American Journal of Case Reports

e-ISSN 1941-5923
© Am J Case Rep, 2021; 22: e931519
DOI: 10.12659/AJCR.931519

Received: 2021.02.06
Accepted: 2021.04.01
Available online: 2021.04.13
Published: 2021.05.17

A Rare Case of Dengue Encephalitis with Raised Procalcitonin

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

ABCDEF 1 Flora Xu
ABCDEFG 2 Krithikaa Nadarajan
ABCDEF 2 Ming Ren Toh

1 Yong Loo Ling School of Medicine, Singapore, Singapore
2 Department of Internal Medicine, Singapore General Hospital, Singapore, Singapore

Corresponding Author: Ming Ren Toh, e-mail: mingren.toh@mohh.com.sg
Conflict of interest: None declared

Patient: Male, 65-year-old
Final Diagnosis: Dengue encephalitis
Symptoms: AMS
Medication: —
Clinical Procedure: —
Specialty: Infectious Diseases

Objective: Rare co-existance of disease or pathology

Background: Dengue virus is a common arbovirus with uncertain neurotropism. Dengue encephalitis is a rare but fatal manifestation of severe dengue. Diagnosis requires high clinical suspicion. It should be routinely considered in patients with encephalopathy, especially in countries where dengue virus is endemic. Unlike other forms of severe dengue, the typical warning signs and biochemical derangements are not reliable markers for dengue encephalitis. Alternative biochemical markers of dengue encephalitis are needed.

Case Report: We present a case of dengue encephalitis with distinctly raised procalcitonin (13.2 µg/L), in the absence of the typical warning signs and biochemical derangements of severe dengue. The patient was a 65-year-old man with fever and sudden loss of consciousness in the absence of other localizing signs/symptoms. Inflammatory markers were raised, with findings of leptomeningeal enhancement on brain computed tomography suggestive of meningoencephalitis. Septic workup was unremarkable (normal renal and liver functions, negative blood and urine cultures). The typical neurotropic microorganisms were not detected in the cerebrospinal fluid. On day 4 of admission, the patient reported abdominal pain and hematuria with a new onset of bicytopenia. Subsequent investigations for dengue infection were positive for serum dengue NS1 antigen and dengue RNA (type 2 strain) in cerebrospinal fluid, confirming the diagnosis of dengue encephalitis. The patient was managed supportively and experienced full clinical recovery.

Conclusions: Dengue encephalitis is a rare condition with nonspecific biochemical and imaging abnormalities. We demonstrated that a raised procalcitonin level can occur in the setting of dengue encephalitis. In endemic countries, this finding may prompt further investigations for dengue encephalitis in patients with meningoencephalitis.

Keywords: Dengue • Encephalitis Viruses • Procalcitonin

Full-text PDF: https://www.amjcaserep.com/abstract/index/idArt/931519

Indexed in: [PMC] [PubMed] [Emerging Sources Citation Index (ESCI)] [Web of Science by Clarivate]

Background

Endemic to the tropics, dengue virus is an arbovirus that infects approximately 100-400 million people yearly [1]. Most infected individuals are either asymptomatic or may experience fever, malaise, retroorbital pain, and arthralgia [2]. Dengue is usually a self-limiting viral illness, but some patients may develop severe dengue infection, circulatory collapse, and end-organ failure. In these cases, the metabolic disturbances, toxin release, and cerebral edema may lead to dengue encephalopathy (clinical syndrome of diminished consciousness). Even more rarely, the virus can infiltrate the central nervous system (CNS) and cause dengue encephalitis. The most common neurological symptoms in dengue encephalitis and encephalopathy are altered sensorium (93.8-100%), headache (63.3%), and seizure (53.3%) [3]. To distinguish dengue encephalitis from encephalopathy, the virus must be isolated in the CNS via serology, polymerase chain reaction, culture, or biopsy [4]. Given that dengue virus is not a neurotropic virus, the diagnosis of dengue encephalitis requires a high index of clinical suspicion. Unlike other severe dengue infections, patients with dengue encephalitis may not show warning signs or deranged biochemical markers typical of severe dengue. There is a need to identify alternative biochemical markers of dengue encephalitis.

