Case report

Mild encephalitis/encephalopathy with reversible splenial lesion (MERS) due to dengue virus

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A R T I C L E  I N F O

Article history:
Received 4 September 2016
Accepted 29 October 2016
Available online xxxx

Keywords:
Dengue
Encephalitis
Encephalopathy
Corpus callosum

A B S T R A C T

A 14-year-old girl presented with encephalopathy, delirium and ophthalmoplegia following a 3 day history of high-grade fever. Brain MRI on day 6 of illness showed diffusion restricted ovoid lesion in the splenium of corpus callosum. Dengue virus encephalitis was diagnosed with positive PCR for dengue virus type-2 in both serum and cerebrospinal fluid. She made a complete recovery from day 10 of illness. Repeat brain MRI on day 12 of illness showed resolution of the splenial lesion. Serial diffusion tensor imaging (DTI) showed normal fractional anisotropy values on resolution of splenial lesion indicating that MERS was likely due to transient interstitial oedema with preservation of white matter tracts. This is the first reported case of MERS following dengue virus infection. It highlights the usefulness of performing serial DTI in understanding the underlying pathogenesis of MERS. Our case report widens the neurological manifestations associated with dengue infection and reiterates that patients with MERS should be managed supportively as the splenial white matter tracts are reversibly involved in MERS.

1. Introduction

Dengue virus infection is the most common mosquito-borne viral infection worldwide [1]. Although dengue is classically considered a non-neurotropic virus, dengue viral neurotropism is seen in some cases with evidence of direct viral invasion of the central nervous system (CNS) [2]. The commonly reported neurological manifestation of dengue virus infection is encephalopathy and encephalitis supported with evidence of direct CNS dengue virus infection in the cerebrospinal fluid (CSF) [2,3]. Brain magnetic resonance imaging (MRI) in dengue encephalitis shows no characteristic findings and is usually normal [4].

There are no reports to date of reversible splenial lesions associated with dengue encephalitis. Mild encephalitis/encephalopathy with reversible splenial lesion (MERS) is a clinical-radiological syndrome [5]. MERS is reported in patients with encephalitis or encephalopathy due to viral infections particularly the influenza viruses, metabolic disorders and withdrawal of antiepileptic drug therapy [6]. Complete resolution of the splenial lesion on repeat imaging with full clinical recovery is the hallmark of this syndrome.

We present a 14-year-old girl with MERS following acute dengue virus encephalitis. To the best of our knowledge this is the first reported case. We also review the current literature and describe the usefulness of diffusion tensor imaging (DTI) in understanding the microstructural white matter tract changes associated with MERS.

2. Case report

A 14-year-old girl presented at day 3 of illness with alteration in behavior after a preceding 3 days of high-grade fever and rigors. Investigation on admission showed normal full blood count, high CRP and normal Brain Computed Tomography. The next day, the patient showed worsening delirious behavior with fluctuating consciousness of Glasgow Coma Scale (GCS) between 7–13/15. Patient continued to be delirious and developed bilateral ophthalmoplegia at day 5 of illness. Contrast enhanced brain MRI revealed a well circumscribed ovoid lesion within the splenium of the corpus callosum (Fig. 1). It demonstrated restricted diffusion on both
At day 5 of illness she had a hemoglobin of 152 g/L (reference: 120–150 g/L), high hematocrit 0.48 L/L (reference: 0.36–0.46 L/L), thrombocytopenia $6 \times 10^9$/L (reference: $150–400 \times 10^9$/L) and leukocytopenia $2.1 \times 10^9$/L (reference: $410 \times 10^9$/L). Her blood serum was positive for both dengue NS1 Ag, anti-dengue IgM, and PCR positive for dengue virus-type 2. Her CSF was also PCR positive for dengue virus-type 2. The rest of her blood investigations were negative for autoimmune screen; viral PCR (herpes simplex virus (HSV)-1, HSV-2, enterovirus, human herpes virus-6, Cytomegalovirus (CMV), Epstein Barr virus (EBV), parvovirus B19, varicella-zoster virus); viral serology (mycoplasma, measles IgM); and anti N-methyl D-aspartate receptor antibody. She did not show evidence of severe plasma leakage or organ impairment.

She was managed conservatively with supportive fluid rehydration and made a full clinical recovery from day 10 of illness with normalisation of all her blood parameters. Repeat brain MRI at day 10 of illness showed complete resolution of the previously seen splenial lesion (Figs. 1 and 2). Serial DTI was also performed to attain the fractional anisotropy (FA) values to evaluate the commissural white matter fibres integrity of the regional tracts. Quantitative axial FA values from the splenium of corpus callosum during the first and second scans were 0.58 and 0.76, respectively (reference: 0.75–0.81) (Fig. 2).

