CASE REPORT

Dengue Encephalopathy or Japanese Encephalitis? Co-Infection or Serologic Cross- Reactivity?

Cheng Keat Moh, Calvin Ke Wen Wong, Hong Bee Ker

Department of Internal Medicine, Hospital Raja Permaisuri Bainun, Jalan Raja Ashman Shah, 30450 Ipoh, Perak, Malaysia, Ministry of Health Malaysia

ABSTRACT

Dengue infection has a wide clinical spectrum ranging from asymptomatic presentation to life-threatening severe dengue with multiorgan failure, and increasingly recognized neurological presentation in the past decade. Japanese encephalitis on the other hand is another common mosquitoes-borne flavivirus infection endemic in Southeast Asia, which share some similar clinical features. We report a case of a 38-year-old male patient who presented to us with complaints of fever and acute encephalitis syndrome with positive dengue NS1 antigen, and positive cerebrospinal fluid serologies for both dengue and JE immunoglobulins. Magnetic Resonance Imaging findings were suggestive of encephalitic changes. Co-infection and serology cross-reactivity of these two flaviviruses is not uncommon in countries where both dengue and Japanese encephalitis are endemic, and thus, the treating clinician should have a high index of suspicion if clinical and serological evidence are present whilst treating the patient.
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Corresponding Author:
Cheng Keat Moh, MD
Email: ckmoh_90@hotmail.com
Tel: +60169864375

INTRODUCTION

Dengue Virus and Japanese Encephalitis (JE) virus are mosquito-borne viruses which cause significant morbidity and mortality especially in South-East Asia where they are endemic. Both viruses are single-stranded enveloped RNA virus which belong to the Flaviviridae family and hence it is not uncommon to have the diagnostic dilemma between them as they share the same vector with several similar clinical features. Studies also show that both flaviviruses cross-react with each other in serological tests. We are here to report a patient with acute encephalitis with positive cerebrospinal fluid serologies for both dengue and JE, as well the diagnostic challenges faced.

CASE REPORT

A previously well 38-year-old Malay gentleman, a religious preacher who travelled frequently preaching around Peninsular Malaysia, with no known co-morbids but an active smoker , was admitted to the hospital with intermittent fever for 4 days, myalgia and malaise. Over the next few days, he developed multiple episodes of vomiting, with altered sensorium and eventually became drowsy. There were no headaches, seizures, abdominal pain, skin rashes or any bleeding tendency prior. His past medical history was unremarkable with no history of chronic medication use or illicit drug ingestion.

Upon his presentation, he was afebrile with stable vital signs. His GCS was 10/15 (GCS: E3, V2, M5) without signs of meningism and had normal reactive pupils of 3 mm bilaterally. Due to his altered GCS, a limited neurological examination found power of all 4 limbs to be 4 over 5, with normal tone with no neck stiffness or rigidity noted. Other systemic examination was unremarkable.

Initial blood investigations on presentation as shown in Table I.

Serum dengue non-structural protein 1 (NS1) antigen was positive while his serum Dengue ELISA serology test was positive for Immunoglobulin G (IgG) and negative for Immunoglobulin M (IgM) (at Day 4 of illness).

An urgent non contrasted CT brain revealed hypodensities over the bilateral cerebellar region with obstructive hydrocephalus. Neurosurgical consult was sought, and an emergency right frontal external ventricular drain (EVD) was inserted. Cerebrospinal fluid (CSF) revealed protein level: 102 mg/L; glucose level: 5.7 mmol/l with

Table I: Initial blood investigations on presentation to Emergency Department

Investigation	Result	Units	Normal Range
White Cell Count	2.2	x 10^9/L	4.0 – 11.0
Haemoglobin	13.1	g/dL	11.5 – 16.0
Haematocrit	40.5	%	35 – 47
Platelet	127	x 10^9/L	150 – 400
Absolute Neutrophils Count (Percentage)	1.45 (65.6)	x 10^9/L %	2.0 – 7.0 40 – 75
Absolute Lymphocyte Count (Percentage)	0.45 (20.4)	x 10^9/L %	1.0 – 3.0 20 – 45
Urea	4.4	mmol/L	2.5 – 6.7
Creatinine	79	µmol/L	50 – 98
Serum Sodium	141	mmol/L	136 – 145
Serum Potassium	3.2	mmol/L	3.5 – 5.1
Total Protein	68	g/L	64 – 83
Serum Albumin	39	g/L	35 – 50
Aspartate aminotransferase (AST)	106	U/L	5 – 34
Alanine aminotransferase (ALT)	69	U/L	< 56.0
Total Bilirubin	5.9	µmol/L	5.1 – 20.5

random blood sugar (RBS) 7.7 mmol/l. Cell count, CSF Gram stain and bacterial cultures were negative. ELISA serology IgM antibodies to dengue virus and JE virus were both detected in his CSF sample while other viral antibodies and GeneXpert for tuberculosis were both negative. DEN 3 serotype was detected via his serum dengue PCR but his serial serum Japanese encephalitis-immunoglobulin M (JE IgM) was found negative. His repeated serum dengue ELISA serology at Day 10 of illness showed both IgG and IgM being positive .

