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New-onset seizure activity in a transplant patient on immunosuppressive therapy

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ABSTRACT

The evaluation of new-onset seizure activity must raise a much broader differential than just epilepsy. This case study highlights that broad differential and identifies an important, but less common, cause of seizure activity in specific patient populations. Information is summarized from recent primary research, case series, literature reviews, and meta-analyses. In the appropriate clinical context, the diagnosis of posterior reversible encephalopathy syndrome (PRES) should be considered as a cause of seizures. Posterior reversible encephalopathy syndrome is a neurotoxic syndrome characterized by posterior cerebral edema on imaging and triggered by a variety of inciting or predisposing factors. This article reviews suggestions for the identification and management of PRES. Because of the myriad factors, nurse practitioners should be familiar with PRES and may encounter it through primary care, emergency or urgent care, hospitalist medicine, or a variety of specialty roles.

Keywords: Cerebral edema; hypertension; immunosuppressants; organ transplant; PRES; renal failure; seizures.

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Introduction

New-onset seizure activity is a frequent acute medical complaint. However, although epilepsy is often considered as a cause of seizure activity, the evaluation of new-onset seizure activity must raise a much broader differential. Additional causes of new-onset seizure–like activity in a general population may include paroxysmal movement disorders, psychogenic nonepileptic seizures, toxic metabolic syndromes, malignancy, metabolic derangements, and vascular pathologies. Specific patient populations may be predisposed to other causes of seizure as well. A detailed history and an awareness of certain risk factors can identify less common causes of seizure.

Case presentation

A 21-year-old woman presented to the emergency department (ED) with slow persistent bleeding from an abdominal site after injecting herself with insulin and enoxaparin. Direct pressure did not stop the bleeding before her presentation.

The patient had a medical history significant for cystic fibrosis, with diabetes and hypertension secondary to cystic fibrosis. She had bilateral lung transplantation 2 months before. Aside from enoxaparin and insulin, her medications included prednisone and immunosuppressants: mycophenolate mofetil and cyclosporine. She took metoprolol for blood pressure and a diuretic, furosemide. In addition, she was prescribed multiple antibiotic and antifungal agents.

Her initial vital signs included a temperature of 36.7°C (98.1°F), heart rate of 91 beats per min, respiratory rate of 22 per min, and blood pressure of 165/111 mm Hg. The patient was alert and oriented. Examination revealed only a small bleeding puncture wound to the abdomen due to a superficial venule. Bleeding was controlled with Surgicel (oxidized cellulose gauze) and local infiltration of lidocaine with epinephrine.

While in the ED, the patient had a muscle spasm of the right upper extremity involving the deltoid, biceps, and triceps muscles. Further discussion revealed that over the day, she had been having multiple similar episodes, with no mental status change. The patient had been experiencing pain and subjective weakness in this distribution since her recent lung transplantation. This had been attributed to a compressed nerve and peripheral neuropathy caused by positioning for surgery. No objective weakness was identified. The patient was given 2.5 mg of diazepam for muscle spasm with good effect. Repeat blood pressure was slightly improved at 154/109 mm Hg.

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No laboratory test results were drawn initially. The patient was discharged to home to follow-up with her transplant team, which had been managing her hypertension. Because hypertension was an established diagnosis managed by her transplant team, no medication changes were made. The patient had no prior blood pressure readings for comparison.

After discharge, the patient had an additional muscle spasm. The spasm progressed down her arm, resulting in 20 s of hand clenching. She subsequently developed generalized tonic–clonic seizure activity. This lasted approximately 60 s, followed by a postictal state. Emergency Medical Services was called, and the patient returned to the ED. Repeat evaluation revealed a blood pressure of 171/113. The patient's neurological status improved. She remained somewhat somnolent but was oriented with no headache or visual changes. She had no further episodes of partial or generalized seizure activity.

