

Dengue Encephalitis associated with symptomatic hyponatremia due to Syndrome of Inappropriate Antidiuretic Hormone Secretion

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SUMMARY

A previously well 21-year-old girl presented to Hospital Teluk Intan, Perak, Malaysia with a short history of fever, vomiting and altered sensorium. She was diagnosed with dengue encephalitis as her dengue NS-1 antigen was positive and her cerebrospinal fluid (CSF) dengue polymerase chain reaction (PCR) was positive with serotype DENV-2. She also had severe hyponatremia due to Syndrome of Inappropriate Antidiuretic Hormone Secretion (SIADH) which caused an episode of seizure. She recovered well with supportive management. SIADH and dengue encephalitis should be considered as one of the differential diagnosis in patients presenting with fever and altered sensorium especially in dengue endemic countries like Malaysia.

INTRODUCTION

The clinical spectrum of dengue fever ranges from undifferentiated mild febrile illness to severe disease with plasma leakage, organ impairment and shock. Neurological complications of dengue are uncommon and can manifest as encephalitis, encephalopathy, myelitis or Guillain-Barre Syndrome. According to Soares et al, dengue virus accounts for 75% of encephalitis with normal CSF cellularity in dengue endemic regions, followed by Herpes Simplex Virus 1 (HSV1).¹ Hyponatremia is a common observation in severe dengue and is believed to be a marker of disease severity.² We describe a case of dengue encephalitis with severe symptomatic hyponatremia.

CASE REPORT

A 21-year-old lady who was previously well, presented with one day history of high-grade fever and multiple episodes of vomiting to Hospital Teluk Intan, Perak, Malaysia. Clinical examination on admission revealed temperature of 38.8°C, blood pressure 130/72 mmHg and pulse rate 108 bpm. She was restless and confused but still able to obey simple commands.

Initial investigations revealed haemoglobin of 12.4 g/dl, white cell count $9.1 \times 10^3/\text{ul}$ (neutrophil 90%, lymphocyte 3%), haematocrit 35.2% and platelet $190 \times 10^3/\text{ul}$. She also had hyponatremia with sodium level of 120 mmol/l. Her aspartate transaminase (AST) was slightly elevated at 59 u/l while her alanine transaminase (ALT) was normal. Dengue was suspected as her father and brother were also warded for

dengue fever. Her dengue virus NS-1 antigen was positive while dengue IgM and IgG were negative. She had contrasted CT brain done and the finding was normal with no meningeal enhancement. She was diagnosed with dengue encephalitis and admitted.

Nine hours after admission, she developed one episode of generalized tonic clonic seizure which lasted for 40 seconds. Repeated serum sodium was 117 mmol/l with a calculated serum osmolality of 242 mOsm/kg. This was despite her not having any more episodes of vomiting and was on 1.2 mls/kg/hr of normal saline infusion since admission. Post fitting her Glasgow Coma Score (GCS) reduced to E4V2M5 (total 11/15). Patient was not hypovolemic and perfusion was good. She was given hypertonic saline (3%) correction followed by Sterofundin (balanced isotonic electrolyte solution) as maintenance drip. Her sodium level improved gradually to 128 mmol/l. Urine sodium and urine osmolality were not taken prior to correction. Post correction her urine sodium was 170 mmol/l and urine osmolality was 124 mOsm/kg.

The conscious level of the patient did not improve despite correction of her serum sodium. Lumbar puncture was performed. Cerebrospinal fluid (CSF) analysis showed no cells, no growth on culture, normal CSF protein (0.43 g/l) and CSF glucose 3.6 mmol/l (random blood sugar was 6.0 mmol/l). CSF for dengue PCR was tested positive and DEN-2 serotype was identified.

She was given symptomatic treatment and closely observed in the intensive care unit. There was no further episode of seizure. Her conscious level returned to normal on day 3 of admission. Her platelet count decreased progressively in trend but there was no evidence of hemoconcentration. She started to develop transaminitis on day 4 of admission with highest AST level reaching 1237 u/l and ALT 1280 u/l but remained asymptomatic. Her bilirubin and alkaline phosphatase remained normal throughout admission. Her fever only began to settle on day 6 of illness with concurrent improvement of her transaminases.

