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Viral Diseases of the Central Nervous System

Phillip A. Swanson II and Dorian B. McGavern

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

Abstract

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.

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, 2**). One route of entry is via the blood supply. Viruses that are inhaled such as measles and mumps or ingested like human

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Corresponding author: Dorian B. McGavern, Ph.D., NIH / NINDS, 10 Center Drive, Bethesda, MD 20892, Phone: (301) 443-7949, mcgavernd@mail.nih.gov.

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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 [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 [21-24]. 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, 2**). These virus-induced diseases will be discussed in more detail below.

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 following intracerebral injection [44-46]. LCMV is likely transmitted from rodents to humans through ingestion of urine or fecal-contaminated food or exposure through an open wound. Most infections result in mild or no symptoms, and in rare cases of severe disease, immunocompetent individuals typically recover with supportive care [47,48]. However, LCMV infection can be fatal in immunocompromised individuals, such as solid-organ transplant recipients [49]. As an animal model of CNS disease, immunocompetent mice are infected intracerebrally with LCMV [50]. Following infection, mice uniformly develop fatal meningitis 6-7 days post-infection, which is characterized by heavy immune cell infiltration and vascular pathology within the meninges [51]. We have shown that this fatal disease is mediated in part by antiviral CD8⁺ T cells that directly release chemoattractants in the meninges, which promotes synchronous extravasation of innate myelomonocytic cells (i.e., monocytes and neutrophils) (**Figure 3**) [45]. As these innate cells extravasate through blood vessels, they open the tight junctions, contributing to dysregulation of CNS homeostasis and fatal edema [45]. Importantly, type I interferon (IFN-I) signaling is responsible for nearly all innate immune gene expression in the LCMV infected brain and sets the stage for the ensuing fatal immunopathology [52]. In fact, blockade of IFN-I signaling completely prevents LCMV meningitis and may therefore represent a therapeutic target to dampen pathogenic antiviral immune activity in the CNS [53,54].

ENCEPHALITIS

Viruses that infect neurons within the CNS can induce intense inflammation of the parenchyma (encephalitis) as well as the meninges (meningoencephalitis), leading to headache, fever, and neurological dysfunction (**Figures 1, 2**). HEVs and alphaviruses, such as Eastern, Western, and Venezuelan equine encephalitis viruses (EEEV, WEEV, VEEV) primarily infect neurons within the CNS, which has a cytopathic effect. HEVs are responsible for a large percentage of worldwide viral encephalitides [1]. Some examples include poliovirus (PV) outbreaks in Africa and Asia [55], EV71 in southeast Asia [56,57], and the recent EV68 outbreak in the United States [58]. EEEV, WEEV, and VEEV are insect transmitted viruses affecting different regions of the Americas, which can induce intense CNS disease mostly among young children and the elderly [59]. Post-mortem analysis of EV71-infected brains revealed virus-infected neurons, heavy immune cell infiltration, and destruction of nerve cells by phagocytes along the medulla, thalamus, hypothalamus, dentate nucleus, and cerebral cortex [56], consistent with experimental data [60]. The cytopathic effect of enteroviruses, which is likely one of the main drivers of inflammation and disease, has been linked to viral protein-induced apoptosis [61].

Alphavirus infection can similarly induce apoptosis within neurons [62]. Furthermore, alphaviruses can also indirectly cause neuronal death through the release of pro-inflammatory cytokines [63] and excitatory amino acids, which can lead to excessive activation of *N*-methyl-D-aspartate-subtype (NMDA) glutamate receptors [64]. Another possible factor contributing to the pathogenesis of human enteroviruses is how they migrate throughout the CNS. For example, CVB3, which can cause a devastating encephalitis in infants, targets neuronal stem cells in the subventricular zone of infected neonatal mice [65]. Over time, the infected stem cells continue to differentiate as they migrate along the rostral migratory stream, seeding the parenchyma with virus, before eventually succumbing to apoptosis. Many viruses are known to target neuronal stem cells because of their enhanced proliferative potential.

