Journal of Neuroinfectious Diseases

Solomon, et al., J Neuroinfect Dis 2016, 7:2
http://dx.doi.org/10.4172/2314-7326.1000220

Review Article Open Access

Neuropathology of Zika Virus Infection

Isaac H Solomon, Danny A Milner and Rebecca D Folkerth*

Department of Pathology, Brigham and Women's Hospital, Boston, USA

***Corresponding author:** Rebecca D Folkerth, Department of Pathology, Brigham and Women's Hospital, 75 Francis Street, Boston, MA 02115, USA, Tel: +16177325500; E-mail: rfolkerth@partners.org

Rec date: Jun 02, 2016; **Acc date:** Jun 20, 2016; **Pub date:** Jun 23, 2016

Abstract

Zika virus (ZIKV) is a member of the Flaviviridae family that had been associated only with mild disease prior to the 2015 outbreak in Brazil. A dramatic increase in reported cases of microcephaly and Guillain-Barré syndrome during this time prompted significant research into possible associations with ZIKV and its neurotropic properties. Infection of neural progenitor cells and organoids have been shown to induce apoptosis and dysregulation of growth, and mouse studies have demonstrated viral replication in brain tissue in adults, as well as vertical transmission resulting in embryonic brain abnormalities. Large case series of clinical and radiological findings of congenital ZIKV infection have begun to be published; however, pathology reports have been limited to two case reports and two small case series. Thus far, the findings have largely been restricted to the brain and include diffuse grey and white matter involvement consisting of dystrophic calcifications, gliosis, microglial nodules, neuronophagia, and scattered lymphocytes. Mild chronic villitis was observed in the placental tissue in some cases, and the remaining organs were essentially uninvolved. Larger, systematic studies, including correlation of histological findings with gestational age at the time of maternal infection, will be required to determine the full range of Zika virus-induced abnormalities and to help guide future clinical decision making.

Keywords: Zika virus; Microcephaly; Guillain-Barré syndrome; Neuropathology; Histology

Introduction

ZIKV (ZIKV) is a member of the *Flaviviridae* family, first identified in the Zika Forest of Uganda in 1947 [1]. Only rare cases were reported in humans prior to outbreaks on the Yap Island in the Federated State of Micronesia in 2007 and French Polynesia in 2013-2014. Cases were first recognized in Brazil in early 2015, and phylogenetic analysis determined that the virus isolates were most closely related to strains from South East Asia and the Pacific islands, suggesting spread via travelers from affected areas. Until the 2015 outbreak in Brazil, infection with ZIKV was predominantly observed to be asymptomatic or associated with a mild disease course including acute onset of fever with maculopapular rash, arthralgia, myalgia, headache, and conjunctivitis, affecting all age groups. Transmission is typically mediated by *Aedes* species mosquitoes, but virus can also be transmitted perinatally, in utero, sexually, or through transfusion products; virus has been detected in urine, saliva, and breast milk [2-5]. Diagnosis relies on a high degree of suspicion due to overlap in symptoms and geographic region with other arboviral infections, including Chikungunya and Dengue. The diagnosis is confirmed by serology and detection of viral nucleic acids by RT-PCR [6]. Treatment of symptomatic infections is supportive only, as no vaccines are currently available. While deaths from acute infection are rare, ZIKV has been associated with Guillain-Barré syndrome (GBS), which can lead to paralysis and death [7].

Neurological Disease Associated with ZIKV Infection

The investigation of a 20-fold increase in cases of microcephaly (defined as a head circumference less than 2 standard deviations below the mean), in Brazil in 2015 suggested a possible connection to ZIKV infection during pregnancy, prompting intense research worldwide [8]. Active ZIKV infection has since been reported in over 48 countries and territories in South and North America, and numerous other countries have reported cases in travelers returning from areas with active infection. The Centers for Disease Control and Prevention (CDC) recently released a statement declaring ZIKV to be the proven cause of microcephaly based on the accumulated epidemiological evidence [9]. Through May 19, 2016, 1,384 confirmed and 3,332 suspected ZIKV-associated microcephaly cases and 88,545 suspected and 31,616 confirmed ZIKV infections have been reported in Brazil, suggesting a rate of microcephaly to total cases of 1%-4% [10]. A study of symptomatic pregnant women with laboratory confirmed ZIKV infections reported ultrasound detection of fetal abnormalities in 12/42 (29%) cases [11]. Although microcephaly had not been associated previously with ZIKV infection, retrospective studies of the 2013-2014 outbreak in French Polynesia identified an increase in incidence of microcephaly and other congenital brain abnormalities (8 cases of microcephaly with 8,750 suspected and 383 laboratory confirmed ZIKV infections) during the period of time with active infection [12,13]. The vast majority of cases of congenital ZIKV infections have been reported in Brazil (1384/1401, 98%), while a few scattered cases have been identified in Colombia, Martinique, Panama, Puerto Rico, and the United States [10]. Studies to identify environmental and genetic co-factors impacting the rate and severity of congenital infections are ongoing.

Prior to the current epidemic, neurological illness associated with ZIKV had previously been limited to scattered cases of GBS [7]. In addition to congenital microcephaly and ocular disease in fetuses and infants and a large number of GBS cases in adults, scattered reports of acute myelitis and meningoencephalitis have been published, indicating a broader range of neurological presentations or sequelae may exist [14-16]. The potential neurotropic properties of ZIKV have

been known for decades due to early mouse studies [17]. More recent experiments utilizing mice deficient in interferon response, due to knockout of IFN-α/β+/-IFN-γ receptors or treatment with IFNAR1-blocking monoclonal antibodies, have demonstrated rapid viremic dissemination and severe brain pathology [18-21]. Mouse models have