbamazepine 400 mg TID. Of note, these medications had been tolerated for many years and initially prescribed for a remote history of staring spells that was poorly defined in prior notes thought to be complex partial seizures. He had no prior EEG or head imaging on file, and collateral information was unable to be obtained.

The evening of POD 6, the patient continued to have maximum temperature of 37.5 °C on scheduled acetaminophen. His mean arterial pressure declined to 42, and he required phenylephrine infusion. He remained off sedation and analgesia without change in examination. He was scheduled for tracheostomy the following day. In the morning, his levetiracetam was decreased to 500 mg BID by the surgical team, although it was not felt to be the cause of his poor mental status by the neurology team. At this time, prolonged EEG was recommended by the neurology service due to his persistent encephalopathy, poor examination, and change in antiepileptic drug (AED) dose. We also requested evaluation of his spinal cord stimulator to more aggressively investigate the possibility of MRI and a retrial of high-dose thiamine supplementation.

The patient underwent EEG monitoring for 3 h prior to tracheostomy. Due to technical constraints, the EEG data was reviewed after the procedure save for a preliminary reading of the first 30 min that did not identify any seizures. Prior to the procedure, the background consisted of 3–7 Hz activity and abundant GPDs with triphasic morphology often occurring in runs lasting between 3 and 12 s (Fig. 1b). The EEG was interpreted as worse than his prior EEG in the NICU given the slower background activity and more prevalent discharges. The GPDs were interpreted to also be on the ictal–interictal continuum, possibly more suggestive of ictal activity than before. While at times the frequency of the GPDs was more rhythmic up to 2 Hz, the runs did not evolve further and thus were not considered consistent with electrographic seizure.

After the surgical procedure, the background was initially diffusely low amplitude and the GPDs were occasional at 0.25–0.5 Hz, likely due to the propofol received. Several hours later, the background amplitude and activity improved from 3–4 to 6–7 Hz activity over the course of the day. During this time, likely as the sedation wore off, the GPDs reappeared but less often and with shorter runs than prior to the procedure. They were considered frequent, and the occasional runs lasted between 1 and 3 s. By early the next morning, there were occasional GPDs with long periods of time without GPDs. By late morning, the GPDs were rare and the background was 5–7 Hz activity, up to 8 Hz at times. Over the course of the subsequent day, the background continued to improve and the GPDs resolved. At 48 h, the patient's EEG was diffusely slow at 6–8 Hz activity with no discharges (Fig. 1c).

The patient's mental status and examination concomitantly improved over the next 24 h after the procedure. The primary team reported the patient was waking up over the course of the day. On neurological evaluation the following morning, he was opening eyes to minimal stimulation, intermittently following simple commands with his upper extremities, mouthing words to pain, and his extraocular movements were intact. He notably had mild end-gaze nystagmus when looking right. Over the course of the second day, the patient's mental status continued to recover and his examination returned to baseline with resolution of his nystagmus.

Given the clinical and electrographic improvement after the procedure, we investigated potential causes. The only medications administered in the interim were propofol infusion at 10 mg/mL and rocuronium for the procedure only. He returned to the CT-ICU off sedation with no other medication changes or events. His levetiracetam remained at 500 mg BID and carbamazepine at 400 mg TID. Given his improvement in mental status to baseline, we did not think any further adjustments were necessary.

The patient completed a full course of antibiotics for his pneumonia, and the rest of his hospital course was relatively unremarkable. The patient was eventually decannulated from his tracheostomy and discharged on the same doses of his AEDs (carbamazepine 400 mg TID and levetiracetam 500 mg BID). He remained at baseline neurological function at follow-up 2 months from discharge. It was at that follow-up that we were able to clarify that his history of seizures began after a remote history of head trauma and that he had not had any seizures in years.

Discussion

This case report encompasses the concept of GPDs with triphasic morphology representing epileptic phenomenon and reports the first time this has been associated with isolated loss of the VOR.