A second group of insect-transmitted encephalitic viruses (referred to as flaviviruses) can also target CNS neurons and cause cytopathology. However, unlike enteroviruses and alphaviruses, the immune response following infection of the CNS by flaviviruses seems to play a much larger role in disease pathogenesis. There are a range of disease susceptible hosts available to flaviviruses. Historically, Japanese encephalitis virus (JEV) is more likely to cause encephalitis in children, whereas the elderly are more susceptible to encephalitis following SLEV and West Nile virus (WNV) infection [66]. Pathological data from individuals who succumbed to WNV encephalitis revealed sparse but widely distributed lesions of neuronal cell death, gliosis, and innate immune cell infiltration found within the brain stem, cortex, hippocampus, and cerebellum [67]. Additionally, vasculitis and breakdown of the BBB was also observed following WNV infection [68]. Immune cell infiltration consisting of lymphocytes and macrophages in the brain stem, cerebellum and cortex is quite prominent following infection by tick-borne encephalitis virus (TBEV) and JEV [69,70]. Many focal areas of tissue necrosis can be found in JEV encephalitic brains, giving a “punched out” appearance.

At the cellular level, WNV antigen is primarily found within neurons and CD11b⁺ myeloid cells [71]. Infection of neurons induces apoptosis via a caspase3-dependent pathway [72]; however, necrosis due to excessive viral budding has also been observed [73]. Pro-inflammatory cytokines and reactive oxygen species (ROS) released from WNV-infected neurons [74] and activated microglia may also contribute to neurotoxicity [25,75]. JEV and TBEV trigger a similar detrimental innate immune reaction characterized by ROS production from macrophages [76,77]. In addition, *in vivo* treatment of infected mice with anti-inflammatory drugs confers protection [77,78]. Differences, however, among the flaviviruses have been noted regarding the role of the immune system in disease pathogenesis. For example, CD8⁺ T cells can contribute to pathogenesis during TBEV encephalitis [79], whereas lymphocytes have a protective role following WNV and JEV infections [80,81]. Thus, there are both positive and negative aspects of immune function to consider following flavivirus infection.

While many of the aforementioned viruses are directly neuropathic, viral encephalitis can also result from indirect mechanisms that disrupt neuronal function. This is best exemplified by HIV-1. Nearly 50% of HIV-1 infections lead to neurological complications that fall under the umbrella of HIV-associated neurocognitive disorders (HAND) [82]. HIV-1

encephalitis (HIVE) underlies the most serious of these disorders called HIV-associated dementia (HAD), which is characterized by major cognitive and motor impairment [83]. HIV-1 enters the CNS within days of primary infection [84] via infected, circulating immune cells or as free virions. Infection and replication occurs primarily in perivascular macrophages and microglia [85] following genetic mutations that shift the virus towards a more macrophage-tropic phenotype with less reliance on the CD4 co-receptor for infection [86]. This compartmentalization of HIV-1 genetic variants is a major driver of HIVE [87]. The pathophysiology of HIVE is largely unknown, but there is evidence of neuronal death during this condition [88]. Because HIV-1 does not infect neurons, HAD is thought to occur due to the creation of a toxic environment for neurons rather than direct cytolysis. Many *in vitro* experiments have shown that exogenous addition of HIV-1 proteins (tat and gp120) have the ability to kill cultured neurons and promote release inflammatory cytokines [89-91]. However, it is currently debated whether the extracellular concentrations of these proteins would be high enough to achieve the same effect *in vivo*. In addition to viral proteins, activated macrophages and microglia could contribute to neuronal death via the release of inflammatory cytokines and free radicals or through the excessive activation of NMDA glutamate receptors [92], similar to alphaviruses.

Although the advent of antiretroviral therapy (ART) has greatly reduced the frequency of HAD, milder HAND disorders still persist [82]. This is likely due to a combination of longer life spans for HIV-infected individuals and a build-up of damage from continued low level inflammation. HIV-1 mRNA can still be detected in various brain regions of individuals on ART [93], possibly due to the fact that HIV-1 infects long lived CNS populations such as microglia and astrocytes [94]. Furthermore, pathology data from individuals on ART demonstrates widespread activation of CNS innate immune cells [95]. This chronic state of immune activation despite reduced viral loads likely disrupts CNS homeostasis and contributes to neurological dysfunction.

