ISSN: 2755-0125

Journal of Virology Research & Reports

SCIENTIFIC Research and Community

Research Article

Open Access

# SIADH (Syndrome of Inappropriate ADH Secretion): Perplexing Look of Dengue Fever

**Richmond Ronald Gomes**

Associate Professor, Medicine, Ad-din Women's Medical College Hospital, Dhaka, Bangladesh

**ABSTRACT**

Dengue is a mosquito-borne disease (female mosquitoes of the Aedes genus, principally Aedes aegypti) caused by any one of four closely related dengue viruses. It is endemic in tropical and subtropical continent. World health organization (WHO) currently estimates there may be 50 -100 million dengue infections worldwide every year with over 2.5 billion people at risk of dengue. Symptomatic dengue virus infection may manifests as undifferentiated fever, classical dengue fever (with or without unusual hemorrhages), and dengue hemorrhagic fever (with or without shock). Isolated organopathy or expanded dengue syndrome (EDS) was coined by WHO in the year 2012 to describe cases, which do not fall into either dengue shock syndrome or dengue hemorrhagic fever. The atypical manifestations noted in expanded dengue are multisystemic and multifaceted with organ involvement, such as liver, brain, heart, kidney, central/peripheral nervous system, gastrointestinal tract, lympho reticular system. Dengue virus has long been considered as a non-neurotropic virus, as animal studies have shown that virus does not cross blood brain barrier. 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 40 years old male who was 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 and addition of tolvaptan. He recovered completely and was discharged after one week. Thus, all clinicians should keep in mind the possibility of SIADH as a part of expanded dengue syndrome.

***Corresponding author**

Richmond Ronald Gomes, Associate Professor, Medicine, Ad-din Women's Medical College Hospital, Dhaka, Bangladesh. Ph: 8801819289499. E-mail: rrichi.dmc.k56@gmail.com

**Received:** November 08, 2021; **Accepted:** November 20, 2021; **Published:** November 25, 2021

**Keywords:** Expanded Dengue, Extravasation, Non-Neurotropic, Blood Brain Barrier, Tolvaptan

## Introduction

Dengue is an arboviral infection common in tropical countries, including South and Southeast Asia and Western Pacific regions [1]. It is caused by the dengue pathogen, which is an enveloped ribonucleic (RNA) virus, from the Flaviviridae family2. The infection caused by the dengue virus causes a wide spectrum of diseases that can be life-threatening, such as dengue with hemorrhagic manifestations and severe dengue triggering dengue shock syndrome [2]. Severe dengue (dengue hemorrhagic fever-DHF and dengue shock syndrome-DSS) is a potentially deadly complication due to plasma leaking, fluid accumulation, respiratory distress, severe bleeding, or organ impairment. The World Health Organization (WHO) has coined the term-expanded dengue to describe cases, which do not fall into either dengue shock syndrome or dengue hemorrhagic fever. This has incorporated several atypical findings of dengue. In clinical practice, the occurrence of atypical presentation should prompt us to investigate for dengue. Various atypical complications of severe dengue are myocarditis, encephalitis, acute motor weakness, Guillane-Barre like syndrome, acute liver failure, lupus erythematosus, hem phagocytic syndrome, acute kidney injury, acute pancreatitis, immune thrombocytopenic purpura, acalculus cholecystitis and so on [3]. It is critical that physicians who monitor dengue illnesses, should be aware and alert to these atypical manifestations [4]. We have come across varied presentations of dengue fever in clinical practice and the present article throws light on one of the atypical manifestations of dengue. 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 hyper osmolality. Here we report a 35 years old female with expanded dengue syndrome presenting as SIADH.

