7 Herpes Simplex Encephalitis

Gene M. Weinstein, Juan E. Small

INTRODUCTION

Herpes simplex encephalitis (HSE) is the most common cause of fatal sporadic encephalitis worldwide. In adults and older children, most cases of HSE are caused by the herpes simplex virus 1 (HSV-1) virus. Patients initially present with nonspecific neurologic signs, including altered mental status, focal cranial nerve defects, hemiparesis, dysphagia, aphasia, ataxia, and seizures, usually with accompanying fevers.[1] Symptoms of encephalopathy then progress with devastating results; the mortality rate exceeds 70% without treatment, with only 11% of survivors returning to baseline function.[2] Acyclovir has been the mainstay of treatment for HSE, and the estimated mortality reduction is 70% to 28%.[3] The percent of survivors who return to normal function is also higher among acyclovir-treated cohorts.[4] Delayed initiation of acyclovir therapy is directly associated with poorer outcome.[5] Thus early recognition of HSE and aggressive

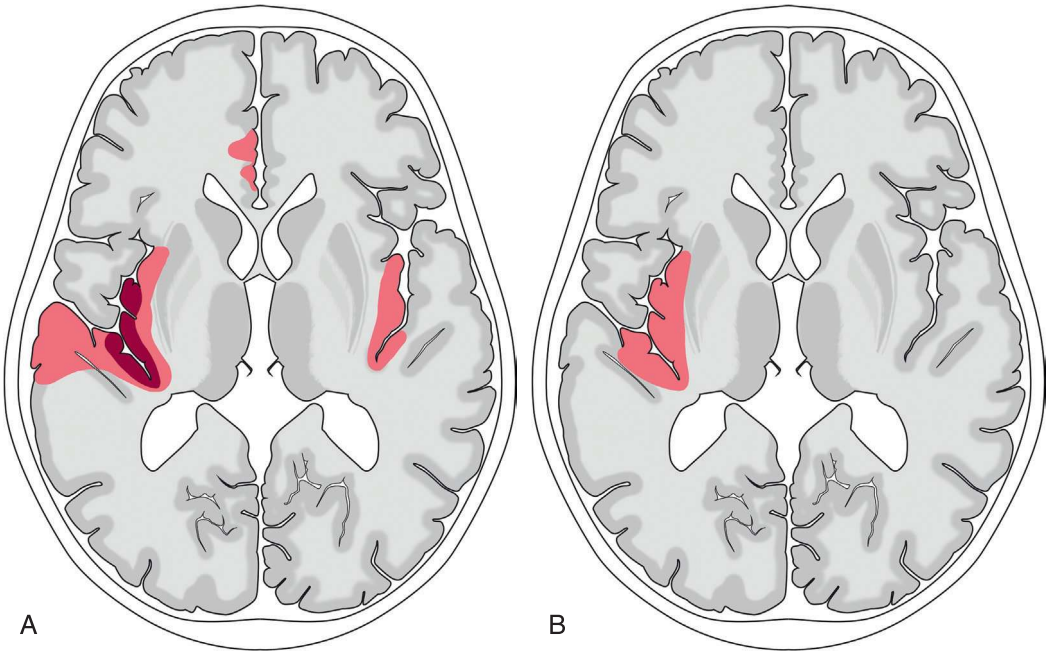

Figure 7.1. Typical MRI features of herpes simplex encephalitis. (A) On presentation there may be unilateral or bilateral asymmetric involvement of limbic system structures, including the temporal lobes, insulae, and cingulate gyri. Restricted diffusion, representing areas of necrosis, is a characteristic feature but not always present. Extensive FLAIR hyperintensity is typically seen. Areas of enhancement or hemorrhage are sometimes seen. (B) Follow-up imaging after several months shows parenchymal volume loss and some residual FLAIR hyperintensity in the regions most severely affected.

empiric treatment with acyclovir is vital to improve morbidity and mortality.

