Acquired Pathology

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Andrew Chiu and Michael Zeineh

Temporal Lobe Epilepsy With or Without Hippocampal Sclerosis

Temporal lobe epilepsy (TLE) is one of the most common forms of intractable epilepsy, with the frontal lobe the most common extratemporal site of seizure origin. Temporal lobe epilepsy can be further characterized as mesial temporal lobe epilepsy (mTLE) if there is an involvement of the amygdala, hippocampus, and/or entorhinal cortex. Of these, hippocampal or mesial temporal sclerosis (MTS) is one of the most common treatable causes of TLE. Sommer first characterized hippocampal sclerosis in 1880 [1], but the ability to diagnose this entity improved with noninvasive neuroimaging. This hardening or sclerosis of the hippocampus is the most commonly reported lesion in surgical and autopsy reports of temporal lobe epilepsy (TLE), occurring in up to 50% of cases of temporal lobe epilepsy. MTS is pathologically characterized by neuronal loss of pyramidal cells in the cornu ammonis, as well as dentate hilar neuronal loss. Patients may have a prior history of infection, trauma, or infantile febrile seizures.

Hippocampal sclerosis (HS) may be further classified by histopathologic cell loss in the hippocampal subfields of the cornu ammonis (CA1-CA4) and dentate gyrus [2]. HS Type 1 is the most common subtype and is characterized by predominant cell loss in CA1 and CA4, with varying degrees of cell loss in the other CA subfields. HS Type 2 is characterized by predominant cell loss in CA1. HS Type 3 is characterized by neuronal cell loss in all subfields except for CA1, with preferential cell loss in CA4 and the dentate gyrus, considered end folium sclerosis. All MTS subtypes demonstrate gliosis by pathology. Approximately 20% of TLE cases do not show significant cell loss and only show gliosis [3], classified as "no-HS" [2]. MTS can be seen on MRI as a combination of hippocampal atrophy, T2 signal hyperintensity, and architectural distortion (Figs. 41.1, 43.1, and 43.2). It is important to note that CA4 and the dentate gyrus are inseparable by MR imaging.

While up to 50% of cases of TLE are cases of MTS, the remainder of TLE cases may not demonstrate abnormality by imaging. In either situation of lesional or non-lesional TLE by MR imaging, there is a significant association of PET hypometabolism localizing to the interictal focus [4]. The degree of hypometabolism is more severe in cases of lesional MRI versus normal MRI [4], regardless of the underlying pathology. Patients with focal temporal hypometabolism by PET have better outcomes versus those with extratemporal hypometabolism on preoperative FDG-PET which are associated with poorer postsurgical outcomes [5–7]. Patients with unilateral temporal lobe epilepsy, but found to have bilateral temporal hypometabolism on PET, also tend to have poorer postsurgical outcomes [8–10].

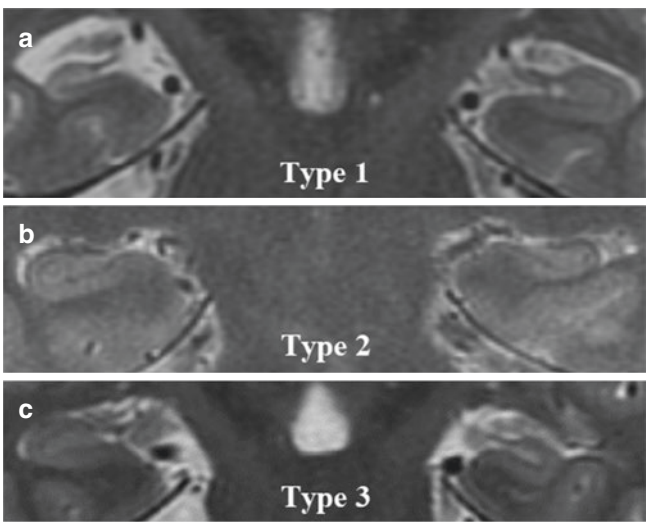

Fig. 43.1 Coronal views demonstrating HS Type 1 (**a**) in the right hippocampus (left side of the image), HS Type 2 (**b**) in the left hippocampus, and HS Type 3 (**c**) also in the left hippocampus. Note the preferential loss of CA1 in HS Type 2

