Chapter 16
Seizures

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Clinical Problem

A 49-year old woman presented to the Emergency Department with confusion, severe headache and altered mentation. She had received a cadaveric renal transplant 2 years earlier and was immunosuppressed with tacrolimus. She was hypertensive at 210/105 mmHg and she was tachycardic at 105 bpm. She was febrile at 38.3 °C and had reduced air entry at the right base with consolidation on chest radiograph suggestive of pneumonia. While in the Emergency Department she suffered a generalized seizure. Initially a head CT was performed and was reported as normal. Due to high suspicion of posterior reversible encephalopathy syndrome secondary to tacrolimus a MRI was requested. This confirmed mild bilateral cortical vasogenic edema in occipital lobes. The patient was admitted to ICU for blood pressure control, treatment of pneumonia, and seizure monitoring. Treatment with tacrolimus was temporarily withheld. The neurological symptoms improved and MRI performed 4 days later demonstrated complete resolution of bilateral occipital lobe changes.

Seizures are defined as abnormal excessive or synchronous neuronal activity that interferes with normal brain function. They can manifest as convulsive or non-convulsive phenomena. Seizures occur in 3.3 % patients in ICU and approximately 90 % of these cases present as generalized tonic-clonic convulsions or status epilepticus. Non-convulsive seizures are less common. However, as they may present non-specifically as altered mental status, obtundation or coma, they are difficult to recognize and their frequency is likely to be underestimated.

Seizures may be caused by a variety of neuropathological processes, which are summarized in Table 16.1. Neuroimaging can play a crucial role in their initial diagnosis. Unenhanced computed tomography in particular plays a crucial role in

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Table 16.1 Common causes of seizures secondary to intracranial pathology

Neurovascular	Ischemic stroke
	Hemorrhage (traumatic or non-traumatic)
	Subarachnoid
	Intracerebral (hemorrhagic stroke, contusion)
	Subdural
	Arteriovenous malformation
	Cortical vein thrombosis
	Dural venous sinus thrombosis
	Posterior reversible encephalopathy syndrome (PRES)
	Hypoxic ischemic encephalopathy
Infection	Meningitis
	Encephalitis
	Brain abscess
	Ventriculitis
Tumors	Primary brain tumors (especially cortically-based)
	Metastases
Autoimmune and inflammatory	Antibody-mediated encephalitis
	Acute disseminated encephalomyelitis (ADEM)
	Multiple sclerosis
	Vasculitis
Other	Primary epilepsy
	Seizures post neurosurgical procedures

the early detection of intracranial complications. New onset of seizures, change in the seizure pattern, or refractory epilepsy should be considered as indication for neuroimaging, especially if accompanied by additional changes in neurological status or a new focal deficit. New seizures occurring in patients admitted to ICU following neurosurgery should always be seen as a potential harbinger of complications and urgent imaging should be requested to exclude a postsurgical intracranial catastrophe.

In patients admitted to ICU with no previous history of neurological disease the majority of seizures are secondary to systemic or metabolic factors associated with critical illness or its treatment. Precipitating factors include hypoxia, hypoglycemia, sepsis, fever, drug toxicity (bronchodilators, antibiotics, antidepressants or antipsychotics), substance abuse (amphetamine, cocaine) or drug withdrawal (alcohol, opioids, benzodiazepines), as well as electrolyte imbalance (such as hyponatremia, hypocalcemia, hypophosphatemia, or acidosis). With few exceptions, these conditions do not have specific imaging appearances and are diagnosed and managed based on history, clinical and biochemical findings. However, neuroimaging may be required to exclude intracranial complications arising de novo, most often of neurovascular origin.

Lastly, prolonged seizure activity causes profound metabolic stress to the brain. That may exacerbate an existing injury, and imaging may be required to assess for consequences such as cerebral edema or encephalopathy.

Imaging Techniques

Owing to its speed and availability unenhanced computed tomography (CT) is the mainstay of acute neuroimaging in ICU. The main advantage of unenhanced CT is in the detection of acute hemorrhage, hemorrhagic transformation of an ischemic infarct, or a new intraaxial or extraaxial hemorrhage. Even inexperienced observers readily appreciate a large bleed. Small intracerebral hemorrhages in the posterior fossa and adjacent to the skull may be difficult to detect because of partial volume averaging and beam-hardening artifacts from adjacent bone.