TEMPORAL EVOLUTION: OVERVIEW

The HSV enters the brain via the cranial nerves. Clinical presentation is usually with an acute onset of encephalopathy, with fever being present in almost all cases. Recruitment of local inflammatory responses leads to cytotoxic edema, presenting as restricted diffusion, which is the most apparent imaging finding in the early stage. The initial site of HSE involvement is usually the medial temporal lobes, either unilaterally or bilaterally (in which case it is often asymmetric; Fig. 7.1). HSE has a strong predilection for the limbic system[6] and spreads along these pathways to involve the contralateral medial temporal lobe, anterior temporal lobe, parahippocampal gyrus, amygdala, orbitofrontal gyri, mammillary bodies, insula, and fornix. The thalamus, parietal lobes, and occipital lobes may occasionally also be affected. The basal ganglia and brainstem are characteristically spared.

As the disease progresses the restricted diffusion normalizes and T2/FLAIR signal increases. Hemorrhage and enhancement can be variably present on imaging, but generally do not impact prognosis. However, fulminant hemorrhagic necrosis of the affected areas leads to a high mortality rate. Survivors often have long-term sequela, manifesting as regional parenchymal volume loss and encephalomalacia on follow-up imaging. A small subset of patients has recurrence of symptoms that is felt to be immune mediated.

TEMPORAL EVOLUTION: IN GREATER DEPTH

It is unclear whether HSE is caused by reactivation of a latent HSV-1 infection or if it represents a primary infection. Latent HSV-1 remains in the trigeminal ganglia of asymptomatic patients after the acute illness subsides,[7] and it is postulated that the encephalitis is a result of reactivation of the latent virus.[8] An alternative theory is that HSE is a primary infection in which the virus travels to the brain either through the trigeminal nerves or olfactory tracts. The latter is supported by studies demonstrating that in at least half of cases of HSE the strain of the virus identified is different from the one responsible for herpes labialis in that individual,[9] as well as studies demonstrating that the percent of HSE patients that provide a history of herpes labialis is not higher than in the general population.[10]

Regardless of the timing of inoculation, the most widely accepted theory is that the virus gains access to the central nervous system via the cranial nerves, either through the olfactory or trigeminal nerves. Once the virus breaches the brain parenchyma, it triggers an immune reaction that may itself contribute to cell death and tissue destruction.

Clinically, HSE presents with nonspecific neurologic findings of an acute (<1 week) duration.[11] Neurologic findings include hemiparesis, dysphagia, aphasia, ataxia, or focal seizures. Fever is the most discriminating finding, present in 90% of patients.[12] Patients often have a prodromal syndrome of upper respiratory tract infection.[13]

Although head CT examination is often obtained in the setting of encephalopathy, in most patients, no abnormality is detected in the first 4 to 6 days of disease.[14] MR is much more sensitive than CT, especially early in the disease course. HSE leads to early development of cytotoxicity, and diffusion-weighted imaging is therefore sensitive in the acute and subacute phase of the disease.[15] In the early disease phase, DWI increases the conspicuity of lesions identified on CT and demonstrates many more areas of signal abnormality in regions that appear normal on CT.

DWI remains the most sensitive sequence for detection of HSE until approximately 2 weeks of disease duration, at which point FLAIR shows more pronounced signal abnormality (Figs. 7.2–7.4). Hemorrhage, both of the large intraparenchymal and petechial variety, is present in less than half of cases.[16] Contrast-enhancement can be seen on CT and MR but is less frequent than

