

Acute Viral Encephalitis Neuroimaging Spectrum

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ABSTRACT

Acute viral encephalitis involves inflammation of the brain caused by multiple different viruses, with CT of the head and MR imaging of the brain involved in the initial diagnostic work-up. Although viral encephalitis may have nonspecific findings on neuroimaging, some imaging patterns have been identified in viral subtypes on MR imaging. The most common cause of encephalitis is herpes simplex virus, with the typical imaging features demonstrating unilateral medial temporal lobe signal abnormalities. Bilateral temporal lobe, cerebellum, and brain stem signal abnormalities are seen in herpes simplex virus 2, with associated edema, necrosis, and hemorrhage. Signal abnormalities are commonly seen in the bilateral basal ganglia, thalami, and mesial temporal lobes in West Nile virus encephalitis. HIV encephalitis is associated with symmetric signal abnormality in the periventricular and deep white matter, which can be differentiated from progressive multifocal leukoencephalopathy by asymmetric U-fiber involvement. The purpose of this article is to present imaging findings associated with typical and atypical cases of viral encephalitis to guide diagnosis, promote early intervention, and improve clinical outcomes.

Learning Objective: Identify unique radiologic findings associated with different types of viral encephalitis to guide diagnosis and improve clinical outcomes.

INTRODUCTION

Acute viral encephalitis involves inflammation of the brain secondary to viral infection, with spread of infection via a hematogenous or neural route. Patients typically present with altered mental status, fever, headache, seizures, and neurologic deficits. Acute viral encephalitis affects approximately 3.5–7.5 of 100,000 people per year.¹ The most common viral etiology of encephalitis is herpes simplex virus (HSV), which is identified in 50%–75% of cases and includes HSV type 1 (HSV-1)

and HSV type 2 (HSV-2).² There are approximately 15 families of viruses and over 100 viruses responsible for encephalitis.³ Other common viral etiologies of encephalitis include varicella zoster virus (VZV), cytomegalovirus (CMV), enterovirus, influenza, HIV, John Cunningham (JC) virus, West Nile virus (WNV), and a variety of arboviruses.

Viral subtypes of encephalitis are associated with certain patient demographics. For example, HSV-1 primarily affects adults, whereas HSV-2 mainly affects

ABBREVIATION KEY

CMV = cytomegalovirus
 HSV = herpes simplex virus
 HSV-1 = HSV type 1
 HSV-2 = HSV type 2
 PCR = polymerase chain reaction
 PML = progressive multifocal leukoencephalopathy
 VZV = varicella zoster virus
 WNV = West Nile virus
 JC Virus = John Cunningham virus

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children. Patients with HIV are at risk for HIV encephalitis, whereas patients who are immunocompromised are at a higher risk for progressive multifocal leukoencephalopathy (PML) via JC virus reactivation. Patients who are immunocompromised, patients with a Glasgow Coma Scale score of ≤ 8 , patients with an initial intensive care unit admission, and patients greater than 65 years old have a poor prognosis when diagnosed with viral encephalitis.²

The initial diagnostic evaluation after a thorough history and physical examination includes imaging of the brain. MR imaging is more specific for identifying neuroimaging findings compared with a CT of the head. Diagnosis is confirmed with polymerase chain reaction (PCR) and cultures of CSF from a lumbar puncture, which may not be readily available due to the length of time required to process the laboratory results. Patients suspected of viral encephalitis should be promptly treated due to its high morbidity and mortality. Management of acute viral encephalitis can vary and typically depends on the etiology. Specific antiviral medications are administered depending on the viral etiology. Acyclovir is often empirically administered when viral encephalitis is suspected and laboratory results are pending. Glucocorticoids have also shown some benefit in treating viral encephalitis.² The ultimate goal in management is supportive care, including prevention of cerebral edema and seizures. This article presents imaging features for select common and uncommon causes of viral encephalitis that have unique imaging findings to guide diagnosis, promote early intervention, and improve clinical outcomes.

NEUROIMAGING IN ACUTE VIRAL ENCEPHALITIS

Although MR imaging provides more detailed information in comparison with CT, CT is typically first-line in diagnostic imaging. A CT of the head is imperative in highlighting findings that may be a contraindication to lumbar puncture, such as a space-occupying lesion with mass effect or herniation. Diagnostic imaging may also provide additional information that can rule out other pathologies, such as hemorrhage or infarct. Nonspecific findings, such as poorly defined and patchy abnormal T2 and FLAIR signal in the gray matter and white matter, may be seen on MR imaging.

Although viral encephalitis may have nonspecific findings on neuroimaging, some specific anatomic sites of involvement have been identified in viral subtypes on MR imaging. In HSV-1, the classic site of involvement is the medial temporal lobe, with additional signal abnormalities seen in the insular cortex, cingulate cortex, and frontobasal cortex. In comparison, HSV-2 involves the bilateral temporal lobes, cerebellum, and brain stem. Abnormalities of the bilateral basal ganglia, thalami, and mesial temporal lobes are seen in WNV encephalitis. HIV encephalitis typically involves the periventricular and deep white matter, predominantly in the frontal lobe and genu of the corpus callosum in comparison with PML, which also involves these anatomic regions, with additional involvement of the U-fibers. Other types of viral

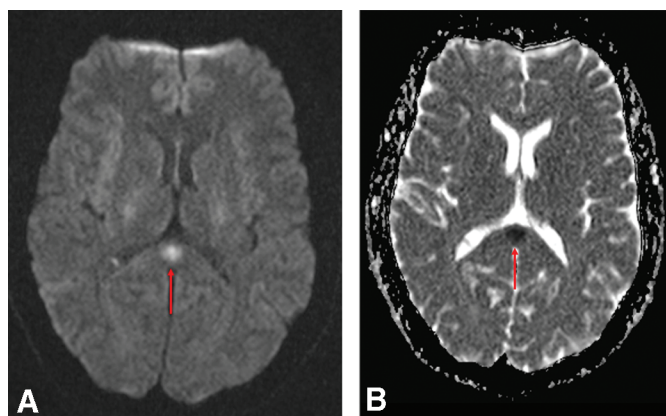


FIG 1. Cytotoxic lesion of the corpus callosum (CLOCC) in WNV encephalitis. A 44-year-old man with fever for 2–3 days and intermittent headache. A and B, An axial DWI and an ADC image demonstrate diffusion restriction of the splenium of the corpus callosum (red arrows). This is a nonspecific finding in viral encephalitis and can be seen in different conditions.

encephalitis, such as influenza, VZV, and CMV encephalitis, have a less specific region of anatomic involvement.

An imaging finding seen in many viral subtypes is the involvement of the corpus callosum, referred to as a cytotoxic lesion of the corpus callosum. This is caused by inflammatory cells that cause cytotoxic edema, which can be visualized on MR imaging as an area of diffusion restriction, typically in the splenium of the corpus callosum (Fig 1).⁴ Cases of cytotoxic lesions of the corpus callosum have been reported with viral encephalitis. However, other inflammatory pathologies, such as malignancy, drugs, toxins, and metabolic derangements, may also present as a cytotoxic lesion of the corpus callosum, which makes it nonspecific to viral encephalitis.

