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DENGUE INDUCED SIADH (SYNDROME OF INAPPROPRIATE ANTIDIURETIC HORMONE SECRETION)

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ABSTRACT
Dengue virus has long been considered as a non-neurotropic virus, as animal studies have shown that virus does not cross blood brain barrier. However, many cases of Dengue encephalopathy have been reported. Hyponatremia may be found in association with dengue fever and is thought to be caused by peripheral fluid extravasation and resulting intravascular hypovolaemia. But hyponatremia due to syndrome of inappropriate secretion of anti-diuretic hormone (SIADH) in Dengue fever is rare. We report a male aged 45 years who presented with altered sensorium since one day, diagnosed as Dengue fever (Dengue Ns1Ag positive) with thrombocytopenia and hyponatremia. He was admitted and further investigations revealed SIADH. He responded well to cautious sodium replacement, recovered completely and was discharged after one week.

INTRODUCTION

The dengue virus is a tropical RNA virus. It is considered to be one of the most important arboviral infections to affect humans. The typical features of dengue infection include headache, arthralgia (break-bone fever), vomiting, fever, thrombocytopenia and elevated liver enzymes. A typical fine measles like rash with occasional petechial spots is classical and can be precipitated with a tourniquet test.

Infection results in increased vascular permeability with subsequent plasma volume loss and haemoconcentration. Patients develop haemostatic defects as a consequence of thrombocytopenia, platelet dysfunction and coagulopathy. Non haemorrhagic neurological involvement is rare but has been noted, the exact aetiology of which remains unclear.

SIADH is a disorder of impaired water excretion caused by inability to suppress the secretion of ADH. SIADH should be suspected in any patient with hyponatremia, plasma hypoosmolality and urine hyperosmolality.

Case Report

A 45 year-old previously healthy male, presented with altered sensorium since one day. For the past 10 days he had complaints of fever with chills, nausea, headache and persistent bodyache. He was diagnosed as Dengue fever (Dengue Ns1Ag positive) with thrombocytopenia few days prior by his family physician.

On admission he was conscious but disoriented, both pupils equal and reacting to light, moving all four limbs, deep tendon reflexes were bilaterally brisk and plantars extensor. His general, cardiovascular, respiratory and alimentary examinations were all unremarkable. There was no visible rash or petechiae or joint swelling. Laboratory investigations (Table 1) revealed hematocrit (0.244), platelet count (1.95 lac/cumm), mild elevation of aspartate transaminase (AST) (170 IU/L) and alanine transaminase (ALT) (93 IU/L) and total bilirubin (1.2 mg/dl) blood urea (10 mg/dl), serum creatinine (0.98 mg/dl) hyponatremia (serum sodium 104 mEq/L), high urine sodium (128 mmol/L) and osmolality (471 mmol/Kg), a low plasma osmolality (220mmol/Kg).

Thyroid function tests and serum cortisol (8am) levels were normal. CT scan and MRI Brain reported no significant abnormality. Electrocardiography and chest x-ray were normal.

He was diagnosed to have SIADH, as he maintained a high urine sodium (128 mmol/L) and osmolality (471 mmol/Kg) despite a low plasma osmolality (220mmol/Kg) hyponatremia (serum sodium 104 mEq/L) in the presence of normal renal, adrenal and thyroid function. Cautious sodium replacement was undertaken using hypertonic 3% saline solution at an rate of 10 ml/hr. Patient's neurological status was improved gradually as hyponatremia was corrected. He responded well to treatment. He was discharged after 15 days and is asymptomatic at 3 months followup.

