A 25-Year-Old Man Presenting With Dengue Encephalitis: A Case Report

Reed Aaron A. Cordova, Alain C. Juayang

Abstract

We present a case of a 25-year-old previously healthy man who came into our emergency department with decreased verbal output and fever. Patient came in febrile, tachycardic and tachypneic. Physical examination was essentially normal; however, patient was noted to be aphasic. Initial diagnostics were requested. Complete blood count (CBC) showed leukocytosis with white blood cell count of $15 \times 10^9/\text{L}$ and normal platelet count of $157 \times 10^9/\text{L}$. Chest X-ray was normal, and so was the urinalysis. Leptospira IgG and IgM showed negative results. Patient was suspected to have bacterial meningitis. He was then given empiric therapy and was started with ceftriaxone and vancomycin. The patient was then referred to the neurology service where a magnetic resonance angiography of the intracranial vessels was made. Results were highly suggestive of viral encephalitis. Lumbar tap for cerebrospinal fluid analysis was performed showing negative test results for cryptococcal antigen, gram stain, acid fast stain, culture and susceptibility, tuberculosis (TB) culture, negative staining, herpes simplex virus 1 and 2, and TB polymerase chain reaction (PCR). Patient was referred to the infectious disease service and a repeat CBC was requested showing leukopenia and thrombocytopenia. Dengue duo was positive together with the CSF dengue RNA-PCR. Platelet went down to as low as $14 \times 10^9/\text{L}$ and patient was transfused with six units of platelet concentrate. Supportive therapy was given and daily monitoring of blood counts was made. The patient started to recover on the fifth day and completely recovered and discharged on the ninth hospital day with normal blood counts and no neurologic deficit.

Keywords: Dengue; Encephalitis; Philippines

Introduction

Dengue fever is an arthropod-borne flaviviridae infection transmitted by either *Aedes aegypti* or *Aedes albopictus*, the same mosquitoes that transmit chikungunya, yellow fever and Zika viruses [1]. Dengue fever is characterized by sudden high fever (40 °C or 104 °F), severe headaches, pain behind the eyes, joint and muscle pain, fatigue, nausea, vomiting and skin rash days after fever [2]. Severe dengue is a potentially deadly complication because primarily of plasma leakage and has warning signs that include severe abdominal pain, persistent vomiting, rapid breathing, bleeding gums, blood in vomit, fatigue and restlessness. The disease is widespread throughout the tropics with variations due to rainfall, temperature and urbanization. Dengue has four serotypes: DEN-1, DEN-2, DEN-3 and DEN-4. The Philippines dengue level of risk is frequent and continuous. This means frequent outbreaks occur or transmission is always ongoing. Recovery from particular serotype provides lifelong protection against that particular serotype. Cross-immunity to other serotypes after recovery is somewhat transient, partial and temporary, but subsequent infections by other serotypes increase the potential of developing severe dengue.

Dengue does not normally cause neurological manifestations and is considered to be extremely rare [3]; however, this condition occurs because of the neurotropic effect of the virus or systemic complications of infection. Murthy and colleagues classified these neurological complications into categories that include metabolic disturbance, viral invasion and autoimmune reactions [4]. Cristiane and Marzia [5] already mentioned that the diagnosis criteria of dengue encephalitis include presence of fever, acute signs of cerebral involvement, reactive IgM dengue antibody, NS1 antigen or positive polymerase chain reaction (PCR) on serum and/or CSF, and exclusion of other viral encephalitis and encephalopathy.

Case Report

A 25-year-old man with no known co-morbidity came in with a chief complaint of fever and decreased verbal output. Patient was apparently well until 4 days prior to consult. He developed undocumented intermittent fever and was temporarily relieved by intake of paracetamol. This was associated with body malaise and decreased appetite. Four hours prior to consult, patient was still febrile, started to complain of having holocranial headache, throbbing in character, non-radiating, not associated with nausea and vomiting with pain score of 6/10. One hour later, patient was noted to have decreased verbal output by his girlfriend. He would not answer questions when asked though he followed some commands and withdrew to pain. Patient
was decided to be brought to the hospital.