We report this case to highlight the potential diagnostic utility of serum procalcitonin in dengue encephalitis.

Case Report

Our patient was a 65-year-old man with a previous medical history of chronic obstructive pulmonary disease who presented acutely with loss of consciousness and fever. Corroborative history from the family revealed a preceding febrile illness of 3 days, associated with chills and rigors. There were no witnessed abnormal limb movements. His vital signs were as follows: temperature 41.0°C, pulse 130 beats/min, blood pressure 120/60 mmHg, and normal oxygen saturation. He was delirious, with a Glasgow Coma Scale score of E2V2M5 and normal pupils (bilaterally equal and reactive to light). There were no signs of meningism. The rest of the physical examination was unremarkable. Blood glucose was 8.9 mmol/L.

Preliminary investigations revealed raised inflammatory markers (total white count 11.1×10^9/dL, procalcitonin 13.2 µg/L, C-reactive protein 74.2 mg/L). The renal and liver function were unremarkable, and the patient had a normal coagulation profile (serum creatinine 0.92 mg/dL, alanine transaminase 18 U/L, aspartate transaminase 28 U/L, hemoglobin 15 g/dL, platelet 230×10^9/L, hematocrit 44.8%, prothrombin time 11.2 s, activated partial thromboplastin time 25.1 s). A brain computed tomography (CT) scan with contrast revealed subtle contrast enhancement equivocal for leptomeningeal enhancement with underlying cerebral edema (**Figure 1A, 1B**). Hence, our initial impression was meningoencephalitis.

Lumbar puncture was performed and empiric intravenous antibiotics and an antiviral (vancomycin, ceftriaxone, ampicillin, and acyclovir) were initiated. Details of the cerebrospinal fluid (CSF) were as follows: raised opening pressure (34 cmH_2O), clear CSF with normal glucose (3.8 mmol/L) and protein levels (0.3 g/L), and an absence of white/red blood cells. No microorganisms were seen on the CSF Gram stain. Polymerase chain reaction tests were also negative for neurotropic viruses (cytomegalovirus, herpes simplex virus, and varicella zoster virus), toxoplasma gondii, and cryptococcus. The patient's blood and urine cultures were also negative for bacterial growth.

A repeat full blood count on day 4 showed that the patient had developed bicytopenia (total white count 3.12×10^9/L and platelet count 57×10^9/L) (**Figure 1D**). The patient also reported abdominal pain and hematuria. We sent off dengue serology, which was positive for NS1 antigen and negative for IgM, prompting suspicion for dengue encephalitis. Residual CSF from the previous lumbar puncture tested positive for dengue RNA (type 2 strain). Hence, we treated the patient supportively for dengue fever and discontinued the antimicrobials. The patient's fever broke on day 9 with gradual recovery of his bicytopenia (**Figure 1D**). Magnetic resonance imaging of the brain done 1 week after the initial brain CT showed resolution of the leptomeningeal enhancement (**Figure 1C**). Serum procalcitonin was normal (0.47 µg/L) prior to discharge. The patient was discharged thereafter. At a subsequent follow-up 1 year later, he remained well without any neurological sequelae.

Discussion

Dengue encephalitis has an incidence of 5.4% to 6.2% in endemic countries and a mortality of 30-52% [3,5]. Early recognition is crucial to minimize the complications of dengue encephalitis. Unfortunately, typical warning signs (eg, abdominal pain, vomiting, lethargy) and significant biochemical derangements (eg, hematocrit, aminotransferases, serum creatinine) may be absent in dengue encephalitis. To complicate matters further, features of dengue encephalitis on brain imaging are also nonspecific and variable, ranging from diffuse cerebral edema and intracranial hemorrhage/microhemorrhages to localized encephalitic changes [6]. Increasingly, procalcitonin has been proposed as a predictor of severe dengue [7,8].