Laboratory results were notable for hyperglycemia (326 mg/dl), hyperkalemia (5.8 mEq/L), and renal insufficiency (blood urea nitrogen 82 mg/dl; Cr 1.6 mg/dl). Alkaline phosphatase was also elevated (252 IU/L). A bolus of normal saline was given to address her renal insufficiency. A computed tomography (CT) scan of the head demonstrated posterior white matter changes. Given her recent transplant status and her immunosuppressive medications, she was admitted to the medical intensive care unit (ICU).

Case review

Given the nonspecific presentation in this case, a broad differential should be considered. Some common differential diagnoses include primary and secondary headache, toxic metabolic syndromes, or vascular pathologies (Faille, Fieuws, & Van Paesschen, 2017). Metabolic derangements, including hyponatremia, uremia, and hypoglycemia, can have similar symptoms. Vascular pathologies include posterior circulation stroke or sinus thrombus (Fugate & Rabinstein, 2015; Granata et al., 2015). Reversible cerebral vasoconstriction is one of the most important alternative diagnoses, with many of the same risk factors and a similar clinical presentation as this case (Fischer & Schmutzhard, 2017). If seen in cancer, causes could include chemotherapy-related demyelination, radiation necrosis, lymphoma, paraneoplastic encephalitis, gliomatosis cerebri, or metastatic disease, often with associated edema (Fugate & Rabinstein, 2015; Granata et al., 2015). Infections, including infectious encephalitis or acute disseminated encephalomyelitis, should be considered in some scenarios (Granata et al., 2015).

In addition, there are myriad of neurologic conditions that should be ruled out. These include subcortical leukoaraiosis, central nervous system vasculitis, progressive multifocal leukoencephalopathy, osmotic demyelination syndrome, acute demyelinating encephalitis, or toxic leukoencephalopathy (Fugate & Rabinstein, 2015). Primary seizure disorder or intracranial hemorrhage should be considered. These may be a consequence of this patient's condition but could also be alternative diagnoses in the differential with similar presentation.

Owing to the broad differential, the clinical picture is still imperfect for identifying this patient's diagnosis. Unfortunately, there is a lack of strict diagnostic criteria, which may complicate its identification (Fischer & Schmutzhard, 2017).

However, based on history and risk factors, the diagnosis of posterior reversible encephalopathy syndrome (PRES) should be strongly considered among these other possibilities. Posterior reversible encephalopathy syndrome is a neurotoxic syndrome characterized by posterior cerebral edema on imaging and triggered by various inciting or predisposing factors. Because of the myriad factors, nurse practitioners (NPs) may encounter PRES through primary care, emergency or urgent care, hospitalist medicine, or a variety of specialty roles (Fugate & Rabinstein, 2015).

Although there are many risk factors for PRES, some particularly clue a clinician in to the diagnosis. Posterior reversible encephalopathy syndrome may be two to three times more common in women, as in this case (Faille et al., 2017; Fischer & Schmutzhard, 2017; Parikh et al., 2017). Also, hypertension is seen in 53–92% of cases (Thompson, Sharp, Pothof, & Hamedani, 2015). The degree of hypertension does not correlate with the extent of edema (Chen et al., 2018), and pressures may be normal or slightly elevated in a significant portion of cases (Fischer & Schmutzhard, 2017). One retrospective review found hypertension to be the most common cause of PRES in 72% of cases, with immunosuppression next most common (20%) (Datar, Singh, Rabinstein, Fugate, & Hocker, 2015). Our case demonstrates both risk factors.

Aside from hypertension, renal failure is seen in over half of cases of PRES. It is unclear whether it is due to other concurrent risk factors: hypertension, cytotoxic medications, and autoimmune disorders. It alternatively may be an independent cause of—or perhaps even a result of—PRES (Fugate & Rabinstein, 2015). Organ transplant, autoimmune disease, chemotherapy, or malignancies are all often associated with PRES (Thompson et al., 2015). In our case, renal insufficiency and solid organ transplant were additional identified risk factors.

Our patient was on prednisone, and at least one study has noted risk of PRES with steroid therapy. Of 99 cases of PRES, steroids were seen in 44%. The short median duration of treatment before the onset of PRES suggested that this might be a common precipitant in these patients (Parikh et al., 2017).

