Open Forum Infectious Diseases

NOVEL ID CASES

Dengue encephalopathy or encephalitis? You decide

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Awareness of neurological sequelae of dengue fever is increasing. However, as this case illustrates, there is a diagnostic conundrum in determining whether certain features are in keeping with dengue encephalopathy, or dengue encephalitis. Further consensus is required.

KEYWORDS (MeSH, 2021): Dengue, Severe dengue, Encephalitis, viral, Brain diseases

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DOI: 10.1093/ofid/ofad490

INTRODUCTION

Cases of dengue fever, the most rapidly-spreading mosquito-borne viral illness, caused by dengue virus (DENV) serotypes 1 – 4, generate a significant burden of morbidity as well as socio-economic impacts. There is increasing awareness of neurological sequelae: between 0.5-21% of patients with dengue fever exhibit neurological symptoms and signs.(1) The World Health Organization (WHO) reclassified dengue syndromes in 2009, incorporating neurological signs as a marker of severe dengue.(2) Here, we present a case that highlights the diagnostic challenges in classification of encephalopathy versus encephalitis in dengue.

CASE REPORT

A 50-year-old female fitness instructor and domestic worker with a history of amlodipine-controlled hypertension presented to a UK teaching hospital with a 2-day history of fever and myalgia with prostration, accompanied by a worsening headache and photophobia. The patient was originally from the Philippines but had lived for many years in the UK with her family. She had travelled for 10 days to Manila, visiting relatives and staying out of the city in the suburbs,. Shereturned to the UK 5 days prior to admission. Whilst she took precautions, she was bitten by mosquitoes; and she noted that a number of friends and relatives had also been hospitalised in the Philippines with dengue fever.

Initial cardio-respiratory and neurological examination was normal with no focal neurological signs, including meningism. No mucosal bleeding or skin rash was seen. Ceftriaxone and acyclovir were commenced as empirical treatment for meningitis and encephalitis. Three blood films and rapid diagnostic tests (RDTs) were negative for malaria parasites. Blood and urine cultures demonstrated no growth. CT brain scan showed no acute intracerebral pathology with normal grey-white matter differentiation. A lumbar puncture was performed within 24h of admission (day 3 of symptoms; platelet count was 239 x 10^9/L. Cerebrospinal fluid (CSF) was acellular (WBC <1/uL, RBC <1/uL) with no organisms seen on microscopy and no growth on bacterial culture. A routine CSF virology PCR screening panel (HSV, VZV, enterovirus) was negative and therefore aciclovir was stopped. An extended-panel respiratory virus PCR throat swab (Supplementary Table 1) was negative. Serology for HIV-1/-2, hepatitis B, hepatitis C, and *Borrelia burgdorferi* infections were negative. Serology for both EBV and CMV showed evidence of previous infection.

A serum sample sent to the reference laboratory for analysis demonstrated IgM and IgG, as well as PCR, positivity for dengue virus (DENV). Serotyping was not performed. Subsequent PCR testing of cerebrospinal fluid demonstrated positivity for DENV RNA. Full details of all tests performed are outlined in Supplementary Table 1.

The patient was transferred to the Infectious Diseases ward for ongoing management. She developed coagulopathy and abnormal liver function tests (transaminitis) midway through her inpatient stay. Ferritin was maximally 48,000µg/L (range 10-120) with ALT 350u/L (0 – 34) and APTT 75s (25 – 35), and platelet nadir 35 $x10^9$/L (135 – 400 $x10^9$/L).

On day 6 of the admission (day 8 of illness), the patient had an unwitnessed fall without head injury after dizziness on mobilising to the toilet. She was noted to be less alert with a Glasgow Coma Scale (GCS) score of 13 (E4, M5, V4), and was unable to obey commands. She was observed to have intermittent vacant episodes and confused speech with word-finding difficulties. Given concurrent thrombocytopaenia, further cerebral imaging was obtained. A repeat CT brain scan showed no acute intracranial pathology. Consequently, a magnetic resonance imaging (MRI) brain scan was performed (Figure 1), which showed ill-defined rounded T2-dependent signal abnormality, without diffusion restriction, in both the left and right middle cerebellar peduncles (the latter being more affected), suggestive of an underlying inflammatory process. There were also multiple small non-specific scattered supratentorial, subcortical, and deep white matter T2-hyperintense foci, most likely representing age-appropriate cerebral micro-angiopathic change.

Her level of coherence and mentation as well as her balance and dizziness normalised spontaneously during the remainder of her stay. All blood parameters improved spontaneously – platelets were normal, and APTT was 48s, by discharge. She was discharged on day 11 of admission. The patient re-presented to the Emergency Department 14 days after this admission with a medication overuse headache secondary to codeine phosphate for post-dengue myalgia and headache. Neurological examination including fundoscopy was normal. CT brain scan at this time was normal with no acute intracranial pathology; MRI was not performed. Symptoms resolved spontaneously on cessation of codeine.

Outpatient interval MRI brain was postponed due to the COVID-19 pandemic but occurred at 15 months post-admission. There was near-complete resolution of the cerebellar changes, temporally related to resolution of the dengue infection. A re-look at initial diffusion-weighted imaging (DWI) sequences did not show any associated micro-haemorrhage. There remained a 2mm siderotic nodule in the region of the right cerebellar peduncle abnormality, likely representing a small fleck of calcification, and consistent with healing of an infective or inflammatory process.