Although there are many viral etiologies of encephalitis, there are nonspecific imaging findings seen with different viral subtypes that are not discussed in this article. Nonspecific imaging findings are associated with cerebral edema, necrosis, and hemorrhage. Frontal and temporal lobe lesions are more commonly identified in cases of encephalitis, whereas lesions in the brain stem and basal ganglia are less commonly identified.⁵ T2 as well as FLAIR imaging sequences have been most beneficial in identifying encephalitis lesions.⁵

HSV

The most common cause of viral encephalitis is HSV, which encompasses HSV-1 and HSV-2. HSV-1 accounts for 95% of cases, which mainly affect adults and is rare in the pediatric population.⁶ The virus infects the oronasopharynx via secretions and remains dormant in the trigeminal nerve ganglion. It reactivates with immunosuppression, emotional stress, and trauma. Common presentations are fever, headache, seizure, altered mental status, and, less likely, neurologic deficits. The fatality rate associated with this virus is 10%–20%, even with treatment.⁷

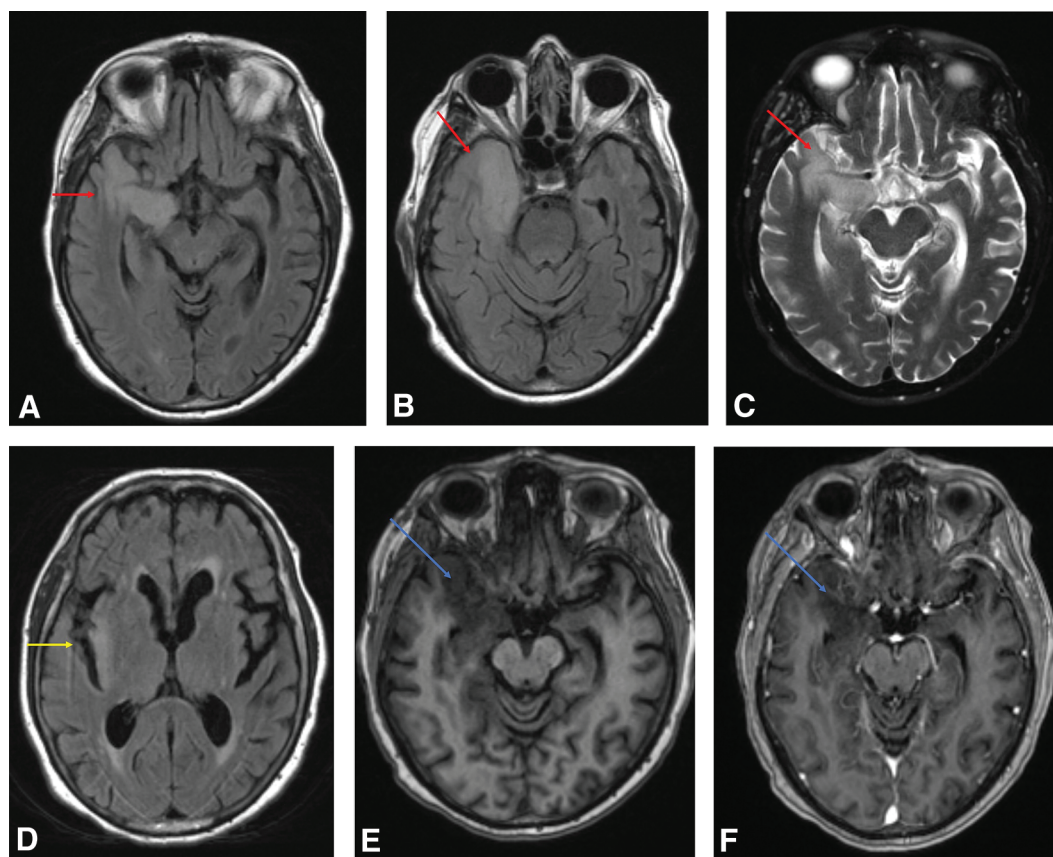


FIG 2. HSV-1. An 82-year-old woman with altered mental status. **A and B,** Axial FLAIR, and **C,** Axial T2 images demonstrate increased signal in the right medial temporal lobe (*red arrows*). **D,** An axial FLAIR image demonstrates increased signal in the right insular cortex (*yellow arrow*), sparing the lentiform nucleus; increased signal is unilateral, with unremarkable appearance of the left temporal lobe and insular cortex. **E and F,** Axial T1 pre- and post-contrast images demonstrate no pathologic enhancement in the area of T2/FLAIR signal abnormality in the right medial temporal lobe (*blue arrows*).

There is a high risk of sequelae, with neurologic involvement and a poor prognosis in the elderly and very young. The diagnosis is suggested by CSF that contains elevated levels of lymphocytes and protein and is confirmed by PCR. Of note, in HSV-1 encephalitis, the initial lumbar puncture may be falsely negative and require a second lumbar puncture.⁸ An electroencephalogram can show a variety of waveforms including increased temporal high voltage discharge. Treatment includes IV acyclovir, an antiviral medication, as well as antiepileptics and supportive care.

In comparison, HSV-2 predominantly affects neonates via maternal genital herpes infection during the peripartum period, with infection less commonly occurring in utero or in the postnatal period, which is associated with more severe long-term consequences. Symptoms include skin, eye, and mouth disease, with progression to CNS dissemination. Two-thirds of patients eventually have involvement of the CNS. Electroencephalogram findings are nonspecific, and CSF analysis can provide the diagnosis. HSV-2 is more deadly in comparison to HSV-1, and, without treatment, 85% of neonates with disseminated disease will die within the first year of life.⁹

In rare cases, HSV encephalitis can lead to the development of “relapsing post-herpes simplex encephalitis,” which occurs in 13%–24% of patients diagnosed with HSV

encephalitis.¹⁰ HSV activation triggers an autoimmune response. Specifically, there is production of N-methyl-D-aspartate receptor antibodies, which have been confirmed by identification of these antibodies in the CSF.¹⁰ This can be a potentially life-threatening complication that may present weeks after antiviral therapy as psychosis, seizures, dyskinesia, hypoventilation, and autonomic instability.¹¹ MR imaging of the brain typically demonstrates no new necrotic lesions and is similar to those findings seen with HSV, including T2 and FLAIR hyperintensities of the frontal and temporal lobes, which may increase or remain the same in intensity.¹⁰ These patients do not improve with administration of acyclovir.

Imaging Findings

In HSV-1, CT is typically normal in early disease. Later in the disease process, low attenuation lesions of the temporal lobes and insula are visualized. The classic findings on MR imaging are T2 and FLAIR hyperintensities in the medial temporal lobe (Fig 2). Additional lesions that are commonly seen in the insular, cingulate, and frontobasal cortex can be present without bilateral temporal lobe lesions and are more common in children and in patients who are immunocompromised.¹² Unilateral involvement occurs in most cases in early disease.¹³ Cortical swelling is demonstrated on T1WI,

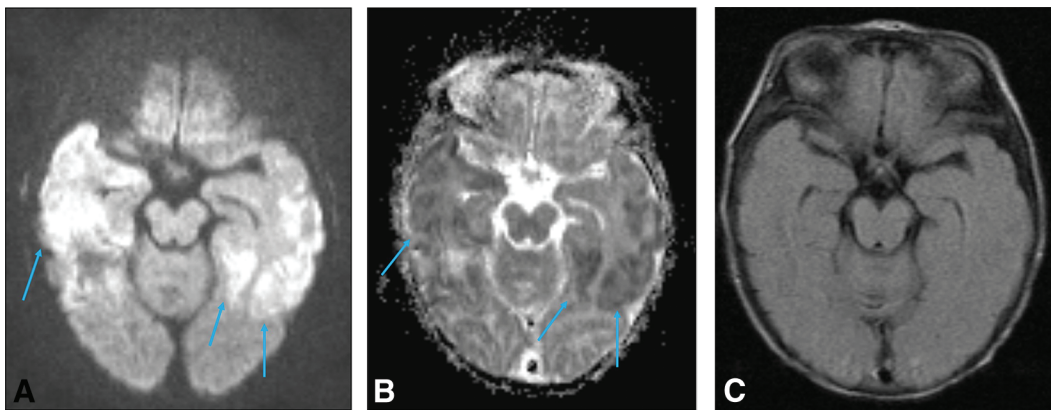


FIG 3. HSV-2. A 2-week-old neonate born via spontaneous vaginal delivery presented with seizures. **A** and **B**, An axial DWI and an ADC image demonstrate diffusion restriction of the bilateral temporal lobes (*blue arrows*). **C**, An axial FLAIR image shows no signal abnormality corresponding to diffusion-restricting lesions.