In addition to risk factors, a suggestive constellation of symptoms can also alert the provider to the possibility of

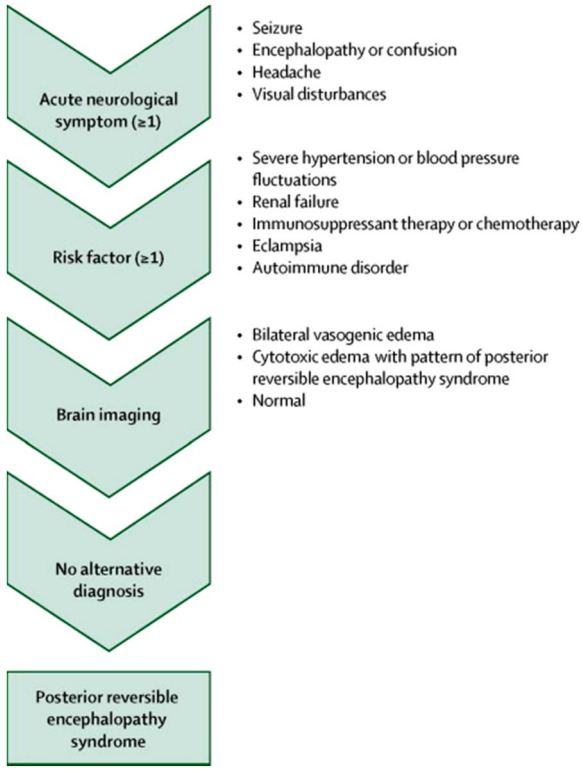

Figure 1. Proposed algorithm for the diagnosis of posterior reversible encephalopathy syndrome (Fugate & Rabinstein, 2015).

PRES in this case. The most common symptoms in PRES are seizure (in 74–92% of cases), encephalopathy (anywhere from 28–92%), headaches (26–83%), or visual disturbances (20–63%) (Thompson et al., 2015). A significant association was seen between PRES and epileptic seizure or encephalopathy in a recent study (Faille et al., 2017). Three to 15% of cases may show status epilepticus (Fischer & Schmutzhard, 2017; Fugate & Rabinstein, 2015). Faille et al. (2017) have reported these symptoms as well, in addition to focal neurologic deficits seen in 43% of cases in their study. This is more than the 5–15% rate of focal symptoms reported by others (Fugate & Rabinstein, 2015). Our patient demonstrated hypertension and seizure activity, while reporting focal symptoms before her secondary generalization. Headache, although common in PRES, is actually poorly predictive of the diagnosis because of poor specificity, with an odds ratio for PRES that did not reach statistical significance (Faille et al., 2017).

A proposed diagnostic algorithm by Fugate and Rabinstein (2015) is shown in **Figure 1**.

Testing and management strategy

Basic laboratory studies should be obtained. Impaired renal function is seen in 55% of cases. Any levels of medications such as immunosuppressants should be measured, although plasma levels of immunosuppressants do not necessarily correlate with the severity of PRES (Fischer & Schmutzhard, 2017). Other laboratory findings that may be seen with PRES include elevated lactate dehydrogenase (Fischer & Schmutzhard, 2017; Fugate & Rabinstein, 2015). There may be hypomagnesemia, elevated liver function studies, and hypoalbuminemia, although no laboratory studies demonstrate adequate sensitivity or specificity to identify the cause of this patient's symptoms (Fischer & Schmutzhard, 2017).

Lumbar puncture should be considered to exclude etiologies such as encephalitis or central nervous system spread of hemato-oncologic diseases. Elevated albumin on lumbar puncture may result from blood–brain barrier disruption in PRES, and in one study, mild albuminocytologic dissociation was seen but with poor specificity (Fischer & Schmutzhard, 2017).

