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Topical Review

Virus and Immune-Mediated Encephalitides: Epidemiology, Diagnosis, Treatment, and Prevention

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ABSTRACT

Virus encephalitis remains a major cause of acute neurological dysfunction and permanent disability among children worldwide. Although some disorders, such as measles encephalomyelitis, subacute sclerosing panencephalitis, and varicella-zoster virus–associated neurological conditions, have largely disappeared in resource-rich regions because of widespread immunization programs, other disorders, such as herpes simplex virus encephalitis, West Nile virus–associated neuroinvasive disease, and nonpolio enterovirus-induced disorders of the nervous system, cannot be prevented. Moreover, emerging viral disorders pose new, potential threats to the child's nervous system. This review summarizes current information regarding the epidemiology of virus encephalitis, the diagnostic methods available to detect central nervous system infection and identify viral pathogens, and the available treatments. The review also describes immune-mediated disorders, including acute disseminated encephalomyelitis and N-methyl-D-aspartate receptor antibody encephalitis, conditions that mimic virus encephalitis and account for a substantial proportion of childhood encephalitis.

Keywords: virus, encephalitis, seizures, epidemiology, autoimmune encephalitis, acute disseminated encephalomyelitis, NMDA

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Introduction

Of the more than 200 viruses that have been linked to human disease, at least 100 can infect the central nervous system (CNS) or induce neurological disorders via immune-mediated mechanisms.[1,2] Although some viral infections associated with neurological disorders, such as measles, mumps, rubella, poliovirus and varicella-zoster, can be prevented by vaccination and a few, such as herpes simplex virus (HSV) encephalitis, can be treated with potent antiviral medications, many other viral infections have no specific therapy or effective means of prevention. Consequently, encephalitis, denoting infection or inflammation of the brain parenchyma, remains a major source of neurological disease and permanent disability among children worldwide.

Viruses, the smallest of the microbes causing human disease, induce neurological disorders during primary (initial) human infection, after reactivation of latent infection or in the case of acute disseminated encephalomyelitis, through immune-mediated mechanisms.[1] Most viral CNS infections reflect primary infection and begin with virus entry and replication in the skin, the conjunctiva, or the epithelial cells of the respiratory or gastrointestinal tracts. The incubation period typically ranges from 1 to 21 days, although in rabies,[3] a year or more may lapse between the exposure to the virus and the onset of symptoms. Because most viruses reach the CNS hematogenously, the likelihood of CNS invasion and encephalitis is influenced by the efficiency of virus replication at systemic sites, the protective effects of innate or adaptive host immune responses, the resulting magnitude or duration of viremia, and the integrity of CNS barriers.[1] Notable exceptions to the hematogenous route of CNS invasion are the HSVs and the rabies virus, which can use neural routes to infect the brain.[1]

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Several factors, including host immune response and the presence of cell surface receptors, determine the likelihood of viral infection of host cells and, in turn, the probability of encephalitis.[1] Host immune compromise, secondary to chemotherapy, immunomodulators, HIV/AIDS, or other factors, can influence the risk of severe or fatal infections, including virus encephalitis. In addition, host genetic mutations may increase the potential for encephalitis with certain viruses. Deficiencies in Toll-like receptors and Toll/interleukin-1R domain-containing adaptor inducing interferon-β protein, as examples, contribute to susceptibility to HSV encephalitis in some children.[4,5]

This review summarizes current information regarding the epidemiology, diagnosis, treatment, and prevention of encephalitis. Although the material focuses on the viruses known to cause encephalitis in infants, children, and adolescents, the review also describes selected emerging viral infections as well as noninfectious disorders that can mimic viral encephalitis, including a fascinating group of immune-mediated disorders, of which anti–N-methyl-D-aspartate (NMDA) receptor encephalitis serves as the prototype. Although other microorganisms, such as *Legionella species*, the cause of Legionnaire's disease; *Bartonella henselae*, the cause of cat-scratch disease; the atypical bacterium *Mycoplasma pneumoniae*; and certain fungi or parasites can also produce disorders that mimic virus encephalitis, these infections are beyond the scope of this review.