In patients with impaired consciousness, the VOR is tested with the OCR or OVR. A normal response, when a patient's eyes rotate counter to the direction of head movement, implies intact brainstem pathways from the vestibular nuclei through the pontine and midbrain paramedian tegmentum [2]. Comatose patients often have impaired or sluggish response due to proximity of the tested brainstem pathways to the ascending arousal system [2]. A more vigorous evaluation of the vestibular response can in turn be done by testing the OVR or cold calorics [2]. After determining that the ear canal is

free of blockage, it is irrigated with up to 50 milliliters of cold water over 5 min and then observed for a response [2]. Cold water into one side should produce the same response as if the patient's head were turned the opposite side—the eyes should deviate slowly toward the tested ear [2]. In awake patients, a compensatory rapid saccade back to the midline is seen, although this does not typically occur in patients who are comatose [2].

The known causes of reversible, isolated loss of OVR include medication toxicity, lead exposure, and thiamine deficiency, but the association with nonconvulsive status epilepticus (NCSE) has never been published [2–5]. Morrow and Young published a case series regarding isolated absent OVR due to high doses of the following sedating medications whose mechanisms of action relate to suppression of the vestibular nuclei: mirtazapine (5-HT1A agonist), baclofen (GABA-agonist), fentanyl (opiate agonist), and clomipramine (tricyclic antidepressant) [3]. Other drugs within these or similar categories of mechanisms of action were noted to be contributory or have potential to cause loss of VOR in toxic doses, such as benzodiazepines, propofol, and barbiturates (GABA-agonists) [3]. The toxic doses of all offending agents were not clarified in the report [3]. For instance, while the propofol dose was mentioned in the patients who had toxicity of baclofen and mirtazapine (case 1) and clomipramine (case 3) (100 mg/mL over 7.5 h and 50 mg/mL for 5.25 h for cases 1 and 3, respectively), it is not clear whether this dose of propofol was directly contributory to the examination finding [3]. Moreover, these patients also received midazolam, which may or may not have been contributory as well [3]. OCR and OVR presumably recover with an antagonist or after a 24-h washout period [3]. Bilateral vestibular failure is also associated with phenytoin and aminoglycoside toxicities [2]. In regards to our case, the patient was comatose for days without any exposure to the aforementioned medications and his thiamine was supplemented without any clinical improvement.

Our patient experienced two separate instances of comatose state with EEGs consisting of GPDs with triphasic morphology that were interpreted differently based on clinical context. Initial EEG demonstrated occasional GPDs with triphasic morphology, but these were interpreted to be a metabolic phenomenon by both the neurointensivist and electroencephalographer given his diagnosis of sepsis and relative infrequency of the findings. The GPDs were not considered ictal or interictal at that time. His examination was noted to have intact OCR at that time. The patient did have an instance of awakening after his treatment of sepsis. Though he was not on EEG at this time, it is clinical evidence that treating sepsis provided some benefit to examination. The second instance when he was comatose was when sedation was weaned a second time, and this is when there was loss of OCR confirmed with OVR. The EEG at this point revealed increased frequency of GPDs with triphasic morphology compared to prior and a slower background, all of which improved after his procedure and exposure to low-dose propofol. Moreover, along with improvement of his EEG, his examination concomitantly improved including recovery of the OCR. With this clinical correlate, his GPDs with triphasic morphology were considered ictal phenomenon. Given this was a realization in hindsight, he was not treated based on preliminary EEG findings, but if the literature existed regarding the relationship of triphasic morphology, NCSE, and loss of VOR, our management likely would have changed.

The debate regarding the significance of GPDs with triphasic morphology is long-standing. The GPDs have a distinct morphology with a triphasic contour from which their name is derived [6]. Traditionally interpreted as metabolic phenomenon, GPDs with triphasic morphology have more recently been associated with drug toxicities and NCSE [6]. They were first introduced in the 1950s as EEG findings associated primarily with hyperammonemia, hepatic and renal failure, later with hyperosmolarity, anoxia, and hypoglycemia [6]. Not until about the 1990s did neurologists consider their potential to reflect ictal activity [6]. The distinguishing factor between the interpretations of the EEG is the clinical correlate.