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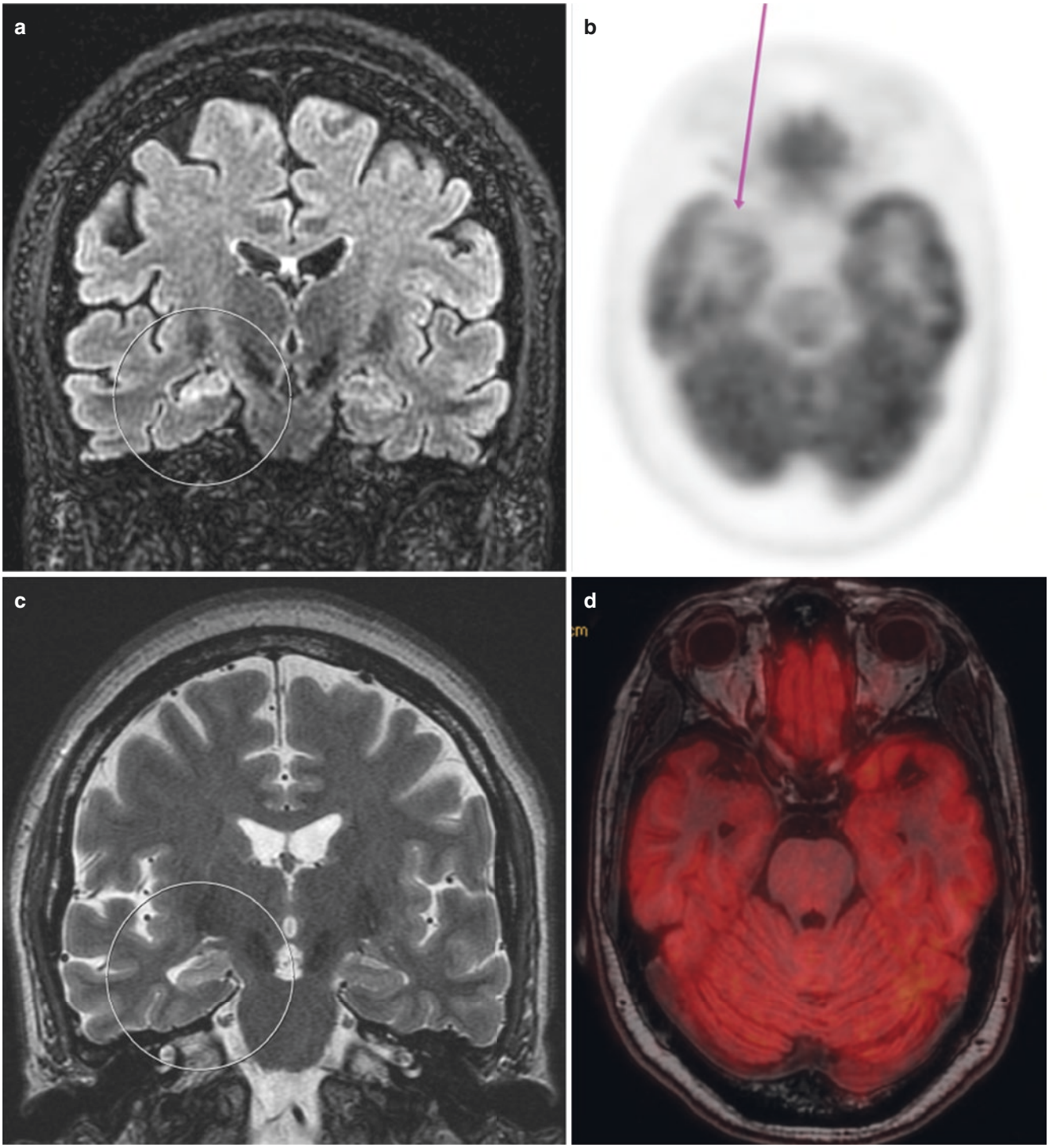

Fig. 43.2 A 41-year-old female with medically refractory seizures. Coronal CUBE FLAIR (**a**) and coronal T2 (**c**) showing right MTS (*circles*). PET/MR images (**b**, **d**) demonstrating localized hypometabolism to the right mesial temporal lobe (*arrow*)

Focal Cortical Dysplasia

Although not truly an acquired cause of seizures in adult patients, FCD may be clinically occult beyond childhood. As seen in pediatric patients, sites of focal cortical dysplasia (FCD) are characterized on MRI as areas of cortical thickening, blurred gray-white matter junction, and increased T2 signal in the subcortical white matter (Figs. 43.3 and 44.1). MRIs are usually abnormal with higher pathologic grades of FCD [11, 12], with FCD Type

