CASE REPORT

Transient splenial lesion due to non-cirrhotic hyperammonaemia in dengue fever

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SUMMARY

Transient splenial lesion(TSL) is seen in a variety of conditions and is detectable only on MRI of the brain. Dengue fever (DF) is a common viral infection encountered in the tropics. The affected patients may face neurological complications like encephalopathy and intracranial haemorrhage, or even ischaemic stroke. Non-cirrhotic hyperammonaemia is a rare scenario; and its occurrence in DF is unknown. The patient being described had DF and developed dysarthria. His MRI brain showed splenial hyperintensity. Further evaluation revealed non-cirrhotic hyperammonaemia. To the best of our knowledge, TSL due to non-cirrhotic hyperammonaemia in DF is an unreported scenario.

BACKGROUND

Transient splenial lesion (TSL) on MRI of the brain has been reported in a wide range of neurologic and non-neurologic conditions. It is self-limiting, and subsides over a period of time, provided the underlying cause has been settled. Dengue fever (DF) is a disease burden of the tropical region. Neurological complications encountered include meningitis, encephalitis and stroke. Hyperammonaemia is a known cause of encephalopathy, and is commonly seen in patients with liver disease. Non-cirrhotic hyperammonaemia can be due to inherited or acquired causes. The condition is uncommon, and unreported in DF. Hyperammonaemia and dengue encephalitis can show as TSL on MRI of the brain.

CASE PRESENTATION WITH INVESTIGATIONS

A 45-year-old man presented to the Medicine department with 5 days history of fever and myalgia. He did not have any comorbidity and was not on any regular medications. On presentation, he was febrile (101°F). Other vitals and systemic examinations were normal. There were no signs of bleeding manifestation. His blood investigations showed leucopenia (3500 cells/cumm with neutrophils 40% lymphocytes 60%), thrombocytopenia (80 000 cells/cumm) and elevated liver enzymes (aspartate transaminase 204 U/L and alanine transaminase 210 U/L). Dengue serology (NS1 antigen and IgM) was positive. Weil Felix, smear for malaria, viral markers (HIV, Hepatitis B surface antigen (HBsAg), anti-Hepatitis C virus (HCV)) and leptospirosis serology were negative. Urine microscopy and other blood investigations like renal functions, electrolytes, glycated haemoglobin (HbA1c), prothrombin time/International Normalized Ratio (PT/INR) and activated partial thromboplastin time (apTT) were normal. Chest X-ray and ECG were also normal. Ultrasound abdomen showed mild hepatomegaly.

Over the next 3 days, he was stable and afebrile, but had a further decline in platelet counts with no bleeding manifestations. On day 5 of admission, he developed dysarthria. Other neurological examinations were normal, with no signs of meningeal irritation. His blood investigations showed worsening thrombocytopenia (25 000 cells/mm^3) with haemoconcentration (haemoglobin 180 g/L, packed cell volume (PCV) 51.4%) and mildly prolonged apTT (test 37.6 s, control 24.4 s). MRI of brain revealed spenial hyperintensity on diffusion sequence (figure 1) and hypointensity of T1W image (figure 2). Cerebrospinal fluid (CSF) analysis was normal (white blood cell count (WBC) 4, protein 32 mg/dL, glucose 62 mg/dL), with Gram stain and culture, dengue IgM, Acid-Fast Bacillus (AFB) stain, India ink, adenosine deaminase (ADA), herpes simplex virus type 1 and 2 (HSV 1 and 2) DNA PCR and Japanese encephalitis virus (JEV) RNA PCR being negative. Blood cultures were sterile. There was no dyselectrolytaemia and antinuclear antibodies (ANA) profile was negative. In view of TSL, serum ammonia level was checked which turned out to be high (107 µmol/L).

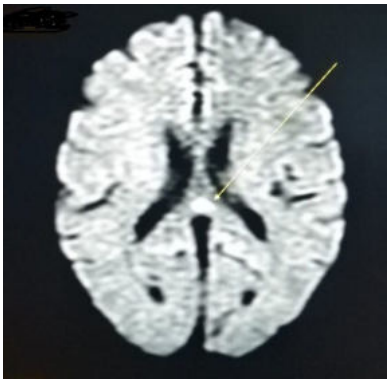

Figure 1 MRI brain diffusion sequence showing hyperintensity in the splenium of corpus callosum.

TREATMENT AND OUTCOME

He was initially managed symptomatically with intravenous fluids, paracetamol, folic acid supplements and pantoprazole. Following the development of dysarthria due to hyperammonaemia, he was given lactulose enema followed by lactulose syrup (30 mL) at night. Within 2 days his ammonia levels started normalising

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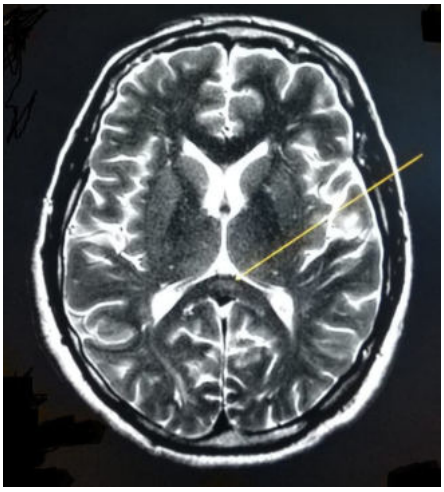

Figure 2 MRI brain T1W image showing hypointensity in the splenium of corpus callosum.

and his speech became normal. His haemoconcentration, thrombocytopenia and liver enzyme levels improved, following which he was discharged on day 10 of admission. His repeat MRI brain after 1 month was normal.