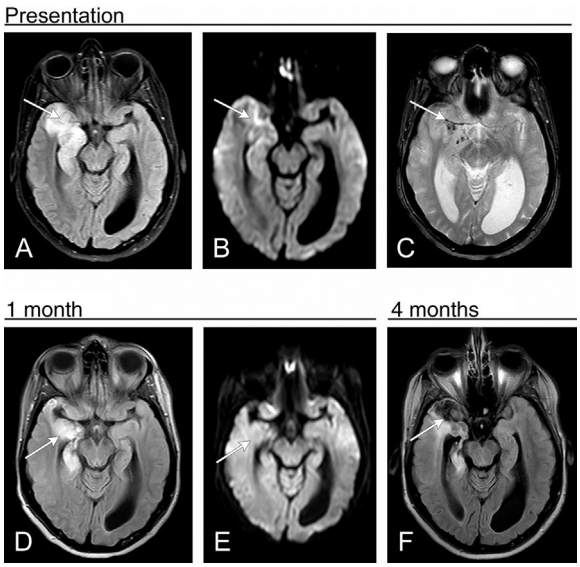

Figure 7.2. Herpes simplex encephalitis, unilateral. (A) FLAIR sequence shows extensive signal abnormality in the right anterior and medial temporal lobe. (B) DWI shows minimal restricted diffusion in the right anterior temporal lobe. (C) Gradient echo (GRE) sequence shows scattered foci of hemorrhage in the right temporal lobe. (D) Follow-up imaging at 1 month shows residual FLAIR hyperintensity with volume loss of the right anterior temporal lobe, with no restricted diffusion on DWI (E). Although the patient had hemorrhage on initial imaging, the small amount of restricted diffusion and rapid initiation of antiviral treatment resulted in a favorable outcome. However, as is often seen even in cases of favorable outcome, follow-up FLAIR sequence at 4 months (F) shows progressive volume loss in the right temporal lobe with cystic change.

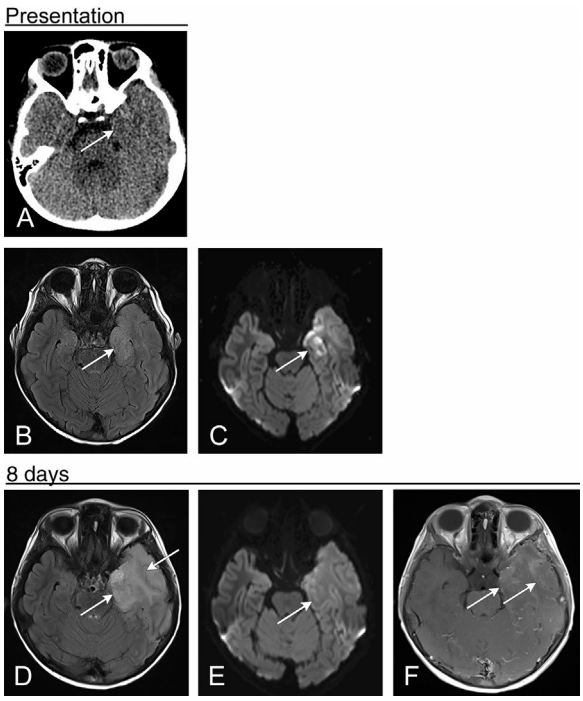

Figure 7.3. Herpes simplex encephalitis with masslike appearance. (A) Noncontrast CT in this 15-year-old immunocompromised patient presenting with encephalopathy shows no abnormality in the left temporal lobe. (B) A FLAIR image performed the same day shows increased signal in the medial left temporal lobe. (C) DWI shows foci of restricted diffusion in the left temporal lobe. (D to F) Follow-up MRI 8 days later shows markedly increased FLAIR hyperintensity (D), with resolution of previously seen restricted diffusion (E). There is associated gyriform cortical enhancement on the postcontrast T1-weighted image (F), typical of herpes simplex virus encephalitis.