In addition to the detection of hemorrhage, CT allows the assessment of the ventricles and extraaxial fluid spaces, as well as of the effacement of cortical sulci and basal cisterns suggestive of diffuse cerebral edema and increased intracranial pressure. Although non-specific, prominence of extraaxial fluid spaces and ventricles in disproportion to the patient's age, as well as cerebellar atrophy, may provide clues of possible chronic alcohol abuse as a seizure precipitant. CT allows assessment of vasogenic edema accompanying intracranial lesions, of the degree of exerted mass effect and midline shift or of uncal herniation. The usefulness of CT in the detection of acute cerebral ischemia presenting as subtle hypoattenuation and loss of grey-white matter differentiation is limited and is strongly dependent on the observer's experience. Established ischemia is easier to appreciate but care should be taken not to misinterpret this as edema if the grey matter is spared. CT can depict advanced global hypoxic ischemic brain injury leading to effacement of cortical sulci and loss of grey-white matter differentiation.

Contrast-enhanced CT may be helpful in the monitoring of intracerebral abscesses, ventriculitis, or intracranial infection. CT angiography is useful in evaluating the patency of intracranial arteries, cerebral ischemia and vasospasm. CT venography has a role to play in the assessment of the patency of the dural venous sinuses.

Due to the practical limitations (see Chap. 4) Magnetic Resonance Imaging of ICU patients is usually reserved for cases in which CT fails to detect the cause of seizures, or if further characterization of abnormal CT findings is needed. The main advantages of MRI stem from its unsurpassed ability to detect changes in brain parenchyma, and to partially categorize them. MRI is more sensitive than CT in the detection of posterior fossa and pituitary abnormalities, as well as pachymeningeal and leptomeningeal enhancement. MR angiography and venography have similar sensitivity to their CT counterparts but are less practical for obvious reasons.

Cortical Vein Thrombosis and Dural Venous Sinus Thrombosis

Cortical vein thrombosis is an uncommon condition presenting with seizures followed by a focal cortical deficit, secondary to cortical venous infarction. The isolated form of this condition (ICVT) is rare, although its frequency is probably underestimated due to the inherent difficulty in establishing the diagnosis. More often,

cortical vein thrombosis occurs in combination (CCVT) with superior sagittal sinus thrombosis due to retrograde thrombus propagation and is accompanied by clinical features such as headache, increased intracranial pressure and papilledema. Predisposing factors include hypercoagulable states, head trauma, parameningeal or meningeal infections, pregnancy and the puerperium, dehydration, nephrotic syndrome, and malignancy.

Imaging findings in ICVT on unenhanced CT include isolated, often hemorrhagic cortical infarction (Fig. 16.1a). The thrombosed cortical vein may be visible as a hyperdense, serpentine structure on the brain surface (the "cord sign," Fig. 16.1b). On MRI, a gradient recalled T2*-weighted sequence is the most sensitive modality and demonstrates low signal intensity in the thrombosed vein (Fig. 16.1c, d). CT venography and MR venography have low sensitivity in detecting cortical vein thrombosis.

Cortical vein thrombosis combined with sagittal sinus involvement (CCVT) should be suspected if there is hyperdensity in the sagittal sinus on unenhanced CT in addition to the above features. As the process is more widespread, multiple cerebral infarcts may be present. The frontal and parietal veins are the most commonly affected. On MRI there is low signal in the sagittal sinus on gradient-recalled echo T2* with "blooming" artifact, and T1 and T2 signal changes depending on the age of the thrombus. Venographic imaging is helpful as the lack of opacification or flow signal in the superior sagittal sinus is unlikely to be an anatomic variant and so indicates occlusion. The main diagnostic pitfall of CTV is the misinterpretation of hyperdense thrombus as normal contrast opacification; an unenhanced CT should always be obtained for reference.

Posterior Reversible Encephalopathy Syndrome

Posterior reversible encephalopathy syndrome (PRES) is a neurotoxic state affecting vascular watershed/junctional zones with a predilection for the posterior circulation, causing a unique pattern of vasogenic cerebral edema. Clinical symptoms include headache, altered mental state, and visual disturbances often associated with seizures or status epilepticus. Cases of PRES were originally described in the context of hypertension (hence the term "hypertensive encephalopathy"), pregnancy, and immunosuppression. It is now recognized to be associated with many different pathological processes (Table 16.2). The underlying pathophysiological cause of PRES is not fully established but it is thought to involve endothelial injury, failure of vascular autoregulation mechanisms, cerebral hyperperfusion or hypoperfusion.

