Annals of Case Reports & Reviews

Case Report

doi: 10.39127/2574-5747/ACRR:1000197
Toh MR, et al. Annal Cas Rep Rev: ACRR-197

A Rare Case of Dengue Encephalitis: Procalcitonin As A Potential Biomarker?

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Citation: Xu F, Nadarajan K, Toh MR (2021) A Rare Case of Dengue Encephalitis: Procalcitonin As A Potential Biomarker? Annal Cas Rep Rev: ACRR-197.

Received Date: 28 January 2021; **Accepted Date:** 08 February 2021; **Published Date:** 15 February 2021

Abstract

Dengue encephalitis is an uncommon but fatal manifestation of severe dengue. Diagnosis requires high clinical suspicion. Unlike other forms of severe dengue, the typical warning signs and biochemical derangements are not reliable markers for dengue encephalitis. We present a case of dengue encephalitis with distinctly raised procalcitonin (13.2ug/L), in absence of the typical warning signs and biochemical derangements of severe dengue. No evidence of bacterial coinfection was noted. Inferring from studies on other forms of severe dengue, we propose the use of procalcitonin as a potential predictor of dengue encephalitis.

Keywords: *Dengue; encephalitis; procalcitonin*

Highlights

- Dengue encephalitis is an uncommon but fatal manifestation of severe dengue.
- Typical warning signs and biochemical derangements are often absent in dengue encephalitis.
- We report a case of dengue encephalitis with significantly raised procalcitonin (13.2ug/L), in absence of the typical warning signs and biochemical derangements.

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 complain of fever, malaise, retroorbital pain and arthralgia [2]. While dengue is usually a self -limiting viral illness, some patients may develop severe dengue infection, circulatory collapse and end-organ failure. Rarely, dengue encephalitis from viral infiltration can occur in severe dengue with central nervous (CNS) involvement. The most common neurological symptoms are altered sensorium (93.8-100%), headache (63.3%) and seizure (53.3%) [3]. In contrast, the classic petechial rash can be absent in many patients (57.1-76.7%) with dengue encephalitis [4]. 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 / 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 summary

Our patient was a 65-year-old Indian male 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 three 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/min, blood pressure 120/60mmHg 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. Rest of the physical examination was unremarkable. Blood glucose was 8.9mmol/L.

Preliminary investigations revealed raised inflammatory markers (total white count $11.1x10^9$/dL, procalcitonin 13.2ug/L, C-reactive protein 74.2mg/L). The renal and liver function were unremarkable and he had normal coagulation profile (serum creatinine 0.92mg/dL, alanine transaminase 18U/L, aspartate transaminase 28U/L, hemoglobin 15g/dL, platelet $230x10^9$/L, hematocrit 44.8%, prothrombin 11.2sec, aPTT 25.1sec). A contrasted Computed Tomography (CT) brain reported 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 / antiviral (vancomycin, ceftriaxone, ampicillin, acyclovir) were initiated. Details of the cerebrospinal fluid (CSF) were as follows: raised opening pressure ($34cmH_2O$), clear CSF with normal glucose (3.8mmol/L) and protein levels (0.3g/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 the neurotropic viruses (cytomegalovirus, herpes simplex virus, varicella zoster virus), toxoplasma gondii and cryptococcus. His blood and urine cultures were also negative for bacterial growth.

A repeat full blood count on Day 4 showed the patient developed bicytopenia (total white count $3.12x10^9$/L and platelet count $57x10^9$/L) (Figure 1D). The patient also complained of 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 was 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 lysed on Day 9 with gradual recovery of his bicytopenia (Figure 1D). A Magnetic Resonance Imaging brain done one week after the initial CT brain showed resolution of the leptomeningeal enhancement (Figure 1C). The patient was discharged thereafter. At a subsequent follow-up one year later, he remained well without any neurological sequala.

Discussion

Dengue encephalitis has an incidence of 5.4 to 6.2% in the endemic countries, and a mortality of 30-52% [3,4]. Early recognition is crucial to minimize the complications of dengue encephalitis. Unfortunately, typical warning signs (e.g. abdominal pain, vomiting, lethargy), and significant biochemical derangements (e.g. hematocrit, aminotransferases, serum creatinine) may be absent in dengue encephalitis. To complicate matters further, features of dengue encephalitis on brain imaging are also non-specific and variable, ranging from diffuse cerebral edema, intracranial hemorrhage/ microhemorrhages, to localized encephalitic changes [5]. Increasingly, procalcitonin has been proposed as a predictor of severe dengue [6,7].

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%) and abdominal pain (18% vs. 30%) [8]. 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 ($160x10^9$/L vs. $144x10^9$/L) and creatinine (1.4mg/dL vs. 1.43mg/dL) [8]. While liver dysfunction (97% vs. 12%) and bleeding (28% vs. 12%) were more common in those with CNS involvement, these findings were not consistently observed in other studies [8]. 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%) [9,10].

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 (13.2ug/L) 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 IL-1β, IL-6 and TNF-α in viral infections can also promote procalcitonin synthesis [11]. Procalcitonin is a well-established predictor of severity in bacterial infections, and increasingly, in viral infections [12,13]. In dengue infections, procalcitonin is raised in patients with severe dengue and those with bacterial coinfections [6,7,14]. Cutoffs of 0.3-0.7ug/L and 1.14ug/L are used to predict severe dengue and bacterial coinfections respectively [6,7,14]. Raised procalcitonin is also associated with death in patients with severe dengue ($p=0.021$) [7]. For our patient, the degree of procalcitonin elevation most likely signified the severe dengue rather than a bacterial coinfection. He did not have any localizing symptoms/signs to suggest other infection sources and his microbial cultures were negative.