During this time, her creatine kinase was also found to be markedly elevated at 37,490 U/l. She did not have any muscle aches or myoglobinuria and her renal profile was normal with good urine output. Echocardiography was not done as she was improving clinically with no chest pain,

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Table I: Investigation chart of the patient

Day of Admission	1	2	3	4	5	6	7	8	9	10
TWC (x10 ⁹ /l)	9.1	5.7	3.5	2.0	2.0	1.9	2.4	1.8	2.4	2.1
Hb (g/l)	12.4	12.0	13.8	13.5	13.4	13.1	12.2	11.1	11.1	10.1
Hct (%)	35.2	32.9	37.5	37.1	38.1	35.7	33.4	31.7	36.5	36.5
Plt (x10 ⁹ /l)	190	174	135	104	63	60	55	87	87	221
Urea (mmol/l)	1.9	1.3	1.6	2.2	2.8	2.8	2.4	1.6	1.8	1.4
Na (mmol/l)	120	117	129	127	125	127	133	137	136	139
K (mmol/l)	2.8	3.4	3.5	4.2	3.9	3.8	3.4	3.8	3.5	3.9
Creatinine (mmol/l)	47	40	41	40	44	43	49	50	42	35
Calculated serum osmolality (mmol/kg)		242								
Urine Na (mmol/l) post correction		170								
Urine Osmolarity (mmol/kg) post correction		124								

tachycardia or failure symptoms. The creatine kinase gradually improved. She was discharged well after nine days in the ward. Upon discharge, her WCC was 4.35 x 10³/ul, platelet count 488 x 10³/ul, AST 51 U/l, ALT 70 U/l and creatine kinase 195 U/l.

DISCUSSION

The main symptoms of dengue encephalitis are headache, altered sensorium and seizures. As in our patient, dengue encephalitis can present as early as day one of illness. The criteria for dengue encephalitis are: i) fever; ii) acute signs of cerebral involvement; iii) presence of anti-dengue IgM antibodies or dengue genomic material in the serum and/or cerebrospinal fluid; iv) exclusion of other causes of viral encephalitis and encephalopathy.³ Dengue virus has four serotypes (DENV-1, DENV-2, DENV-3 and DENV-4). The serotypes most frequently implicated in causing neurological complications are DEN2 and DEN3.⁴ Although MRI brain is the imaging modality of choice in encephalitis, it is not specific nor essential as a plain CT scan can rule out other life-threatening complications like intra-cerebral bleeding. A MRI brain was not done for our patient as our centre does not have this facility.

Hyponatremia is a common electrolyte disturbance and may play an important role in the prognosis of dengue fever and associated complications. The incidence of CNS and bleeding complications have been reported to be higher with severe hyponatremia.² Our patient had severe hyponatremia which caused seizure and altered sensorium. The degree of hyponatremia appeared to be disproportionate to her vomiting which had already stopped upon admission and normal saline drip commenced. The cause of hyponatremia could have been due to Syndrome of Inappropriate Antidiuretic Hormone Secretion (SIADH) as her serum osmolality was less than 280 mOsm/kg. Although urine osmolality and urine sodium was not done before correction, the diagnosis of SIADH was suspected as her serum sodium dropped further following hydration. In SIADH restriction of fluid is the recommended treatment. Urine sodium post correction was elevated likely due to the sodium load from the 3% saline infusion. Her urine osmolality was still above 100 mOsm which in the context of serum hypo-osmolality suggests arginine vasopressin (AVP) excess.

The occurrence of SIADH with encephalitis is a known association. Other mechanisms of hyponatremia postulated in association with dengue fever are excess water from increased metabolism, decreased renal excretion, or the influx of sodium into the cells as a result of dysfunction of sodium potassium pump.⁵

The patient's conscious level was slow to respond to the correction of hyponatremia. Recovery from neuropsychiatric effects of hyponatremia may be delayed. Therefore, it is possible that acute hyponatremia was the cause of the neurological manifestation of the patient instead of dengue encephalitis.

Another interesting finding in our patient was the markedly elevated creatine kinase of above 30,000 U/l in the absence of symptoms as well as other laboratory evidence of rhabdomyolysis like hyperkalemia. Dengue fever, although commonly causes muscle aches and joint pains, rarely causes creatine kinase to be raised to this degree. Seizures can also cause elevation of creatine kinase. However, very raised levels are usually seen after a violent status epilepticus. Our patient's fit only lasted for 40 seconds. Other causes of markedly elevated creatine kinase are rhabdomyolysis, myositis and myocarditis, all of which have been reported before in complicated dengue fever. As the patient was clinically well, it was decided that she did not warrant further investigations like an echocardiography or muscle biopsy.

The management of dengue fever and its complications remain mainly supportive. Careful monitoring of symptoms and a high index of suspicion for its myriad complications is important. The outcome of dengue encephalitis is variable with many studies showing good recovery.

CONCLUSION

Dengue encephalitis is increasingly being recognized as a complication of dengue fever. It should be suspected in all patients with fever and altered sensorium in dengue endemic areas. It can be confirmed by CSF dengue PCR and treatment is supportive. Dengue fever can also be associated with SIADH leading to symptomatic hyponatremia which can present with seizures and altered conscious levels.

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