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Case Report

Dengue encephalitis featuring "double-doughnut" sign - A case report

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ABSTRACT

Introduction: Dengue is a common febrile illness caused by Dengue virus and spread by *Aedes* mosquitoes. The neurological complications like encephalopathy or encephalitis or immune-mediated neurological syndromes are uncommon though. Discrete neuroimaging findings in this setting are even rarer. We report a case of dengue encephalitis with uncommon MRI features in a young female.

Case presentation: The patient presented with complains of fever, vomiting, weakness in all limbs and difficulty in speech. Neurological examination revealed bilateral horizontal gaze palsy with impaired oculo-cephalic reflex, bulbar dysarthria and quadriplegia with bilateral planters up-going. Laboratory reported anemia, thrombocytopenia and positive NS1 antigen while excluding other tropical and immunological diseases. Brain MRI revealed extensive thalamic involvement as unique "double-doughnut" sign along with lesions in brainstem. The patient received supportive treatment in intensive unit and was discharged following improvement in clinical condition and laboratory reports.

Clinical discussion: Dengue can infect the central nervous system directly as encephalitis or can have neurological consequences following multi-organ dysfunction and shock as encephalopathy or post-infection immunological syndromes as Guillain-Barré Syndrome or cerebrovascular complications or dengue muscle dysfunction. The MRI appearance of "double-doughnut" sign points towards dengue encephalitis in appropriate setting.

Conclusion: A high index of suspicion is required to make a diagnosis of dengue encephalitis. The "double-doughnut" sign in MRI sequences has the potential to become a diagnostic marker for dengue encephalitis.

1. Introduction

Dengue is an arthropod borne febrile illness caused by Dengue virus (DENV 1,2,3 & 4) and transmitted via the bite of an infected *Aedes* species (*Ae. aegypti or Ae. albopictus*) [1]. Dengue fever affects over 4 billion people worldwide, with roughly 100 million cases of symptomatic dengue occurring annually [2]. Nepal is also burdened with increasing dengue case load over time. The case incidence was 140 times higher in 2019 as compared to the incidence in 2016 [3].

Neurological complications of dengue virus can be broadly divided into encephalopathy; encephalitis, meningitis, myositis, and myelitis; and auto-immune reactions including acute disseminated encephalomyelitis, optic neuritis, and Guillain-Barre syndrome [4]. Among them, encephalopathy and encephalitis are the most common ones [5,6]. The frequency of neurologic manifestations is approximately 1% in case series [7]. We describe a case of a young girl with dengue encephalitis who presented with fever, vomiting, quadriparesis, horizontal gaze palsy and dysarthria along with a positive NS1 antigen and distinctive changes in MRI, namely "double-doughnut" sign. The sign is highly specific for dengue encephalitis, however, it is also associated with other viral encephalitides such as Japanese Encephalitis, herpes simplex, rabies and West Nile virus encephalitis [8]. Serum or cerebrospinal fluid serology can aid in diagnosis.

2. Case Presentation

An eighteen-year-old female presented in the emergency department with complaints of fever and vomiting of two days and weakness of all

Abbreviations: NS1, Nonstructural protein 1; FLAIR, Fluid-attenuated inversion recovery; DWI, Diffusion-weighted imaging; ADC, Apparent Diffusion Coefficient; GRE, Gradient echo sequence.

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four limbs and difficulty in speech of one day. On evaluation, her temperature was 101.4 °F while the other vital signs were within normal limit. Her GCS was 15/15. On neurological examination, the fundoscopy findings were normal. She had bilateral horizontal gaze palsy with impaired oculo-cephalic reflex, bulbar dysarthria and quadriplegia with bilateral planters up-going. There were no signs of meningeal irritation. Because of the speech and motor abnormality, other neurological examinations were limited. Chest, precordial and abdominal examinations were unremarkable.

Complete blood count revealed anemia, decreased packed cell volume and thrombocytopenia. Cerebrospinal fluid (CSF) analysis revealed normal cell counts with all the cells being lymphocytes, and slightly elevated protein levels. The patient had a positive serum NS-1 antigen, however anti-dengue IgM and IgG were not detected.

However, MRI brain showed T1 low, T2/FLAIR high signal intensity area in bilateral thalamus, pons, medulla, and left cerebellum with intense restriction of diffusion on diffusion-weighted imaging (DWI) and blooming in central region in gradient echo sequence (GRE) giving double doughnut sign, which is rare yet very specific radiological finding of dengue meningoencephalitis (see Fig. 1). Acute infarct in right frontal lobe white matter was also present. Japanese encephalitis, being a close differential to dengue encephalitis in terms of MRI brain findings, was tested for with CSF serology which came out to be negative. Workup for vasculitis and other tropical diseases were also negative. Hence, the diagnosis of dengue encephalitis was made.