Clinically, if the patient and EEG markedly improve with treatment of NCSE, one would conclude that the pattern of GPDs with triphasic morphology on EEG was likely ictal [6]. Both clinical and EEG improvement must occur because treatment for seizures (i.e. benzodiazepines) can improve GPDs with triphasic morphology on EEG in a metabolic encephalopathy, although the patient may not clinically improve. A case series of 15 patients admitted for various reasons but who were all very ill and encephalopathic all had triphasic waves (their descriptive term at the time) on their EEG and determined to have NCSE due to their response to treatment [7]. After the administration of diazepam 10 mg, the triphasic waves disappeared and consciousness was improved in all patients, although at varying times with delays attributed to their primary source of illness [7].

Although propofol has not been studied in this situation, it does have anti-epileptic properties and given our patient's remarkable clinical improvement and resolution of EEG findings, it is possible that propofol had inadvertently treated our patient, implying that perhaps he was in NCSE [8]. Prior cases implicating propofol given its mechanism of action could potentially cause loss of VOR in toxic doses did not clarify at what dose, and cases where propofol may have been contributory involve other offensive agents considered to be the culprits [3].

The dose of 10 mg/mL received by our patient with the absence of other sedating medications may be considered a therapeutic trial which may be why he responded in the way he did.

The patient's history of complex partial seizures predisposed him to seizures, especially with provoking factors which lower seizure threshold such as infection and de-escalated doses of one of his home AEDs. In the midst of his clinical situation (inability to obtain MRI, persistent low-grade fever on acetaminophen and hypotension, and reported history of delayed awakening from sedation), this conclusion was not as apparent. The propofol administration was incidental, but his clinical and electroencephalographic improvement is convincing that the GPDs with triphasic morphology were interpretable as NCSE and it carried a relationship with a reversible loss of OVR.

Subsequent to his procedure, his AED doses were not increased as his examination was improving. To the point that an AED or benzodiazepine "trial" for NCSE without increase in maintenance AEDs would not be standard treatment, we hypothesize that the sustained exposure to propofol—a cumulatively higher dose than an equivalent "trial" of AED or benzodiazepine—may have been enough to resolve his seizures. While we would not recommend a prolonged exposure to low-dose propofol in the future as an AED trial in a similar scenario, it appeared to have been an effective treatment in our case. Without further provoking factors to allow for additional seizures, the patient was continued on his modified doses of AEDs without issue.

His subsequent nystagmus after the procedure which eventually resolved was also suspicious for a post-ictal phenomenon, providing evidence for this hypothesis. Furthermore, the patient's loss of VOR could not be explained by other known reasons such as drug toxicity, thiamine deficiency, or structural lesion [3, 7]. He had not received any of the aforementioned offending medications to cause loss of VOR and despite being off any sedation for 24 h, did not improve.

While this may have been witnessed by other clinicians, this is the first report of a potential association between the reversible loss of VOR and NCSE. The art of interpretation of GPDs with triphasic morphology is a secondary factor in our partially delayed diagnosis, in addition to sparse reports regarding reversible causes of OVR. Clinical suspicion, correlate, and EEG interpretation should be carefully reconsidered in a comatose patient without obvious explanation. AED trial may provide diagnostic and therapeutic results.

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Author Contributions
Jennifer Kang was the lead author and performed the literature review with substantive contributions of expertise and editing by Joel Morgenlander and Aatif Husain. Jennifer Kang and Joel Morgenlander identified the case on clinical rounds. Aatif Husain obtained the necessary figures. All authors finalized the last version.

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Compliance with Ethical Standards

Conflict of interest
The authors declare there were no conflicts of interest.

Ethical Approval
This article does not contain any studies with human participants performed by any of the authors.

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