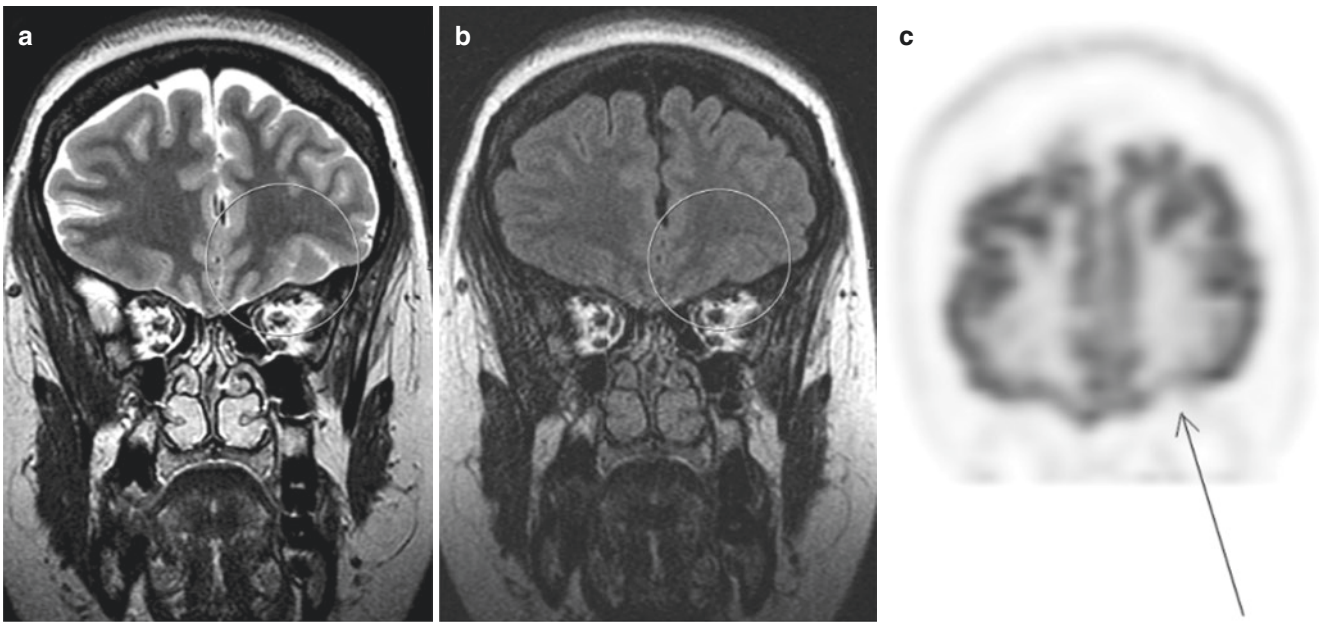

Fig. 43.3 A 30-year-old female with medically refractory epilepsy and prior EEG localizing to the left frontal lobe. Coronal T2 (**a**) and FLAIR (**b**) demonstrate a subtle area of blurring of the gray-white matter junction in the left frontal lobe (*circle*) with associated tiny linear signal abnormality. Coronal PET (**c**) showing corresponding mild hypometabolism in this region (*arrow*). Surgical resection was curative of epilepsy, with pathology revealing FCD Type IIB

II more likely to demonstrate discrete imaging findings as opposed to FCD Type I which may present with a non-lesional MRI.

FDG-PET imaging is especially helpful with epileptogenic localization in patients with non-lesional MRI, with research showing that PET is more sensitive than MRI in patients with mild degrees of cortical dysplasia [13]. A different study also showed that the degree of FDG-PET hypometabolism also correlated with the degree or grading of cortical dysplasia, with FCD type II showing more severe hypometabolism [14]. Additionally, a larger extent of PET hypometabolism beyond the focal lesion on MRI is associated with poorer postsurgical prognosis, possibly indicating a more extensive area of underlying neural network alteration [15].

Encephaloceles

Another potential cause of seizures are focal protrusions of intracranial contents through defects in the overlying dura or skull base, also known as encephaloceles (Fig. 43.4). Potential etiologies of encephaloceles include congenital defects, posttraumatic, iatrogenic, infectious/inflammatory, pseudotumor cerebri, or even neoplastic.

Temporal encephaloceles have been found in 2–4% of patients with medically refractory epilepsy [16, 17], but as high as 12.5% in a more recent study [18]. This rarer and underappreciated cause of epilepsy can be overlooked on initial imaging, but with improved recognition when utilizing isotropic 3D MR imaging or high-resolution thin slice CT imaging through the skull base.

Surgical resection of the epileptogenic encephalocele can prove highly effective or curable in these patients as encephaloceles can contain abnormal brain tissue that is typically gliotic, possibly the source of seizures [19–22]. One study [16] showed that 75% of their epilepsy surgical candidates with temporal encephaloceles demonstrated ipsilateral temporal lobe hypometabolism (Fig. 43.5).

Vascular Malformations

Of the various types of intracranial vascular malformations, arteriovenous malformations and cavernous malformations are the two that are most associated with epilepsy. Various multifactorial mechanisms of epileptogenicity have been proposed, such as blood-brain barrier dysfunction and accumulation of albumin in perilesional astrocytes [23]. In patients with arteriovenous malformations and seizures, it has been shown that there is an associated impaired cerebrovascular reserve in the surrounding brain parenchyma with concomitant venous congestion [24], more so than in patients with arteriovenous malformations without seizures.

