Case Report

Dengue encephalopathy – still an enigma?

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Abstract

Dengue encephalopathy or dengue hemorrhagic fever (DHF) with neurological involvement was once considered to be one of the rarer presentations of this infectious agent. In recent years, many such clinical cases have been reported, though they still remain isolated. We hereby report a case of confirmed dengue fever with features of encephalopathy with previously unreported cranial magnetic resonance imaging findings suggestive of extensive involvement of the bilateral cerebellar region, brainstem, and thalami along with peculiar rim enhancement but normal cerebrospinal fluid analysis.

Key words: dengue infection; encephalopathy; magnetic resonance imaging.

J Infect Dev Ctries 2014; 8(8):1076-1078. doi:10.3855/jidc.4762

(Received 24 January 2014 – Accepted 27 February 2014)

Introduction

The dengue virus is a single-stranded ribonucleic acid (RNA) virus of the *Flaviviridae* family, causing varied clinical manifestations including dengue fever (DF) and dengue hemorrhagic fever (DHF) [1]. Encephalopathy is a rare though well-known neurological complication of dengue infection. Dengue encephalitis is a different entity, which possibly occurs due to direct neuronal infiltration by the dengue virus [2,3]. We hereby report a case of dengue fever with encephalopathy with previously unreported brain magnetic resonance imaging (MRI) findings.

Case Report

A 35-year-old female patient was referred with a history of fever for the last ten days associated with generalized headache, followed by two episodes of seizures on day 4 of illness and subsequent altered sensorium. On admission she was febrile (101°F), without any signs of respiratory distress, skin rash, icterus, or skin/mucosal bleeds. She was drowsy with a Glasgow Coma Score (GCS) of 7/15 (E2V2M3) but without any meningeal signs. The rest of the systemic examination was within normal limits.

She was admitted with a bedside diagnosis of infectious encephalitis in view of persistent fever with history of seizures and altered sensorium. She was initially managed conservatively and started on suitable antibiotics and empirical parenteral antimalarial preparation (for cerebral malaria) along with antiepileptics.

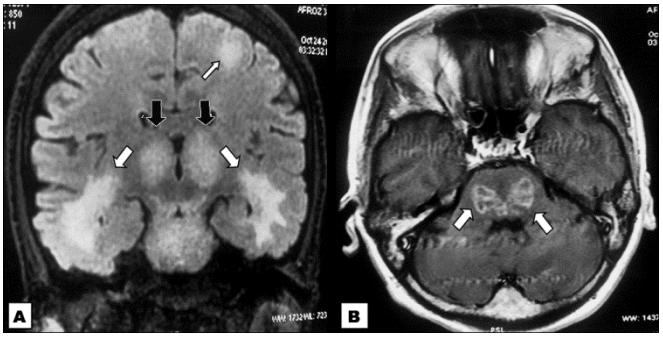
Her outside investigations were reviewed and suggested evidence of low platelet count, high liver enzymes, and positive serum Widal titers (TO titer 1/320 and TH 1/320) (Table 1).

An urgent non-contrast computerized tomographic (NCCT) scan was done; it was suggestive of white matter edema in the bilateral temporal and occipital lobes and the bilateral basal ganglia, without any intracranial bleed. Her repeat blood investigations also revealed a similar laboratory picture along with severe coagulopathy (Table 1). An etiological work-up later revealed positive dengue IgM (Immunochromatographic kit, Standard Diagnostics Inc.,Yongin, Korea) and NS1 antigen (ELISA kit, PanBio Diagnostics, Brisbane, Australia) tests with negative rapid malarial antigen (sandwich immunoassay kit, Microgene Diagnostics and Access Bio. Ltd., Mumbai, India,) (antimalarials were subsequently stopped), typhoid IgM (immunochromatographic kit, DG diagnostics Ltd., Mumbai, India) and blood culture test. Common infectious agents including herpes virus, Japanese encephalitis virus, and neurocysticercosis were excluded with relevant tests including cerebrospinal fluid (CSF) analysis, but due to lack of facilities, tests for other infectious agents such as West Nile Virus could not be done. There was no facility for dengue virus detection in CSF.

The MRI brain scan, done on a 1.5 T Signa Excite MR scanner (GE Healthcare, Milwaukee USA), later showed extensive parenchymal hyperintense lesions in the white matter of the bilateral cerebellum, bilateral occipital, and temporo-parietal lobes on T2 and fluid attenuated inversion recovery (FLAIR) images. An altered T2/FLAIR hyperintense signal involving the brainstem, midbrain, and bilateral thalami was also noted and showed low signals on T2/susceptibility weighted images suggestive of focal hemorrhage (Figure 1A). On post-contrast imaging, atypical rim-enhancing areas involving the bilateral cerebellum, thalami, and brainstem region were observed without leptomeningeal enhancement (Figure 1B).