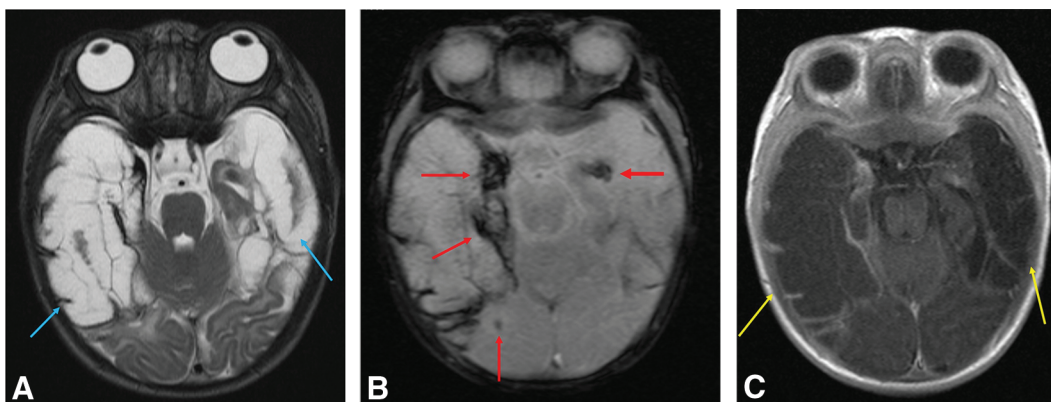


FIG 4. Twenty days after an HSV-2 diagnosis in the same patient as Fig 3. **A**, An axial T2WI shows increased signal intensity of the bilateral temporal lobes (*blue arrows*) related to cystic necrotic change. **B**, An axial gradient recalled-echo image shows hemorrhage in the bilateral temporal lobes (*red arrows*). **C**, An axial T1 postcontrast image demonstrates low signal intensity of the bilateral temporal lobes due to liquefactive necrosis (*yellow arrows*).

associated with loss of the gray-white matter junction. In the acute phase, lesions in the limbic system will restrict diffusion on DWI, although it is not beneficial to use this sequence when differentiating from other neurologic pathologies.¹² In the subacute phase, findings are best seen on T2 and FLAIR. Isolated hippocampal involvement makes a diagnosis of HSV-1 unlikely.

In HSV-2 acute viral encephalitis, CT findings are nonspecific and involve diffuse hypoattenuation of the white matter due to necrosis and hemorrhage. A CT of the head may also be negative. On MR imaging, findings demonstrate T1-hypointense and T2-hyperintense lesions, with loss of gray-white matter differentiation. T2-hyperintense lesions are seen most commonly in the bilateral temporal lobes, cerebellum, and brain stem, with diffusion restriction of lesions on DWI (Fig 3).¹³ Additional areas of abnormal signal involvement include deep gray nuclei and superficial cortex. Enhancement of the gyri or leptomeninges can be seen with administration of gadolinium. DWI is more sensitive than FLAIR alone in detecting lesions (Fig 3).¹³ HSV-2 encephalitis is highly associated with vasogenic and cytotoxic edema, necrosis, and

hemorrhage. Hemorrhage is also commonly seen on gradient T2* (Fig 4). DWI is best used to evaluate the extent of cytotoxic injury.¹³ Later findings of the disease include dystrophic calcification and cystic encephalomalacia (Fig 4).⁹

WNV ENCEPHALITIS

WNV encephalitis is caused by a virus from the *Flaviviridae* family, transmitted via mosquitos. Most people affected by this virus are asymptomatic (80%).¹⁴ Those who develop symptoms typically present with a mild febrile syndrome (20%), including fever, fatigue, headache, and arthralgia. It is reported that 1 of 150 people affected with WNV progress to encephalitis and develop neurologic symptoms, such as seizure, altered mental status, weakness, flaccid paralysis, and coma.¹⁴ These symptoms are most severe in the elderly and patients who are immunocompromised. The diagnosis is confirmed via PCR testing on CSF. Treatment is supportive, including antipyretics, hydration, and antiseizure medication. WNV encephalitis became well known after the 2002 epidemic, which was the largest arbovirus meningoencephalitis outbreak in the Western hemisphere.¹⁵ Of the

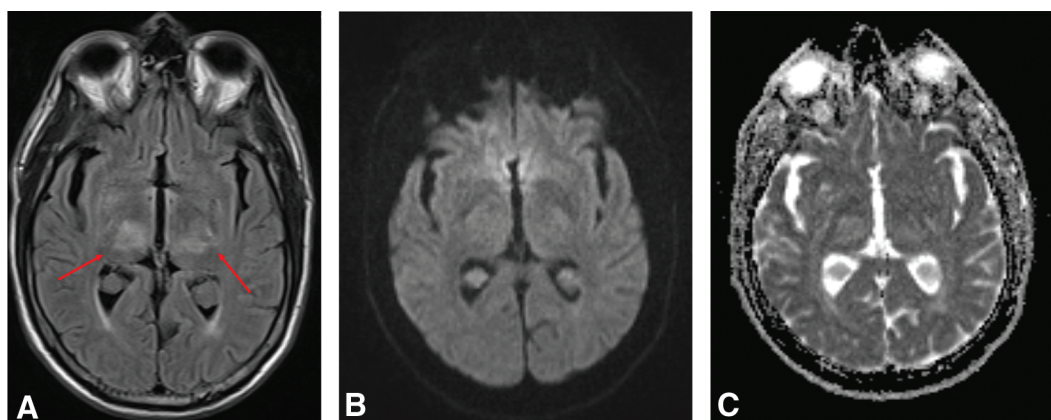


FIG 5. WNV encephalitis. A 50-year-old man presented with altered mental status. **A**, An axial FLAIR image demonstrates high signal intensity of bilateral thalami (*red arrows*). **B** and **C**, An axial DWI and an ADC image show that bilateral thalamic lesions do not restrict diffusion.

