Ischemic Stroke During Dengue Infection: A Report of 2 Cases

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Case series

Patient: Female, 51-year-old • Male, 50-year-old
Final Diagnosis: Dengue • ischemic stroke
Symptoms: Altered state of consciousness • dysarthria • facial palsy • fever • paresis
Clinical Procedure: N/A
Specialty: Neurology

Objective: Rare disease

Background: Involvement of the central nervous system during infection with dengue virus (DENV) is recognized. However, ischemic stroke is rarely reported. Herein are described 2 cases of patients with ischemic stroke in which DENV infection was demonstrated.

Case Reports: The first patient was a 51-year-old woman that presented altered consciousness, monoparesis, facial palsy, dysarthria, Babinski sign, and syncope 7 days from the onset of fever. She had a history of carotid artery atherothrombosis and previous stroke. Magnetic resonance imaging (MRI) showed an acute infarction of the right middle cerebral artery. DENV was confirmed by the presence of NS1 and IgM in serum. The patient was treated with intravenous fluids and recovered well, with only right facial paresis still present at discharge. The second patient was a 50-year-old man who presented with headache, altered consciousness, and mutism after a febrile episode 1 week prior. This patient had a previous history of stroke, glioblastoma resection, epilepsy, hypothyroidism, and diabetes. MRI demonstrated a subacute ischemic event. The diagnosis of dengue was confirmed by serum NS1 and IgM and by RT-PCR in serum and cerebrospinal fluid. DENV-1 serotype was observed in serum and cerebrospinal fluid. The patient was treated with intravenous fluids and was discharged in good condition. In both patients, thrombocytopenia and leukopenia was demonstrated, and hemoconcentration was demonstrated in the second patient.

Conclusions: In tropical and subtropical countries, DENV infection can represent a potential cause of ischemic stroke in patients with a history of comorbidities, including stroke.

Keywords: Case Reports • Dengue • Ischemic Stroke

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Background

Dengue is an arbovirus of importance worldwide, belongs to the family Flaviviridae (genus Flavivirus), and is transmitted by mosquitoes of the *Aedes* genus, mostly *A. aegypti*. In Colombia, dengue infection is highly prevalent, with an average of 76,292 cases per year between 2016 and 2020 [1]. There are 3 dengue infection classifications: (1) without warning signs, (2) with warning signs, and (3) severe dengue. Severe dengue infection includes the following conditions: severe plasma leakage leading to shock and fluid accumulation with respiratory distress; and severe bleeding and severe organ involvement, such as the liver, central nervous system, heart, and other organs [2].

The neurological complications of dengue infection include encephalitis, meningitis, acute disseminated meningoencephalitis, Guillain-Barré syndrome, epilepsy, pituitary apoplexy, progressive tetraparesis, hypokalemic quadriparesis, and stroke. However, ischemic stroke associated with dengue infection has rarely been reported [3-12]. A possible cause is the difficulty in diagnosing the neurological complications associated with dengue virus (DENV). RT-PCR has lower sensitivity in the cerebrospinal fluid (CSF) than in serum, owing to a lower CSF viral load and low IgM antibodies titers detected in the CSF [6]. On the other hand, in Colombia, there is no report of this event in the available literature. Herein, we report 2 cases of patients presenting with ischemic stroke associated with dengue infection.

Case Reports

Case 1

The first patient was a 51-year-old woman. She was a tobacco smoker with a history of carotid artery stenosis and ischemic stroke. The patient consulted medical help owing to the onset of the following neurological manifestations: altered consciousness, monoparesis, central facial palsy, dysarthria, Babinski sign, and syncope associated with the onset of a febrile episode 7 days prior. There were no meningeal signs during the evaluation. The severity of the stroke according to the National Institute of Health Stroke Scale (NIHSS) was grade 2 (mild dysarthria and mild central facial palsy) and her Glasgow coma score was 15/15. On day 3 of hospitalization, her blood pressure was 79/51 mm Hg, and her heart rate was 56 beats per min. Her platelet counts on admission, day 4, and day 7 were 104,000 cells/mm$^3$, 78,000 cells/mm$^3$, and 44,000 cells/mm$^3$ (reference value (RV): 150,000-400,000 cells/mm$^3$). On the same days, her leukocyte counts were 2800 cells/mm$^3$, 2480 cells/mm$^3$, and 6700 cells/mm$^3$, respectively (RV: 4500-11,000 cell/mm$^3$), and hematocrit values were normal at 36.6%, 37.4%, and 38%, respectively (RV: for female, 36.1% to 44.3%). Kidney function was normal, and lupus erythematosus was ruled out. CSF analysis was not performed. MRI showed acute cerebral infarction in the right middle cerebral artery (Figure 1). Cerebral angiography showed occlusion in the communicating segment of the right internal carotid artery and 50% stenosis in the communicating segment of the left internal carotid artery. The electrocardiogram did not present alterations, and the chest X-ray was normal. The patient developed a healthcare-associated urinary tract infection. Dengue fever was confirmed by non-structural protein 1 (NS1) and IgM antibodies using enzyme-linked immunosorbent assay (ELISA). In addition, IgG antibodies were positive, indicating secondary infection. The patient was treated with intravenous fluids. Ceftriaxone was prescribed for urinary tract infection. The patient had a good recovery; only right facial paresis was still present at discharge. The patient was hospitalized for 10 days. The final diagnosis was an ischemic stroke associated with dengue infection. The patient was discharged.