The patient gradually responded to conservative management and was later discharged after full neurological recovery on day 14 of admission as dengue infection with neurological manifestations (encephalopathy).

Figure 1. A. Coronal FLAIR image of brain showing hyperintensities involving the white matter of bilateral temporal lobes (thick white arrows) and thalami (black arrow) and left parietal lobe (thin white arrow). **B.** Axial contrast-enhanced T1-weighted image in the same patient demonstrating multiple coalescent rim-enhancing lesions in the brainstem (arrows).



Discussion

Dengue virus, classically labeled as a non-neurotropic virus [3], is associated with numerous rare neurological manifestations of dengue infection such as transverse myelitis, Guillain–Barré syndrome, acute disseminated encephalomyelitis, and myositis [4,5]. Dengue encephalopathy is now a well-recognized, though uncommon, entity with incidence ranging from 0.5% to 6.2% [6]. Plausible explanations for neurological symptoms include liver failure (hepatic encephalopathy), cerebral hypoperfusion (shock), cerebral edema (vascular leak), deranged electrolytes, and intracranial bleeding due to thrombocytopenia or coagulopathy [4,5]. In a few cases, neurological symptoms remain unanswered; here, direct neuronal infiltration by the virus may be the key to pathogenesis.

In last few years, multiple clinical cases have been reported, especially from the tropics [2,6]. In the study described by Misra *et al*. [6], out of eleven patients with confirmed dengue infection, eight had evidence of CSF pleocytosis, but no CSF viral study was available. Solomon *et al*. [2] diagnosed dengue encephalitis in nine patients, but could demonstrate virus or antibody in CSF in only two cases.

On admission, our patient had fever with evidence of encephalopathy and deranged liver functions, which subsequently improved spontaneously. Usual causes of neurological impairment including intracranial

Table 1. Trend of laboratory parameters at various time frames.

Parameter	Outside	Day 1	Day 7
Hemoglobin (g/dL)	9.5	9.8	10
TLC (cells/mm^3)	10,500	4,500	5,600
DLC (N/L/E/M) (%)	45/50/3/2	80/15/2/3	55/43/1/1
Platelets (1000×mm^3)	20 --- > 67	95	112
Bilirubin (T/D) mg/dL	3/2.1	0.6/0.4	-
AST/ALT (IU/L)	1800/1442	103/63	-
SAP (IU/L)	342	113	-
INR	1.3	2.8	1.3
BU/Cr. mg/dL	42/0.6	21/0.3	-
Na/K (Meq/L)	138/4.1	138/3.5	-
CSF study	-	Color: clear Coagulum: absent Cells: nil Sugar: 68 mg/dL Protien: 20 mg/dL ADA: 0.58 U/L (< 5 IU/L)	-

ALT: alanine aminotransferase; AST: aspartate aminotransferase; GGTP: gamma glutamyl transpeptidase; g/dL: grams per deciliter; Hb: hemoglobin; IU/L: international units per liter; Meq/L: milliequivalents per liter; mg/dL: milligram per deciliter; mm: millimeter; N/L/E/M: neutrophils/lymphocytes/eosinophils/monocytes; SAP: serum alkaline phosphatase; T/D: total/direct; TLC: total leukocyte count

infections, dyselectrolytemia, and intracranial bleeds were excluded by relevant investigations. Further evaluation revealed normal CSF analysis, but the MRI brain scan showed extensive involvement (bilateral cerebellar, brainstem, and thalamic involvement with foci of hemorrhage), which has been reported in only a few case reports [5]. No clinical study has yet reported rim enhancement as part of the imaging spectrum in dengue infection. Also, evidence of such extensive involvement suggests direct neuronal involvement, but absolutely normal CSF analysis provides evidence against such an explanation. This case, therefore, highlights the lack of a definite scientific explanation of the exact pathogenesis behind neurological syndromes in dengue infection.

Conclusions

Presently, no clear explanation can be put forth for the etiopathogenesis of dengue encephalopathy. Understanding the pathophysiology of dengue encephalopathy, a benign but potentially fatal disease, is crucial toward developing a more effective management strategy [4]. Therefore, larger multicenter prospective studies with detailed virological and radiological evaluation are required to unravel the mystery behind the varied manifestations of this enigmatic condition.

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Conflict of interests: No conflict of interests is declared.