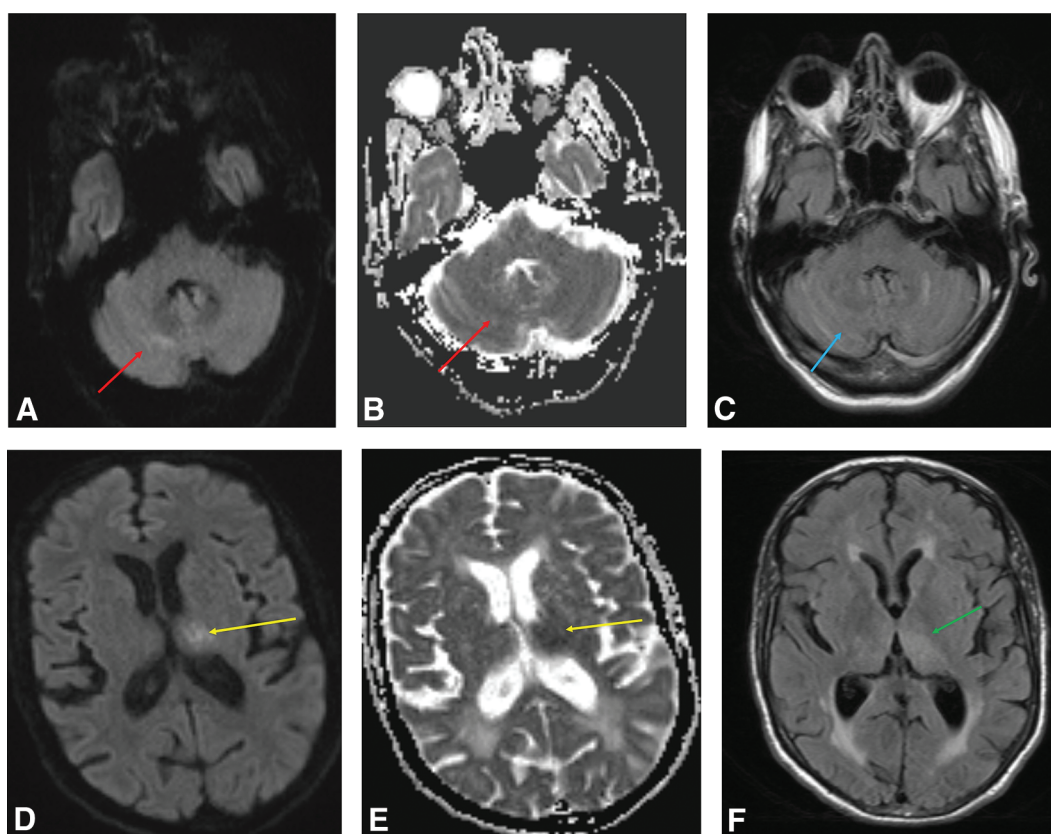


FIG 6. WNV encephalitis. An 85-year-old man presented with speech difficulty and right-sided weakness. **A** and **B**, An axial DWI and an ADC image demonstrate subtle diffusion restriction of the right cerebellar hemisphere (*red arrows*). **C**, An axial FLAIR image demonstrates subtle high signal intensity of the right cerebellum, which corresponds to a diffusion-restricting lesion (*blue arrow*). **D** and **E**, An axial DWI and an ADC image demonstrate diffusion restriction of the left thalamus (*yellow arrows*). **F**, An axial FLAIR image demonstrates high signal intensity of the left thalamus, which corresponds to a diffusion-restricting lesion (*green arrow*).

documented 4,000 cases of WNV during the epidemic, 71% included meningoencephalitis.¹⁵

Imaging Findings

CT of the head is typically unremarkable. Classic MR imaging findings include T2 hyperintensities of the bilateral basal ganglia, thalami, and mesial temporal lobes (Fig 5). Although bilateral thalamic involvement is a classic finding,

unilateral thalamic involvement is an atypical presentation that can be seen (Fig 6). In addition, patchy and poorly demarcated foci of high T2 and FLAIR signal intensity are seen in the cerebral white matter. Other anatomic areas commonly involved include the splenium of the corpus callosum and cerebellum. On DWI, these lesions may restrict diffusion, especially in early disease. WNV can be differentiated from other common cases of encephalitis by the

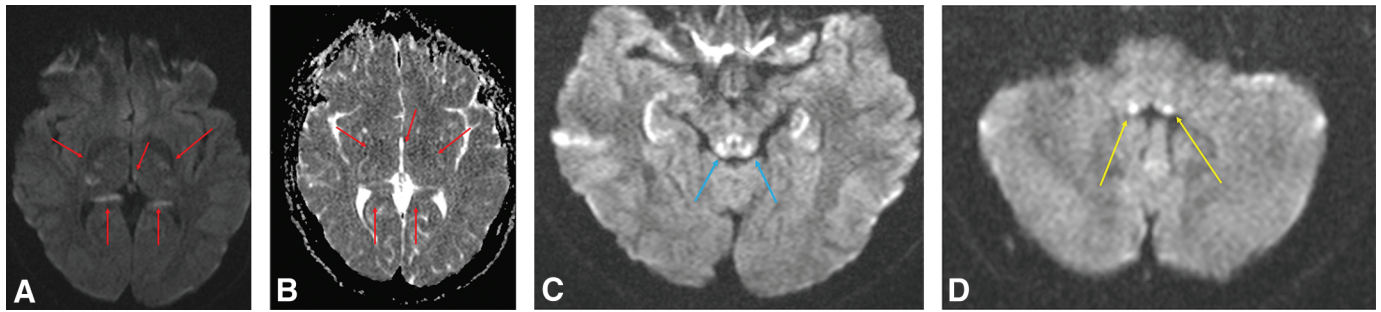


FIG 7. Influenza A encephalitis. A 13-year-old girl who presented with altered mental status, bilateral vision loss, fevers, nasal congestion, and cough. **A and B,** An axial DWI and an ADC image shows diffusion restriction of the lateral thalami bilaterally, left medial thalamus, and bilateral hippocampi (**red arrows**). **C,** An axial DWI shows diffusion restriction of periaqueductal gray matter (**blue arrows**). **D,** An axial DWI shows diffusion restriction of bilateral facial colliculi (**yellow arrows**).

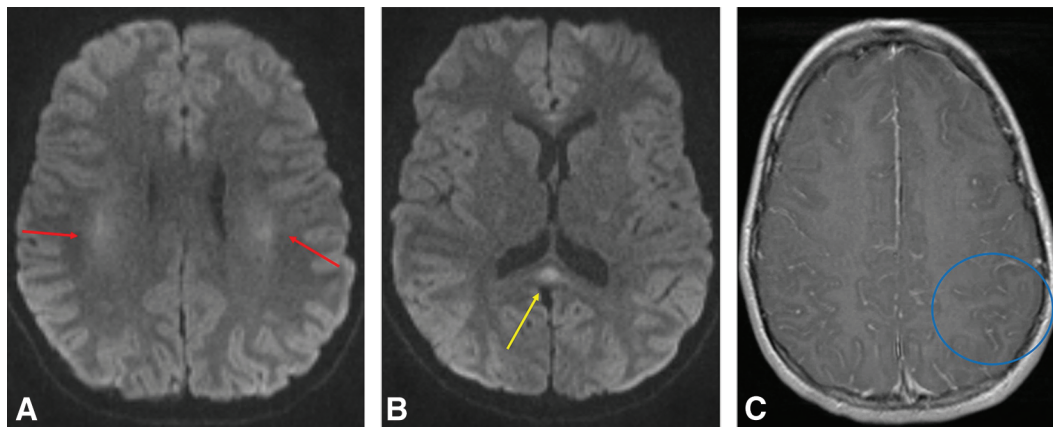


FIG 8. Influenza B encephalitis. An 11-year-old girl who presented with fever, headache, and neck pain. **A,** An axial DWI demonstrates symmetric signal abnormality in the bilateral central semiovale (**red arrows**). **B,** An axial DWI demonstrates restriction in the splenium of the corpus callosum (**yellow arrow**). **C,** A postcontrast axial T1 image demonstrates leptomeningeal enhancement (**blue circle**). These findings are common in all viral subtypes of influenza and are not specific to the subtype of influenza B encephalitis.

absence of isolated involvement of the mesial temporal lobe or necrosis, which are findings commonly seen in HSV encephalitis. Spinal cord involvement on MR imaging can be seen and is clinically associated with flaccid paralysis. Gray matter lesions are seen, which predominantly involve the ventral horns and the conus medullaris, and these areas can enhance. Enhancement is also seen in the cauda equina. Lesions in the cauda equina and conus medullaris may restrict diffusion on DWI.