Given the new onset of seizure, imaging studies should be pursued. Computed tomography was obtained initially in this case and is likely a first-line imaging modality. Noncontrast CT can identify vasogenic edema in parieto-occipital regions bilaterally in some patients (Fugate & Rabinstein, 2015). However, magnetic resonance imaging is the preferred imaging because of the increased sensitivity (Fischer & Schmutzhard, 2017; Fugate & Rabinstein, 2015). Magnetic resonance imaging usually demonstrates vasogenic edema in a suggestive distribution (Faille et al., 2017; Fugate & Rabinstein, 2015) with the subcortical white matter universally affected and often with cortical involvement (Fugate & Rabinstein, 2015). Magnetic resonance imaging may also identify restricted diffusion in 15–30% of cases, usually as small areas within larger regions of edema. This is associated with irreversible structural damage and worse prognosis. Intracranial hemorrhage can be identified in 10–25% of cases (Fugate & Rabinstein, 2015). Most of these hemorrhages are intraparenchymal and generally smaller punctate hemorrhages (Thompson et al., 2015). The addition of magnetic resonance angiography—or, alternatively, computed tomography angiography or cerebral angiography—may identify cerebral vasoconstriction (Fugate & Rabinstein, 2015).

Advanced workup in consultation with neurology may include electroencephalography (EEG) to distinguish encephalopathy and epilepsy. The EEG in PRES may show a number of different patterns, although a generalized slowing of the EEG background in the theta–delta frequency is common (Datar et al, 2015; Fischer & Schmutzhard, 2017). Angiography may also be pursued with radiology or vascular specialists and can demonstrate vasoconstriction or vasospasm, either focal or diffuse in distribution (Fischer & Schmutzhard, 2017).

There are no adequate interventional trials to guide specific pathophysiologically guided therapies, so much controversy and variation in treatment persist (Fugate & Rabinstein, 2015).

It is essential to lower any significant hypertension and stabilize variations using hemodynamic monitoring (Fischer & Schmutzhard, 2017). Titratable antihypertensive medications may be used, with a target of no more than 25% reduction to avoid adverse effects on cerebral autoregulation (Fischer & Schmutzhard, 2017; Thompson et al., 2015) The specific antihypertensive medication is guided by recommendations for hypertensive crisis or urgency (Fischer & Schmutzhard, 2017). Nitroglycerin should be specifically avoided because of reports of worsening cerebral edema, and calcium channel blockers or beta blockers remain first line (Thompson et al., 2015). However, there remains no direct evidence that strict blood pressure control limits neurologic injury or significantly reverses clinical or imaging findings (Fischer & Schmutzhard, 2017).

Seizures are frequently seen early in the disease course (Datar et al., 2015). Antiepileptic medications are frequently required, but the best agents or duration of therapy is unknown (Fischer & Schmutzhard, 2017). Thompson et al. (2015) recommend benzodiazepines for seizures in PRES, with second-line options such as fosphenytoin or phenobarbital. Refractory seizures may require propofol or pentobarbital. Magnesium level should be assessed because it is frequently low in patients with PRES. Magnesium supplementation may serve as prophylaxis against seizures and has a cerebral vasodilatory effect (Fischer & Schmutzhard, 2017). Pre-eclampsia and eclampsia may be associated with PRES in pregnant patients as well, and, if it is diagnosed, will similarly benefit from magnesium therapy. Magnesium may lessen the risk of cerebral vasospasm or constriction, but additional systemic or local intra-arterial calcium antagonists can be considered (Fischer & Schmutzhard, 2017).

Perhaps, most important when managing PRES is the elimination of triggers, especially the cytotoxic and immunosuppressant medications that are often associated with it. There remains controversy regarding whether discontinuation, tapering, or reducing dosage is most appropriate, and how to restart treatment after the resolution of PRES (Fischer & Schmutzhard, 2017). The elimination of pharmacological treatment is not uniform, however, and some autoimmune diseases may be the cause of PRES and, therefore, could theoretically warrant increased immunosuppression rather than discontinuation (Fischer & Schmutzhard, 2017).

About 40% of patients require ICU monitoring (Fischer & Schmutzhard, 2017).

Prognosis

Patients and families must understand that there is significant uncertainty around PRES, which even includes uncertainty regarding pathophysiology (Fischer & Schmutzhard, 2017; Fugate & Rabinstein, 2015; Granata et al., 2015). Although it may be seen in a range of settings where NPs practice, the diagnosis can be very challenging. This confounds PRES management. When diagnosed, the NP and other providers should convey the potential for complications such as hemorrhage, the risks of persistent symptoms or poor outcomes, and the potential for reoccurrence of PRES.