In a prospective study of 486 cases of dengue fever, patients with CNS involvement were less likely to present with abdominal symptoms of vomiting (32% vs 45%), diarrhea (7% vs 23%),

Indexed in: [PMC] [PubMed] [Emerging Sources Citation Index (ESCI)] [Web of Science by Clarivate]

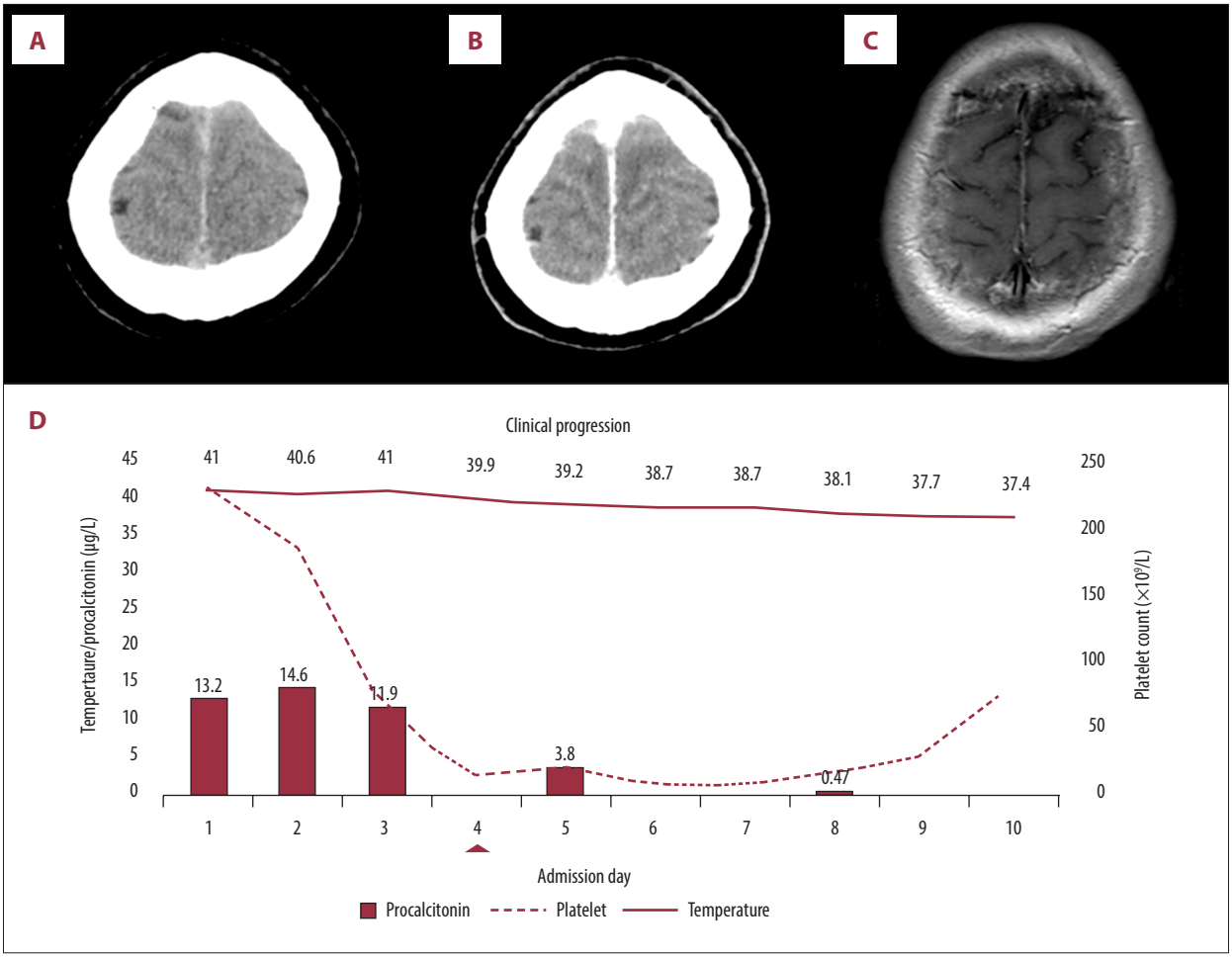

Figure 1. (**A**) Brain computed tomography (CT) without contrast showing crowded cerebral gyri and sulcal effacement and (**B**) brain CT with contrast showing leptomeningeal enhancement. (**C**) Brain magnetic resonance imaging on day 9 of admission showing resolution of cerebral edema and leptomeningeal enhancement. (**D**) Clinical progression of the patient showing the increase in platelets following defervescence, the resolution of delirium (arrowhead), and the procalcitonin trend.

and abdominal pain (18% vs 30%) [9]. Biochemical markers of severe dengue such as hematocrit, platelet count, and serum creatinine also did not differ between those with and without CNS complications; mean serum hematocrit (30.1% vs 31.5%), platelet (160×10^9/L vs 144×10^9/L), and creatinine (1.4 mg/dL vs 1.43 mg/dL) [9]. While liver dysfunction (97% vs 12%) and bleeding (28% vs 12%) were more common in individuals with CNS involvement, these findings were not consistently observed in other studies [9]. A retrospective study of 116 dengue-infected patients showed that patients with neurologic involvement were less likely to develop hepatic dysfunction (60% vs 69.2%), while another study reported similar bleeding rates in both groups (33.3% vs 37.3%) [10,11].

In our case report, the patient did not present with any abdominal or bleeding symptoms and had relatively normal biochemical values. Notably, he had a raised procalcitonin level (13.2 μg/L), which is unusual in dengue fever. Procalcitonin is a calcitonin propeptide synthesized by C cells and secreted by leukocytes in the presence of bacterial lipopolysaccharides and cytokines during sepsis. Upregulation of cytokines such as interleukin (IL)-1β, IL-6, and tumor necrosis factor-α in viral