INFLUENZA ENCEPHALITIS

Influenza is a common viral infection; however, it rarely progresses to encephalitis, with an estimated 0.21 per million population per year affected.¹⁶ Influenza encephalitis is most commonly associated with influenza A, which includes the H1N1 subtype.¹⁶ The incidence of influenza encephalitis increases in children during influenza epidemics.¹⁷ After the H1N1 epidemic in 2009, there was an increase in the number of encephalitis cases associated with influenza.¹⁶ The symptoms of influenza encephalitis are often nonspecific. In addition to typical flulike symptoms, patients can present with confusion, seizures, loss of consciousness, and even coma. A confirmed diagnosis is difficult given that influenza

RNA is rarely detected via PCR of CSF samples from a lumbar puncture. Influenza RNA is also rarely detected in respiratory samples once neurologic symptoms set in. Treatment of influenza encephalitis with oseltamivir is controversial, and treatment is mostly supportive care.¹⁶

Imaging Findings

Imaging can be normal or nonspecific, and, therefore, it is difficult to diagnose based on imaging alone. Head CT findings include hypoattenuating lesions in the brain stem, along with the thalami and pons.¹⁸ MR imaging also has relatively nonspecific findings. A feature often seen with this infection but not specific to it is the cytotoxic lesion of the corpus callosum lesion (previously described) as well as diffusion restriction in the centrum semiovale and thalami, in addition to areas of T2 signal in the thalami, centrum semiovale, and pons.³ Diffusion restriction is a sensitive finding and can be seen in the splenium of the corpus callosum, centrum semiovale, and thalami (Figs 7 and 8).³

VZV ENCEPHALITIS

VZV encephalitis encompasses both varicella encephalitis and herpes zoster encephalitis. Varicella infection initially

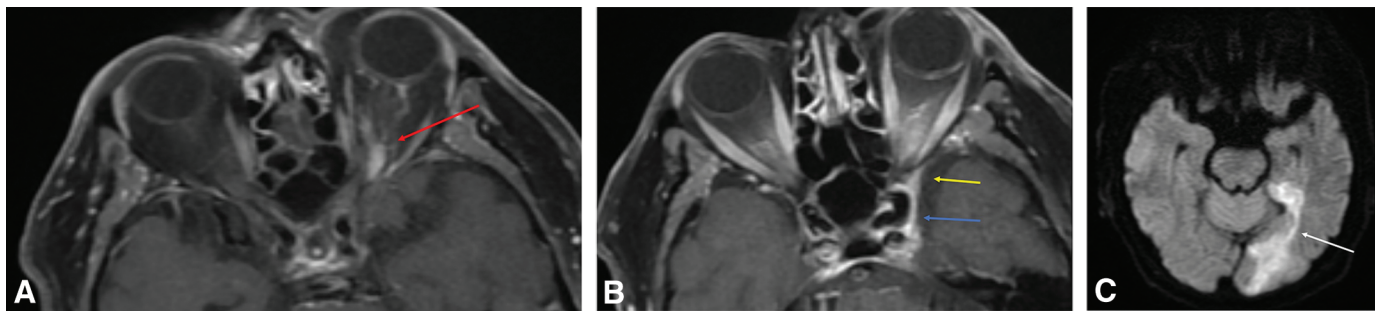


FIG 9. An acute ischemic stroke in a patient with known VZV infection. An 84-year-old man with a history of known VZV infection who presented with ptosis of the left eyelid. **A and B,** Postcontrast MR imaging of the orbits demonstrates indistinct soft-tissue planes in the left orbital apex, with poor definition and mild enhancement of the left optic nerve (*red arrow*). There is a linear enhancing structure extending to the superior lateral aspect of the cavernous sinus (*yellow arrow*), with mild thickening and enhancement that involves the left cavernous sinus (*blue arrow*). After discharge, the patient followed up with an ophthalmologist, completed a course of steroids for cavernous sinus thrombophlebitis, and used prednisolone ophthalmic drops for VZV ophthalmicus. Three months after initial presentation, the patient presented with dizziness and right-sided vision loss. **C,** A large left posterior cerebral artery distribution stroke can be seen on this DWI and involves the left temporal and occipital lobes (*white arrow*).

presents as chicken pox in children, with a diffuse vesicular rash. Once infected, the virus remains dormant in the dorsal root ganglia. Reactivation of the virus in patients who are immunocompromised or in elderly patients manifests as shingles and presents with a painful rash in a dermatomal pattern. Progression to CNS involvement is very rare and occurs approximately 2 weeks after the onset of the rash, and is seen in 1–3 cases per 10,000.³ Those patients with VZV cases that progress to encephalitis are more commonly associated with the elderly and patients who are immunocompromised. The rare cases in patients who are immunocompetent are linked to a more severe diffuse rash.³ However, up to 30% of reported cases have reported no rash before presentation of encephalitis.¹⁹ Neurologic involvement presents most commonly with seizure and less commonly with ataxia, hemiparesis, and sensory changes.

Neurologic complications of VZV include cerebellitis, cranial nerve palsies, transverse myelitis, herpes zoster ophthalmicus, and Ramsay Hunt syndrome. Herpes zoster ophthalmicus is a result of virus reactivation, most commonly in the elderly and patients who are immunocompromised, with involvement of the ophthalmic division of the trigeminal nerve seen in 10%–20% of all VZV cases.²⁰ Ramsay Hunt syndrome occurs due to reactivation of VZV in the geniculate ganglion, with involvement of the facial nerve, and presents with rash, facial palsy, ear pain, and vesicles within the ear canal, and can potentially lead to encephalitis. VZV vasculopathy is one of the most severe complications of VZV encephalitis as a result of inflammation of the cerebral arteries, which causes ischemia. Less common presentations of VZV vasculopathy include cerebral artery aneurysm, intracranial hemorrhage, and arterial dissection.²¹ A diagnosis is achieved with a PCR positive result for VZV antibodies. In addition to supportive care, patients who are affected are treated with IV acyclovir.

Imaging Findings

VZV encephalitis findings may differ, depending on if the patient initially presents with a varicella (chickenpox)

infection or a herpes zoster (shingles) infection. In both infections, findings on head CT are nonspecific and may include cerebellar edema and nonspecific cerebral hypodensity. On MR imaging, there are multifocal areas of involvement, with diffuse high T2 signal seen throughout the cortex. In comparison, zoster primarily affects the brain stem, cortical gray matter, and cranial nerves, and is associated with high T2 signal in the brain stem and cortex.

In both varicella and herpes zoster encephalitis, acute ischemia from vasculitis presents with lesions that restrict diffusion on DWI (Fig 9). Larger ischemic lesions of the MCA as a result of arterial stenosis are commonly associated with patients who are immunocompromised. Patients who are immunocompetent may present with smaller ischemic lesions identified at the gray-white matter junction. Findings of vasculitis without ischemia can be seen on MR intracranial vessel wall imaging as vessel wall thickening and enhancement.