Unenhanced CT may be normal but changes of subcortical low attenuation vasogenic edema can be seen in more severe cases (Fig. 16.2a). Generally, MRI is preferred to CT for the detection of PRES. The typical, parieto-occipital pattern of PRES on MRI consists of symmetrical, T1-hypointense, T2-hyperintense cortical and subcortical regions of vasogenic edema in the posterior circulation (Fig. 16.2b, c). The parieto-occipital white matter is affected in approximately 97 % cases. PRES

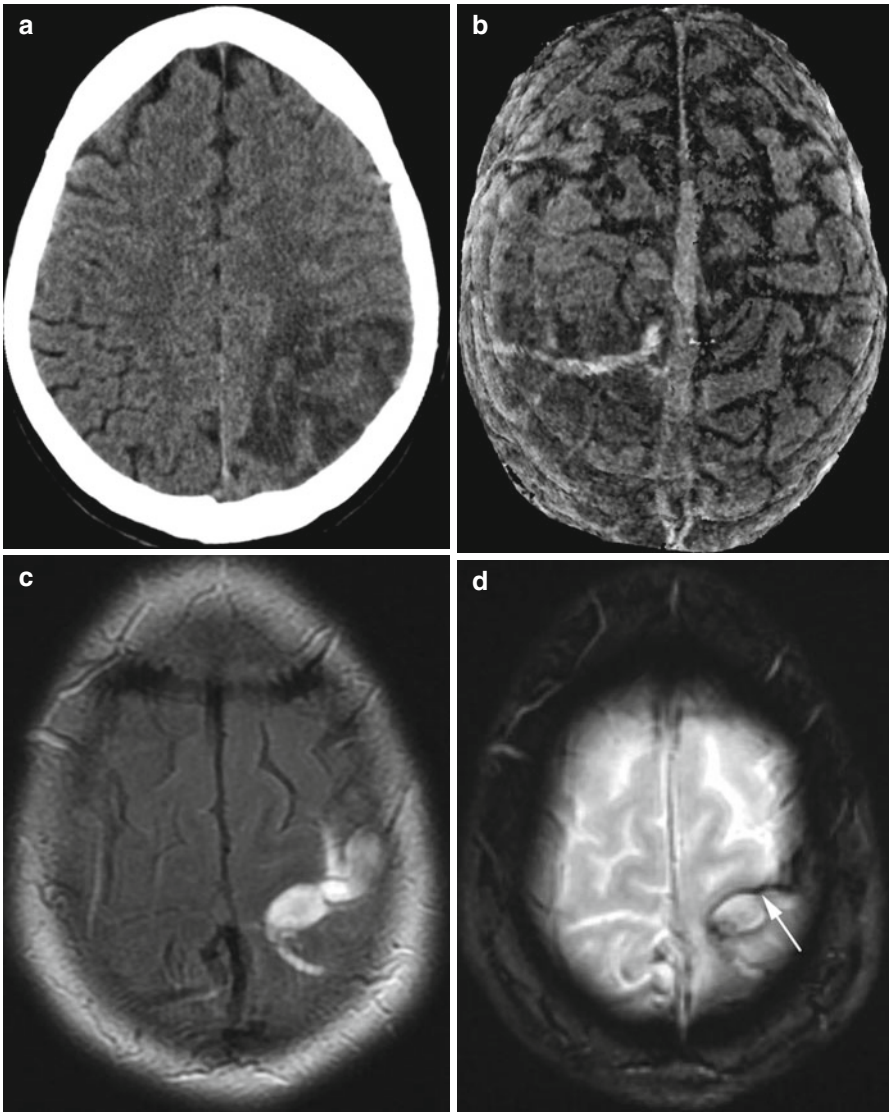

Fig. 16.1 Cortical vein thrombosis. (**a**) CT demonstrates a cortically based infarction in the left parietal lobe. (**b**) 3D reconstruction shows a hyperdense, thrombosed cortical vein ("cord sign") which is difficult to appreciate on axial images. FLAIR (**c**) and gradient recalled echo (**d**) (T2*) images in a different patient demonstrate FLAIR hyperintensity in the region of the left precentral gyrus; T2* images show low signal in the thrombosed cortical vein (*arrow*)

can also affect the basal ganglia and deep white matter. Involvement of the brain stem and cerebellum can cause an obstructive hydrocephalus.