She was intubated and managed conservatively with intravenous fluids, antipyretics and other supportive treatment in medical intensive care unit (MICU) with total nine days of MICU stay. Her general condition and neurological deficits improved steadily and there was correction in hemoglobin and platelet count. She was subsequently extubated and discharged after a total hospital stay of 18 days.

The patient was followed up a month after the discharge. Her neurological status was improving. She could walk with support and articulate speech with clarity.

3. Discussion

Although most dengue infections are asymptomatic or mildly symptomatic, these can lead to life-threatening multi-system dysfunction. In 2009, WHO has classified the illness as dengue without warning signs, dengue with warning signs, and severe dengue [9]. Of the symptomatic ones, most are self-limiting and few progress to severe disease [2]. Severe dengue can manifest as shock from plasma leakage or severe bleeding or severe organ involvement including liver, kidney, heart and/or central nervous system [9]. The access to better health services has limited fatality rates of severe dengue to below 1% in most endemic areas [10].

Severe dengue can have neurological manifestations, with an incidence of 0.5%–21% in dengue-infected hospitalized patients. However, there is little information on the actual burden. Dengue encephalopathy, encephalitis, immune-mediated syndromes, dengue muscular dysfunction, and neuro-ophthalmic disorders are the neurological consequences caused by the virus. Dengue encephalopathy is characterized by impaired consciousness or seizures or focal neurological signs or neck stiffness which can be caused or precipitated by other dengue-associated complications including hepatic failure, renal failure, metabolic acidosis, severe hyponatremia, prolonged shock, disseminated intravascular coagulation, or brain hemorrhage. Dengue encephalitis features similar CNS manifestations caused by direct CNS invasion and neurotropic effects of dengue virus [7]. These entities are the most common neurological presentations of dengue infections and can overlap and CSF analysis can be unremarkable in both manifestations [11].

Soares et al. [12] have proposed following criteria to diagnose dengue encephalitis:

a. Presence of fever;
b. Acute signs of cerebral involvement such as altered consciousness or personality and/or seizures and/or focal neurological signs;

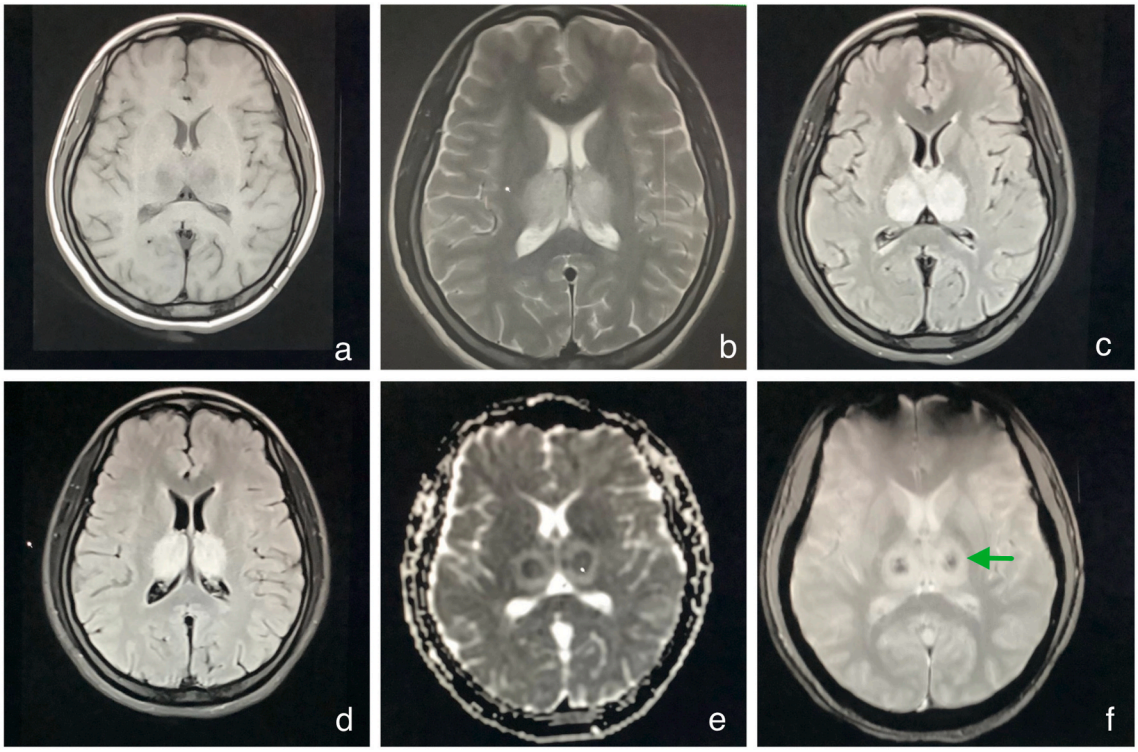

Fig. 1. Axial sections of MRI brain with bilateral thalami showing (a) hypo intense signal in T1-weighted image, (b and c) hyperintense signals in T2 and FLAIR sequences, (d) restricted diffusion in DWI with (e) corresponding low ADC values and (f) blooming in central region in gradient echo sequence, giving the 'double-doughnut' appearance (green arrow). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

c. Reactive IgM dengue antibody, NS1 antigen, or positive dengue polymerase chain reaction in serum and/or CSF;
d. Exclusion of other causes of viral encephalitis and encephalopathy.

