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Review article

Molecular mechanisms of neuroinflammation and injury during acute viral encephalitis

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ABSTRACT

Viral infections in the central nervous system are a major cause of encephalitis. West Nile virus (WNV) and Herpes simplex virus (HSV) are the most common causes of viral encephalitis in the United States. We review the role of neuroinflammation in the pathogenesis of WNV and HSV infections in the central nervous system (CNS). We discuss the role of the innate and cell-mediated immune responses in peripheral control of viral infection, viral invasion of the CNS, and in inflammatory-mediated neuronal injury. By understanding the role of specific inflammatory responses to viral infections in the CNS, targeted therapeutic approaches can be developed to maximize control of acute viral infection while minimizing neuronal injury in the CNS.

Contents

1. Introduction

Viral encephalitis is an important cause of morbidity and mortality in the United States and throughout the world. In the U.S. viral encephalitis results in a mean of 7.3 hospitalizations per 100,000 population, with a disproportionate burden on individuals greater than 65 or less than 1 year of age (George, Schneider, & Venkatesan, 2014a, 2014b). Numerous viruses are associated with encephalitis, but increased vaccination rates and new vaccines have reduced the rates of encephalitis due to previously common pathogens including measles (*Morbillivirus*), mumps (*Rubulavirus*), and poliovirus (Picornavirus) over the last 60 years. Other pathogens that can cause encephalitis

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such as Western Equine Encephalitis Virus and St. Louis encephalitis virus have decreased in incidence over the last 20 years, for reasons that remain poorly understood (Go, Balasuriya, & Lee, 2014).

In studies of encephalitis etiologies, 50–62% of encephalitis cases are due to unknown causes (Glaser, Gilliam, Schnurr, et al., 2003; Granerod, Ambrose, Davies, et al., 2010; George et al., 2014a, 2014b). In these same studies, viruses account for approximately half the cases of encephalitis with an identified etiology (Glaser et al., 2003; Granerod et al., 2010; George et al., 2014a, 2014b). A variety of viruses belonging to a diverse group of viral families cause encephalitis including DNA viruses such as Herpes simplex viruses (HSV) or human cytomegalovirus (CMV) and Varicella-zoster virus (VZV); single stranded RNA viruses such as West Nile virus (WNV), St. Louis encephalitis virus, and Zika virus; and retroviruses such as human immunodeficiency virus 1 (HIV-1). Overall, HSV is the most common cause of sporadic viral encephalitis and WNV the most common cause of epidemic encephalitis in the US (George et al., 2014a, 2014b) (Table 1). While other viruses, including recently emerged Zika virus, cause acute infections of the central nervous system, these viruses are much less common when compared to WNV and HSV.

Given the importance of HSV and WNV as the predominant identified causes of viral encephalitis in the US, this review will focus on the mechanisms of inflammation and neuronal injury during acute WNV encephalitis (WNE) and acute Herpes simplex virus encephalitis (HSE). In general, the clinical outcome of viral encephalitis is the result of a complex interplay between the direct effects of viral infection on the central nervous system (CNS) and the associated innate and adaptive host immune responses to infection. Understanding the interactions between viral infection, inflammation, and injury in the CNS informs our clinical understanding of outcomes and therapeutic interventions in patients with viral encephalitis.

2. West Nile virus encephalitis pathogenesis

West Nile virus (WNV) is a member of the genus flavivirus and is related to other clinically important neuroinvasive flaviviruses including Japanese Encephalitis virus, St. Louis encephalitis virus, and Zika virus. WNV is the leading cause of epidemic encephalitis in North America and has caused recurrent localized outbreaks of viral encephalitis since its introduction in 1999 (CDC.gov/westnile). Following its introduction into the United States, WNV rapidly spread across North America and caused over 41,000 confirmed cases of disease, and nearly 19,000 cases of neuroinvasive infection (encephalitis, meningitis, myelitis). WNV infections now occur as annual epidemics in characteristic areas in the United States (Fig. 1). Mortality among patients with WNV neuroinvasive disease is approximately 9%, with the majority of mortality occurring in patients with encephalitis.