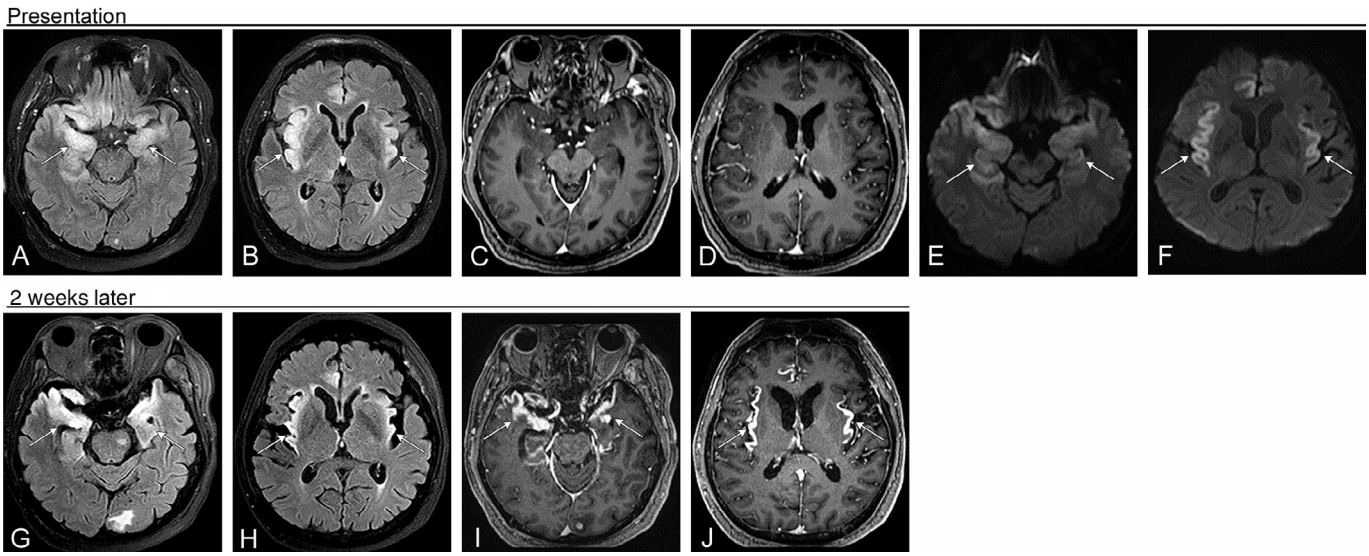

Figure 7.4. Bilateral herpes simplex encephalitis. Elderly female with history of metastatic lung cancer and known brain metastasis presents with mental status change and seizures. (A and B) FLAIR sequences show bilateral but asymmetric signal in both anterior and medial temporal lobes, both frontal lobes (bilateral orbitofrontal cortex and right gyrus rectus) and both cingulate gyri. There is no associated enhancement (C and D). (E and F) DWI sequences show restricted diffusion in the areas of abnormal FLAIR signal, confined to the cortex. Two weeks later, FLAIR signal persists (G and H). (I and J) However, there is now intense cortical enhancement corresponding to the areas of FLAIR hyperintensity. Signal abnormality in the left occipital lobe and left pons is secondary to treated metastatic disease.

FLAIR hyperintensity or restricted diffusion.[17,18] Of all MR imaging findings in the acute stage, the only one that is predictive of disease morbidity is restricted diffusion. The presence of hemorrhage or contrast enhancement does not portend a worse prognosis.[17]

Several months after primary infection there is encephalomalacia in the affected brain, with parenchymal volume loss, frequent cystic changes, and ex vacuo dilatation of the ventricles.[19,20] FDG-PET imaging performed up to months after presentation shows FDG avidity of the affected cortex.[21] Progressive diffuse brain atrophy is a frequent finding of HSE, seen even in patients with resolving neurologic deficits.[22]

ATYPICAL PRESENTATIONS

Typically, acute HSE infection follows a monophasic course. However, more than 10% of patients have a relapse of symptoms, termed post-HSE.[23] Unlike primary HSE, post-HSE is felt to be immune mediated, possibly due to antibodies to the N-methyl-D-aspartate (NMDA) receptor. Contrast enhancement is seen much more commonly in post-HSE.

HSE typically presents with bilateral asymmetric involvement of limbic system structures, with the temporal lobes and orbitofrontal gyri being the most commonly affected sites.[10] Rarely the thalami, parietal lobes, and occipital lobes are affected. In addition, some patients exhibit purely extratemporal involvement.[24]

DIFFERENTIAL DIAGNOSIS

Acute Cerebral Ischemia-Infarction

Acute infarct can have a similar appearance to HSE because both may present with restricted diffusion that progresses to FLAIR hyperintensity (Fig. 7.5). However, the clinical presentation of acute infarct is hyperacute, whereas HSE presents over several days. Furthermore, the symptoms of encephalitis, especially fever and seizure, are not typically seen in acute infarct. In addition, as HSE progresses it spreads to the contralateral side and other vascular territories, whereas infarction frequently is restricted to one vascular territory.