Intracranial hemorrhage is a significant risk with PRES. Intracranial hemorrhage may be seen in 10–32% of cases and predicts worse outcomes. A meta-analysis has found that hemorrhage had a pooled odds ratio of 4.93 for worse outcomes. It is unclear whether hemorrhage is a direct risk factor for poor outcomes or a secondary sequela seen in more severe cases of PRES (Chen et al., 2018).

Some cohorts have reported mortality approaching 20% in patients with PRES, but this does not appear to be a direct result of PRES itself (Fischer & Schmutzhard, 2017). Others find that mortality may be closer to 3–6%, and severe neurologic sequelae or death may be mediated by intracranial hemorrhage, posterior fossa edema and swelling with brainstem compression or hydrocephalus, or even more generalized cerebral edema, and increased intracranial pressures (Fugate & Rabinstein, 2015).

Patient and family must be informed that despite the name "posterior reversible encephalopathy syndrome," the extent of reversibility in PRES remains unclear and may be associated with poor long-term outcomes (Faille et al., 2017; Fischer, & Schmutzhard, 2017). Preexisting diabetes and PRES involving the corpus callosum are reportedly strong predictors of this (Fischer & Schmutzhard, 2017). Findings of restricted diffusion and longer time to control causative factors also predict worse outcomes (Fugate & Rabinstein, 2015). In one study, more than a quarter of patients were discharged from the hospital with residual symptoms, most commonly visual symptoms or seizures (Faille et al., 2017).

Development of epilepsy may be a long-term complication of PRES, but it appears this is rare based on other literature (Fischer & Schmutzhard, 2017; Heo et al., 2016). Although some find the recurrent seizure rate to be 10–15% (Fugate & Rabinstein, 2015), Datar et al. (2015) argue that unprovoked seizures and epilepsy are rare enough that providers should consider discontinuing antiepileptic drugs after PRES has resolved. Most seizures after PRES were provoked, rather than unprovoked, and only 1 patient out of 127 cases was ultimately diagnosed with epilepsy. Most patients with seizures are treated with antiepileptic drugs during hospitalizations, which might have prevented early recurrent seizures. There remains no standard approach to how long these drugs should be continued, and it is ultimately at the discretion of the provider, based on control of risk factors and other potential seizure triggers.

There is a risk for reoccurrence of PRES, although this is estimated at only 5–10% of cases in the first few years after presentation. Recurrent PRES is most common in

uncontrolled hypertensive patients (Fugate & Rabinstein, 2015).

Case conclusion

The patient was given a loading dose of phenytoin, and then transitioned to levetiracetam for seizure prophylaxis. A nicardipine drip was initiated for blood pressure management. Magnetic resonance imaging of the head demonstrated multiple signal abnormalities in the parietal and occipital lobes. Based on these findings, the diagnosis of PRES was made. In light of this imaging and the generalized seizure activity on her return visit, the previously seen spasms of muscle activity were subsequently reinterpreted as simple partial seizure. Blood levels for her immunosuppressant medications were obtained. Her cyclosporine level was elevated at 375 ng/ml (normal 100–200 ng/ml) and was discontinued. Her renal insufficiency gradually resolved with intravenous fluids, and she had no further seizures. She was subsequently transferred to her primary transplant hospital for further care.

Implications for practice

This case is particularly useful to NPs because of the multidisciplinary nature of the diagnosis and treatment. Posterior reversible encephalopathy syndrome is a condition that may be seen across many different practice settings that NPs function in, including primary care, but is easily missed. Its prevalence is unclear, but likely PRES is significantly underreported because of the difficulty making the diagnosis. At the same time, it may be increasing in prevalence, as more patients are exposed to key risk factors. Because NPs are more likely to encounter this important and complex condition, when a patient presents with a history of new-onset seizures, understanding the need for consideration of multiple differential diagnoses and collaboration with other providers is imperative.

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