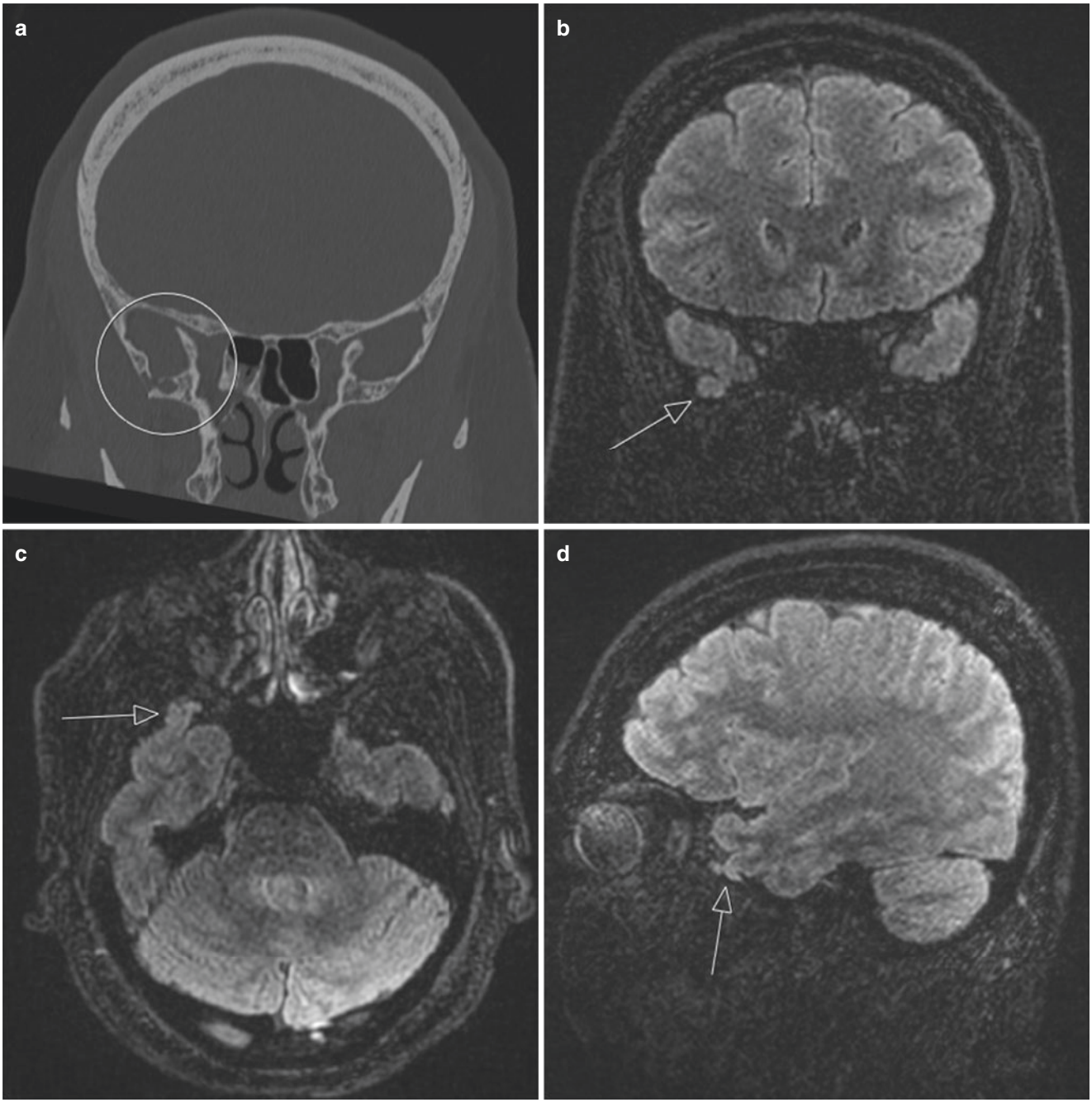

Fig. 43.4 A 49-year-old with a history of medically refractory seizures and bitemporal seizures on EEG. Coronal CT (**a**) shows a clear bony defect at the floor of the right middle cranial fossa (*circle*), with associated bony pitting in the floor of the middle cranial fossa (not shown). Coronal (**b**), axial (**c**), and sagittal (**d**) T2 CUBE FLAIRS showing a small right temporal encephalocele (*arrows*). The patient also had a small left meningocele and additional possible small left meningoencephalocele (not shown)

Between 22.7 and 47% of patients with unruptured arteriovenous malformations demonstrate symptoms consistent with epilepsy [25–27].

Cavernous malformations (Fig. 43.6) are sinusoidal dilated pockets of blood with a thin endothelial layer but without normal intervening parenchyma. Although not intrinsically epileptogenic, the repeated bouts of clinical or subclinical intralesional hemorrhage can lead to chronic hemosiderin deposition and associated gliosis which may be epileptogenic [28–30] (Fig. 43.7).

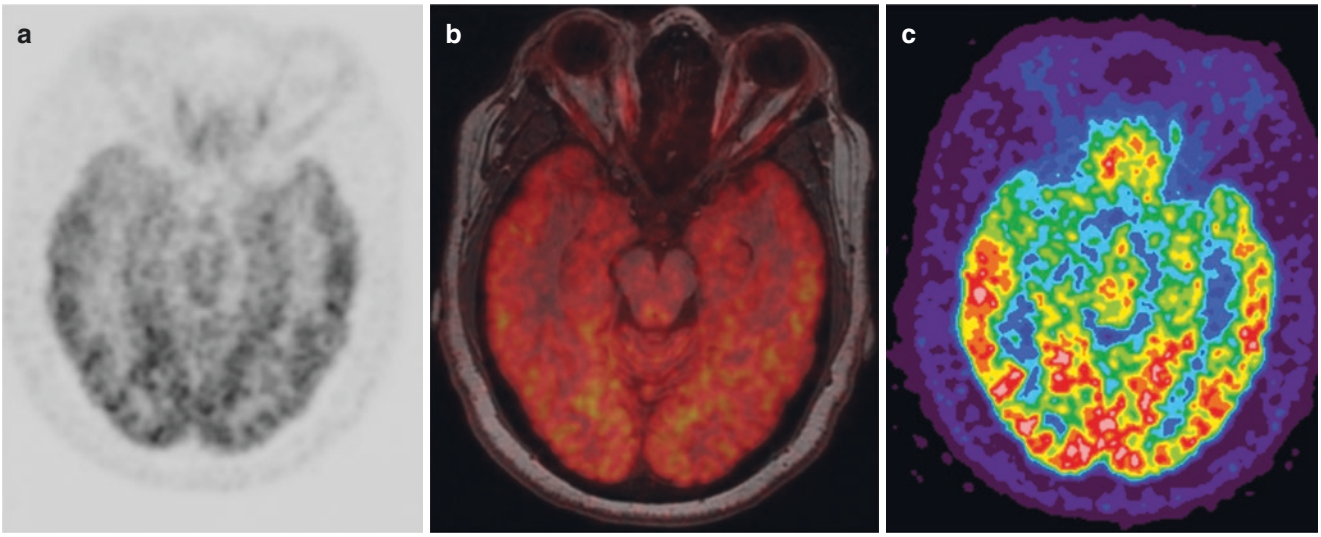

Fig. 43.5 Same patient from the previous figure with encephaloceles (not shown). Axial PET (**a** & **c**) and hybrid PET/MR (**b**) shows mild bitemporal hypometabolism, slightly worse on the right

