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Viral diseases of the central nervous system

Phillip A Swanson II and Dorian B McGavern

Virus-induced diseases of the central nervous system (CNS) represent a significant burden to human health worldwide. The complexity of these diseases is influenced by the sheer number of different neurotropic viruses, the diverse routes of CNS entry, viral tropism, and the immune system. Using a combination of human pathological data and experimental animal models, we have begun to uncover many of the mechanisms that viruses use to enter the CNS and cause disease. This review highlights a selection of neurotropic viruses that infect the CNS and explores the means by which they induce neurological diseases such as meningitis, encephalitis, and myelitis.

Addresses
National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, MD 20892, United States

Corresponding author:

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Introduction

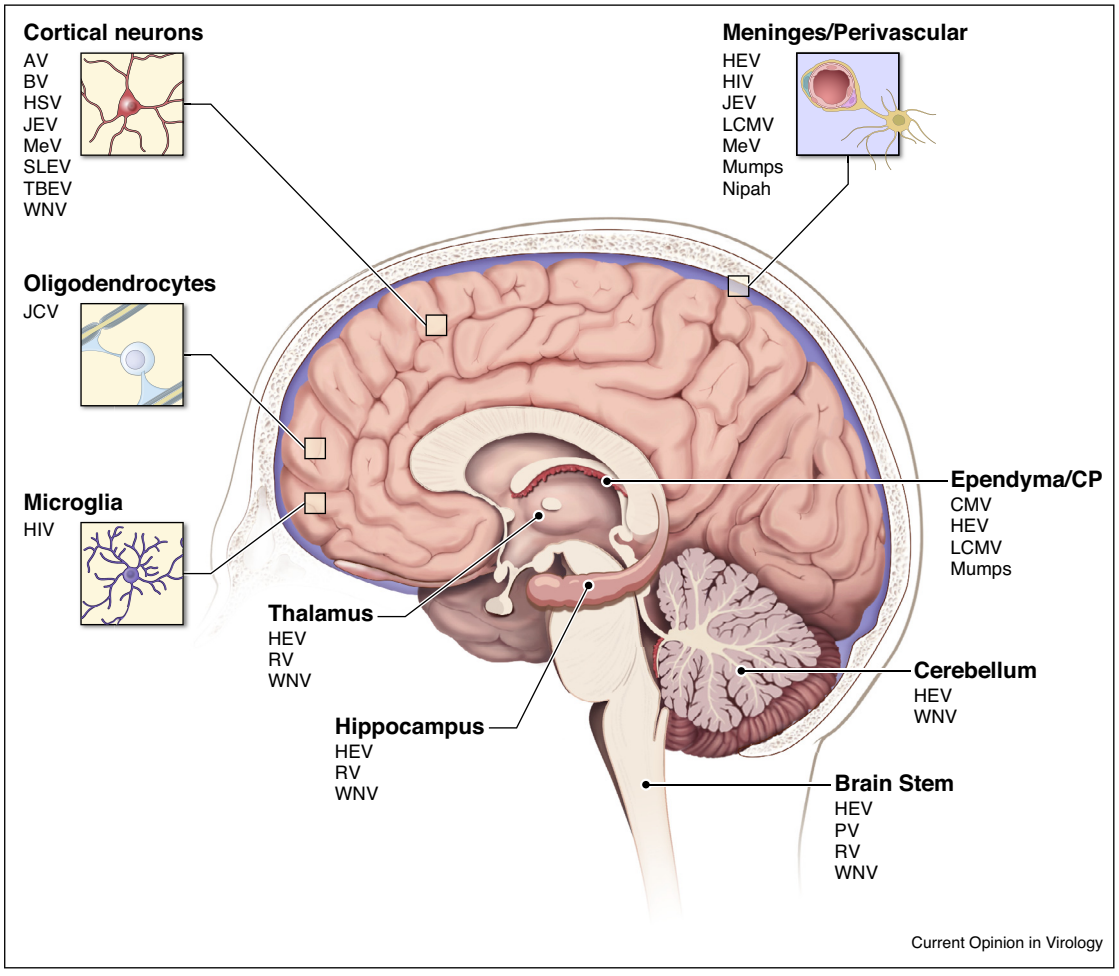
The central nervous system (CNS) is protected by a highly complex barrier system, yet a wide variety of viruses still manage to gain access and induce disease. In fact, the number CNS viral infections each year is greater than all bacterial, fungal, and protozoa infections combined [1]. Following CNS infection, inflammation can arise in distinct anatomical regions such as the meninges (meningitis), brain (encephalitis), and spinal cord (myelitis), or simultaneously in multiple regions (meningoencephalitis, encephalomyelitis). For many neurotropic viruses, viral cytopathology plays a major role in CNS dysfunction. However, experimental animal models have revealed that the antiviral immune response can also under certain conditions be an active contributor to disease. This brief review will break down CNS viral pathogenesis into distinct anatomical regions and discuss selected viruses that drive pathology involved in each.