## Case Report

A 40 year-old previously healthy non-smoker service holder, not known to have diabetes, hypertension, bronchial asthma or coronary artery disease presented with high grade continued fever(maximum recorded as 104o F) not associated with chills and rigor and subsided temporarily after taking anti pyretic along with headache, body ache and retro orbital pain for 4 days. He denied any altered sensorium, convulsion, visual or speech disturbances, cough, chest pain, joint pain, shortness of breath, abdominal pain, loose motion, vomiting or burning micturition. He had also no recent history of travel to malarial endemic area. On examination, he was toxic, conscious, oriented, febrile with temparature102o F, hemodynamically stable. There was diffuse generalized blanching erythema. There was neither active bleeding from any site nor any petechial or purpura. His other general, cardiovascular, respiratory, neurological and alimentary examinations were all unremarkable

Laboratory investigations on admission revealed hemoglobin 14.2 gm%, hematocrit 43%, total white cell count 3.82× 103(normal 4-11× 103) with neutrophil> lymphocyte, platelet count (1.81 lac/cmm(normal 1.5-4.5 lac/cmm,) mild elevation of aspartate transaminase (AST) (150 IU/L, normal <30IU/L) and alanine transaminase (ALT) (83 IU/L, normal <40 IU/L)), serum creatinine (0.98 mg/dl normal 0.6-1.2 mg/dl). Serum electrolytes were normal with serum sodium 141 mEq/L, potassium 3.9 mEq/L. Dengue NS1 antigen was positive. From the very next day, he became afebrile and there was progressive leucopenia and development of thrombocytopenia with total white cell count 2.62× 103(normal 4-11× 103) with neutrophil< lymphocyte, platelet count (91000/cmm(normal 1.5-4.5 lac/cmm,). There was also rise of hematocrit to 51%. Clinically there was development of bilateral pleural effusion and ascites which was later documented by doing chest X ray and ultrasonography of whole abdomen which additionally revealed gall bladder edema. Serum albumin and non fasting cholesterol was low (29.6 g/L, normal 35-52 g/L) and 94 mg/dl(normal 130-200 mg/dl) respectively. On second afebrile day, his BP dropped to 100/90(narrow pulse pressure) mm of Hg with rapid(108 beats/min) low volume pulse. There was no bleeding from any site. The diagnosis of dengue hemorrhagic fever was made and he was resuscitated with appropriate crystalloid saline. On 3rd afebrile day,as he newly complained for anorexia, drowsiness and hiccup, repeat serum electrolyte was done which revealed moderate hyponatremia with serum sodium 124 mEq/L with normal potassium level. Further investigation revealed high urine sodium (184 mmol/L), a low plasma osmolality (251mmol/Kg). Thyroid function tests and serum cortisol (8am) levels were normal. Echocardiograpy was normal. Blood urea was 12.28 mg/dl(normal 16-48 mg/dl),serum creatinine was 0.73 mg/dl(normal 0.6-1.2 mg/dl) and serum uric acid was 3.63 mg/dl(normal 3.7-7.0 mg/dl). He was diagnosed to have SIADH, as he maintained a high urine sodium (184 mmol/L) despite a low plasma osmolality (251mmol/Kg) hyponatremia (serum sodium 124 mEq/L ) in the presence of normal renal, adrenal and thyroid function. As there was evidence of significant plasma leakage,cautious sodium replacement was undertaken using hypertonic 3% saline solution at an rate of 10 ml/hr. Successive next two days serum electrolyte showed mild improvement of serum sodium with 126 mEq/L and 128 mEq/L respectively. 3% sodium chloride was discontinued. But as patients symptoms did not show any significant progress and the patient had passed critical phase of illness with resolved plasma leakage, fluid restriction 1200 ml/day along with tablet tolvaptan 15 mg/day was added. 3 days after adding tolvaptan his serum sodium increases to 138 mEq/L. Tolvaptan was continued for two more days. Patient's neurological status was improved gradually as hyponatremia was corrected. He was discharged after 10 days with serum sodium 141 mEq/L and is asymptomatic at 1 month follow up.