Neurologic complications associated with VZV infection, such as Ramsay Hunt syndrome and herpes zoster ophthalmicus, may present on imaging and are important to identify because they may precede encephalitis in rare cases. Herpes zoster ophthalmicus findings include asymmetric enhancement of the trigeminal nerve root. Orbital apex syndrome seen with herpes zoster ophthalmicus involves damage to the oculomotor, trochlear, abducens, and ophthalmic branches of the trigeminal nerve, which present as enhancement and thickening of the optic nerve on T1 postcontrast MR imaging (Fig 9).²² Increased enhancement of the facial nerve as well as abnormal enhancement of the internal auditory canal and membranous labyrinth are findings seen with Ramsay Hunt syndrome (Fig 10).²³

CMV ENCEPHALITIS

Initial infection with CMV occurs through transmission of bodily fluids spreading to the CNS and leading to encephalitis. It affects approximately 2% of neonates as well as immunocompromised patients.³ Congenital CMV infection is typically asymptomatic, with only 10% of patients

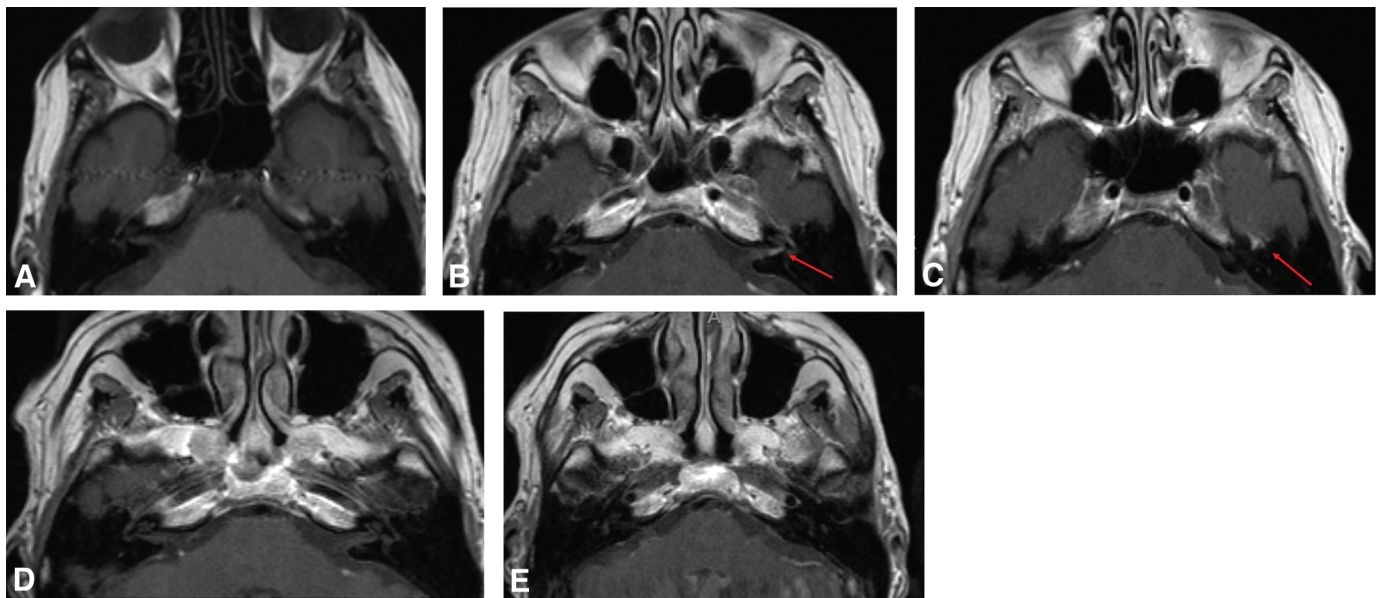


FIG 10. Ramsay Hunt syndrome, confirmed by identification of VZV in CSF. A 56-year-old woman who presented with dizziness and left ear pain. **A**, Precontrast, **B** and **C**, Postcontrast MR images of the internal auditory canals demonstrate enhancement of the intracanalicular and labyrinthine segments of the left facial nerve as well as geniculate ganglion (red arrows). **D** and **E**, Postcontrast images from a follow up study 8 months later demonstrates complete resolution of pathologic enhancement of the left facial nerve.

presenting with symptoms at birth.²⁴ Those children who develop symptoms later in life have neurodevelopmental delay, including hearing loss, microcephaly, and chorioretinitis.²⁴ Other symptoms associated with the infection include altered mental status, cranial nerve palsies, and decreased cognitive function. Patients who are immunocompromised present with neurologic deficits later in the disease as a result of myelitis, retinitis, and ventriculoencephalitis. Immunocompetent adults present with symptoms similar to a mononucleosis-type infection, with rare progression to neurologic involvement. A diagnosis is confirmed with PCR testing of CSF. Standard treatment includes specific antiviral medications appropriate at certain points of the disease. Mortality is high if not properly treated with antiviral medications such as ganciclovir and foscarnet.

Imaging Findings

CMV infection of the brain in infants classically presents on imaging as ventriculomegaly (commonly lateral ventricles), microcephaly, cortical anomalies, subependymal cysts, cerebellar hypoplasia, and periventricular calcifications, with development of white matter abnormalities later in life (Fig 11).²⁴ Specifically, white matter lesions are multifocal and involve deep parietal white matter.²⁴ MR imaging is the most useful imaging technique in identifying the extent of these findings to determine the severity and possible long-term effects of epilepsy and developmental delay. In immunocompetent adults, imaging shows diffuse cerebral and cerebellar volume loss. Classic ventriculoencephalitis MR imaging findings include regions of diffusion restriction and T2 hyperintensities in the deep

periventricular white matter, which may enhance. Focal areas of necrosis may be seen as ring-enhancing nodules on MR imaging. Abnormalities of the choroid plexus and retina may also be seen in association with CMV infection.

EPSTEIN-BARR VIRUS ENCEPHALITIS

Epstein-Barr virus, also known as human herpesvirus 4, is highly prevalent in individuals. However, even when infected, most patients are asymptomatic and the virus it remains latent in lymphoid tissue and B cells. Epstein-Barr virus is responsible for infectious mononucleosis, typically seen in young teenagers or early adolescents, who present with fever, fatigue, sore throat, lymphadenopathy, and splenomegaly. This virus has also been linked to the development of lymphoma in patients who are immunocompromised (ie, AIDS-related lymphoma). Progression to neurologic complications, for example, encephalitis, is rare and is seen in only 0.5%–0.7% of cases.³ There typically is a prodrome of fever and headache, followed by seizures. EBV is also associated with altered mental status, visual hallucinations, and psychosis. A diagnosis is confirmed with PCR from CSF. Treatment of Epstein-Barr virus encephalitis with antiviral medications such as acyclovir and ganciclovir is controversial.

Imaging Findings

MR imaging brain findings may be nonspecific, with multifocal areas of high signal intensity in the subcortical white matter on T2WI. Specific sites of abnormal T2 signal intensity include the cerebellum, thalami, cerebral

