# Chikungunya virus: The neurology

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Chikungunya virus (CHIKV) is an insect-borne virus, of the genus, Alphavirus and the family Togaviridae that is transmitted to humans by virus-carrying *Aedes mosquitoes*[1] and was first recognized in epidemic form in East Africa in 1952-1953.[2,3] In India CHIKV was first isolated in Calcutta in 1963,[4] with several reported outbreaks in India since then. The recent 2005 CHIKV epidemic, caused by the central/eastern African genotype, occurred among the populations of Réunion and other Indian Ocean islands,[5,6] and spread to India, where an estimated 1.4 million people were infected.[7-9] Comparing the earlier outbreaks, the recent episode was massive, spread at a fast pace to wider areas causing serious economic and social impact.[8]

Infection from CHIKV infection typically induces a mild disease in humans, characterized by fever, myalgia, arthralgia, and rash. During the recent epidemic, previously unreported severe forms of CHIKV infection were observed in adults, complicated by multi-organ involvement.[10-15] The maximum estimated incidence of severe CHIKV infection was 34 cases per 200,000 population (less than 0.02%).[13] This epidemic also witnessed the first ever CHIKV associated deaths and mother to child transmission.[5,8,14,15]

CHIKV infection was first reported to affect the nervous system in the 1960s;[16] in the early 1970s it was found to be associated with meningoencephalitis, myelitis, and choroiditis.[17] The re-emergence of CHIKV infection in areas with efficient clinical facilities has allowed CHIKV-related neurological disease to be better defined both in adults and children. Various neurological complications described in the recent epidemic include: meningo-encephalitis, meningo-encephalo-myeloradiculitis, myeloradiculitis, myelitis, myeloneuropathy, Guillain-Barre' (GB) syndrome, external opthalmoplegia, facial palsy, sensorineural deafness, and optic neuritis.[14,15,18-24] Optic nerve involvement in CHIKV infection included papillitis, retrobulbar neuritis, and neuroretinitis.[20] Encephalitis appears to represent the most common clinical manifestation and occurs either simultaneously or within few days of onset of systemic symptoms, during the period of viremia. A delay of more than two weeks had been reported with other complications like myelitis, GB syndrome, and optic neuritits.[14,20,24]

The pathophysiology of human CHIKV infection and the neurological complications associated with the disease has so far remained essentially unknown. Animal experimental studies suggest that the fibroblast is the cell chiefly targeted by CHIKV and this accounts for its tropism for muscles, joint, and skin connective diseases closely resembling the cell/tissue tropism observed in biopsy samples of CHIKV infected humans. These studies also identified two critical factors influencing viral replication: neonatal age and defective type-I interferon (IFN) signaling.[25] In the recent epidemic in the Reunion Island, vertical transmission of CHIKV was seen in the neonates born to the mothers infected with the virus intrapartum.[26] Viral inclusions have been demonstrated in Kupffer cells of liver and myocytes, respectively by Lemant *et al.*[15] in patients with severe disease, thus proving hepatic and myocardial tropism. Ziegler *et al.*[27] observed the presence of virus in the leg muscles even after the disappearance of viraemia, which lasted for 6-7 days.

CHIKV is strongly suspected to have neurotropism but has not been well studied like other neurotropic arboviruses including alphaviruses species, such as Eastren equine encephalitis and Venezuelan equine encephalitis.[28] In the experimental studies, Couderc *et al.*[25] had showed that CHIKV disseminates to the central nervous system in severe cases, where it specifically targets the choroid plexuses and the leptomeninges. In contrast, microvascular endothelial cells that constitute the blood-brain barrier were not infected. The only pathological study had not shown any evidence for the neurotropism for CHIKV. The pathological changes were more of non-specific of encephalitis.[29] Diffusion weighted (DWI) magnetic resonance imaging (MRI) in adult patients with encephalopathy showed multiple small restricted diffusion lesions.[14,29] Contrast MRI imaging showed meningeal enhancement (unpublished personal observations).[29] The most distinctive MRI abnormalities observed in the course of neonatal chikungunya encephalopathy were exclusively located in the white matter and consisted of areas of reversible diffusion restriction, a pattern classically associated with transient ischemia with cytotoxic edema,[26] that does not imply neuronal death.[30]

In patients with CHIKV infection with neurological complications, both adults and children, cerebrospinal fluid (CSF) was positive for real-time polymerase chain reaction (RT-PCR) (which detects the genome of virus particles during an active infection) and IgM serology (which looks for an immune response to recent infection).[14,15,24,29,31,32] Five of the babies born to mothers infected with the virus intrapartum had CSF RT-PCR positive for CHIKV (mean viral load 184,000 copies/ml of CSF), but normal for chemistry and cytology.[26] One may argue that positive RT-PCR or IgM in CSF could be as the result of contamination with peripheral blood. The detection of a very high level of viral genomes ($1.5\times10^{[8]}$ copies/ml) in the CSF seven days after symptom onset in a fatal case of CHIKV infection cannot be explained by this argument.[32] In few cases CHIKV has been isolated from the CSF in patients with CHIKV encephalitis.[33]

Thus, there exists some evidence in both neonates and adults CHIKV exhibiting a neurotropism. However, we still need a conclusive proof for the neurotropism of CHIKV in the form demonstration of neuronal inclusion bodies as has been shown in myocytes and Kupffer cells of liver.

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