Limbic Encephalitis

Limbic encephalitis (Fig. 43.8) can be infectious or autoimmune in etiology. In some cases of autoimmune encephalitis, the cause is due to an underlying malignancy, termed paraneoplastic syndrome. Patients with limbic encephalitis may have general psychiatric symptoms, fever, aphasia, memory loss, as well as seizures [31]. Although there are characteristic MRI findings of limbic encephalitis as described below, sometimes MRI may be negative or normal. In these cases, hybrid FDG-PET/MRI can increase the diagnostic confidence of identifying patients with limbic encephalitis, as well as identify more patients with limbic encephalitis as compared to MRI alone [32].

Infectious/Viral (HSV)

Herpetic encephalitis, the most common etiology of viral encephalitis, can present with seizures, often also presenting with fever, altered mental status, and aphasia. Prompt recognition is important as early treatment with acyclovir can prevent serious complications, including death. Clinically, patients with herpetic encephalitis are more likely to present with acute onset of symptoms, including fever, as compared with patients with autoimmune epilepsy [31].

MR imaging findings classically demonstrate edema and T2 hyperintensity involving the insula and temporal lobe diffusely. While this finding can also be seen in cases of other forms of encephalitis, sparing of the basal ganglia is characteristic of herpetic encephalitis.

Autoimmune Epilepsy

Another underrecognized cause of epilepsy in patients is autoimmune epilepsy (AE), a condition in which neurologic autoantibodies cause encephalopathies with associated seizures. This entity should be considered when other more common etiologies of seizures are excluded, as prompt and early immunotherapy treatment may prevent chronic neurologic damage. The exact prevalence of autoimmune epilepsy is still under investigation, but early studies have demonstrated anywhere from 11% to 20% of patients with epilepsy [33, 34].

There are two major groups of neurologic autoantibodies, those attaching to extracellular surface antigens and others attaching to intracellular antigens. Although both may present with varying forms of seizures with or without classically associated limbic encephalitis, it is the extracellular autoantibodies that are more often associated with epilepsy [35]. Examples of antigen targets include the extracellular voltage-gated potassium channel complex (VGKCc), glycine receptor (GlyR), N-methyl-D-aspartate receptor (NMDAR), gamma-aminobutyric acid receptor (GABAR), alpha-amino3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors, and the intracellular protein glutamic acid decarboxylase (GAD) [33, 35].