Patient came in wheelchair borne, awake, drowsy and in cardiopulmonary distress. Patient was febrile with temperature of 40 °C, tachycardic at 124, tachypneic at 24 and normotensive at 128/89. Physical examination was unremarkable, and neurologic examination was not fully assessed because he was uncooperative. The patient was aphasic though he followed some commands. He was immediately hydrated and sepsis workup was done. The patient was requested for complete blood count (CBC), chest X-ray portable, blood culture at two sites, urinalysis, serum sodium and potassium, serum blood urea nitrogen (BUN), serum creatinine, capillary blood glucose, prothrombin time (PT) and partial thromboplastin time (P TT), erythrocyte sedimentation rate (ESR), alanine aminotransferase (ALT)/aspartate aminotransferase (AST), leptospira IgG/IgM, 12-lead electrocardiogram (ECG) and arterial blood gas. Patient was started on ceftriaxone 2 g intravenous (IV), vancomycin 1,200 mg IV (with estimated weight of 80 kg) and IV paracetamol. The patient was then referred to the neurology service where a magnetic resonance angiography of the intracranial vessels was made.

Baseline CBC revealed leukocytosis at $15 \times 10^9$/L, with increased hemoglobin of 179 g/L and platelet count of $157 \times 10^9$/L. Patient was noted to be hypotensive at 131.70 mmHg and hypokalemic with result of 2.8 mmol/L which was corrected with potassium chloride drip. PT is prolonged at 54.7 s and PTT at 14.5 s which is within reference interval. ESR was normal at 2.00 mm/h, urinalysis was also normal and chest X-ray was noted as unremarkable. Leptospirosis IgG and IgM were negative. AST/SGOT, blood urea nitrogen and creatinine were elevated with result of 112.00 U/L, 27.20 mg/dL and 2.85 mg/dL, respectively. Patient was referred to nephrology for consult and for clearance for the gadolinium scan. Nephrology consult was requested and showed positive results both for IgM and IgG. CSF was also submitted for dengue RNA-PCR and was also found positive.

Vancomycin, acyclovir and ceftriaxone were discontinued. CBC was monitored every day. On the third hospital day, patient was transfused with 6 units of platelet concentrate because platelet dropped down to $14 \times 10^9$/L.

Patient was discharged on the fifth hospital day with platelet count of $275 \times 10^9$/L and with no neurologic deficit.

Discussion

Dengue fever is not new in the Philippines, and every year a large number of dengue suspected cases are reported by the country’s Department of Health (DOH) [6]. Yearly reports from the Department of Health’s Public Health Surveillance Division gave approximation in the number of dengue suspected cases both nationally and by region. Such that cases of dengue from 2015 to 2018 went respectively from 200,415, 220,518, 208,805 and 216,190. But this goes way up in the first 8 months of 2019 with 217,480 cases prompting the department to declare national dengue epidemic [7]. Though a dengue endemic country, this may be the first published report of dengue encephalitis on an adult patient in the Philippines.

Majority of the dengue cases in the Philippines are of the classical dengue or break bone fever with clinical presentations that include fever, influenza-like syndrome characterized by headache, retro-ocular and joint pain, rash and lymphadenopathy [2]. Following the febrile case, the disease may progress to dengue hemorrhagic characterized by thrombocytopenia, pleural and abdominal effusion and dengue shock syndrome [2]. The cardinal feature or hallmark of dengue hemorrhagic fever identified as plasma leakage potentially arises from pro-inflammatory cytokine-inflicted damage to the endothelium. It occurs late and coincides with clearance of viremia suggesting mediation through host response rather than direct virally mediated tissue damage [8].