infections can also promote procalcitonin synthesis [12]. Procalcitonin is a well-established predictor of severity in bacterial infections and increasingly in viral infections [13,14]. In dengue infections, the procalcitonin level is raised in patients with severe dengue and those with bacterial co-infections [7,8,15]. Cutoffs of 0.3-0.7 μg/L and 1.14 μg/L are used to predict severe dengue and bacterial co-infections, respectively [7,8,15]. Raised procalcitonin is also associated with death in patients with severe dengue (P=0.021) [8]. For our patient, the degree of procalcitonin elevation most likely signified severe dengue rather than a bacterial co-infection. He did not have any localizing symptoms/signs to suggest other infection sources and his microbial cultures were negative.

Indexed in: [PMC] [PubMed] [Emerging Sources Citation Index (ESCI)] [Web of Science by Clarivate]

Besides being a biomarker of severity, procalcitonin is a mediator of sepsis and possibly dengue encephalitis. It upregulates surface markers on neutrophils/lymphocytes and upregulates cytokines and reactive oxygen species (ROS) [12]. This positive feedback between procalcitonin and the proinflammatory cytokines subsequently culminates in an overwhelming systemic inflammatory response [12]. The increased ROS can disrupt the blood-brain barrier, contributing to cerebral edema and CNS infections [12]. In severe dengue, neurological complications of dengue infection were previously attributed to the pathophysiology of severe dengue infection (ie, prolonged plasma leakage and hemorrhage causing hepatic encephalopathy, cerebral edema, and intracranial hemorrhage) [3]. We postulate that in dengue encephalitis, the elevated procalcitonin may further disrupt the blood-brain barrier and aggravate cerebral edema. Another possible mechanism is a direct CNS invasion by the dengue virus through the compromised blood-brain barrier. The direct neurotropism of the dengue virus has recently been illustrated with the isolation of the virus RNA in the CSF, also evidenced in our case report [16].