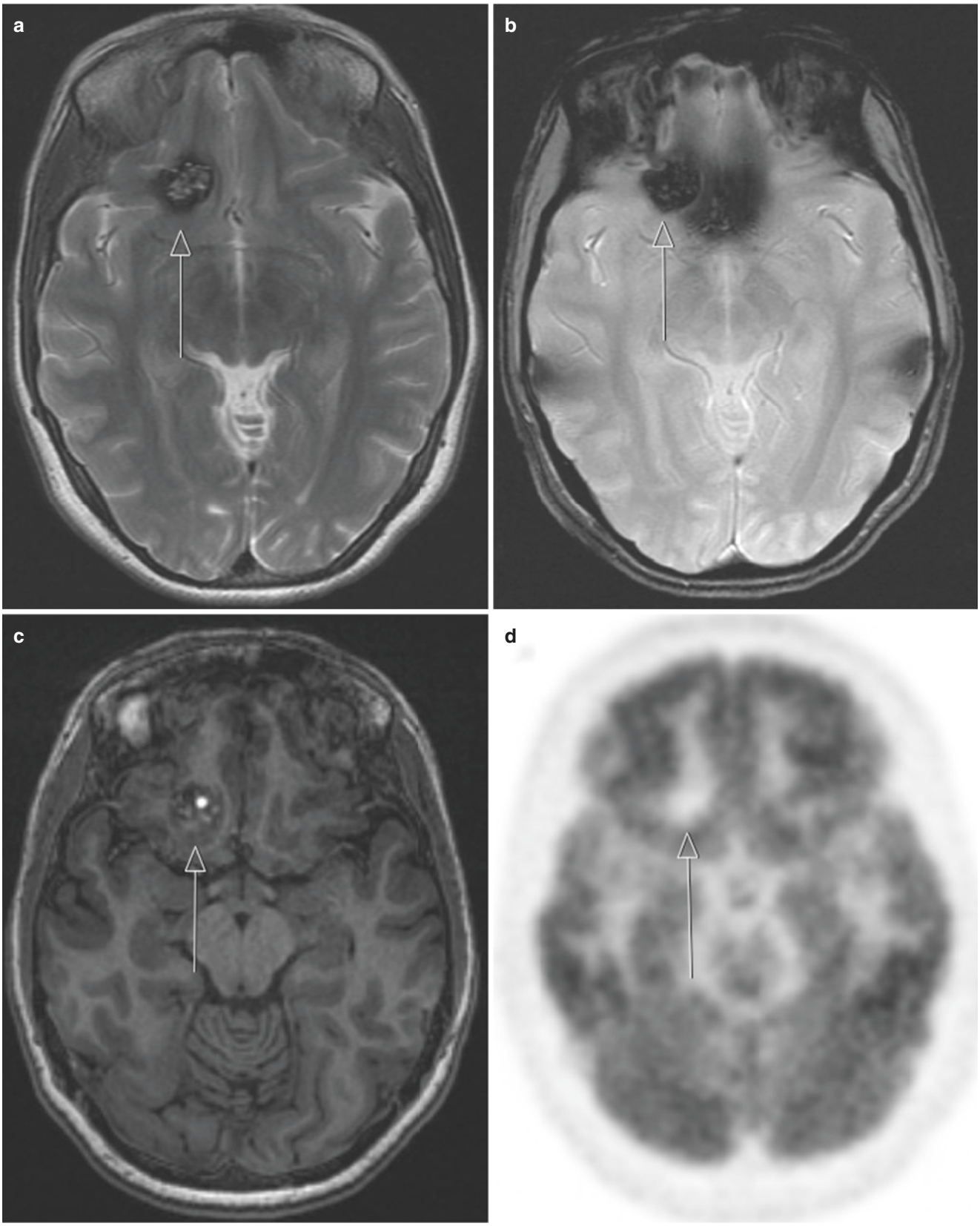

Fig. 43.6 Axial T2 (**a**), GRE (**b**), and T1 (**c**) showing a right orbitofrontal cavernous malformation (*arrow)* which characteristic peripheral hemosiderin staining and internal hemorrhagic blood products of varying age. Concurrent interictal PET (**d**) image showing focal hypometabolism

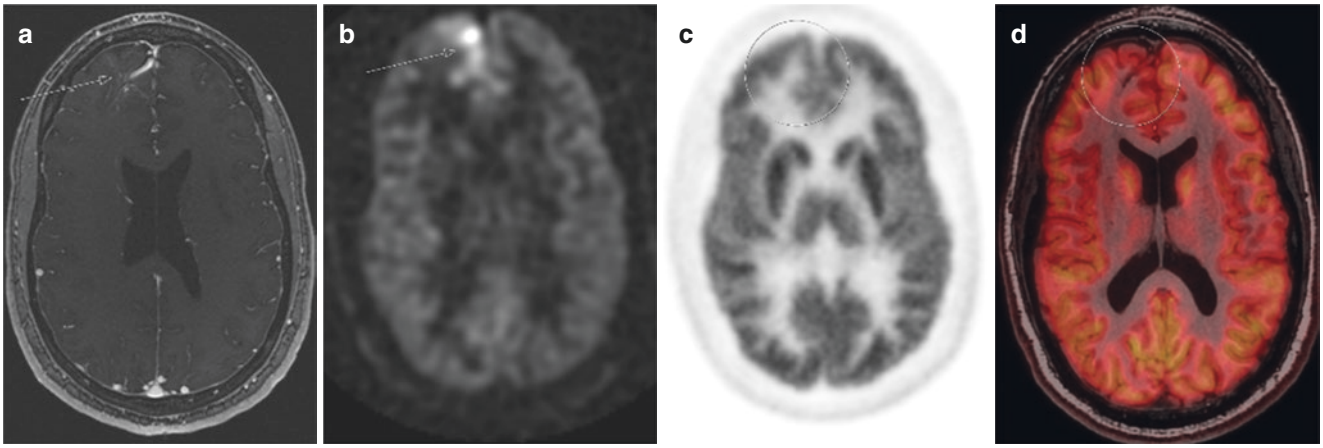

Fig. 43.7 Axial postcontrast (**a**) and ASL (**b**) demonstrating a right frontal venous anomaly with associated shunting (*arrow*), possibly reflecting a transitional venous anomaly. The concurrent PET portion of hybrid PET/MR (**c**, **d**) showing mild relative hypometabolism in the right frontal lobe (*circle*). The patient's EEG (not shown) revealed seizure localization to the right cerebral hemisphere

Anti-NMDAR encephalitis most often presents in young women with ovarian teratomas [36, 37]. Many of these patients have symptoms of psychosis, hallucinations, speech difficulties, and epileptic seizures [36, 38]. Brain MRIs are often normal but when abnormal demonstrate T2 hyperintensity and edema in the mesial temporal lobe. There may also be transient contrast enhancement of the cortex, meninges, or basal ganglia [37, 39]. Like in many of the other autoimmune epilepsy syndromes, there may be focal hypermetabolism in the acute phase. On PET examinations, there may be a characteristic anteroposterior gradient pattern of relative hyper to hypometabolism when comparing the frontotemporal to the (abnormal) parietooccipital lobes (Fig. 43.9) [35, 40–43].

