Infectious Diseases of the Central Nervous System

Vincent Doussset¹, Alain Bonafé²

¹ Department of Neuroimaging, University of Bordeaux Segalen, CHU of Bordeaux, Bordeaux, France
² Department of Neuroradiology, University of Montpellier, CHU Gui de Chauliac, Montpellier, France

Introduction

Infectious diseases affecting humans have greatly decreased in recent decades thanks to antibiotics and the increased level of hygiene. However, the central nervous system (CNS) must be seen has a potential target from many external organisms that have the ability to produce severe diseases with striking symptoms. New viruses or bacteria affecting both animals and humans are spreading around the world and may affect the CNS (avian flu, H1N1 influenza, chikungunya arbovirus, etc.). New therapies used for immunological disorders may also favor the development of CNS infections. This is the case in some natalizumab-treated multiple sclerosis (MS) patients who may develop progressive multifocal leukoencephalopathy (PML) due to John Cunningham virus (JCV). It also has been established that following treatment for infections, clinical worsening may occur due to an immune reconstitution inflammatory syndrome (IRIS).

Imaging technology – computed tomography (CT) and, even more so, magnetic resonance imaging (MRI) – have led to an enhanced ability to characterize infectious processes. MRI techniques such as T2-weighted fast imaging and fluid-attenuated inversion-recovery (FLAIR) make it possible to depict lesions in the brain, spinal cord, and meninges. Techniques such as diffusion-weighted imaging (DWI) and MR spectroscopy (MRS) have been applied to imaging inflammatory and infectious lesions, bringing new capabilities for in vivo characterization. Such techniques assist in making a positive diagnosis and understanding the disease process. Multiple factors affect the appearance of inflammatory lesions, including type of organism, mode of spread, host response, and histopathologic findings. There are three potential mechanisms by which infections can spread to the CNS:

Hematogenously: This occurs either through the choroids plexus or through the blood brain barrier (BBB); this is now the most frequent origin of CNS infection.

Direct spread: This occurs from adjacent structures, such as the sinuses, nasopharynx, or mastoid air cells.

Retrograde axoplasmic flow: This occurs along cranial or peripheral nerves by some viral agents, such as herpes.

Imaging features of CNS infections can be classified by the organisms, the location of the lesion, and the host response:

Organisms include viruses, mycotic agents, parasites, and bacteria (pyogenes).

Lesion location might be one or several of the following: cerebrospinal fluid (CSF), meninges, parenchyma, arteries, veins, cranial cavities (sinuses, mastoid); it is thus important in an imaging study to look for several locations.

Host response:

Immunocompetent patients (children and adults): The response is immunologic, and most often, symptoms and in vivo images are related to the response rather than to the infectious agent himself. This means that common imaging features are present for several organisms, making the specific diagnosis somewhat difficult. There is now evidence for a strong role in the individual genetic background for the development of an organism in the CNS. Not only do prions develop in susceptible individuals; many more organisms are probably infective for some individuals and not others. Transient decrease in the level of immunity may also be responsible for disease development.

Immunocompromised patients: This can be caused by several factors, such as HIV infection that, without treatment, leads to severe immunodeficiency; anticancer chemotherapy; diabetes mellitus; long-term steroid administration; and, more rarely, congenital immunodeficiency. In these patients, opportunistic agents develop, meaning that these germs might be present in nonimmunocompromised people in whom they do not have the ability to develop. HIV has infected more than 60 million people worldwide, with 26 million in Africa alone. In the CNS of HIV-positive patients, numerous and some very specific infective agents may develop: HIV virus, toxoplasma gondii, JCV, tuberculosis (TB), cytomegalovirus (CMV), and cryptococcus being the most frequent. CNS type B lymphoma can also develop. In immunocompromised non-HIV patients, organisms such as Candida albicans, mucormycosis, or Nocardia may become pathogenic for the CNS.
Viral Infections

CNS viral infections can be caused by a wide variety of agents. These diseases are typically diffuse and often involve the meninges and spinal cord as well as the brain. Viral agents most commonly gain access to the CNS hematogenously. Retrograde perineural spread along cranial nerves may also occur. Viral illnesses are most often acute and self-limiting. Chronic or slow viral infections are most commonly seen in immunocompromised patients. Many of these disorders produce only subtle and diffuse changes in the brain and are therefore difficult to identify and characterize with CT and MRI imaging.