Limbic Encephalitis

Limbic encephalitis is an autoimmune inflammatory condition that affects the limbic system. It can be seen as a paraneoplastic process or in the absence of underlying malignancy. Imaging features are often similar to HSE, with increased FLAIR signal in the mesial temporal lobes and other areas of the limbic system.[25] Bilateral temporal lobe involvement is more common with limbic encephalitis (Fig. 7.6),[26] whereas hemorrhage and restricted diffusion are more common with HSE. Symptom onset is typically slower than with HSE, progressing over weeks to months rather than days.

Human Herpesvirus 6 Encephalitis

Human herpesvirus 6 (HHV-6) is common, with more than 90% of the human population being seropositive by age 2.[25] Unlike HSV, HHE-6 encephalitis almost always occurs in immunocompromised patients, usually in those undergoing transplantation. The presentation is similar to HSV, with change in mental status, short-term memory loss, and seizures being the most common symptoms. Imaging findings also overlap with HSV (Fig. 7.7). However, HHV-6 encephalitis is more likely to have a normal initial CT, and hemorrhage and extratemporal involvement are less common than in HSV.

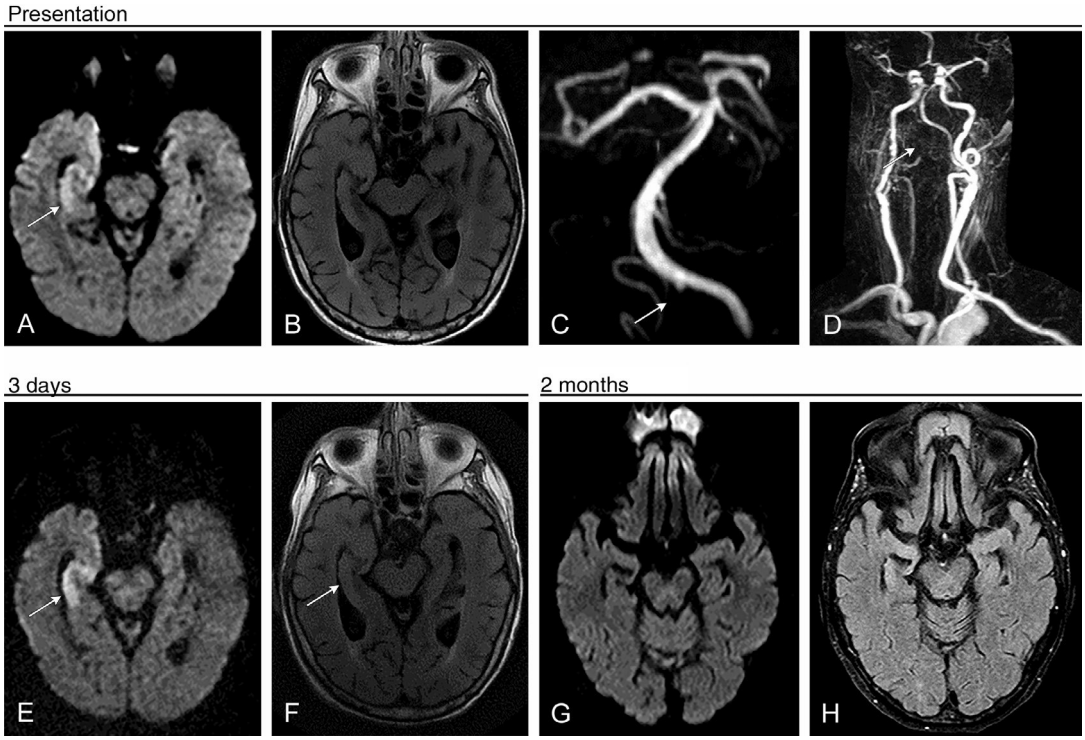

Figure 7.5. Hippocampal infarction in the setting of vertebral artery dissection. Elderly female presented with acute left sided weakness. Initial DWI (A) showed restricted diffusion in the right mesial temporal lobe *(arrow)*. Initial FLAIR image is normal (B). MRA shows loss of flow-related enhancement in the intradural right vertebral artery (C and D), consistent with dissection. Follow-up imaging in 3 days shows persistent restricted diffusion (E), with increased FLAIR signal (F). There was not associated enhancement or hemorrhage. Two months later, there is resolution of restricted diffusion (G), persistent FLAIR hyperintensity, and (H) volume loss in the region of the hippocampus.