**Discussion**

Hyponatremia—defined as a serum sodium concentration of less than 135 mEq/L—is a common and important electrolyte imbalance that can be seen in isolation or, as most often is the case, as a complication of other medical illnesses. The normal serum sodium concentration is 135-145 mEq/L. Joint European guidelines classify hyponatremia in adults according to serum sodium concentration, as follows5 :mild: 130-134 mmol/L, moderate: 125-129 mmol/L, profound: < 125 mmol/L. Hyponatremia can be classified according to effective osmolality, as follows: hypotonic hyponatremia, isotonic or pseudo hyponatremia, hypertonic or translocational hyponatremia. Hypotonic hyponatremia can be further sub classified according to volume status, as follows: Hypovolemic hyponatremia: decrease in total body water with greater decrease in total body sodium, euvolemic hyponatremia: normal body sodium with increase in total body water and hypervolemic hyponatremia: increase in total body sodium with greater increase in total body water. SIADH is one of the important cause of euvolemic hypotonic hyponatremia.

SIADH is characterized by excessive unsuppressible release of antidiuretic hormone (ADH) either from the posterior pituitary gland, or an abnormal non-pituitary source [5, 6]. Unsuppressed ADH causes an unrelenting increase in solute-free water being returned by the tubules of the kidney to the venous circulation. The incidence of SIADH rises with increasing age. Residents of nursing homes are at highest risk [7]. The condition was first described at separate institutions by William Schwartz and Frederic Bartter in two people with lung cancer [8,9]. Criteria were developed by Schwartz and Bartter in 1967 and have remained unchanged since then [8, 10].

The causes of SIADH are grouped into six categories:1) central nervous system diseases that directly stimulate the hypothalamus, the site of control of ADH secretion [infections(meningitis, encephalitis, brain abscess, rocky mountain spotted fever, AIDS), perinatal asphyxia, mass / bleed(trauma, subarachnoid hemorrhage, subdural hematoma, cavernous sinus thrombosis), hydrocephalus, guillain–barré syndrome, acute porphyria (acute intermittent porphyria, hereditary coproporphyria, variegate porphyria), multiple system atrophy, multiple sclerosis, 2) various cancers that synthesize and secrete ectopic ADH[ Carcinomas(lung cancers (small-cell lung cancer, mesothelioma), gastrointestinal cancers (stomach, duodenum, pancreas), genitourinary cancers (bladder, urethral, prostate, endometrial), lymphoma, sarcomas (Ewing's sarcoma),3) various lung diseases[infection(pneumonia, lung abscess),asthma, COPD, cystic fibrosis 4) numerous drugs that chemically stimulate the hypothalamus( chlorpropamide, clofibrate, phenothiazine, cyclophosphamide, carbamazepine, oxcarbazepine, valproic acid, selective serotonin reuptake inhibitors, 3,4-methylenedioxymethamphetamine (MDMA, commonly called Ecstasy.) oxytocin, vincristine, morphine, amitriptyline (5) inherited mutations; and 6) miscellaneous largely transient conditions(endurance exercise, general anesthesia, sarcoidosis, idiopathic) [11].

Dengue virus has long been regarded as a non-neurotropic virus [12]. And animal studies have confirmed that the dengue virus is unable to cross the blood brain barrier [13]. 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 [14, 15]. There are also reports of the dengue virus being isolated from the CSF of infected patients [15].

Hyponatremia is commonly found in association with dengue fever and is thought to be caused by peripheral fluid extravasation and resulting intravascular hypovolaemia. 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 8.1 times more common in dengue patients [16]. 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, but this has not been conclusively demonstrated. Interestingly, this patient met all

criteria for both dengue haemorrhagic fever [17]. And syndrome of inappropriate secretion of anti-diuretic hormone [18].
Despite this, controversy remains as to whether this was, in fact, a true case of SIADH. Physiological teaching suggests that anti-diuretic hormone 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. This means that in the shocked patient, a hypovolemic stimulus will override a hypotonic inhibition and volume will be conserved at the expense of tonicity [19]. This mechanism would account for the rapid fall in sodium levels while the patient was symptomatic, whilst microcapillary leakage could explain the preceding hyponatraemia. Our patient was clinically euvolaemic and haemodynamically stable, further supporting a diagnosis of SIADH.