Another relevant inducer of disease in the CNS parenchyma is rabies virus. Encephalitic (furious) rabies accounts for nearly 80% of all CNS disease arising from rabies virus infection [19]. Interestingly, autopsies from patients who have succumbed to rabies encephalitis revealed very little immunopathology [96,97]. The disease is characterized by sporadic edema as well as mild perivascular infiltration, gliosis, and microglia nodules occurring mainly in the brainstem and thalamus. A number of factors have been proposed to contribute to this interesting phenotype, including active immune suppression [98-100] and neuronal dysfunction [101-103]. Apoptosis of neuronal cells has been proposed to contribute to pathogenesis [104,105]; however, these findings were based on infections using attenuated strains of virus, whereas wild type strains fail to induce neuronal apoptosis [105,106].

CNS disease is also induced by viruses that establish latent or persistent infections. Over half of the adult population is infected by one such virus called John Cunningham virus (JCV) [107]. Most individuals are completely asymptomatic; however, during states of immunosuppression, JCV can cause progressive multifocal leukoencephalopathy (PML). This once rare disease characterized by infection of oligodendrocytes leading to multiple foci of demyelinated neurons in the brain has become more prevalent with the emergence of

acquired immunodeficiency syndrome (AIDS) as well as various immunosuppressive treatments for autoimmune disorders. Currently, there are no animal models for PML, so our understanding of this disease comes entirely from human pathological data. Although the precise events that give rise to PML are not completely understood, the current hypothesis is that neurotropic JCV is reactivated from a peripheral latent reservoir following immunosuppression, particularly of CD4 T cells [108]. JCV then migrates to the CNS, possibly in B cells [109], where it crosses the BBB and infects oligodendrocytes. Before ART the prognosis for AIDS patients also suffering from PML was quite grim, but now with treatment 50% of patients survive greater than 12 months [110]. The prognosis is close to 80% survival for PML patients on immunosuppressive drugs such as natalizumab [111].

HSV-1, which establishes latency in trigeminal ganglia following primary infection, is responsible for over 90% of the cases of HSV encephalitis (HSE) [112]. HSE most often affects the elderly as well as young children and can have a mortality rate, especially if left untreated [113,114]. However, it is still unknown whether HSE results from primary HSV-1 infection or reactivation of latent virus. Histological analysis of brain tissue from patients who succumbed to HSE revealed perivascular inflammatory infiltrates, HSV-infected neurons, and engulfment of neurons by microglia [115], typically in the frontal-temporal lobe [116]. Interestingly, there is also intense eosinophilia, although the role of eosinophils is unclear [115]. Despite these histological data, the mechanisms that drive HSE remain unknown. Some studies implicate a protective role for the immune system, as individuals with genetic deficiencies in IFN-I signaling [117] or those with immunosuppression are more susceptible to HSE [118]. However, others have shown that the innate immune response can be detrimental [119].

Measles virus (MeV) can also establish a persistent infection in the CNS, which results in a disease called subacute sclerosing panencephalitis (SSPE). As many as 1:1700 children who contract measles before the age of 5 are at risk for SSPE [120]. The range of onset for SSPE is between 6-13 years [121], with early disease often going undiagnosed. Symptoms begin with cognitive defects, followed by seizures, neurological deterioration, and coma [4]. At the cellular level, neurons and glial cells are infected by MeV, and there is a large infiltration of both innate immune cells and lymphocytes [122,123]; however, this response is unable to clear virus. Several hypotheses have been put forth to explain the mechanism(s) of viral persistence. Viral transmission can occur via cell-cell fusion between infected and uninfected neurons [124], which would effectively thwart the neutralizing antibody response. Alternatively, the antibody response might also contribute to MeV persistence by altering the primary immune response or modulating CNS immunity [4]. Evidence for this theory comes from experiments showing that passive transfer of MeV-specific antibodies rescues infected rats from acute disease, but leads to persistent viral infection and chronic encephalitis [125].

MYELITIS

Some neurotropic viruses primarily impact brain tissue, whereas others cause disease in the spinal cord (**Figure 2**). A prototypic example of the latter is poliomyelitis. Poliomyelitis derives from the ancient Greek words for “gray” (referring to the gray matter of the spinal

cord) and “inflammation”. In the strictest definition of the term, it refers to inflammation of the spinal cord caused by poliovirus. However, this term is frequently used to phenotypically describe other cases of virus-induced myelitis with similar pathology, such as WNV and EV71. Poliovirus, EV71, WNV, TBEV, and JEV infections have all been associated with acute flaccid paralysis. In each case, viral antigen was found in neuronal cell bodies residing in the anterior horn of the spinal cord (**Figure 2**), often coupled with intense perivascular inflammation [56,126-130]. Experiments using hamsters have shown that WNV migration to the spinal cord via peripheral neurons [131] and subsequent injury to anterior horn neurons is responsible for limb paralysis [132]. Although virus-induced cytopathology is undoubtedly contributing to the destruction of motor neurons, the role of immune-mediated pathology in this disease remains unknown.