The most common feature of dengue infection is thrombocytopenia and leucopenia. Thrombocytopenia is an effect of the dengue NS1. Thrombocytopenia is the criterion used by the WHO guidelines as a potential indicator of clinical severity [9]. Platelet count significantly decreases on the third day or up to the seventh day and starts to increase to normal levels on the eighth or ninth day. Dengue NS1 directly induces platelet activation and apoptosis, binds to platelets and activates platelets through TLR4 signal transduction, enhances platelet aggregation in the presence of subthreshold dose of ADP, increases platelet adherence to endothelial cells and phagocytosis of macrophages and causes aggregated complex formation and cell death [10]. Hypothesis on the occurrence of leucopenia is that dengue infection destroys or inhibits myeloid progenitor cells. Leucopenia starts to occur on the second day of fever and peaks on the fifth day. Then it starts to go back to normal.
cellularity on the convalescent phase of dengue [11]. A dengue duo testing was done and revealed positive IgM and IgG banding. This indicates recent secondary dengue infections that induce antibody dependent enhancement that makes the heterotypic non-neutralizing antibodies form complexes with dengue virus. In effect, this allows the virus to infect mononuclear phagocytes with enhanced efficiency, thus contributing to development of certain complications including neurologic conditions [12]. Neurologic complications are rare and normally occur 2 to 30 days after the onset of fever. What is unique in this patient’s case is the presence of leukocytosis in the fourth day of fever that suddenly plummeted on the fifth day accompanied with neurological manifestations. In usual dengue pathophysiology, leukocytosis is noted during the early stage of symptomatic infection. This is usually followed by leukopenia starting on the second day with marked leukopenia on the fifth day. Normal leucocyte levels are regained as the infection resolves.

Although very rare (1-5% of dengue cases), neurological involvement on dengue infections has been increasingly reported in dengue epidemics in other countries. The neurologic complication can occur in patients with few or no signs of previous dengue infection. For almost 20 years, dengue virus neurotropism in the human host was considered non-neurotropic [13, 14] or only as an opportunistic characteristics, but a number of evidences support that the virus is neurovirulent [4]. The most usual involved serotypes in neurotropism are the DEN-2 and DEN-3. Dengue encephalopathy is just a secondary manifestation of dengue fever and is frequently associated with multisystem derangement found later in the course of illness somehow leading to encephalitis that occurs due to the direct invasion of the virus and during the viremic phase of the illness [3].

Central neurological system complications are diagnosed by assessing the patient with fever, acute signs of cerebral involvement, presence of anti-DENV immunoglobulins (IgM), detecting viral RNA or non-structural protein 1 (NS-1), or isolating the virus from the CSF after excluding other causative agents of viral brain disease [3]. It should also be noted that not all dengue encephalitis have abnormal CSF cellularity just like in the present case. According to Cristiane and Marzia [4, 5], it is known that absence of pleocytosis has been described in more than 5% of viral encephalitis especially the early infectious stage. It has also acute signs of cerebral involvement, normal or high CSF protein and mostly normal signal changes in involved regions using CT or MRI. It should also be noted that MRI has advantages over CT in revealing cerebral lesions in dengue encephalitis [4]. In the current case, MRI revealed nonspecific T2W/FLAIR hyperintensity with restricted diffusion in the splenium of the corpus callosum. This can be seen in cases of virus-associated encephalopathy.

There is no specific treatment for dengue fever [1, 14], may it be symptomatic or critical phase. Thus, dengue infections are managed symptomatically or on supportive care [15] because there are no specific or effective drugs as of the moment against the dengue virus. Proper fluid balance is still the cornerstone in the management. Also, improved outcomes and complications are reduced when plasma leakage is identified and managed early [16].

Though neurological involvement is rare or low in frequency, this report emphasizes the importance of considering dengue in the diagnosis of patients with features of encephalitis especially in a dengue endemic region. A combination of clinical signs and basic laboratory tests such as routine blood counts will provide clues for diagnosis and proper monitoring.

Conclusion

Dengue encephalitis is a rare complication of dengue. In a dengue endemic country, where the disease is present all throughout the year with seasonal spikes, and patients present in the emergency room with chief complaint of fever accompanied with focal neurologic symptoms, it is prudent to include dengue as a differential diagnosis.

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Conflict of Interest

The authors declare that they have no conflict of interest.

Informed Consent

Not applicable.

Author Contributions

RAAC conceptualize the design of work, acquisition, analysis and interpretation of data. ACJ did the analysis, helped the interpretation of data and drafted the report. Both RAAC and ACJ approved the final version of the report.

Data Availability

The authors declare that data supporting the findings of this study are available within the article.

References