DISCUSSION

The splenium is the thickest and posterior most portion of the corpus callosum. Clinically, the lesions involving the splenium present as ataxia, headache, confusion, dysarthria, seizures, hemiparesis and increased muscle tone.[1] TSL has been observed in a variety of conditions, which has been outlined in table 1. These lesions are only detectable on the MRI and present in two distinct patterns: the 'dot sign' which appears as a well circumscribed, small, oval lesions in the midline within the splenium; or the 'boomerang sign' which is a more extensive less regular lesion extending throughout the splenium and into the adjacent hemispheres. Several mechanisms have been implicated for TSL which include transient breakdown of blood–brain barrier, intramyelinic oedema due to inflammation and migration of inflammatory cells, extrapontine osmotic myelinolysis due to sodium and glucose imbalance, a direct viral invasion of neurons, cytokine-mediated immunological reaction resulting in microvascular endothelial injury and toxicity or hypersensitivity to antiepileptic drugs. These lesions appear isointense or hypointense on T1-weighted image without enhancement and hyperintense on T2 and FLAIR images. The changes in diffusion-weighted imaging (DWI) appear earlier compared with T2 and FLAIR images. They are fully reversible and disappear after a few weeks.[2]

Table 1 Causes of TSL

Infection	Viral	Influenza, measles, herpes, mumps, adenovirus, varicella, rotavirus, HIV
	Bacterial	Salmonella, rickettsial infection, Legionnaires' disease
	Mycobacteria	Tuberculous meningitis
	Spirochetes	Leptospirosis
Epilepsy	Seizures, overdose or sudden stoppage of antiepileptic drugs	
Demyelination	Multiple sclerosis, acute disseminated encephalomyelitis, SLE	
Metabolic	Hypoglycemia, electrolyte imbalance (eg, hyperammonaemia, hyperatraemia and hyponatraemia), hemolytic-uremic syndrome, hepatic encephalopathy, Marchiafava-Bignami disease, osmotic demyelination, Wernicke encephalopathy, Wilson disease	
Vascular	Posterior reversible encephalopathy syndrome, cerebrovascular accident, pre-eclampsia, post cardiac arrest	
Drugs	Cyclosporine, metronidazole, fluorouracil	

SLE, systemic lupus erythematosus; TSL, transient splenial lesion.

Ammonia is produced by the bacterial hydrolysis of intestinal urea and other nitrogenous compounds, the purine nucleotide cycle, the transamination of amino acid in skeletal muscle and other metabolic processes which take place in the liver and kidneys. Neurological disorders are seen when excess ammonia crosses the blood–brain barrier. The primary cause for hyperammonaemia is congenital defect in enzymes of the urea cycle. Secondary hyperammonaemia is seen in patients with liver disease, Reye's syndrome, infection in a neurogenic bladder and ureterosigmoidostomy. Certain drugs, in toxic amounts, like cyanide, valproic acid, carbamazepine and iron, can disrupt the mitochondrial pathways, thereby resulting in secondary hyperammonaemia. Non-cirrhotic hyperammonaemia has been noticed in patients receiving chemotherapy drugs like cyclophosphamide, 5-fluorouracil, cytarabine, vincristine, L-asparaginase and etoposide. It has also been reported in cases of gastric bypass surgery. Patients with acute leukaemia, multiple myeloma and solid organ tumours can also have hyperammonaemia as a rare complication.[3–11]

According to the WHO, DF is the most rapidly spreading viral infection in the world. Recently, several neurological complications like Guillain Barre syndrome, hypokalemic periodic paralysis, myositis, brachial neuritis, encephalopathy, opsoclonus-myoclonus syndrome, acute disseminated encephalomyelitis, Parkinsonism and cerebellar ataxia have been reported in DF.[12–14] Oligoclonal bands have also been noticed in the CSF of patients with viral encephalitis, suggesting an immune-mediated mechanism.[15 16] Thrombocytopenia in DF can result in intracranial haemorrhage. Ischaemic stroke is rare, and can be due to a transient hypercoagulable state or meningovasculitis.[17–19]

Our patient presented with DF. Following acute onset dysarthria, he was found to have spenial lesion on MRI brain. Such lesion can be seen in dengue encephalitis. However, his CSF analysis was normal. He had elevated ammonia levels in the absence of liver disease. After administration of lactulose, his ammonia levels normalised and his speech became normal. His repeat MRI brain did not show any splenial lesion. The above findings are suggestive of TSL due to non-cirrhotic hyperammonaemia; the onset and resolution of TSL co-inside with the patient's blood ammonia level. The occurrence of non-cirrhotic hyperammonaemia in DF is unknown and must be due to fever-induced catabolic state resulting in protein breakdown.[20] TSL in this scenario could be due to cytokine release or direct viral invasion causing a disruption of the blood–brain barrier.

Learning points

- Transient splenial lesion (TSL) can occur in neurological and non-neurological conditions.
- Dengue encephalitis and hyperammonaemia can show TSL on MRI brain.
- Non-cirrhotic hyperammonaemia is an unknown presentation in dengue fever and can be due to the fever-induced catabolic state.
- Hyperammonaemia should be considered in cases of acute encephalopathy and TSL even in the absence of liver disease.

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