![Figure 1](image_url). Case 1. Acute right middle cerebral artery infarction localized to the corona radiata (arrow) (A) Diffusion-weighted imaging. (B) Apparent diffusion coefficient. (C) Fluid-attenuated inversion recovery.
with antiplatelet therapy and a statin for secondary stroke prevention. Additionally, she was sent to physical and occupational therapy. Five months later, she was recovered of the monoparesia and dysarthria.

Case 2

The second patient was a 50-year-old man with a history of glioblastoma resection 13 years prior, epilepsy, hypothyroidism, dyslipidemia, diabetes mellitus, and ischemic stroke. The patient was hospitalized presenting with headache, altered state of consciousness, decompensation of his epilepsy, and mutism after a febrile episode 1 week prior. The patient was lethargic upon physical examination, with nominal aphasia and Parinaud syndrome. There were no meningeal signs during the evaluation. Upon admission, his temperature and blood pressure were 37°C and 111/75 mm Hg, respectively, and his Glasgow coma score was 9/15. He presented a febrile episode on the second day of hospitalization. His platelet counts on admission, day 2, day 3, and day 5 were 114,000 cells/mm$^3$, 65,000 cells/mm$^3$, 30,000 cells/mm$^3$, and 124,000 cells/mm$^3$, respectively. On the same days, his leukocyte counts were 3790 cells/mm$^3$, 2500 cells/mm$^3$, 3900 cells/mm$^3$, and 5400 cells/mm$^3$, respectively, and hematocrit values were 48.8%, 52.6%, 48.9%, and 44.3%, respectively (RV: for male 40.7% to 50.3%). These data showed a hematocrit of 15.8%. Aspartate aminotransferase levels on day 0, day 3, and day 5 were 106 U/L, 127 U/L, and 93.9 U/L, respectively (RV: 8-33 U/L), and alanine aminotransferase levels were 36 U/L, 46.6 U/L, and 48 U/L, respectively (RV: 4-36 U/L). Other data included hyponatremia (sodium level of 123 mmol/L [RV: 135-145 mmol/L]), potassium 4.3 mmol/L (RV: 3.70-5.20 mmol/L), chlorine 98.5 mmol/L (RV: 96-106 mmol/L), magnesium 2.1 mmol/L (RV: 1.7-2.2 mmol/L), serum glucose 90 mg/dL, creatinine 1.14 mg/dL (RV: 0.7-1.3 mg/dL), and elevated levels of C-reactive protein at 6.9 mg/dL (RV: 0.3 mg/dL). CSF protein concentration was elevated, at 57 mg/dL (RV: 15-45 mg/dL), there was an absence of pleocytosis, and low glucose was present, at 40 mg/dL (RV: 50-80 mg/dL). These findings excluded the presence of bacterial infection. Hence, the risk of bacterial meningitis was considered low. MRI showed subacute right middle cerebral artery infarction and post-surgical changes due to a left temporal lobectomy (Figure 2). Electroencephalogram demonstrated encephalitis without ictal activity. His chest X-ray was normal, and bacterial infection was ruled out. Dengue fever was confirmed by NS1 and IgM antibodies in serum using ELISA. DENV-1 serotype was detected in serum and CSF by real-time multiplex RT-PCR based on the TaqMan assay, using dengue-specific primers and probes provided by the U.S. Centers for Disease Control. The serotype DEN-1 was detected in serum and CSF. The cycle threshold values for virus detection in serum and CSF were 29 and 32, respectively [13]. In addition, IgG antibodies were negative, indicating primary infection. The patient was treated only with intravenous fluids, according to the guidelines of the World Health Organization, and was discharged on day 6 of hospitalization in good condition. The final diagnosis was stroke and encephalitis associated with dengue infection. The patient was discharged with antiplatelet therapy and a statin for secondary stroke prevention. At the time of this report, the patient was being followed because he had refractory epilepsy, but there had not been any new stroke event.