This febrile patient had gross neurological deficits showing acute cerebral involvement along with positive NS1 antigen in serum and exclusion of other common causes of encephalitis, thus fulfilling the criteria.

Dengue infection can also involve nervous system as post-dengue immune mediated syndromes (acute transverse myelitis, acute disseminated encephalomyelitis, Guillain-Barré Syndrome) or cerebrovascular complications or dengue muscle dysfunction (e.g., inflammatory myopathies, rhabdomyolysis) or neuro-ophthalmic complications (optic neuropathy, maculopathy, retinal vasculitis, retinal hemorrhages, exudative retinal detachment, vitritis) [7]. The involvement of CNS in dengue indicates more severe disease with poorer recovery [13].

Only few case reports and case series featuring dengue encephalitis describe extensive MRI brain findings. They mostly report involvement of bilateral thalamus, brainstem, cerebellum, basal ganglia, medial temporal lobes and cortical and cerebral white matter [14,15]. The "double-doughnut" sign in dengue encephalitis is characterized by symmetrical T2/FLAIR high signal intensity area in bilateral thalami with restriction of diffusion on DWI and ADC and blooming in central region in gradient echo sequence due to hemorrhagic residues and have only been reported in few reports and case series [16–20]. Dengue virus inflicts direct neuronal injury leading to cerebral edema and hemorrhage secondary to vascular leak, which usually involves bilateral basal ganglia and thalamus complex and manifests neuro-radiologically as "double-doughnut" sign [14]. Compared to the case by Ramineni et al. that shows similar clinical picture of febrile illness followed by acute neurological symptoms, alike laboratory picture of thrombocytopenia and cerebrospinal fluid analysis findings and identical MRI characteristics of classic "double-doughnut" sign, our case had presentation resembling locked-in syndrome while their patient showed symptoms of typical meningoencephalitis i.e. altered sensorium and seizures. The prognosis is similar as the patients achieved full recovery in both instances, however, our case had some delay to achieve the improvement owing to the severity of neurological insult at the beginning [20]. Similar MRI findings have been reported in cases of Japanese encephalitis [8,21]. However, for a typical clinical setting such as acute febrile thrombocytopenia, this finding can point towards dengue encephalitis, thus helping in cases with severe thrombocytopenia where lumbar puncture may be risky. This patient, however, had no evidence of JE on immunological tests.

It is difficult to conclude whether this sign can be a diagnostic marker for dengue encephalitis, owing to rarity of incidence of dengue encephalitis and scarcity of strong evidence regarding the MRI findings. Also, MRI is not easily accessible to all suspected encephalitic patients in lower and middle income countries in tropics where dengue along with other encephalitic viruses are most prevalent. However, in cases where other serological and biochemical diagnostic tests remain inconclusive, the presence of this sign can help in directing clinicians' suspicion towards dengue encephalitis.

4. Conclusion

Dengue encephalitis is an uncommon complication of dengue infection. The clinical features can point towards wide range of diagnoses. However, with high degree of suspicion under appropriate circumstances, one can make a diagnosis of dengue encephalitis. The treatment remains supportive until the patients improves substantially.

Ethical approval

Case reports are exempt from ethical approval in our institution, Tribhuvan University Institute of Medicine, Maharajgunj.

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Author contribution

All the authors contributed equally for the preparation of this case report. Aashish Shrestha (AS), Niraj Gautam (NG), Bikram Prasad Gajurel (BPG) = study concept and therapy for the patient. Anupama Pandeya (AP), Devansh Upadhyay (DU), Bikram Oli (BO), Monika Parajuli (MP), Nitesh Silwal (NS) = Data collection, obtaining consent from patient's party, review of previous literatures, editing and writing of the manuscript. BPG = Senior author and manuscript reviewer. All the authors individually did the final proof-reading of the manuscript before submission.

Trial registry number

1. Name of the registry:
2. Unique Identifying number or registration ID:
3. Hyperlink to your specific registration (must be publicly accessible and will be checked):

Guarantor

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Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Provenance and peer review

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Declaration of competing interest

There are no conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.amsu.2022.103939.

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