Patients with anti-VGKCc associated autoimmune epilepsy can present with a characteristic seizure semiology of faciobrachial dystonic seizures (FBDS) [44, 45]. Primarily non-paraneoplastic, the antibodies associated with anti-VGKCc autoimmune epilepsy have been further characterized as targeting cell surface proteins LGI-1 (leucine-rich glioma inactivated (1) or CASPR2 (contactin-associated protein (2) associated with the VGKC complex [44]. Although MRI may be normal in these patients, when abnormal the MRI findings include unilateral or bilateral amygdala and/or hippocampal enlargement with abnormal T2 hyperintensity on MRI, similar to other limbic encephalitides [46], as well as possible hyperintensities in the basal ganglia. These patients may also go on to develop mesial temporal sclerosis [46]. In the acute phase, patients with anti-VGKCc with FBDS may demonstrate hypermetabolic activity on FDG-PET (Fig. 43.10) in the basal ganglia and/or in the mesial temporal lobes [45].

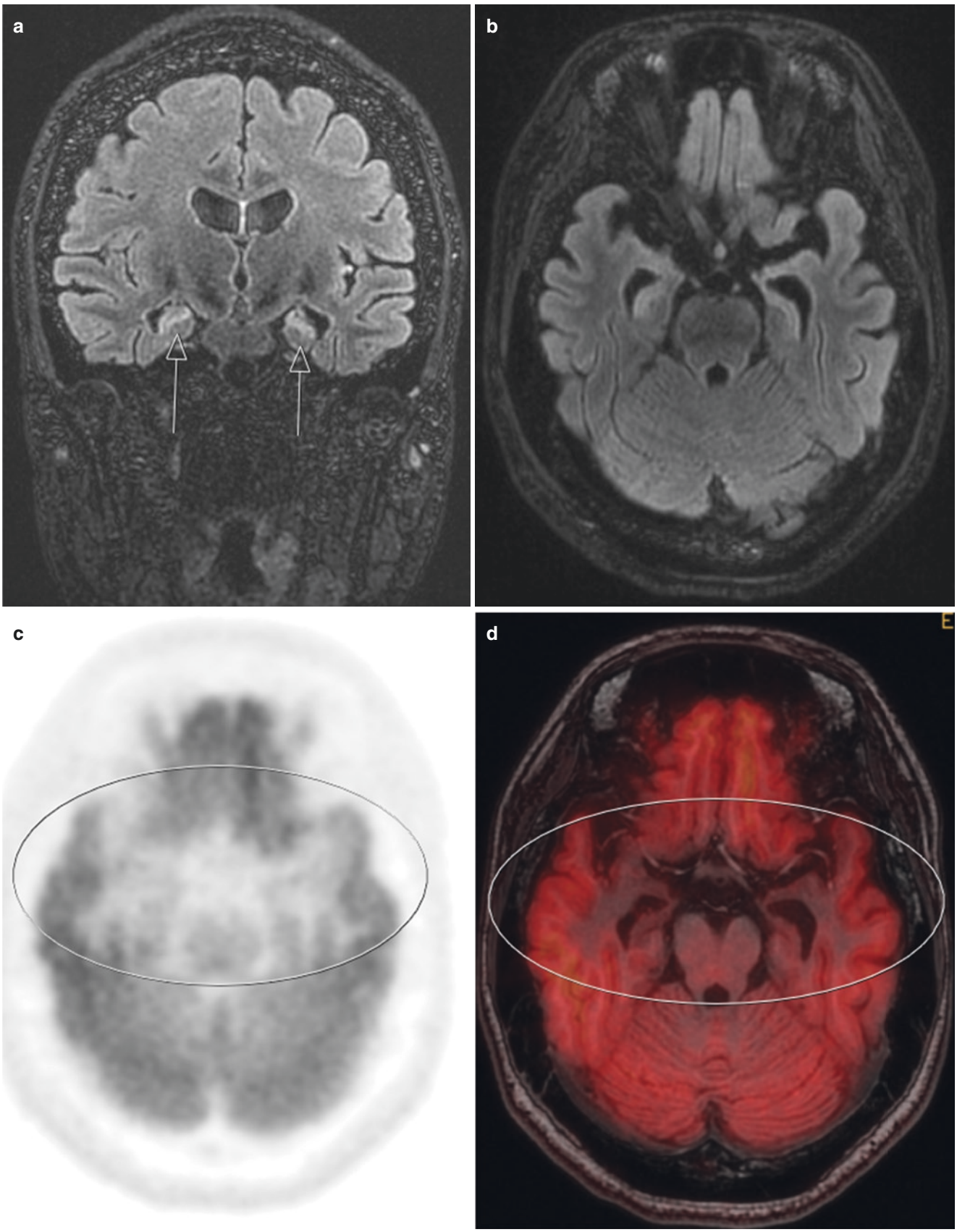

Fig. 43.8 A 23-year-old female with chronic limbic encephalitis. Hybrid PET/MR demonstrating bilateral mesial temporal lobe signal abnormality (*arrows*) and marked atrophy of bilateral amygdala and hippocampi for patient's age on coronal (**a**) and axial (**b**) CUBE FLAIR images. PET portion of the exam (**c**, **d**) demonstrated corresponding decreased FDG uptake in the bilateral mesial temporal lobes (*ellipses*)