### 3. Discussion

This is the first reported case fulfilling the diagnostic criteria for MERS associated with dengue virus. To date, there are only two adult reports from India and Japan (Japanese language case report with English language only in abstract form) reporting the possible association between splenial lesion with dengue virus infection [7,8]. These reports however do not meet the diagnostic criteria of MERS as no serial MRIs were performed in these 2 patients to show the resolution of the splenial lesion. In addition, a diagnosis of presumptive dengue encephalitis was made with no CSF findings available to show definitive evidence of dengue virus in the CSF unlike our case with CSF PCR positive for dengue virus type-2.

Clinically MERS patients present with non-specific prodromal symptoms and then subsequently develop encephalopathic symptoms including speech difficulties, drowsiness, delirium and seizures. A multi-center study performed in Japan showed that the most common neurological symptom is a delirious behavior seen in 54% of patients which was also seen in our patient [9]. Some authors postulate that the delirium is as a result of disconnection of the bilateral cerebral hemispheres leading to disruption of the higher cortical function [10].

Brain MRI is required to make the diagnosis of MERS. The typical MRI features of MERS are T2 signal prolongation and restricted DWI with decreased ADC values in the splenium of corpus callosum. Majority of the reported MERS resolve within 2 weeks associated with full resolution of clinical symptoms [11–13]. The proposed diagnostic criteria for MERS requires the following 5 features: (1) Clinical onset associated with neuropsychiatric symptoms, such as impaired consciousness within 1 week after fever onset; (2) Complete recovery without sequelae, mostly within 10 days after the onset of neuropsychiatric symptoms; (3) High-signal-intensity lesion in the splenium of corpus callosum; (4) Lesion may involve the entire corpus callosum and the cerebral white matter in a symmetric fashion; (5) Lesion disappearing within 1 week, with no residual signal changes or atrophy [14]. Our patient fulfills this diagnostic criteria.

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**Fig. 1.** Contrast enhanced MRI brain performed at day 5 (A, B, C) and day 12 (D, E, F). Arrow showing a well-defined ovoid lesion in the splenium of the corpus callosum measuring $0.7 \times 1.0 \times 1.2$ cm which was hyperintense on axial T2-weighted (A), sagittal T2-weighted (B) and coronal T2 FLAIR (C) images. Complete resolution of the splenial lesion on repeat MRI as demonstrated on axial T2-weighted (D), sagittal T2-weighted (E), and coronal T2 FLAIR (F) images.

**Fig. 2.** Diffusion weighted imaging (DWI) and apparent diffusion coefficient (ADC) showing decreased ADC values and hyperintense lesion in the splenium of the corpus callosum (A, B, C).
The exact underlying pathophysiology of MERS is unknown. Various mechanisms have been proposed including changes in vascular distribution, direct viral invasion and arginine vasopressin suppression [11–13]. DTI enables the use of FA to evaluate the intrinsic directionality of water diffusion within fibrous structures of myelinated neural axons and is thus able to detect microstructural white matter changes better than DWI [15]. To date there are only 3 published studies of 5 patients that have evaluated MERS during the acute and recovery phase using serial DTI studies [5,16,17]. Our study complements the previous published studies and is the first to be performed MERS caused by dengue virus. The findings of FA in the acute phase are mixed with 3 cases showing reduced FA (including our patient), 2 cases showing normal FA and 1 case showing increased FA. Thus it is difficult to interpret the significance of DTI findings in MERS during the acute stage due to the variable timings in the acute illness of the FA evaluation. However, all these 6 cases (including our case) have shown that repeat FA is normal upon resolution of the corpus callosum lesion clearly indicating that MERS is a non-degenerative disorder. Hence, these serial DTI findings indicate that MERS is likely due to transient interstitial oedema with preservation of the white matter architecture.

4. Conclusion

This is the first reported case of MERS following dengue infection. Our case report widens the phenotype of the neurological manifestations associated with dengue infection and reiterates that these patients should be managed supportively as the DTI findings indicate that the splenial white matter tracts is reversibly involved in MERS.

Conflict of interest/disclosures

The authors declare that they have no financial or other conflict of interest in relation to this research and its publication.

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Please cite this article in press as: Fong CY et al. Mild encephalitis/encephalopathy with reversible splenial lesion (MERS) due to dengue virus. J Clin Neurosci (2016), http://dx.doi.org/10.1016/j.jocn.2016.10.050

Please cite this article in press as: Fong CY et al. Mild encephalitis/encephalopathy with reversible splenial lesion (MERS) due to dengue virus. J Clin Neurosci (2016), http://dx.doi.org/10.1016/j.jocn.2016.10.050