Neurological Complications of Dengue: Beware of Striking Similarities with Severe COVID-19

In the recent publication by Kulkarni, *et al*., from Western India, authors have retrospectively analyzed all the patients with neurological complications of dengue fever.[1] The frequency of various manifestations determined by the authors in their cohort is consistent with the known prevalence of dengue complications from past studies. Most common being encephalopathy, followed by encephalitis and hemorrhagic stroke. Syncope and acute symptomatic seizures are also highlighted by authors. However, syncope and seizures may be secondary to severe dengue-related homeostatic abnormalities and may not be independent diagnostic entities. The various post-dengue immune-mediated entities are also consistent with the known information. Additional information regarding the time of onset of neurological symptoms after the onset of dengue-related symptoms could have helped to understand the para-infectious and post-infectious nature of neurological involvement.

Since, the increased vascular permeability and coagulation abnormalities in severe dengue are transient and occurs around the second week of illness, the timing of neurological complication of severe dengue fever assumes importance. Such large data-set of dengue patients can also be utilized to statistically determine factors or variables that could potentially predispose a patient to neurological complications. However, the study assumes importance in view of a large sample size and information regarding the outcome of encephalopathy and encephalitis patients.

In 2009, the World Health Organization (WHO) classified dengue fever into dengue fever without warning signs, with warning signs and severe dengue.[2] The traditional way of classification of dengue fever into dengue fever, dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS) also had reasonable sensitivity and specificity to detect severe cases.[3] However, the 2009 classification identify patients with end-organ damage like liver failure, heart and other organ involvement and neurological involvement in addition to those with hemorrhagic manifestations and circulatory failure as cases of severe dengue.[2] The clinical implication of identifying patients with severe dengue fever is to provide early and intensive care to these patients.

Neurological complications of dengue fever are seen in 0.5% to 21% of all laboratory confirmed dengue cases.[4] Encephalopathy is the most common and the most neurological manifestation of severe dengue. Encephalopathy occurs primarily secondary to metabolic abnormalities, coagulation abnormalities (systemic and brain hemorrhages), circulatory failure, cerebral edema, and secondary to organ failure like anoxia, liver or renal failure. Post-mortem studies have shown evidence of cerebral congestion, edema, focal hemorrhages and multiple microhemorrhages. Usually, there is no evidence of elevated protein or cells in the cerebrospinal fluid (CSF).[4] After 1990, there were increasing reports of encephalitis secondary to dengue fever. This led to the evidence of neurotropic nature of dengue virus.[5] There were multiple reports of isolation of dengue virus from neural tissue and CSF in patients with dengue encephalitis.[4] The clinical manifestation of encephalitis is difficult to differentiate from encephalopathy because both presents with reduced level of consciousness and seizures.

However, the presence of focal signs in form of limb weakness and cranial neuropathies, meningeal signs and evidence of inflammation in the CSF are pointers towards encephalitis. A number of post-mortem studies in patients with encephalitis where dengue virus was isolated from CSF or dengue antigen was demonstrated with immunohistochemical staining of neural tissue showed histochemical evidence of meningitis, encephalitis, necrosis, perivenular inflammation in addition to cerebral edema and hemorrhages.[6-8] The outcome of dengue encephalopathy and dengue encephalitis is variable and multi-factorial. While most patients with either of the diagnosis showed spontaneous recovery, many patients had fatal outcome.[9,10] Associated circulatory failure or hemorrhagic manifestations and lack of supportive care were factors associated with fatal outcome.[9]

Acute disseminated encephalomyelitis (ADEM), acute necrotizing encephalitis, cerebral hemorrhages and ischemic stroke, optic neuritis, retinal involvement, Guillain-Barré syndrome, isolated cranial neuropathy and dengue myositis have been well reported in patients with dengue fever.[4] Most of these manifestations are immune-mediated post dengue syndromes. Intracranial hemorrhage is usually seen during the convalescent stage of dengue fever.[11] Cerebral hemorrhage, cerebellar and brainstem hemorrhage, multiple punctate hemorrhage, subarachnoid hemorrhage and acute subdural hematoma are described in patients with dengue fever.[3] Coagulation abnormalities associated with dengue fever may be held responsible for hemorrhagic stroke. Ischemic stroke is less common.

Most post-dengue immune mediated neurological manifestations are temporally related to dengue fever and it often remains difficult to assess the cause-to-effect relationship. CSF examination rarely shows positive PCR

or other serological tests are usually negative for the dengue virus. Muscle involvement secondary to dengue fever may range from myalgia to benign transient muscle weakness to severe life-threatening rhabdomyolysis. Dengue myositis is usually associated with mild to moderate proximal muscle weakness, elevated creatine phosphokinase (CPK) levels and no specific abnormality on electromyography. Most patients show complete recovery.[12] However, severe rhabdomyolysis may present with severe muscle weakness, myoglobinuria, very high levels of CPK and fatal outcome.[13] Rarely, acute muscle necrosis has also been shown on muscle biopsy from patients with rhabdomyolysis.[13]

Pathophysiology of neurological manifestations secondary to the dengue virus is not clearly known. Severe dengue is characterized by leaky blood vessels and coagulopathy that leads to bleeding manifestations and circulatory failure. Phenomenon of cytokine storm is responsible for these manifestations. After the mosquito bite and introduction of the dengue virus to the epidermal and dendritic cells, these cells produce proinflammatory cytokines that determines local inflammation, and also regulates replication and dissemination of the virus by recruiting virus-susceptible cells to the inoculation site.[14] Some of the released cytokines like matrix metalloproteinase (MMP)-2 and MMP-9 may facilitate migration of dendritic cells to local lymph nodes thereby facilitating entry of virus into the circulation.[14] Once the virus enters circulation, it incites innate immune response. The dendritic cells, monocytes, macrophages, natural killer cells and host of other cells responsible for innate immunity elaborates proinflammatory environment by releasing various cytokines like interferon gamma and tumour necrosis factor (TNF)-alpha, and contributes to the disease severity.[14] The activation of adaptive immune response that primarily helps in containing the viremia may also enhance the production of various cytokines. In patients with DHF and DSS, elevated levels of TNF-alpha and interleukin-10 have been seen. Both these cytokines may produce increased vascular permeability and activation of coagulation cascade.[14]

Neurological manifestations of Covid-19 and dengue fever have striking similarities. The most common neurological symptoms in Covid-19 are headache and anosmia or ageusia. The common severe neurological complication of Covid-19 is encephalopathy, arterial and venous stroke. Meningitis, encephalitis and transverse myelitis are infrequent. Common peripheral nervous system manifestations are Guillain–Barré syndrome, Miller Fisher syndrome, rhabdomyolysis and myositis.[15] Covid-19 and severe dengue also have strikingly similar pathophysiology, like capillary leak, thrombocytopenia, and coagulopathy. Severe Covid-19 and severe dengue have similar host severe immunological response also referred as the cytokine storm. In both, the cytokine storm is mediated by pro-inflammatory cytokines such as tumor necrosis factor and interleukin-6. In severe dengue, the destruction of platelets is predominant cause of thrombocytopenia which may result in coagulopathy, disseminated intravascular coagulation, and in some cases, even death.[16,17] Lately, many cases of cerebral venous thrombosis with thrombocytopenia after SARS-CoV-2 vaccination have been reported.[18] Physicians working in India, a country with huge numbers of both dengue and Covid-19, need to be familiar with these similarities to avoid catastrophic consequences resulting out of ignorance.

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