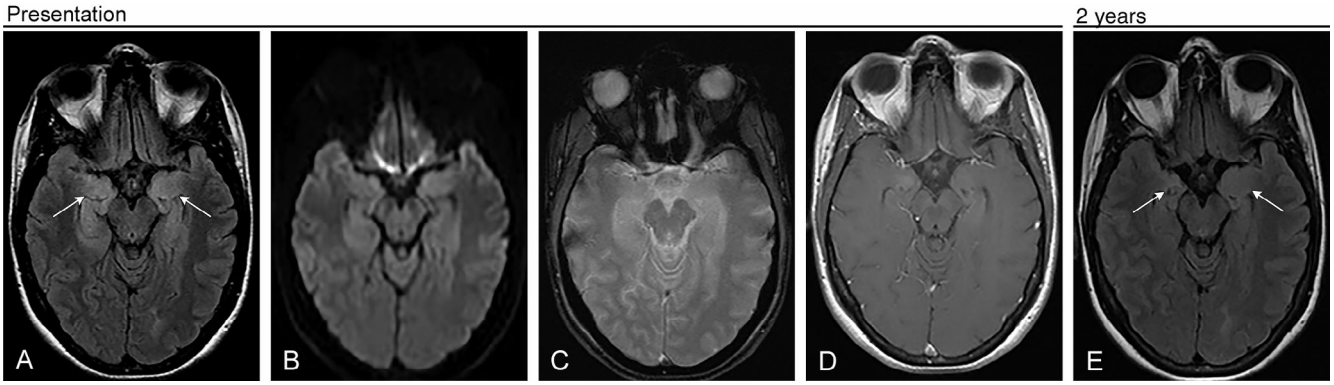

Figure 7.6. Limbic encephalitis. A 29-year-old female presented with several months of hallucinations, seizures, hypersomnolence, and amnesia. (A) FLAIR sequence shows increased signal in both mesial temporal lobes. DWI (B), gradient echo (C), and postcontrast T1-weighted images (D) show no restricted diffusion, hemorrhage, or enhancement. CSF was positive for voltage-gated potassium channel antibodies, and a diagnosis of voltage-gated potassium channel antibody–induced limbic encephalitis was made. Follow-up FLAIR sequence performed 2 years later (E) shows minimal residual FLAIR hyperintensity in the mesial temporal lobes without associated volume loss.