Diagnosis is based on clinical and laboratory findings of low serum osmolality and low serum sodium [20]. Urinalysis reveals a highly concentrated urine with a high fractional excretion of sodium (high sodium urine content compared to the serum sodium) [21]. A suspected diagnosis is based on a serum sodium under 138. A confirmed diagnosis has seven elements: 1) a decreased effective serum osmolality - <275 mOsm/kg of water; 2) urinary sodium concentration high - over 40 mEq/L with adequate dietary salt intake; 3) no recent diuretic usage; 4) no signs of ECF volume depletion or excess; 5) no signs of decreased arterial blood volume - cirrhosis, nephrosis, or congestive heart failure; 6) normal adrenal and thyroid function; and 7) no evidence of hyperglycemia (diabetes mellitus), hypertriglyceridemia, or hyperproteinia (myeloma) [22]. There are nine supplemental features: 1) a low BUN; 2) a low uric acid; 3) a normal creatinine; 4) failure to correct hyponatremia with IV normal saline; 5) successful correction of hyponatremia with fluid restriction; 6) a fractional sodium excretion >1%; 7) a fractional urea excretion >55%; 8) an abnormal water load test; and 9) an elevated plasma AVP [11].

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.

Antidiuretic hormone (ADH) is released from the posterior pituitary for a number of physiologic reasons. The majority of people with hyponatremia, other than those with excessive water intake (polydipsia) or renal salt wasting will have elevated ADH as the cause of their hyponatremia. However, not every person with hyponatremia and elevated ADH has SIADH. One approach to a diagnosis is to divide ADH release into appropriate (not SIADH) or inappropriate (SIADH). Appropriate ADH release can be a result of hypovolemia, a so-called non-osmotic trigger of ADH release. This may be true hypovolemia, as a result of dehydration with fluid losses replaced by free water. It can also be perceived hypovolemia, as in the conditions of congestive heart failure (CHF) and cirrhosis in which the kidneys perceive a lack of intravascular volume. Appropriate ADH release can also be a result of non-osmotic triggers. Symptoms such as nausea/vomiting and pain are significant causes of ADH release. The combination of osmotic and non-osmotic triggers of ADH release can adequately explain the hyponatremia in the majority of people who are hospitalized with acute illness and are found to have mild to moderate hyponatremia. SIADH is less common than appropriate release of ADH. While it should be considered in a differential, other causes should be considered as well [23]. Cerebral salt wasting syndrome (CSWS) also presents with hyponatremia, there are signs of dehydration for which reason the management is diametrically opposed to SIADH. Importantly CSWS can be associated with subarachnoid hemorrhage (SAH) which may require fluid supplementation rather than restriction to prevent brain damage [24].

The management of this case required careful consideration. Inappropriate antidiuretic hormone 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 to create a negative balance in order to restore osmolality. However, in this patient with haemorrhagic fever, ongoing capillary leakage coupled with fluid restriction would have precipitated worsening intravascular hypovolaemia. The decision was made to treat her with 3% hypertonic saline and addind tolvaptan (an antagonist of the V2 vasopressin receptor 15 mg once daily for 5 days to maintain perfusion pressures and prevent further hyponatremia-induced cerebral edema. A regime of low volume, hypertonic saline resuscitation was used with a rate of correction of less than 10mmol over the first 24 hours to avoid osmotic demyelination.

## Conclusion

To our knowledge, this report describes the third case of SIADH caused by dengue hemorrhagic fever and highlights the association of hyponatremia with the dengue virus. Prompt 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.

**Conflict of Interest:** None declared.

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