Epidemiology

Viral encephalitis

Rates of virus encephalitis, generally higher among children than adults, range from 3 to 30 or more per 100,000 persons of all ages annually, depending upon the location of the epidemiological study.[1,6] The herpesviruses, tick- or mosquito-borne viruses (arboviruses), and nonpolio enteroviruses account for the majority of encephalitis cases in many regions of the world.[1,6] HSV causes approximately 10% of encephalitis cases in humans, affecting approximately 1 in every 250,000-500,000 children and adults worldwide.[7] Swedish investigators observed that the incidence of herpes simplex encephalitis among patients ranging from less than 1 year to greater than 90 years of age was 2.2 cases per million population per year.[8] In the United States, approximately 260,000 encephalitis-caused hospitalizations from all viral infections occurred between 1998 and 2010, corresponding to slightly more than 20,000 children and adults with encephalitis requiring hospitalization annually or ~6 cases per 100,000 persons/year.[9]

Before the appearance of West Nile virus in the United States, only 200-500 cases of arboviral encephalitis were reported to the Centers for Disease Control and Prevention (CDC) annually. In 1999, West Nile virus emerged in the United States, and by the end of 2003, the year in which West Nile virus activity peaked, the CDC had received reports of more than 14,000 cases of human West Nile virus infections in the United States and nearly 6,000 cases of West Nile virus–mediated neuroinvasive disease.[10,11] In 2003, 2006, and 2012, the years of greatest West Nile virus activity in the United States, 13 or more states reported an incidence of neuroinvasive disease exceeding 1 case/100,000 inhabitants, mostly among older adults.[10] By contrast, rates of encephalitis from other US arboviruses, such as La Crosse virus and eastern equine encephalitis virus, although varying from year to year, remained relatively constant.

Although rare in the United States and other resource-rich nations, human rabies cases in Africa and India average between 1/100,000 and 1/1 million inhabitants annually and result in over 25,000 deaths annually in Africa alone.[12,13] In the United States, six or fewer indigenously acquired cases of human rabies occur annually,[14] and certain regions, such as Australia, much of Europe, New Zealand, and several other island nations, are rabies-free.[15] Children and adolescents compose approximately 40% of human rabies cases[16]; dogs and bats serve as the principal sources of human rabies in Africa and the United States, respectively.

Encephalitis from environmentally derived pathogens, such as the tick- or mosquito-borne encephalitis viruses (collectively called arboviruses because of being *ar*thropod-*bo*rne), occurs when vectors are active, typically in the late spring, summer, or fall, and patients often display distinct geographic patterns unique to the distribution of vectors. Travel to or residence in regions endemic for selected viral pathogens, such as Japanese encephalitis virus or tick-borne encephalitis viruses, agents endemic to Asia and Europe, respectively, increase the risk of encephalitis with these viruses.[17,18] Outdoor activities, such as camping or hiking, and occupations such as herding or lumbering increase the probability of several vector-borne infections, including La Crosse virus, endemic to the Midwestern United States, and tick-borne encephalitis viruses. By contrast, infection with human-derived viruses, such as the herpesviruses and nonpolio enteroviruses, requires direct contact with infected humans or with fomites contaminated with infected human secretions. Although infections with these viruses can occur throughout the year, some, such as chickenpox, peak in the late winter or early spring[19] and others, such as the nonpolio enteroviruses, peak during the summer and fall.[20]

Emerging infections

Periodically, viruses emerge and cause serious or widespread human disease. Recent examples include the West Nile virus, a mosquito-borne flavivirus that appeared in Africa in the 1930s and remained relatively dormant until the 1990s when it caused outbreaks in the Middle East, Europe, and the United States[10,11,21]; Nipah virus,[22] a paramyxovirus endemic to India, Bangladesh, and South Asia; chikungunya, a mosquito-borne alphavirus endemic to Africa, India, and Southeast Asia that has recently emerged in the western hemisphere[23]; and parechovirus, a picornavirus that can cause severe disease in neonates.[24]

Several factors, including host behaviors, travel, climate, natural disasters, gene mutations, or recombination of genomic material, contribute to the phenomenon of virus emergence. The emergence of human viral diseases is often multifactorial, reflecting changes in human behaviors, the genetics of microorganisms, and the epidemiology of