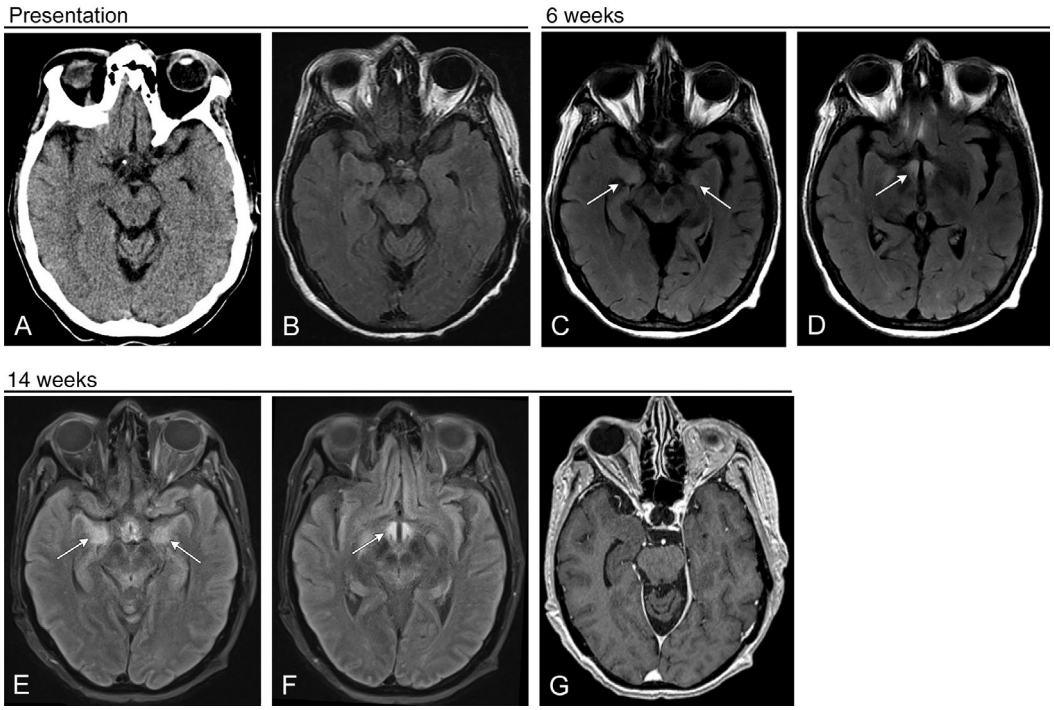

Figure 7.7. Herpes simplex virus 6 (HHV-6) encephalitis. A 58-year-old female with history of bone marrow transplant presents with recurrent episodes of altered mental status. Initial CT (A) and MRI (B; FLAIR) show no abnormality. Follow-up MRI performed 6 weeks later shows FLAIR hyperintensity in the hippocampi (C) and hypothalamus (D). There was no corresponding restricted diffusion or enhancement (not shown). Follow-up MRI performed 8 weeks later shows increasing FLAIR hyperintensity in the hippocampi (E) and hypothalamus (F). Parenchymal volume is preserved. Postcontrast T1-weighted image shows no abnormal enhancement (G). At this time, cerebrospinal fluid sample was obtained and was positive for HHV-6.

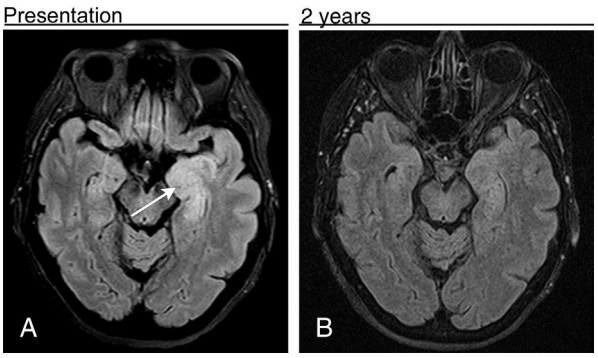

Figure 7.8. Transient temporal lobe postictal changes. Adult female with history of metastatic breast and endometrial carcinoma presenting with seizures. Nonenhancing FLAIR hyperintense signal abnormality is seen within the medial left temporal lobe at the time of presentation (A; *arrow*). Complete interval resolution of left temporal lobe signal abnormality is noted 2 years later (B). In light of resolution of imaging findings, as well as the documented normal EEG, normal spinal fluid, and normal paraneoplastic screen, these findings most likely represent resolution of transient postictal edema.

Postictal Changes

Transient MR signal changes have been reported in patients in the postictal state.[27] These changes are thought to be due to vasogenic and/or cytotoxic edema or altered perfusion patterns and consequently manifest as T2/FLAIR hyperintense signal that is sometimes associated with restricted diffusion and enhancement. When presenting in the hippocampus, these changes may mimic of the appearance of HSE (Fig. 7.8). However, unlike HSE, they commonly resolve within weeks to months.