The two main features are meningitis and encephalitis. Neurological symptoms will depend on the location of the organism:

- Meningitis due to viruses, the most frequent infectious disease of immunocompetent hosts, has little imaging manifestations. Waiting for results of imaging modalities may unnecessarily delay lumbar puncture and treatment. Enhancement of meninges is rare.

- Encephalitis results from reactivation of latent virus in the CNS. The most sensitive targets are the myelin proteins, leading to acute disseminated encephalomyelitis (ADEM). This includes cross-reaction to viruses or bacteria following systemic infection or vaccination. Vasculitis may also be of immunologic origin in response to systemic organism leading to cerebral infarct. Some granulomatosis diseases can be included in this group, which cause normal immunologic cells to form abnormal collection in the CNS, mostly in the meninges, facial cavities, or cavernous sinus. These include inflammatory pseudotumor, sarcoidosis, etc.

In certain conditions, usually following acute treatment after immunodepression (HIV/AIDS-related patients) or immunological drug withdrawal/removal, an IRIS may occur, with a clinical worsening that also may affect survival.

We now describe infections by type of organisms affecting the CNS: viruses and prions, bacteria, parasites, fungi, and granulomatous or immunologic reaction. The immunologic state of the host and infection location is discussed in each section.

Viral encephalitis is usually associated with seizure, decreased consciousness, or focal symptoms such as motor or sensory deficits. Mild mass effect may be seen during the acute phase. Enhancement is often absent early in the course of acute encephalitis unless there is associated meningitis. Cell damage produced by the virus leads to increased intracerebral viscosity that restricts water motion and diminishes the apparent diffusion coefficient (ADC).

Viruses in Immunocompetent Patients

Viruses that belong to herpes virus, enterovirus, and arbovirus groups may affect both immunocompetent and immunocompromised patients: neonates, children, and adults.

Herpes Viruses

Herpes viruses are DNA viruses, and many can cause CNS infections in humans. These include herpes simplex viruses (HSV) 1 and 2, varicella-zoster virus (VZV), Epstein-Barr (EBV) virus, and cytomegalovirus (CMV):

- HSV is the most common cause of sporadic viral encephalitis. Clinical manifestations include fever, headache, neck stiffness, seizures, focal deficits, and depressed mental state. Because antiviral acyclovir therapy is safe, it is recommended that the drug be given on the basis of clinical findings. The virus has a mortality rate >50% if untreated. Therapy with acyclovir is effective if given early (<3 days after diagnosis). Encephalitis results from reactivation of latent viral infection of the gasserian (fifth cranial nerve) ganglion. From here, the infection spreads to the parenchyma. The virus has a predilection for the medial area of the temporal lobes, the frontal lobes, and the insular lobes. On CT, low densities are seen in affected areas. There is no enhancement; only the adjacent meninges may show some congestive changes, with very little contrast agent uptake. On MRI, hyperintensities are encountered in the temporal, frontal, or insular areas, and the bilateral nature of the process is frequent. The acute phase of HSV 1 encephalitis is much more easily appreciated with FLAIR and DWI. Initially, the infection may appear unilateral on imaging studies, but over time, involvement of the contralateral temporal and frontal lobes will become apparent. Gross hemorrhage is absent in most cases. Generalized atrophy is encountered in severe cases. HSV 2 is the most common cause of neonatal encephalitis. Infection occurs when the fetus passes through the birth canal of a mother with genital herpes. Imaging findings reflect rapid brain destruction. Rare observations have been made in adults.

- VZV produces two distinct clinical syndromes: chickenpox and herpes zoster. Diffuse encephalitis is a rare complication of chickenpox, but it is more common in adults. It is usually mild. Herpes zoster may lead to...