DISCUSSION

In 2009, the World Health Organization (WHO) reclassified dengue virus (DENV) clinical cases, incorporating neurological signs and symptoms as a manifestation of severe dengue.(2) In one review, neurological complications occurred in 0.5 – 5.4% of confirmed dengue cases

originating in southeast Asia;(3) and in other studies, up to 20% of cases of encephalitis presenting at hospitals were diagnosed with dengue.(1)

In the above case, impairment of consciousness ("severe organ involvement") categorises the patient as having severe dengue. Currently, no clear diagnostic criteria exist for distinguishing dengue encephalopathy from encephalitis, and the terms are often used interchangeably.(1) There have long been calls for standardised criteria to define these conditions in dengue.(1, 3, 4) A classification of dengue involvement of the central nervous system has been proposed recently,(1) but there is debate as to the possibility of under-diagnosis.(4)

Encephalopathy, an altered conscious level, is the most commonly-reported neurological complication of dengue, ordinarily exhibiting normal CSF cell counts; however, in a number of reported case series, no PCR testing of CSF for DENV was performed.(1) Dengue encephalopathy may result from shock, cerebral oedema, electrolyte abnormality, acute liver or kidney injury, or cerebrovascular complications such as microhaemorrhages.(1)

Whilst not previously thought to be the case, it is now known that DENV, like other flaviviruses exhibits tropism for neural cells, including direct neuroinvasion.(5) In our case, DENV RNA was concomitantly detected in blood, but previous cases where CSF PCR alone was positive again suggest active neuroinvasion, rather than vascular leakage or permeation across the blood-brain barrier.(1) In some instances of encephalitis, a lymphocytic pleiocytosis may add weight to the diagnosis, but in others CSF cellularity is reported to be normal(6), as here, and this does not exclude viral encephalitis.(1, 5) Timing of the lumbar puncture in the course of the illness may have affected this result. Brain imaging may show heterogeneous changes, or appear normal, in dengue encephalitis cases.(1, 5, 6) Dengue cerebellitis has also been described.(7)

In this case, there was evidence of acute dengue infection (serum IgM positivity, epidemiological risk), dengue CNS involvement (altered GCS), and evidence of DENV (positive RNA PCR) in CSF that was otherwise acellular (and therefore unlikely to be passively contaminated with DENV RNA from a traumatic tap). Although present, the degree of liver function abnormality was not sufficient to explain the patient's symptoms. However, there was no CSF pleiocytosis. The brain lesions found on MRI are non-specific but temporally were associated with the initial infection, appear inflammatory in nature, and improved to resolution on subsequent imaging. EEG was not performed in this case; nor was there evidence of seizure activity, focal or generalised, in contrast to other cases of CNS dengue classified as encephalitis.(3) Histopathology demonstrating viral inclusions with inflammation and/or necrosis might have been declarative – but sampling in this case was not undertaken.

In summary, there is no clear expert consensus on classification of encephalopathy versus encephalitis syndromes in dengue infection. Differentiation between dengue encephalopathy and encephalitis will be of increasing importance, especially with increasing dengue prevalence. Studies have shown an increased risk of encephalitis in secondary (compared with primary)

dengue, and higher mortality rates in cases classified as dengue encephalitis.(8) One may presume that patients suffering from encephalitis might have a higher burden of long-term neurological and other sequelae than those with encephalopathy, but further research on this would be required. Formulation of consensus criteria would therefore aid identification of dengue severity, standardise workup, and assist with stratified prognostication and early treatment planning (such as transfer to an inpatient or secondary/tertiary centre), as well as providing another benchmark against which to test vaccine candidates. In a similar way, dengue must be considered in patients presenting with encephalitis, in order to ensure prompt diagnosis of dengue.

This case fulfils the proposed neurological Koch's postulates for viral aetiologies of encephalitis.(9) In the absence of any other discernible cause, this case could be classified as probable or confirmed dengue encephalitis by some criteria(4, 9) – a diagnosis that may not be as rare as previously thought. Disagreement exists in particular as to inclusion of CSF pleiocytosis and imaging changes, and, as discussed, their prevalence in dengue encephalitis cases is variable. Further global expert consensus is therefore required to clarify the dengue encephalopathy versus dengue encephalitis distinction.

Abbreviations

ALT – alanine aminotransferase

APTT – activated partial thromboplastin time

CMV – cytomegalovirus

CSF – cerebrospinal fluid

CT – computed tomography

DENV – dengue virus

DWI – diffusion-weighted imaging

EBV – Epstein-Barr virus

EEG – electro-encephalogram

FLAIR – fluid-attenuated inversion recovery

GCS – Glasgow Coma Score

HIV – human immunodeficiency virus

HSV – herpes simplex virus

MRI – magnetic resonance imaging

PCR – polymerase chain reaction

RIPL – Rare & Imported Pathogens Laboratory, Porton Down, UK

RBC – red blood cells

RDT – rapid diagnostic test

RNA – ribonucleic acid

VZV – varicella zoster virus

WBC – white blood cell

WHO – World Health Organization

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflict of interest statement

The Authors have no competing interests to declare.

Patient consent statement

A copy of the consent form signed by the patient is available for viewing by the Editors.

Acknowledgements

The Authors are grateful for the kind permission of the patient to publish their case. With thanks to Dr. Jane Osborne, Consultant Clinical Scientist, and the Team at the Rare & Imported Pathogens Laboratory (RIPL), Porton Down, UK, for their involvement in processing and interpreting samples.

Author contributions

SMD: Conceptualisation, Writing – Original draft preparation, Writing – Review & editing, Patient care.

ALdS: Writing – Original draft preparation, Patient care (Imaging review).

NWSD: Writing – Review & editing, Patient care (Specialist Review).

SS: Writing – Review & editing, Supervision, Patient care (Named Consultant).

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Figure 1: (a) Axial MRI FLAIR image, day 7 of illness, demonstrating ill-defined areas of T2 weighted signal hyperintensity in both cerebral peduncles (arrows). (b) Axial FLAIR image 15 months later demonstrating resolution of the abnormal signal in the cerebral peduncles.