Rabies virus can also cause disease in the spinal cord. Paralytic (dumb) rabies is much less common than furious rabies [19]. Nevertheless, one pathological study noted that symptoms associated with paralytic rabies began with pain in bite area, followed by motor weakness in the affected limb, and progressed to rapid onset motor paralysis in other limbs [133]. Similar to poliomyelitis, this was associated with heavy inflammation in the anterior horns of the spinal cord, which was associated with motor neuron loss. Dorsal root ganglion neurons are also infected. Rabies virus can eventually give rise to segmental demyelination in peripheral and spinal cord nerves, and electrophysiological experiments have implicated peripheral nerve demyelination as the cause for rabies paralysis [134].

CONCLUSION

Great strides have been made to identify viruses that infect the CNS and mechanisms they use to cause disease. However, many viruses that drive CNS disease remain unidentified and thus it is imperative to survey cohorts of patients with neurological diseases suspected to have an infectious etiology [135]. While human pathology studies have been instrumental in identifying CNS regions affected by neurotropic viruses, the development of experimental animal models are often critical for the discovery of immunological and virological mechanisms that lead to CNS diseases. For example, *in vitro* and *in vivo* models have helped uncover the role of apoptosis and specific viral proteins in the pathogenesis of enterovirus, alphavirus, and flavivirus infection of neurons. Animal models have also shed light on the immunological mechanisms that contribute to tissue damage and neurological dysfunction following CNS infection. The immune system is initially mobilized to defend the CNS from a viral invader, but can sometimes participate in devastating pathological reactions. Despite the diversity of viruses that invade the CNS, many infections induce common pathogenic cascades such as break down of CNS barriers and release of potentially detrimental mediators (e.g. TNF- α , IFN-I, ROS, and glutamate) that can cause neurotoxicity. These universal mediators could serve as therapeutic targets to lessen the pathogenesis associated with many different CNS viral infections. The IFN-I pathway, for example, plays an important role in the CNS defense against most viral infections [136], and modulation of this pathway might provide a therapeutic means to control the magnitude of CNS inflammatory responses. Many advances in our understanding of neurotropic viruses have been made thus far, but more research is required to improve our ability to rapidly diagnose and then treat CNS infections [137], especially for viruses like JCV that have no animal model. Viral

diseases of the CNS represent a significant burden to the global community, and the only way to lessen this burden is through a concerted research effort that involves pathogen discovery, animal model and therapeutic development, and intervention studies.

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HIGHLIGHTS

- A diverse spectrum of viruses can enter the CNS, causing acute and chronic neurological disorders
- Virus-induced CNS diseases are influenced by routes of viral entry, viral tropism, and immune responses
- CNS immune reactions limit the spread of virus, but can also cause severe pathology
- Viruses can directly injure or disable cells of the CNS resulting in disease
- New animal models and therapeutic interventions are required to lessen the burden of CNS viral infections worldwide

Figure 1. Immunopathogenesis of fatal meningitis induced by LCMV

A) On day 5 post-infection, small numbers of antiviral CD8⁺ T cells begin to infiltrate the subarachnoid space and engage virus-infected targets such as meningeal stromal cells, leading to chemokine release. There is little pathology in the meninges and brain parenchyma at this time point, although reactive microglia can be observed. B) On day 6 post-infection, large numbers of CD8⁺ T cells migrate into the subarachnoid space, which amplifies chemokine release and gives rise to massive, synchronized extravasation by innate myelomonocytic cells. This results in disruption of vascular tight junctions, breakdown of the glial limitans, cellular pathology, edema, and ultimately death.

Figure 2. Brain regions affected by viruses that cause meningitis and encephalitis

Abbreviations: AV, alphaviruses, BV, bunyaviruses, CMV, cytomegalovirus, 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.

Figure 3. Spinal cord regions affected by viruses that cause myelitis

Abbreviations: HEV, human enteroviruses, JEV, Japanese encephalitis virus, PV, poliovirus, RV, rabies virus, TBEV, tick-borne encephalitis virus, WNV, West Nile virus.