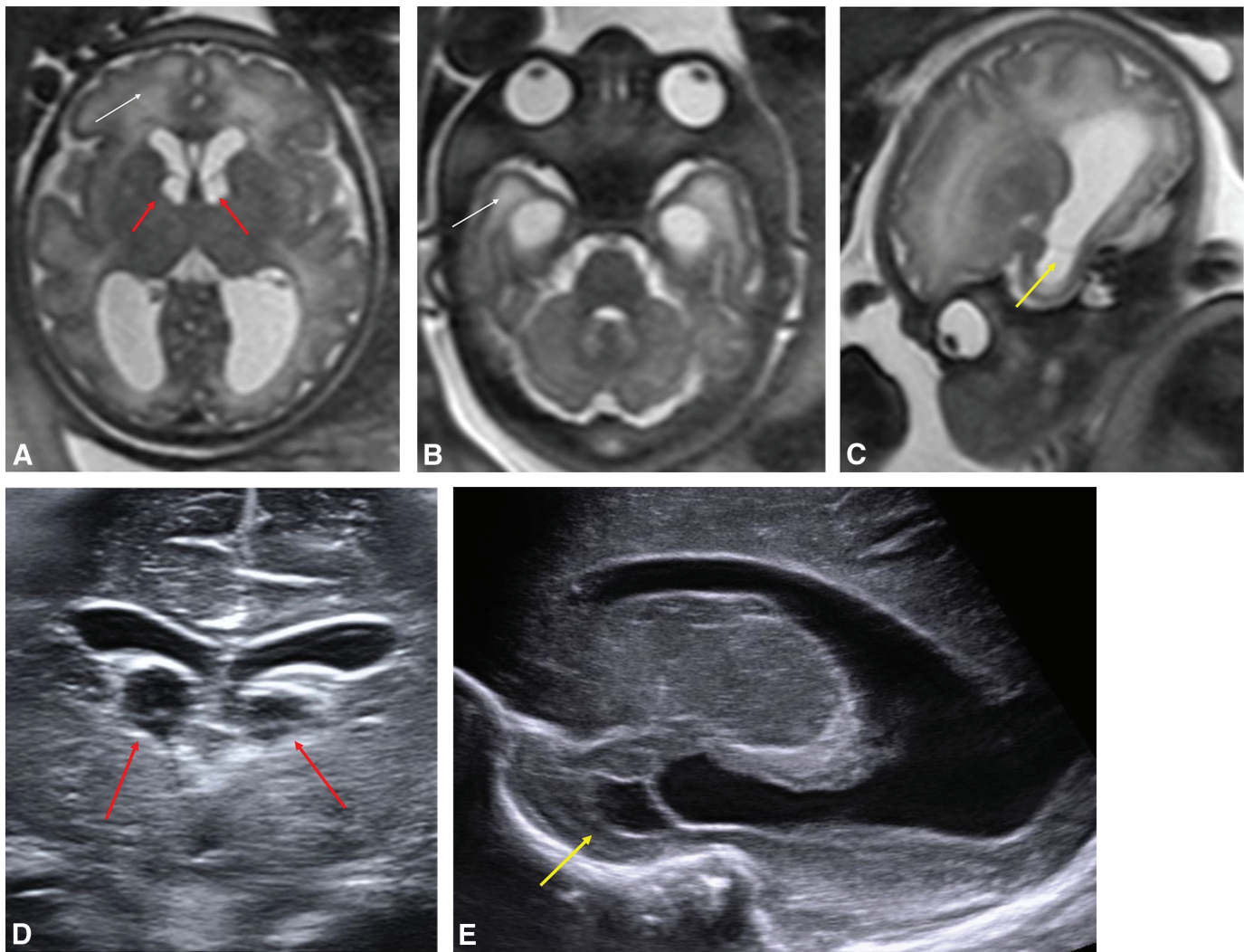


FIG 11. Neonatal CMV encephalitis. Patient with ventriculomegaly on fetal ultrasound was referred for exclusion of hemorrhage. **A** and **B**, Axial HASTE T2, and **C**, Sagittal HASTE T2 images as part of a fetal MR imaging, demonstrate ventriculomegaly that involves the lateral ventricles and occipital horns of the lateral ventricles, abnormal septation in the temporal horns (*yellow arrow*), increased T2 signal in the white matter (*white arrows*), and subependymal cysts (*red arrows*) near the frontal horns. Concern for CMV was raised on this fetal MR imaging, and maternal serology was performed, which demonstrated elevated immunoglobulin M (IgM) for CMV. **D** and **E**, A follow-up neonatal sonography of the head demonstrates persistent ventriculomegaly of the lateral ventricles and occipital horns of the lateral ventricles. There are subependymal cysts (*red arrows*) as well as septation or a cyst in the temporal lobe (*yellow arrow*).

peduncles, pons, and corpus striatum. Hemorrhagic lesions as well as white matter lesions have been reported. A higher rate of sequelae has been reported when signal abnormalities are seen in the thalami and limbic system.³

HIV ENCEPHALITIS

HIV encephalitis is the result of the direct infection of the brain by HIV type 1. It is seen in 33%–67% of adult patients with AIDS and 30%–50% of pediatric patients with AIDS.²⁵ The virus infects the microglia and macrophages and causes neurologic deficits. Initially, patients present with impairment of fine motor control, verbal fluency, and short-term memory. This may progress to behavioral deficits, such as depression, delirium, confusion, dementia,

and eventual vegetative state. This is a diagnosis of exclusion after CSF evaluation for CMV, cryptococcus, and syphilis. Patients are treated with highly active antiretroviral therapy (HAART), which decreases the severity of the infection.

Imaging Findings

Findings on head CT include diffuse cerebral atrophy, with symmetric, low attenuation of periventricular and deep white matter, without mass effect or enhancement. MR imaging also shows diffuse cerebral atrophy. Patchy or confluent T2 hyperintensities of the periventricular and deep white matter predominantly in the frontal lobe as well as the genu of the corpus callosum are unique to this infection. These lesions may also be associated with diffusion

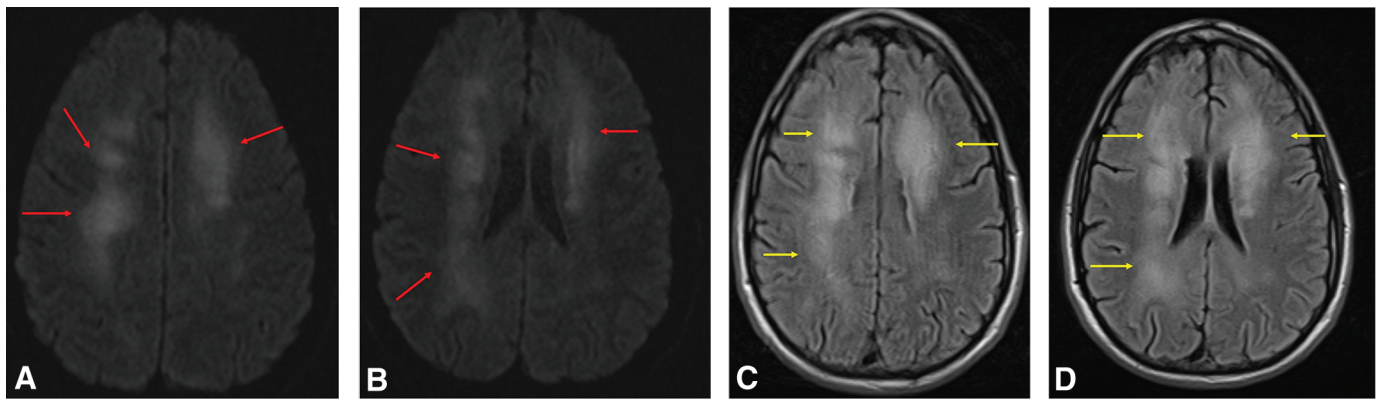


FIG 12. HIV encephalitis. A 34-year-old man brought to the emergency department by his mother for altered mental status, strange behavior, and difficulty walking for the past 2 months. **A** and **B**, Axial DWI images demonstrate diffusion restriction of bilateral white matter, with sparing of U-fibers (*red arrows*). **C** and **D**, Axial FLAIR images demonstrate deep and periventricular white matter hyperintensities (*yellow arrows*).

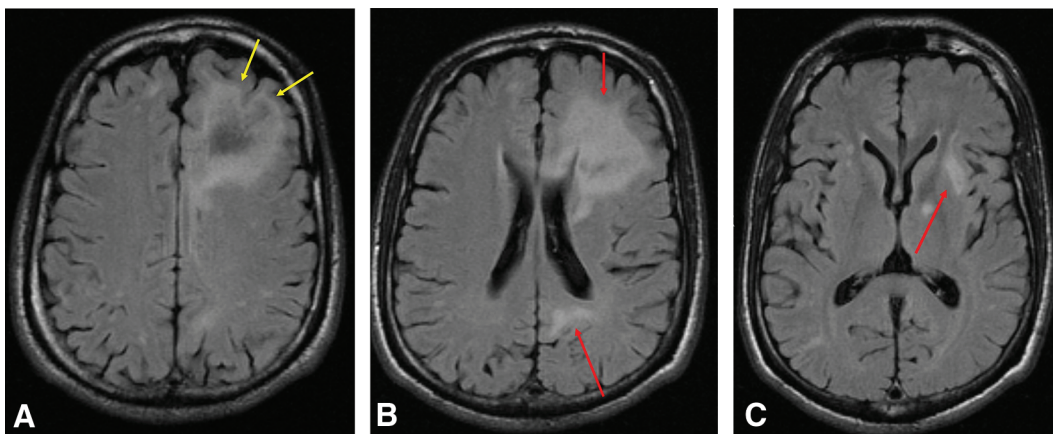


FIG 13. PML in HIV. A 43-year-old man with HIV presented with confusion and speech difficulties. **A–C**, Axial FLAIR images demonstrate high signal intensity in subcortical and deep white matter (*red arrows*) with U-fiber involvement (*yellow arrows*).