Conclusions

Dengue encephalitis is a rare condition. In endemic countries, it should be routinely considered in patients with encephalopathy. Clinicians should bear in mind that typical warning signs and biochemical derangements may be mild or absent in dengue encephalitis. CNS imaging may also be inconclusive. A raised procalcitonin level can occur in the setting of dengue encephalitis, prompting dengue serology investigation and dengue RNA testing in CSF. Large-cohort studies are needed to elucidate the diagnostic utility of procalcitonin in dengue encephalitis.

Conflict of Interest

None.

References:

1. Bhatt S, Gething PW, Brady OJ, et al. The global distribution and burden of dengue. Nature. 2013;496(7446):504-7
2. Lee IK, Liu JW, Yang KD. Clinical characteristics and risk factors for concurrent bacteremia in adults with dengue hemorrhagic fever. Am J Trop Med Hyg. 2005;72(2):221-26
3. Saluja M, Swami YK, Chittora S, Vimlani H. Central nervous system involvement in dengue: A tertiary care centre study. Curr Med Res Pract. 2019;9(2):45-48
4. Varatharaj A. Encephalitis in the clinical spectrum of dengue infection. Neurol India. 2010;58(4):585
5. Pancharoen C, Thisyakorn U. Neurological manifestations in dengue patients. Southeast Asian J Trop Med Public Health. 2001;32(2):341-45
6. Cam B, Fonsmark L, Hue N, Phuong N, et al. Prospective case-control study of encephalopathy in children with dengue hemorrhagic fever. Am J Trop Med Hyg. 2001;65(6):848-51
7. Thanachartwet V, Desakorn V, Sahassananda D, et al. Serum procalcitonin and peripheral venous lactate for predicting dengue shock and/or organ failure: A prospective observational study. PLoS Negl Trop Dis. 2016;10(8):e0004961
8. Sani H, Syazana N, Azhar ZI, et al. Procalcitonin and clinical factors associated with severe dengue infection in hospitalised adults in Malaysia. Infection, Disease & Health. 2018;23:S20
9. Sahu R, Verma R, Jain A, et al. Neurologic complications in dengue virus infection: A prospective cohort study. Neurology. 2014;83(18):1601-9
10. Misra UK, Kalita J, Mani VE, et al: Central nervous system and muscle involvement in dengue patients: A study from a tertiary care center. J Clin Virol. 2015;72:146-51
11. Domingues RB, Kuster GW, Onuki-Castro FL, et al. Involvement of the central nervous system in patients with dengue virus infection. J Neurol Sci. 2008;267(1-2):36-40
12. Gautam S, Cohen AJ, Stahl Y, et al. Severe respiratory viral infection induces procalcitonin in the absence of bacterial pneumonia. Thorax. 2020;75(11):974-81
13. Simon L, Gauvin F, Amre DK, et al. Serum procalcitonin and C-reactive protein levels as markers of bacterial infection: A systematic review and meta-analysis. Clin Infect Dis. 2004;39(2):206-17
14. Alkholi UM, Abd Al-Monem N, Abd El-Azim AA, Sultan MH. Serum procalcitonin in viral and bacterial meningitis. J Glob Infect Dis. 2011;3(1):14-18
15. Chen CM, Chan KS, Chao HC, Lai CC. Diagnostic performance of procalcitonin for bacteremia in patients with severe dengue infection in the intensive care unit. J Infect. 2016;73(1):93-95
16. Ngwe Tun MM, Muthugala R, Nabeshima T, et al. Complete genome analysis and characterization of neurotropic dengue virus 2 cosmopolitan genotype isolated from the cerebrospinal fluid of encephalitis patients. PLoS One. 2020;15(6):e0234508

Indexed in: [PMC] [PubMed] [Emerging Sources Citation Index (ESCI)] [Web of Science by Clarivate]