REFERENCES

1. Baringer JR. Herpes simplex infections of the nervous system. *Neurol Clin*. 2008;26:657–674, viii.
2. Whitley RJ, Lakeman F. Herpes simplex virus infections of the central nervous system: therapeutic and diagnostic considerations. *Clin Infect Dis*. 1995;20:414–420.
3. Whitley RJ, Alford CA, Hirsch MS, et al. Vidarabine versus acyclovir therapy in herpes simplex encephalitis. *N Engl J Med*. 1986;314:144–149.
4. Skoldenberg B, Forsgren M, Alestig K, et al. Acyclovir versus vidarabine in herpes simplex encephalitis. Randomised multicentre study in consecutive Swedish patients. *Lancet*. 1984;2:707–711.
5. Raschilas F, Wolff M, Delatour F, et al. Outcome of and prognostic factors for herpes simplex encephalitis in adult patients: results of a multicenter study. *Clin Infect Dis*. 2002;35:254–260.
6. Kapur N, Barker S, Burrows EH, et al. Herpes simplex encephalitis: long term magnetic resonance imaging and neuropsychological profile. *J Neurol Neurosurg Psychiatry*. 1994;57:1334–1342.
7. Steiner I, Spivack JG, O'Boyle DR 2nd, et al. Latent herpes simplex virus type 1 transcription in human trigeminal ganglia. *J Virol*. 1988;62:3493–3496.
8. Davis LE, Johnson RT. An explanation for the localization of herpes simplex encephalitis? *Ann Neurol*. 1979;5:2–5.
9. Whitley R, Lakeman AD, Nahmias A, et al. DNA restriction-enzyme analysis of herpes simplex virus isolates obtained from patients with encephalitis. *N Engl J Med*. 1982;307:1060–1062.
10. Steiner I, Benninger F. Update on herpes virus infections of the nervous system. *Curr Neurol Neurosci Rep*. 2013;13:414-013-0414-8.
11. Levitz RE. Herpes simplex encephalitis: a review. *Heart Lung*. 1998;27:209–212.
12. Whitley RJ, Soong SJ, Linneman C Jr, et al. Herpes simplex encephalitis. Clinical Assessment. *JAMA*. 1982;247:317–320.
13. Steiner I. Herpes simplex virus encephalitis: new infection or reactivation? *Curr Opin Neurol*. 2011;24:268–274.
14. Dutt MK. Computed tomography and EEG in herpes simplex encephalitis. *Arch Neurol*. 1982;39:99.
15. Sawlani V. Diffusion-weighted imaging and apparent diffusion coefficient evaluation of herpes simplex encephalitis and Japanese encephalitis. *J Neurol Sci*. 2009;287:221–226.
16. Rodríguez-Sainz A, Escalza-Cortina I, Guio-Carrión L, et al. Intracerebral hematoma complicating herpes simplex encephalitis. *Clin Neurol Neurosurg*. 2013;115:2041–2045.
17. Singh TD, Fugate JE, Hocker S, et al. Predictors of outcome in HSV encephalitis. *J Neurol*. 2016;263:277–289.
18. Weisberg LA, Greenberg J, Stazio A. Computed tomographic findings in acute viral encephalitis in adults with emphasis on herpes simplex encephalitis. *Comput Med Imaging Graph*. 1988;12:385–392.
19. Lee JW, Kim IO, Kim WS, et al. Herpes simplex encephalitis: MRI findings in two cases confirmed by polymerase chain reaction assay. *Pediatr Radiol*. 2001;31:619.
20. Soto-Hernandez JL. Follow-up in herpes simplex virus encephalitis. *Clin Infect Dis*. 2000;31:206–207.
21. Wong KK, Tolia B, Bohnen N. Chronic sequelae of herpes simplex encephalitis demonstrated on interictal F-18 FDG PET/CT. *Clin Nucl Med*. 2008;33:443.
22. Soto-Hernandez JL. Follow-up in herpes simplex virus encephalitis. *Clin Infect Dis*. 2000;31:206–207.
23. Sköldenberg B, Aurelius E, Hjalmarsson A, et al. Incidence and pathogenesis of clinical relapse after herpes simplex encephalitis in adults. *J Neurol*. 2005; 2006;253:163–170.
24. Wasay M, Mekan SF, Khelaeni B, et al. Extra temporal involvement in herpes simplex encephalitis. *Eur J Neurol*. 2005;12:475–479.
25. Eran A, Hodes A, Izbudak I. Bilateral temporal lobe disease: looking beyond herpes encephalitis. *Insights Imaging*. 2016;7:265–274.
26. Lawn ND, Westmoreland BF, Kiely MJ, et al. Clinical, magnetic resonance imaging, and electroencephalographic findings in paraneoplastic limbic encephalitis. *Mayo Clin Proc*. 2003;78:1363–1368.
27. Kim J, Chung J, Toon P, et al. Transient MR signal changes in patients with generalized tonicoclonic seizure or status epilepticus: periictal diffusion-weighted imaging. *AJNR Am J Neuroradiol*. 2001;22:1149–1160.