Viral Infections and White Matter Lesions

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KEYWORDS

• Viral infection • White matter • Magnetic resonance • Diffusion weighted • Brain • Pathology

KEY POINTS

- Viral infections with white matter involvement are mainly divided into viral infectious and noninfectious diseases.
- Magnetic resonance imaging provides many clues for the specific diagnosis and differential diagnosis in infectious and noninfectious encephalitis/encephalopathy.
- Understanding the underlying disorder and pathophysiology is useful for the image interpretation and treatment.

INTRODUCTION

White matter diseases related to viral infections are divided into 2 major types: (1) infectious encephalitis/encephalopathy caused by direct viral infection to the central nervous system (CNS), and (2) noninfectious encephalitis/encephalopathy mainly caused by an autoimmune-mediated mechanism.[1,2]

Although viruses are the most common causes of infectious encephalitis/encephalopathy, the causative virus can be unknown in up to 60% of cases.[1] There are many known viral CNS infections involving white matter.[1–7] Herpes simplex virus (HSV) and varicella-zoster virus (VZV) are the most common causes of acute infectious encephalitis. Human immunodeficiency virus (HIV) can cause either leukoencephalopathy or encephalitis. In immunocompromised patients, there are many types of viral infection involving the white matter, including VZV vasculitis/vasculopathy, cytomegalovirus (CMV) infection, John Cunningham virus (JCV) producing progressive multifocal leukoencephalopathy (PML), human herpes virus (HHV) 6 encephalitis, and Epstein-Barr virus (EBV) encephalitis/encephalopathy and EBV-associated neoplastic conditions. Subacute sclerosing panencephalitis (SSPE) is a slow virus infection caused by the measles virus. Newer viral encephalitides such as West Nile virus (WNV) encephalitis and HHV6 encephalitis are emerging because of human host modification of viral agents,[1,8,9] which potentially increases the ability to infect the CNS.

Noninfectious encephalitis/encephalopathy includes acute disseminated encephalomyelitis (ADEM), acute hemorrhagic leukoencephalopathy (AHLE), Bickerstaff brainstem encephalitis (BBE), acute necrotizing encephalopathy, and mild encephalitis/encephalopathy with a reversible splenial lesion (MERS).[1,2,8,10]

Acute viral encephalitis is a medical emergency. It requires prompt diagnosis and specific antiviral treatment or symptomatic treatment.[2,11] Thus, differentiating between infectious and noninfectious CNS involvement is imperative because noninfectious immune-mediated CNS involvement

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is mainly treated with corticosteroids. Symptoms are often nonspecific, including an acute onset of altered mental status, fever, headache, focal neurologic deficit, and possible seizures. Cerebrospinal fluid (CSF) findings of acute viral encephalitis usually show lymphocytic pleocytosis, with increased protein and normal glucose. However, CSF findings can be similar in noninfectious virus-associated CNS diseases. Prompt introduction of treatment has a significant influence on survival and the extent of permanent brain injury. Although the confirmation of the diagnosis often needs the detection of specific viral antigen or serologic markers in CSF, neuroimaging, especially magnetic resonance (MR) imaging, provides many clues for the specific diagnosis and differentiation from noninfectious encephalitis/encephalopathy.

This article discusses neuroimaging findings with the emphasis on MR imaging, including diffusion-weighted imaging (DWI) of infectious and noninfectious white matter lesions associated with various viral infections. It discusses the characteristic distribution and underlying disorder and pathophysiology.

INFECTIOUS VIRAL WHITE MATTER DISEASES

HIV Infection

Initial case reports of what would later become known as acquired immunodeficiency syndrome (AIDS) first appeared in 1981.[12] HIV was first described as the putative cause for AIDS in 1983.[13] HIV is a single-stranded ribonucleic acid (RNA) retrovirus that is lymphotropic and neurotropic. CNS is a primary target for HIV. Between 20% and 30% of patients with AIDS progress into AIDS dementia complex, characterized by neurocognitive impairment, emotional disturbance, and motor abnormalities.[14] The diagnosis of HIV infection is made through detection of HIV antibody using enzyme-linked immunosorbent assay (ELISA) and Western blot, which are usually detectable within 4 weeks of inoculation. Polymerase chain reaction (PCR)–based tests measure the load of replicating HIV virus within the blood stream, which is useful both for testing for HIV before seroconversion and as a quantitative estimate of viral load. CD4 count is used to stage HIV infection. Circulating monocytes carry the virus across the blood-brain barrier. In the CNS, HIV-infected or activated monocytes differentiate into HIV-infected or activated macrophages and microglia, which produce neurotoxic viral proteins and increased concentration of excitotoxic glutamate via astrocyte activation, resulting in neurodegeneration.[14]

The pathologic hallmark of HIV encephalopathy/encephalitis is multinucleated giant cells of macrophage/microglia origin. HIV encephalopathy is characterized pathologically by diffuse myelin breakdown, astrogliosis, multinucleated giant cells, and little inflammation. The corpus callosum can be spared. HIV encephalitis is identified in 26% in neuropathologic AIDS autopsies and is characterized by perivascular inflammation, microglial nodules, and multinucleated giant cells. Brains frequently show overlap of encephalopathy and encephalitis.[15–17]

MR imaging shows parenchymal volume loss and diffuse periventricular white matter lesions (**Fig. 1**). T2-weighted and fluid-attenuated inversion recovery (FLAIR) images show diffuse periventricular hyperintensity, with no mass effect or contrast enhancement.[18] DWI shows high signal with increased apparent diffusion coefficient (ADC) (T2 shine-through). In some cases, brainstem, basal ganglia, and corpus callosum are involved, which suggests the presence of HIV encephalitis (**Fig. 2**). Patients with HIV have a small

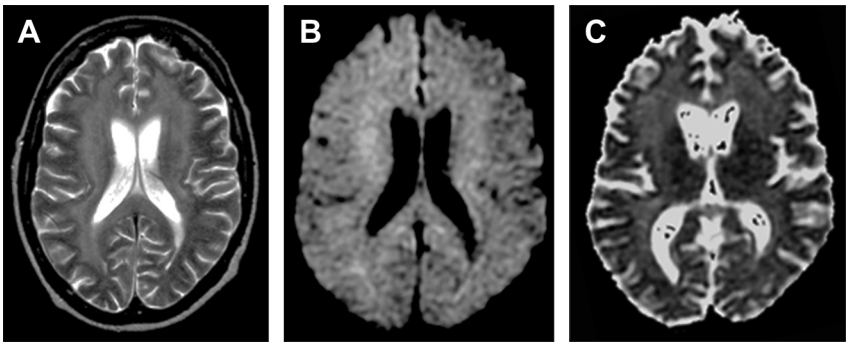

Fig. 1. HIV encephalopathy. A 46-year-old man with AIDS dementia complex. T2-weighted image (*A*) shows diffuse periventricular hyperintense lesions. U fibers are spared. DWI reveals these lesions as mild hyperintensity (*B*). Apparent diffusion coefficient (ADC) map shows these lesions as increased ADC (*C*). Mild hyperintensity on DWI is caused by a T2 shine-through effect.