The main differential diagnosis is ischemic stroke. Diffusion weighted imaging can help differentiate PRES from ischaemia. Angiographic studies may demonstrate

Table 16.2 Risk factors for developing PRES

Preeclampsia/eclampsia
Immunosuppression with cyclosporin or tacrolimus after bone marrow or solid organ transplantation
High-dose multidrug cancer chemotherapy
Autoimmune diseases
Nephrotic state
Thrombotic microangiopathies
Sepsis
Shock
Moderate to severe hypertension

diffuse vasoconstriction or focal areas of vasoconstriction and vasodilatation with a "string of beads" appearance due to vasospasm or vasculopathy. Characteristically, imaging changes and clinical symptoms are fully or near fully reversible after normalization of blood pressure or cessation of other causative factors.

Antibody-Mediated Encephalitis

Antibody mediated encephalitis is a rare condition primarily affecting the hippocampus and limbic region ("limbic encephalitis"). Patients typically present with amnesia, confusion, seizures and personality changes or psychosis. It can be associated with a variety of antibodies directed at neuronal cell surface proteins or intracellular targets. The presence of these antibodies is frequently associated with malignancy, particularly in small cell lung carcinoma, breast and testicular cancers, as well as thymoma. Encephalopathy with NMDA receptor antibodies was first identified in young women with ovarian teratomas.

Seizures are a major feature of encephalitis associated with antibodies directed against VGKC, NMDA and GABA-B receptors, as well as with high titers of GAD65. Of note, a growing body of evidence suggests that some of the autoantibodies may play a role in chronic epilepsy without manifesting limbic encephalitis symptoms.

MRI can be normal in up to 45 % of patients. If present, imaging findings include unilateral or bilateral temporal lobe FLAIR hyperintensity (Fig. 16.3a, b). NMDA receptor antibodies may cause a more diffuse process extending beyond the temporal region. In later stages the process may evolve into mesial temporal sclerosis leading to chronic temporal lobe epilepsy. Suspicion of antibody-mediated encephalitis should prompt a thorough search for an underlying malignancy, which may include pelvic or testicular ultrasound, mammography, CT, and PET.