restriction (Fig 12). Additional areas of T2 hyperintensity, although less specific, include the basal ganglia, cerebellum, and, brain stem. On FLAIR, diffuse periventricular as well as subcortical white matter hyperintensities are seen. The imaging may improve after initiation of HAART.²⁵

Progressive Multifocal Leukoencephalopathy

PML is caused by reactivation of the JC virus in immunocompromised patients. The JC virus commonly infects many children and young adults without identifiable symptoms.³ Patients who are immunocompromised and at risk of developing PML include patients with AIDS, organ transplantation, MS, and who had chemotherapy, along with those patients with MS and rheumatoid arthritis treated with alpha-integrin inhibitors (eg, natalizumab).²⁶ However, among immunocompromised patients, patients with HIV are most commonly infected by PML, which is seen in approximately 82% of cases.³ Symptoms include progressive neurologic deficits and cognitive decline. There is no cure. However, the goal of treatment is to restore immune function once diagnosed. Specifically, patients with AIDS/HIV are treated with HAART. Immunosuppressive medications are

discontinued in patients with MS and rheumatoid arthritis. These patients may undergo plasma exchange for further management of the disease.²⁶

PML may progress to CNS immune reconstitution inflammatory syndrome (IRIS), which is an exaggerated inflammatory response seen in patients with HIV anywhere from weeks to years after initiation of HAART. Patients present with worsening symptoms of HIV despite taking antiretroviral medication. Laboratory tests demonstrate reconstitution of the immune system. PML–IRIS in patients who are HIV positive is reported in approximately 18% of patients seen 1 week to 26 months after initiating HAART.²⁶ Patients are treated with steroids.

Imaging Findings

Imaging findings reflect involvement of the white matter due to the demyelinating mechanism of the virus. A CT of the head shows asymmetric focal subcortical and periventricular low attenuation white matter changes. This is a differentiating factor from HIV encephalitis, which is associated with symmetric lesions of these regions. On MR imaging, T2-hyperintense and T1-hypointense areas are seen in

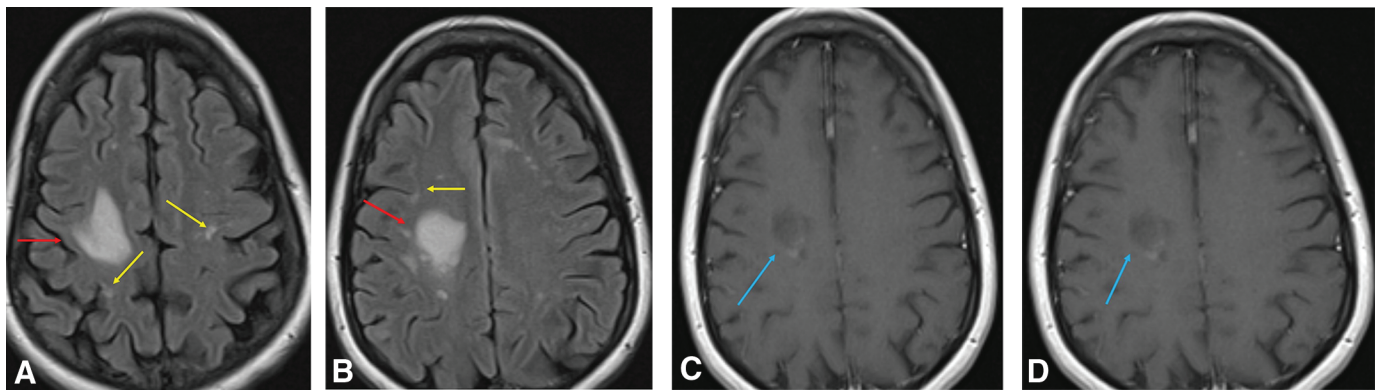


FIG 14. Progressive Multifocal Leukoencephalopathy in a patient treated for MS. A 46-year-old woman with MS, being treated with natalizumab. **A** and **B**, Axial FLAIR images demonstrate hyperintensities of subcortical deep white matter (red arrows) with U-fiber involvement (yellow arrows). **C** and **D**, Axial T1 post contrast images demonstrate incomplete rim enhancement of the lesions (blue arrows).

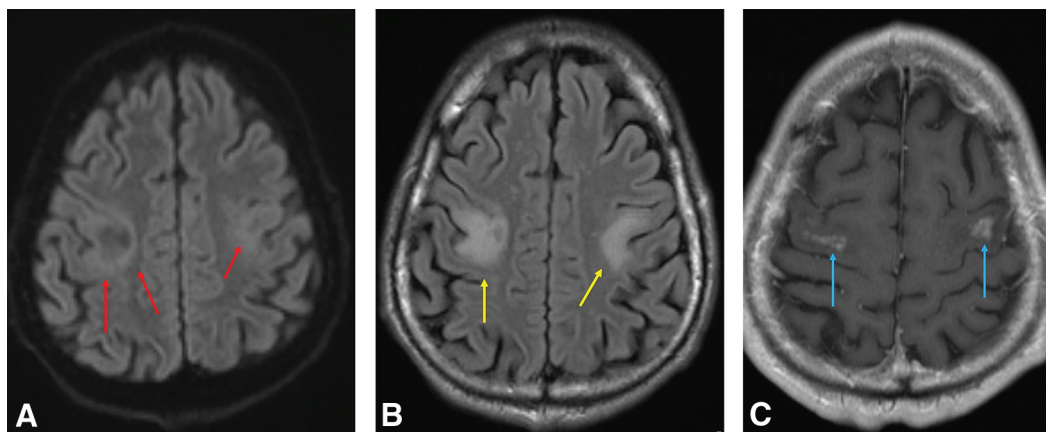


FIG 15. PML-immune reconstitution inflammatory syndrome (IRIS). A 52-year-old man with HIV on HAART presented with new-onset seizure. **A**, An axial DWI demonstrates diffusion restriction of deep and subcortical white matter with U-fiber involvement (red arrows). **B**, An axial FLAIR image demonstrates increased signal with U-fiber involvement, which corresponded to previously described DWI lesions (yellow arrows). **C**, An axial T1 postcontrast image demonstrates partial enhancement of these lesions (blue arrows).

subcortical and periventricular white matter. Most lesions do not enhance, and edema and hemorrhage are rarely seen.³ A differentiating and unique finding includes U-fiber involvement (Figs 13 and 14). In PML-IRIS, enhancement is much more common (reported in 56% of patients) and can be seen with associated mass effect (Fig 15).

CONCLUSIONS

Acute viral encephalitis can present clinically with multiple, nonspecific neurologic deficits, such as fever, mental status change, and headache. There are many different viruses responsible for viral encephalitis, with the most common being HSV. However, certain viruses may be responsible for viral encephalitis in certain patient populations, such as those who are immunocompromised, children, and those infected by HIV. The diagnosis is confirmed by using PCR and cultures of CSF from lumbar punctures. However, neuroimaging findings may aid in the diagnosis, with certain findings specific to different viral etiologies of encephalitis. Radiologists should be aware of

these findings, both common and uncommon, to provide an accurate diagnosis in a timely manner to ensure early therapeutic management.

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