Magnetic resonance imaging (MRI & MRA) of brain was performed and showed post-operative intraventricular haemorrhage with cerebellar micro-haemorrhages. No abnormal leptomeningeal enhancement seen. On day 2 of admission, he had a blocked EVD with worsening hydrocephalus and subsequently underwent an insertion of a left frontal external ventricular drain (EVD). Post operatively, the patient was admitted to the Intensive Care Unit (ICU) for further therapy. He eventually underwent tracheostomy due to poor GCS recovery and prolonged ventilation and subsequently was transferred out to the general medical ward for further care and rehabilitation. He was discharged home after 1 month of hospitalization with a recorded GCS of 13/15 (GCS: E4, V3, M6), still wheelchair bound and carer dependent due to motor function impairment, with bilateral upper limbs power 3/5, while lower limbs power 4/5 upon discharge.

DISCUSSION

Patients with dengue fever although typically presents with fever, generalized myalgia, arthralgia and headaches, it is worth noting that some may be asymptomatic or present with undifferentiated fever mimicking many other diseases. Although dengue fever has been considered to be non-neurotropic in the past, neurological involvement like encephalopathy, meningoencephalitis, intracranial haemorrhages or thrombosis, myelitis and Guillain–Barre syndrome have been increasingly noted in recent years. The WHO Dengue Guideline in Year 2009 proposed that dengue infection with CNS manifestation(s) are classified as "severe dengue", but there was no consensus reached on the diagnostic criteria and management guidelines for dengue encephalitis and dengue encephalopathy.

Japanese encephalitis (JE) virus, which is a known neurotropic virus, associates itself with significantly high mortality at around 30% among those with encephalitis, with another 30%–50% of survivors suffering from permanent neurologic, cognitive, or psychiatric complications, reported by CDC (Centres for Disease Control and Prevention). Meanwhile, most of the JE infections are asymptomatic or have mild undifferentiated symptoms, and only less than 1% go on to develop neurological disease.

This patient first presented with viral fever and neurological manifestations, no meningeal irritation sign on admission clinically, with positive serum Dengue NS-1 on admission. The working diagnosis upon admission was severe dengue with dengue encephalopathy. Along the way, his CSF JE virus IgM and Dengue virus IgM turned positive and created confusion. Clinical manifestations for dengue encephalopathy are not readily distinguishable from Japanese Encephalitis. This raised the dilemma of whether this is a co-infection, sequential infection or serological cross-reactivity.

Nuegoonpipat et al. from Thailand reported cross-reactivity of IgM to both dengue and JE viruses in both serum and CSF samples, where they found that 24 (9%)

of 258 serum samples from Dengue IgM positive patients had JE-IgM Positive results as well while 13 (13%) of 99 serum samples and 4 (11%) of 37 CSF samples with JE IgM positive also noted to be Dengue IgM positive as well. (1). Another large retrospective study done by Singh et. al from July 2008 to October 2011 involving 1410 patients that presented with suspected viral meningoencephalitis, 129 (9.14%) patients were tested co-positive for both Dengue IgM and JEV IgM. Among those co-positive cases, 8 out of the 76 cases had co-positive Dengue and JE virus by reverse transcriptase polymerase chain reaction (RT-PCR) (Six in serum only and two in both serum and CSF). (2).

Singh et. al demonstrated that co-infection versus antigen cross-reactivity can be differentiated by comparing anti-DENV and anti-JEV IgM antibodies titre in paired sera and CSF sample, for which titres are high above cut off level is considered to be the infecting virus (or co-infection if both high titres) (2). And this hypothesis is more significant in endemic countries where both dengue and JE infection are prevalent. The diagnostic confirmation of co-infection can be done through RT-PCR (2). However, sera and CSF antibodies titre for both pathogens and JE PCR result were unfortunately not sent for this case. There was also absence of Anti-JEV Immunoglobulins in serial sera sample and hence, we are unable to ascertain whether this patient was having a single dengue infection with serological cross-reactivity, or sequential infection. Facing such diagnostic dilemma, plaque reduction neutralization test (PRNT) is the gold standard serological assays for differentiating serological cross-reactivity or co-infection between DENV and JE virus, as well for other flaviviruses by quantifying the neutralizing antibody titres, even in those vaccinated population. (5). However, PRNT testing is time consuming and labour intensive, used mainly for clinical research practice in Malaysia and thus, not readily available in most centres.

Neuroimaging finding in dengue encephalopathy or encephalitis are diverse and non-specific. (3). Many observed intracranial haemorrhages and cerebral oedema among the predominant manifestation seen in those with encephalopathy (3), which is similar to this case, in which supports our diagnosis of dengue encephalopathy. Few isolated case reports did describe presence of intracranial haemorrhage involving thalami and basal ganglia seen in JE (4) and also dengue encephalitis (3).

CONCLUSION

Due to the endemicity and similar clinical features with a possibility of serology cross reactivity, definitive diagnostic differentiation between dengue encephalopathy versus encephalitis and as well between dengue encephalitis and Japanese Encephalitis is indeed important as the management and trajectory of recovery varies between the two. MRI findings or ELISA serological studies for diagnosis are not specific enough to differentiate, while labour-intensive PRNT assays while useful, are not practical in daily clinical practice. Treating clinicians in endemic regions should always have a high index of suspicion for the atypical manifestation of both infections.

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