CNS invasion

Although viruses breach protective barriers a number of different ways, there are basically two main routes of entry into the CNS (Figures 1 and 2). One route of entry is via the blood supply. Viruses that are inhaled such as measles and mumps or ingested like human enteroviruses are able to move quickly past mucosal epithelial barriers and establish infection in oropharyngeal or small bowel lymphoid tissues [2–4]. Arboviruses that enter the skin after an insect bite are picked up by Langerhans cells, which then migrate to the draining lymph node [5•,6]. Once in secondary lymphoid tissues, viruses are often shed into the blood stream, resulting in systemic infection. The delicate CNS parenchyma is protected from harmful substances in the blood by an elaborate barrier network called the blood brain and blood cerebrospinal fluid barriers [7••]. However, viruses have adapted one or more ways to overcome this obstacle [8•]. Some viruses directly infect vascular endothelial cells, which allow direct passage across the blood brain barrier (BBB) into the CNS [9–11]. Additionally, there are areas of the CNS such as the choroid plexus and circumventricular organs that are not completely protected by the BBB and serve as entry points for several viruses [12,13]. Infected hematopoietic cells are also used as 'Trojan horses' to transport virus into the CNS via the blood supply [14•,15]. Finally, systemic viral infection can lead to inflammation-induced breakdown of the BBB [16,17], allowing viruses to literally slip through the cracks into the CNS.

As a second major route of CNS entry, some viruses infect and migrate through peripheral nerves. While rabies virus initially infects myocytes after a bite from an infected animal, and poliovirus infects mucosal epithelial cells after ingestion, they both use peripheral motor neurons to make their way into the CNS (Figure 2) [18,19]. Herpes simplex virus (HSV)-1 initially infects keratinocytes before migrating to peripheral sensory neurons. HSV-1 has also been proposed to reach the CNS via olfactory sensory neurons whose dendrites are directly exposed to airways in the nose [20]. Nipah virus, influenza virus, and rabies virus have also been proposed to enter the CNS via olfactory nerves [21•,22–24]. It is important to note, however, that while some viruses have a preference for the hematogenous or peripheral nerve route to CNS entry, other viruses are able to take advantage of both [25,26]. Once viruses reach the CNS, viral tropism and the ensuing immune response combine to shape the resulting disease. Viruses that remain within cells of the meninges or ventricular lining often induce meningitis, whereas those that infect the CNS parenchyma give rise to meningoencephalitis, encephalitis, or myelitis (Figures 1 and 2). These virus-induced diseases will be discussed in more detail below.

Figure 1



Brain regions affected by viruses that cause meningitis and encephalitis. *Abbreviations*: AV, alphaviruses; BV, bunyaviruses; CMV, cytomegalovirus; CP, choroid plexus; HEV, human enteroviruses; HIV, human immunodeficiency virus; HSV, herpes simplex virus; JCV, John Cunningham virus; JEV, Japanese encephalitis virus; LCMV, lymphocytic choriomeningitis virus; MeV, measles virus; Mumps, mumps virus; Nipah, Nipah virus; PV, poliovirus; RV, rabies virus; SLEV, St. Louis encephalitis virus; TBEV, tick-borne encephalitis virus; WNV, West Nile virus.

Meningitis

Aseptic meningitis is classically defined as non-bacterial inflammation of the tissues lining the brain. Any inflammation or pathology that also involves the parenchyma is referred to as meningoencephalitis or encephalitis (discussed below). The vast majority of aseptic meningitis cases are caused by human enteroviruses (HEV) [27,28] that mostly target children [29,30]. However, many other viruses have the ability to cause meningitis including St. Louis encephalitis virus (SLEV) [31], bunyaviruses [32–34], mumps virus [35], lymphocytic choriomeningitis virus (LCMV) [36], HSV-1 and 2 [37,38], and human immunodeficiency virus (HIV)-1 [39]. Because most adult infections resolve without long term sequelae, pathological data are scarce. Common symptoms such as fever, headache, and neck stiffness are usually treated with supportive care, and these symptoms are driven in part by pleocytosis and elevated cytokines in the cerebrospinal fluid [40].

Animal models have helped elucidate some of the mechanisms that drive the pathogenesis of viral meningitis. Neonatal humans are especially at risk for developing severe morbidity and mortality following infection by group B coxsackieviruses and echoviruses [41,42]. A pathological report of a child who succumbed to coxsackievirus B5 noted intense inflammation around the choroid plexus as well as the lateral and fourth ventricles [43]. This is consistent with experimental data showing that the choroid plexus in coxsackievirus B3 (CVB3)-infected neonatal mice is heavily populated with virus-infected myeloid cells undergoing apoptosis [15]. Similarly, LCMV targets the choroid plexus and ependymal cells as well as stromal and innate immune cells in mice