Table 1. Observations

Serum Biochemistry	Day from onset of fever								
	11(admitted)	12	13	14	15	16	17	18	24
Sodium	104	110	105	112	111	115	121	125	136
Potassium	3.3	3.5	3.7	3.8	3.9	3.7	4.5	4.2	4.4
Urea	10	-	-	-	-	-	-	-	-
Creatinine	0.98	-	-	-	-	-	-	-	-
Osmolality	220	-	-	-	-	-	-	-	-
Haemoglobin (g/L)	9.1	-	-	-	-	-	-	-	-
TLC	3800	-	-	-	-	-	-	-	-
Platelets(lacs/cumm)	1.95	1.94	-	-	2.1	-	-	-	-
Urine Biochemistry									
Sodium (mmol/L)	128	-	-	-	-	-	-	-	-
Osmolarity (mmol/kg)	471	-	-	-	-	-	-	-	-

DISCUSSION

Dengue virus has long been regarded as a non-neurotropic virus [1], and animal studies have confirmed that the dengue virus is unable to cross the blood brain barrier [2]. Involvement of the central nervous system may be secondary to microcapillary fluid extravasation, cerebral oedema, hypoperfusion, hyponatraemia, liver failure and renal failure. Despite this there have been many reports of encephalopathy associated with the dengue virus where no metabolic cause can be found [3],[4]. There are also reports of the dengue virus being isolated from the CSF of infected patients [4].

Hyponatremia may be found in association with dengue fever and is thought to be caused by peripheral fluid extravasation and resulting intravascular hypovolaemia [5]. Previous studies have identified that Dengue patients are 9.7 times more likely to have clinically significant hyponatremia (Na <130mmol/L) than patients with similar febrile illnesses. Hypovolaemia, confirmed by a urine sodium of <20mmol/L, was also found to be more common in patients with dengue fever [6]. Patients who present with dengue associated hyponatremia with a normal or elevated urine sodium have been hypothesised to have transient syndrome of inappropriate secretion of anti-diuretic hormone (SIADH). Causes of SIADH can be classified as hereditary, acquired and idiopathic. In the acquired variant causes includes CNS disorders like stroke, trauma, psychosis and hemorrhage, Malignancies like Small cell carcinoma of lung, head and neck cancer, Olfactory neuroblastoma, extrapulmonary small cell carcinoma, Drugs like cisplatin, vinblastine, SSRI, carbamazepine, vincristine,etc Surgical procedures like cardiac catheterization, transsphenoidal pituitary surgery, Pulmonary diseases like pneumonia, asthma, atelectasis, pneumothorax, acute respiratory failure, Hormone deficiencies like hypothyroidism, hypopitutarism.

There are 4 variants of SIADH of which type A which is characterized by erratic unregulated release of ADH is most common. ADH secretion results in concentrated urine and therefore reduced urine volume. In most patients with SIADH ingestion n of water does not adequately suppress ADH, hence urine remains concentrated and there is water retention. This further causes increase in Total body water leading to increase in ECF volume and increased urinary sodium excretion causing hyponatremia

Anti-diuretic hormone (ADH) release is controlled by both osmoreceptors and baroreceptors. Hypothalamic osmoreceptors are extremely sensitive and respond to as little as 1% variation in tonicity whereas baroreceptors are much less sensitive but far more potent stimulators of ADH release. In the patient with shock, a hypovolaemic stimulus will override a hypotonic inhibition and volume will be conserved at the expense of tonicity. This mechanism may account for the rapid fall in sodium levels in patients of Dengue shock syndrome. Our patient was clinically euvolaemic and haemodynamically stable, further supporting a diagnosis of SIADH. Inappropriate ADH initially causes an increase in water retention followed by a secondary solute loss mediated by a normal renin-angiotensin-aldosterone system. Providing excess salt is not lost from another source, such as the gastrointestinal tract or from cerebral salt wasting, the

patient's intravascular volume is maintained. Treatment therefore involves fluid restriction and high solute intake to create a negative balance in order to restore osmolality. He was treated with 3% hypertonic saline to maintain perfusion pressures and prevent further hyponatraemia-induced cerebral oedema.

A regime of low volume, hypertonic saline resuscitation was used with a rate of correction of less than 10 mmol over the first 24 hours to avoid osmotic demyelination.

CONCLUSION

Hyponatremia due to syndrome of inappropriate secretion of anti-diuretic hormone (SIADH) in Dengue fever is rare. We have presented this case to sensitize the treating physician to the possibility of this treatable metabolic complication in Dengue fever. Persistent hyponatremia in Dengue fever should alert the physician and SIADH should be ruled out. Treatment modalities involve fluid restriction and solute replenishment as and when necessary.

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