Spectrum of Neuroimmunological Manifestations of Dengue Fever

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Introduction

Dengue fever (DF) is a viral disease caused by the bite of the *Aedes aegypti* female mosquito, with a wide range of signs and symptoms, similar in most cases to flu-like syndrome.[1] However, in a minority of cases, there may be serious complications, generating haemorrhagic manifestations, shock, and neurological disorders.[1,2] Neurological manifestations reportedly occur in 0.5%–21% of dengue virus-infected patients.[3] Among the dengue serotypes, dengue virus (DENV) 3 is responsible for the largest number of neurological complications.[3]

In Brazil, there is currently a notable dengue epidemic. According to the latest updated data from the Brazilian Ministry of Health,[4] in 2024 there are 2,965,988 probable cases and 1,117 confirmed deaths from dengue, in addition to 1,806 deaths under investigation to determine whether there is a relationship with the disease. The incidence rate of dengue currently in the country, for every 100 thousand inhabitants, is 1460,6.[4] Unfortunately, expectations for improvement in this scenario are low. The government has been trying to develop a vaccination campaign against the virus, however, sanitation problems and a shortage of vaccines put the success of this campaign at risk.[5]

So, due to the wide range of neurological complications of DF and, the current dengue epidemic that the country is experiencing, this study aimed to describe the main neuroimmunological manifestations that this disease can cause.

Main Neuroimmunological Manifestations

Guillain-Barre syndrome (GBS) is an acute demyelinating autoimmune syndrome, with areflexia, ascending motor paralysis, and cytological albumin dissociation in the CSF.[6] GBS and its variants represent 5% of neurological complications in paediatric patients with DF.[6] The axonal variant of GBS has also been described in two brothers simultaneously and is associated with DENV infection, although neither had the typical clinical symptoms of DF.[7] The latest case report corroborates a possible genetic predisposition associated with this complication of DF. As most GBS cases occur after the acute dengue stage (Table 1), having an autoimmune process that causes the disease.[6,8] It is believed that both diseases present the same pro-inflammatory substances, facilitating the onset of SBG after a DF case.[6,7] Interleukins, tumour necrosis factor alpha, and complement proteins may play important roles in the pathogenesis of GBS after dengue infection.[8] Moreover, due to a cross-immune response, an attack by defence cells occurs against the myelin and axon of the spinal cord roots.[8]

Encephalopathy, as a manifestation of DF, is more commonly secondary to multisystemic disorders of infectious involvement, such as shock, hepatitis, coagulation disorders, and even bacterial infection concomitant.[9] However, in the case of encephalitis, this is not a mechanism.[9] The most widely accepted hypothesis is that dengue-related encephalitis is caused by DENV neuronal infiltration that induces neurological disorders by the virus or through immunological mechanisms.[9] This inflammation occurs mainly in the viremic stage of DF, whereas other encephalopathies occur later. In the study by Bhushan et al.[10] (Table 1), 13 of 79 patients

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Table 1. Characteristics of Guillain-Barre Syndrome and Encephalitis Among Patients with Dengue Fever.

Author	Country	Disease	Study Design	n	Main Findings
Sahu et al.[3]	India	GBS	Prospective cohort	486 dengue cases	Forty-five patients developed neurologic complications. Among them, 9% presented GBS as a complication
Bhushan et al.[10]	India	GBS	Cross-sectional	1,627 dengue cases	Two hundred and thirty-eight patients developed neurologic complications. Among them, four patients presented GBS as a complication
Sil et al.[6]	India	GBS	Cross-sectional	71 dengue cases	Twenty-eight percent of patients presented with neurological complications. Among them, 5% had GBS as a complication
Sahu et al.[3]	India	Encephalitis	Prospective cohort	486 dengue cases	Forty-five patients developed neurologic complications. Among them, 33% presented encephalitis as a complication
Sil et al.[6]	India	Encephalitis	Cross-sectional	71 dengue cases	Of the total, 28.1% of patients presented neurologic complications Among them, 30% presented encephalitis as a complication
Misra et al.[15]	India	Encephalitis	Retrospective cohort	116 dengue cases	Of the total, 79% of the patients presented neurological complications. Among them, 19% presented encephalitis as a complication
Li et al.[14]	China	Encephalitis	Prospective cohort	183 children with acute viral encephalitis-like symptoms	Of the total, 15.8% of the patients were diagnosed with dengue infection

Note: GBS: Guillain-Barre syndrome.

with immune-mediated neurological complications had encephalitis associated with DENV infection. In the same study, 24 patients had encephalitis associated with direct neurotropic invasion.[10] Neuroimaging in dengue-related encephalitis usually does not show changes,[11] some peculiar findings have been related to this condition on brain magnetic resonance imaging (MRI), such as the 'double doughnut sign' and the 'Jack-o'-lantern sign'.[11] Immunoglobulin M (IgM) testing of the CSF uses the enzyme-linked immunosorbent assay test for DF antibodies, which has high sensitivity and specificity (92% and 99%, respectively) and is used in diagnostic investigations.[12] The gold standard is the virus isolated from cell culture with fluorescence-antibody identification.[13,14] In terms of treatment, although an effective antiviral agent is still lacking, acyclovir and corticosteroids are occasionally used to manage dengue-related encephalitis.[12,14,15]

Transverse myelitis (TM) despite being serious, is an uncommon complication of DENV infection.[15] It may involve clinical recovery conditions that lead to long-term disability.[16] TM-related symptoms include weakness of the limbs, urinary retention, and sensory system alterations.[16] Initially, owing to the direct viral action on the spinal cord, the TM symptoms may result from an immune reaction in the spinal cord.[15] The direct viral invasion diagnosis is supported by IgG and IgM test results or by isolation of the virus at very early stages in the CSF.[17] A study of 10 patients with neurological complications of DF revealed that seven individuals had IgM-positive antibodies and nine were IgG-positive for DENV in the CSF.[16] Controversy persists regarding treatment decisions for TM. Even with proper therapy, neurological function takes months to resume in many patients and may involve residual symptoms. High-level evidence to support the use of intravenous corticosteroids is lacking; however, pulse therapy with methylprednisolone remains the main option, and therapeutic plasma exchange can be a second choice.[18] Although myelitis is rarely associated with DF, clinicians must be aware of its existence as a possible complication to investigate it in the face of neurological symptoms in patients with typical dengue symptoms.[18]

Conclusion

DF has become a relevant cause of CNS and PNS pathologies, with possible mechanisms involving invasion of the virus or cross-immune response complications. The disease may have disabling neurological diseases that can be self-limiting and have a better prognosis when properly managed. DF is not just an emerging infectious disease, but a well-established disorder, with almost half of the population susceptible to its infection. In the tropical and subtropical regions, such as Brazil, especially in the most contagious seasons, the diagnosis of DF should be considered in symptomatic patients, who must be tested to avoid poor outcomes, in

addition to early recognition of neurological manifestations that can be potentially disabling or fatal.

Authors' Contribution

All authors contributed equally.

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