Besides being a biomarker of severity, procalcitonin is a mediator of sepsis and possibly, dengue encephalitis. It upregulates surface markers on neutrophils / lymphocytes, upregulates cytokines and reactive oxygen species (ROS) [11]. This positive feedback between procalcitonin and the proinflammatory cytokines subsequently culminates in an overwhelming systemic inflammatory response [11]. The increased ROS can disrupt the blood-brain barrier and contribute to cerebral edema / CNS infections [11]. In severe dengue, neurological complications of dengue infection are previously attributed to the pathophysiology of severe dengue infection, (i.e. prolonged plasma leakage and hemorrhage causing hepatic encephalopathy, cerebral edema and intracranial hemorrhage) [3]. We postulate that

in dengue encephalitis, the elevated procalcitonin may have further disrupted the blood-brain barrier and aggravated 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 [15].

Conclusion

Dengue encephalitis is a rare condition. In endemic countries, this should routinely be 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 may be a relevant biomarker-mediator of dengue encephalitis, considering its role in severe sepsis and severe dengue. Large cohort studies will be needed to elucidate the diagnostic utility of procalcitonin in dengue encephalitis.

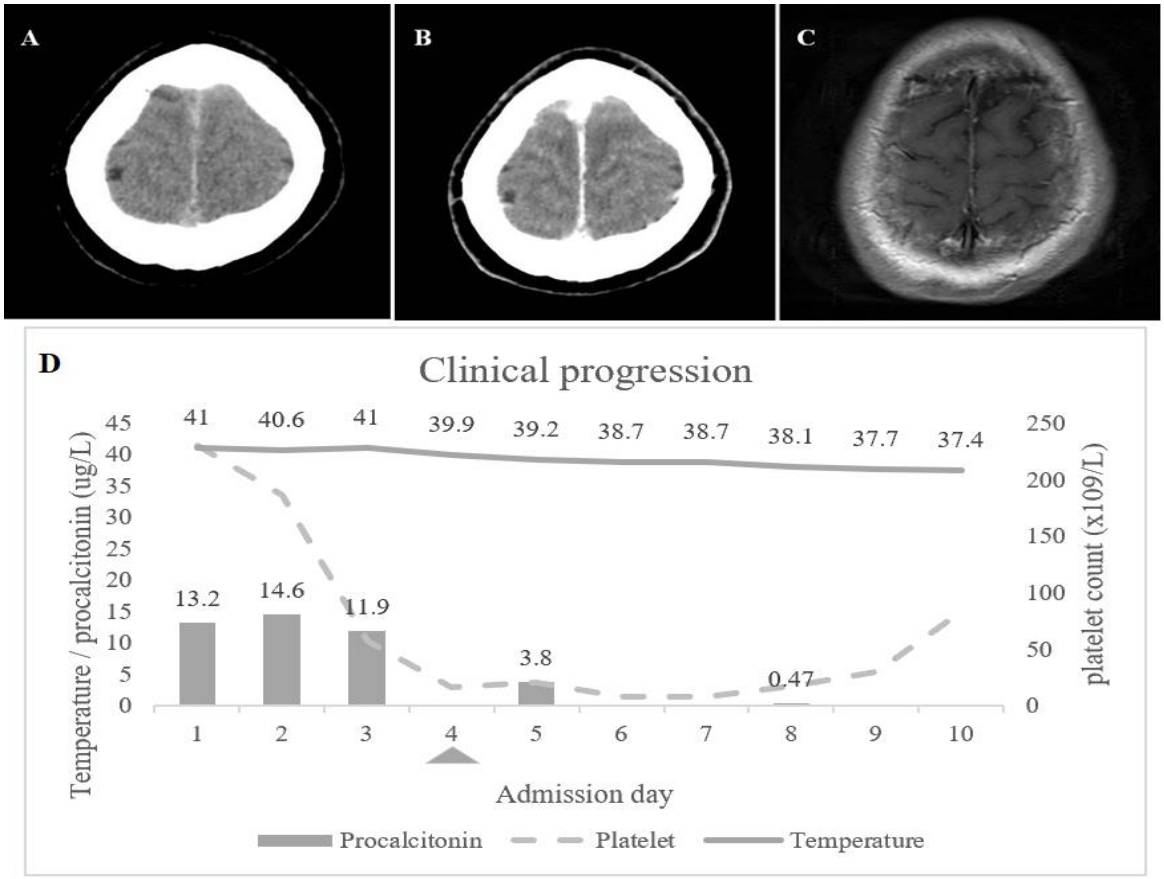

Figure 1: (A) non-contrasted CT brain showing crowded cerebral gyri and sulcal effacement and (B) contrasted CT brain showing leptomeningeal enhancement. (C) MRI brain Day 9 of admission showing resolution of cerebral edema and leptomeningeal enhancement. (D) Clinical progression of the patient showing the rise of platelets following defervescence, the resolution of delirium (arrowhead) and the procalcitonin trend.

Conflict of interest
All authors declare no conflict of interest.

Funding source
No funding was involved.

Ethical approval
Ethical approval and patient consent were obtained for the case report.

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