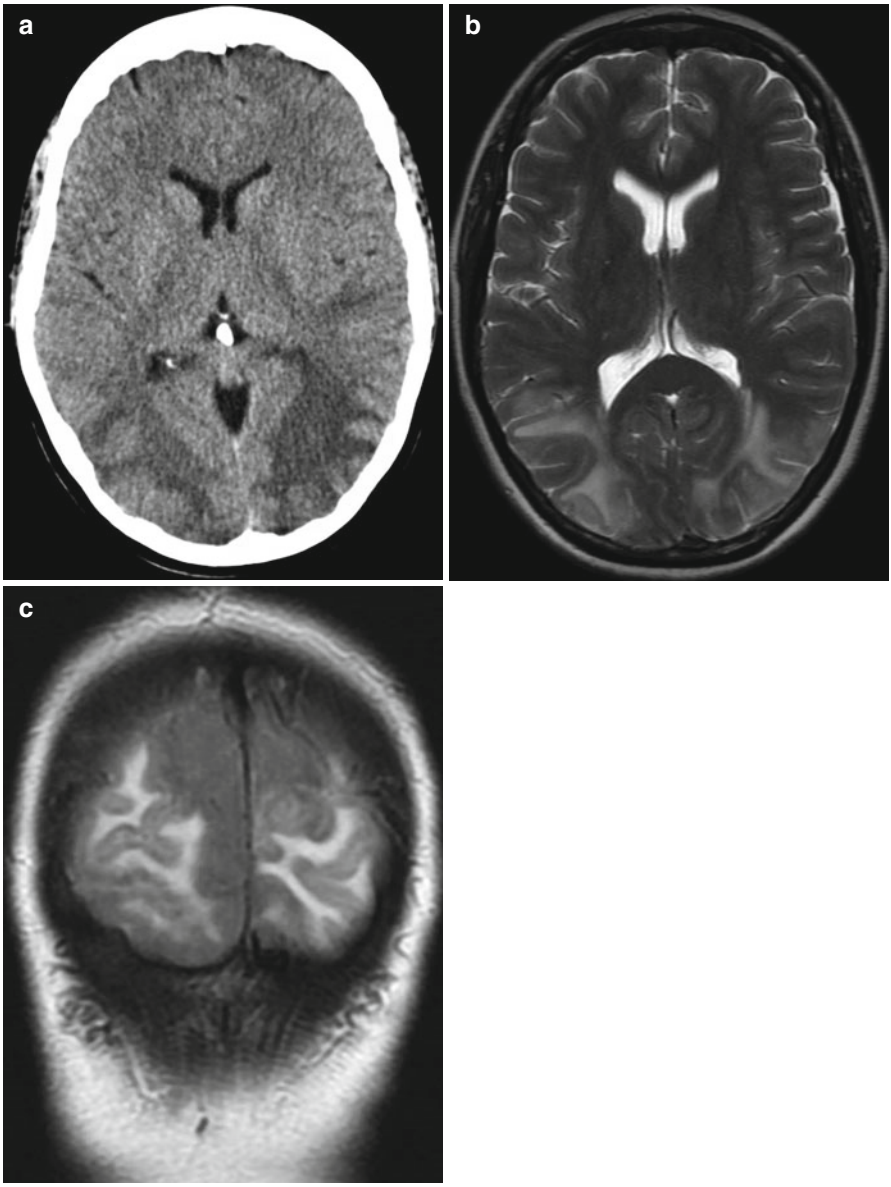

Fig. 16.2 Posterior reversible encephalopathy syndrome. (**a**) CT demonstrates bilateral areas of cortical and subcortical low attenuation in occipital lobes; corresponding T2-weighted (**b**) and coronal FLAIR (**c**) images of the most typical distribution

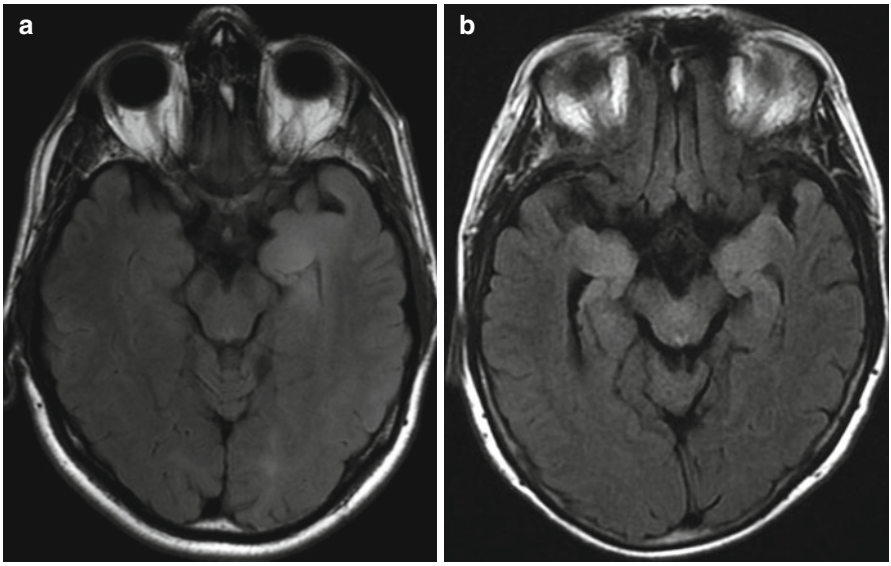

Fig. 16.3 Antibody-mediated encephalitis. (**a**) Unilateral high signal intensity in a patient with NMDA-receptor mediated encephalitis on a background of ovarian teratoma. (**b**) Bilateral changes in a patient with potassium channel antibodies

Transient Postictal Changes

Seizure activity causes many pathophysiological changes in the brain including hyperperfusion and increased blood-brain barrier permeability with the development of focal cytotoxic or vasogenic edema. On CT this manifests as focal gyral swelling, effacement of cortical sulci, as well as a region of low attenuation in the area of epileptogenic discharge. On MRI several characteristic postictal imaging patterns have been described depending on the location of the seizure focus and the underlying cause (Fig. 16.4a–c):

- A hippocampal pattern can be seen in temporal lobe epilepsy as restricted diffusion and enlargement of the hippocampus, usually unilateral and involving the side of seizure focus but can be bilateral. In some cases this may develop into hippocampal atrophy.
- A cortical pattern can be seen following hypoxia or hypoperfusion and is characterized by restricted gyral diffusion in the cortex corresponding to the seizure focus as well as functionally connected regions such as the ipsilateral posterior thalamus and the contralateral cerebellar hemisphere (crossed cerebellar diaschisis).
- The third pattern can be associated with bitemporal seizures, seizures related to metabolic factors, as well as antiepileptic drug withdrawal, and manifests as restricted diffusion in the splenium of corpus callosum.