WNV is naturally maintained in an enzootic cycle in avian hosts, primarily passerine species of birds including crows, jays, and sparrows, with transmission by *Culex* and other mosquito species. Infection of humans usually occurs following the bite of mosquito but transmission can also occur by less frequent means such as blood transfusion or organ donation. Humans are typically "dead-end hosts" because infection does not produce a viremia of sufficient magnitude to infect subsequent biting mosquitoes. After inoculation via an infected mosquito, WNV replicates in dendritic cells and macrophages in the dermis near the bite site. Infected inflammatory cells spread virus to regional lymph nodes and into the lymphatic system. Following localized replication, patients develop a primary viremia with subsequent seeding of reticuloendothelial organs such as the spleen where continued replication results in a secondary viremia that facilitates spread of virus to the CNS (Petersen, Brault, & Nasci, 2013). Following entry to the CNS, WNV directly infects neurons, with a predilection for cells in subcortical regions including the basal ganglia, thalamus, midbrain, and cerebellum. WNV can also infect the motor neurons of the anterior horn of the spinal cord. Injury in these subcortical regions results in the distinctive features of WNV encephalitis that can include altered mental status, Parkinsonian features (tremor, bradykinesia, rigidity), ataxia, myoclonus, and acute flaccid paralysis (Sejvar, Haddad, Tierney, et al., 2003; Debiasi & Tyler, 2006).

The inflammatory process following WNV infection can be divided into responses in the periphery that limit primary and secondary viremia, inflammatory processes associated with invasion of the CNS, and inflammatory responses in the CNS responsible for clearing virus. Due to extensive research in mouse models of disease, the pathophysiology of the immune response following WNV infection is increasingly well characterized (Reviewed by Suthar, Diamond, & Gale, 2013b).

3. Peripheral innate responses

Interferon responses are the primary, early responses required to control WNV infection of a susceptible host and prevent viral invasion of the CNS. Mice lacking interferon receptors (IFNAR−/−) exhibit increased susceptibility to WNV infection, as do mice lacking key components in downstream IFN signaling pathways including interferon regulatory factor-3 (IRF3) (Daffis, Samuel, Keller, et al., 2007). Recent work in mouse models of WNV encephalitis have shown that viral RNA acts as a pathogen-associated molecular pattern (PAMP) that is recognized by cytosolic innate immune pathogen recognition receptors or PRRs (reviewed in Suthar, Aguirre, & Gernandez-Sesma, 2013a). One such PRR is called the retinoic-acid inducible gene-I (RIG-I)-like receptor or RLR. RLRs recognized non-self RNA signatures and interact with mitochondrial antiviral (MAVs) signaling protein to induce type I interferon (IFN), proinflammatory cytokines, and express IFN-stimulated genes (ISGs) such as 2′-5′ oligoadenylate synthetase 1 (OAS1). In many cells types, RLRs like RIG-I or myeloma differentiation factor 5 (MDA5) are critical for detecting and responding to flavivirus infections including West Nile virus (Fredericksen et al., 2008). While the fundamentals of pathogen detection and IFN responses are present in the periphery and in the CNS, it is the peripheral IFN-dependent restriction of WNV that is critical to limiting viral invasion of the CNS.

Once type 1 interferon is induced, it can restrict additional viral replication through induction of interferon stimulated genes (ISGs) which directly restrict viral infection. For example, T1IFN-induced induction of 2′-5′-oligoadenylate synthase 1 (OAS1) and RNaseL results in direct

Table 1
Viral encephalitis case numbers.

Virus	US cases (dates)	Fatalities	Mortality rate
WNV	~44,000 total cases and 20,265 Neuroinvasive cases (2000–2015) Cdc.gov/westnile	1783	4%
HSV	1.2–7.3 out of 100,000 persons (annual incidence) (George et al., 2014a, 2014b; Jouan, Grammatico-Guillon, Espitalier, et al., 2015)	N/A	5.5–11.9%
St. Louis encephalitis	92 reported cases (2004–2013) cdc.gov/sle	2	2%
Eastern equine encephalitis virus	85 reported cases (2004–2013) cdc.gov/easternequineencephalitis	34	40%
Zika virus	5040 reported cases in Continental US and 48 cases of fetal infection in 1047 Zika virus-infected pregnant women (2015–2016)	5 (Pregnancy loss)	10%[a]

[a] Calculated as known number of fetal loss cases/total reported fetal infections.

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