Discussion

The neurological manifestations associated with dengue infection are a challenge to its diagnosis and timely management,
Ischemic stroke associated with DENV infection is rare. When a stroke is observed, hemorrhagic stroke is the most common [4,6,14-20]. Ischemic stroke, on the other hand, is considered rare [21-30]. However, this may be because it is not usual for patients with ischemic stroke to be screened for the presence of DENV. In fact, recent studies that take this into account have described a higher incidence of ischemic than hemorrhagic stroke in dengue cases [28,31].

Ischemic stroke during dengue infection is an acute neurological manifestation, and neurological symptoms can occur at any phase of dengue infection or after the general symptoms of dengue infection, according to other authors [21-31].

DENV-3 and DENV-2 serotypes have been associated with neurological manifestations and, to a lesser extent, DENV-4 [12] and DENV-1 [10], with the last in concordance with our findings. However, why the serotype of DENV is more frequently associated with ischemic stroke is still not clear.

Ischemic stroke associated with DENV infection is more common in male patients, patients older than 60 years, patients with a history of comorbidities, and in patients with severe dengue or with dengue hemorrhagic fever [19,21-23,25,27,28,31,32], which is in keeping with the patients in the present study. Additionally, like in the study of Chang et al [31], both of our patients had a history of ischemic stroke. Chang et al observed that patients with a history of ischemic stroke have a greater risk of hemorrhagic and ischemic stroke associated with dengue infection [31].

None of the studied patients died and one of them had a mild sequela. The current literature does not offer a clear picture of the lethality and sequelae in patients with ischemic stroke during dengue infection [21-31]. These differences could be explained by the type of study population (case report or cohort study), circulating serotypes, or epidemiological context, among other factors. Therefore, further investigation of these variables is needed. One of the patients presented ischemic stroke and encephalitis, features also observed in previous studies [26,27], which suggests extensive involvement of the central nervous system by DENV infection.

The physiopathology of ischemic stroke associated with dengue is not yet clear. The mechanisms proposed are immune-mediated arteritis and a transient hypercoagulable state following plasma leakage [17,21,23,30]. In line with the previously described immune-mediated response, the improvement in clinical symptoms and vasculitis with the use of corticosteroids seems to support this proposal [24].

It has been described that NS1 contributes to coagulation disorders observed in dengue through several mechanisms, such as cytokine storm by activation of macrophages and complement, contributing to endothelial damage and increased permeability [33,34]. These mechanisms lead to hemorrhages and plasma leakage characteristic of dengue infection, which may explain the higher reported incidence of hemorrhagic stroke than of ischemic stroke associated with DENV. Other components such as the loss of endothelial non-thrombotic factors and the expression of thrombomodulin by infected endothelial cells facilitate procoagulant hemostasis in dengue infection [30]. However, both immune-mediated arteritis and a transient hypercoagulable state need to be studied in ischemic stroke patients with dengue.

According to the pathogenesis, neurological manifestations associated with DENV infection have been classified in metabolic derangements, direct invasion by DENV and immune-mediated responses [35]. The first 2 mechanisms are more common in the early stages of the disease. At this point, the therapy relies on supportive care [1]. On the other hand, immune-mediated mechanisms (eg, vasculitis or optic neuritis) occur in the late stage of the disease. Corticosteroids have been used at this phase [12,24,27]. However, their efficacy has not been demonstrated, and currently there is no consensus on the management of ischemic stroke associated with DENV [30]. The management of our patients included supportive care according to World Health Organization guidelines [1], in concordance with other studies [19,21-23,25,29].

Conclusions

Ischemic stroke is a complication of DENV infection. It occurs in the acute phase of the disease and in any clinical form of dengue. This neurological complication occurs in elderly patients with comorbidities, including a prior history of ischemic stroke. These conditions can underestimate dengue infection as a risk factor for ischemic stroke. Therefore, it is important that in tropical and subtropical countries, physicians look for fever in patients that coincides with focal neurological deficits and altered consciousness to exclude DENV infection and give appropriate care. Future studies are needed to determine the measurement of the complexity of the neurological complications of these patients and their economic burden.
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