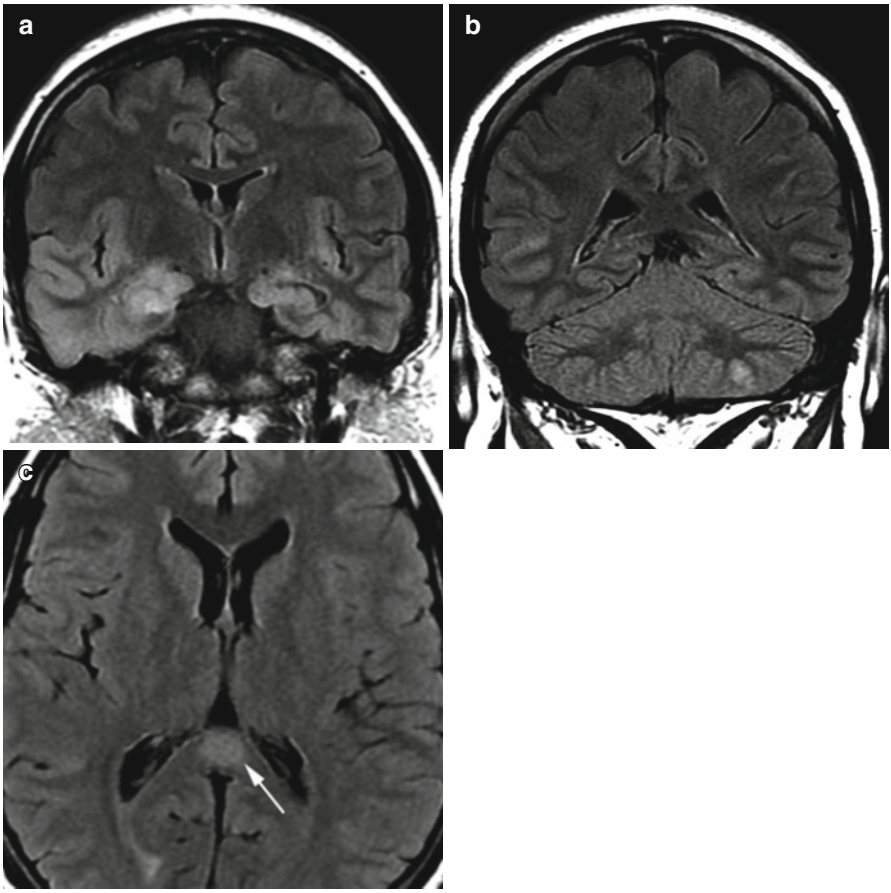

Fig. 16.4 Transient postictal changes. (**a**) Coronal FLAIR images demonstrate bilateral high signal in temporal lobes, more pronounced on the right with associated swelling of the hippocampus. (**b**) Cortically based high signal in contralateral cerebellar hemisphere, likely due to a crossed cerebellar diaschisis. (**c**) FLAIR images in a different patient demonstrating a postictal lesion in the splenium of a corpus callosum (*arrow*)

Awareness of the above imaging findings is important to avoid diagnostic error. Unenhanced CT findings of cortical and subcortical low attenuation can be misinterpreted as ischemic stroke. Cases in which thrombolytic therapy was erroneously administered have been described. MRI appearances may be misleading due to diffusion restriction in the region of seizure-associated cytotoxic edema mimicking an ischemic infarct. CT perfusion or MRI perfusion imaging may be helpful to differentiate these conditions by demonstrating increased blood flow in the region affected by seizures, in contrast to hypoperfusion in ischemia. Depending on the location there may be an overlap of postictal MRI changes with those seen in PRES, limbic

encephalitis, and herpes encephalitis. As these conditions are typically associated with seizures, it may be difficult to know if imaging changes represent the cause, or the result of epileptic discharge.

Teaching Points

1. Seizures may be seen in critically ill patients with or without preexisting intracranial pathology.
2. New onset seizures, change in the seizure pattern, and refractory epilepsy should be considered as indications for neuroimaging, especially if associated with changes in neurological status or a new focal deficit.
3. The suggested first line investigation is an unenhanced CT, which allows exclusion of hemorrhage and gross structural changes.
4. MRI has an advantage in evaluating the brain parenchyma and plays a crucial role in the diagnosis of posterior reversible encephalopathy syndrome and encephalitis as the cause of seizures.
5. Postictal imaging findings need to be differentiated from ischemic stroke, posterior reversible encephalopathy syndrome, and encephalitis.