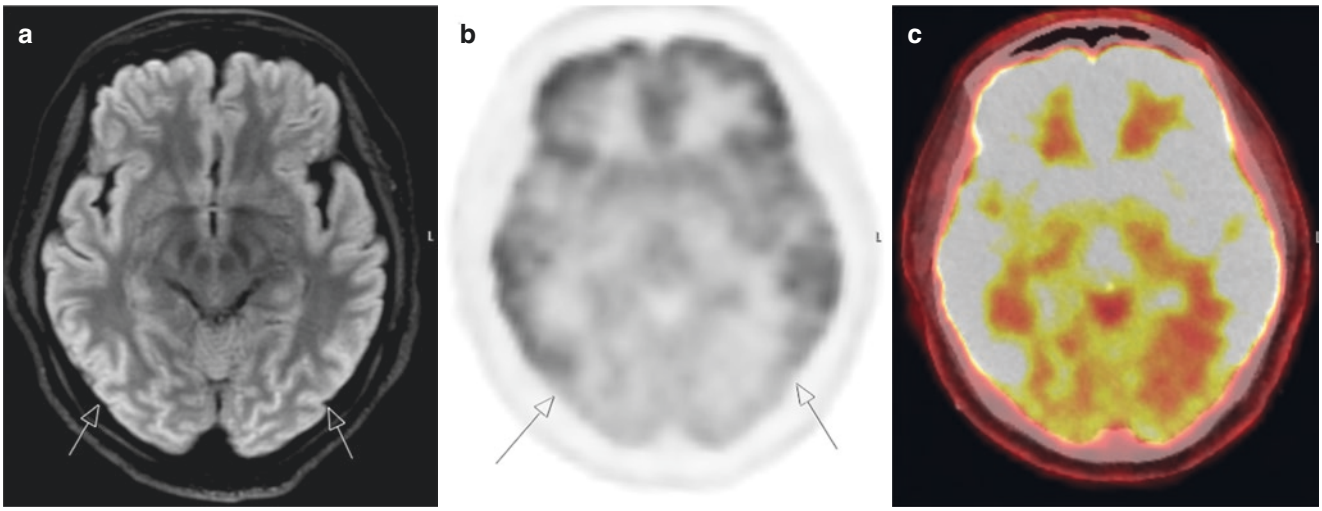

Fig. 43.9 A 43-year-old with confirmed NMDA encephalitis. Axial CUBE FLAIR (**a**) demonstrates increased cortical and leptomeningeal signal in the bilateral posterior occipital lobes (*arrows*). PET/CT (**b**, **c**) shows a characteristic anteroposterior gradient of hyper to hypometabolism when comparing the frontotemporal to parietooccipital lobes

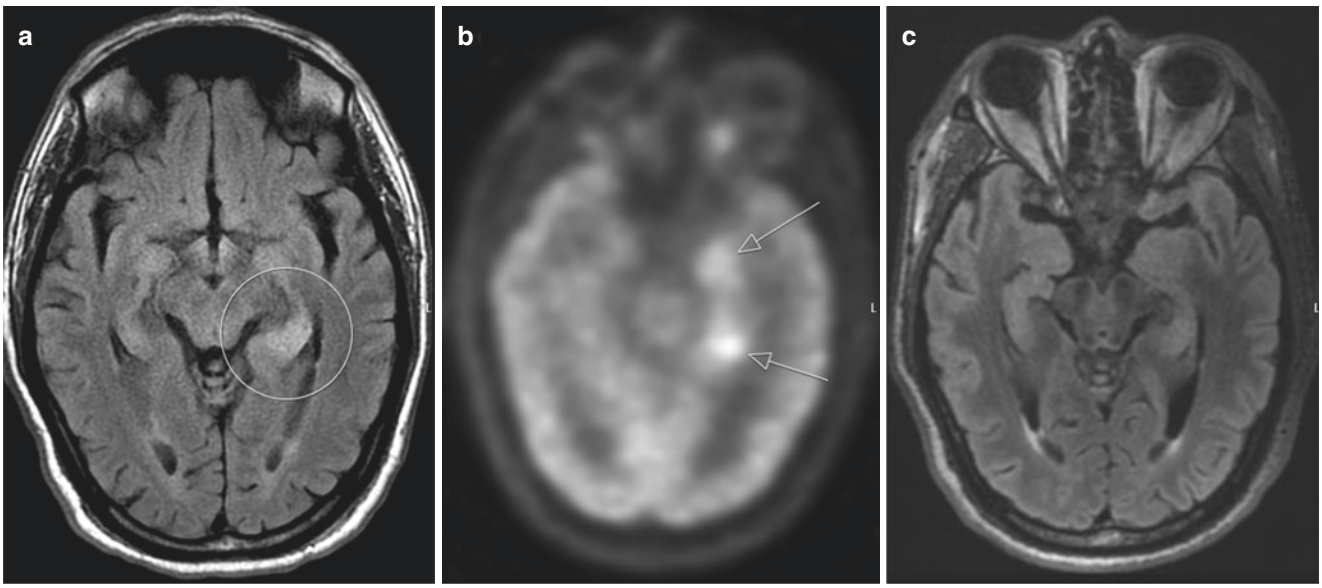

Fig. 43.10 A 66-year-old male with LGI1 encephalitis diagnosed by CSF analysis who presented with active clinical symptoms. Axial T2 FLAIR (**a**) and PET portion of a PET/CT (**b**) performed during initial presentation shows a hyperintense signal abnormality in the left hippocampal body (*circle*) and corresponding increased metabolic activity in the left hippocampal head and body (*arrows*). Axial T2 CUBE FLAIR (**c**) from follow up MRI 2 months later after treatment demonstrating interval resolution of signal abnormality in the left hippocampus

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