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Significance of Serum Electrolyte Pattern in an Eastern Sudanese Dengue Fever Patients Population

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Abstract

Background: Dengue virus (DENV) infection is caused by an arboviral strain and is transmitted by the mosquito *Aedes Egyties* which is found in Sudan especially Red Sea and Kassala states in the east. In the year 2020 there was a significant outbreak in the both states. The disease is known to cause renal and electrolyte disturbances and a thorough understanding of that which will potentially help in the prediction, diagnosis and treatment of the disease. **Methods:** This study is a prospective observational cross sectional study conducted in the Eastern Sudan College of Medical Science and Technology and Port Sudan Teaching Hospital. 200 confirmed Dengue virus infection patients along with 200 healthy appearing adults (as a control) were enrolled for the study. Statistical analysis was carried out after the collection of patients' demographic, clinical, and investigational data including electrolyte values. **Results:** The highest incidence of DENV infection was observed in individuals of the middle age group (29%). Although fallen within reference ranges found in the literature, mean serum electrolyte values differed significantly between patients and controls and between different categories of the disease. For our patients, hyponatraemia was seen in 43.5%, hypokalaemia in 37%, hypocalcaemia in 30%, hypophosphataemia in 12% and low magnesium concentrations in 13%. Mean serum sodium concentration differed in the control (138.2 mmol/l) from in the test (132.5 mmol/l) (P. value 0.02). Similarly, mean serum potassium in the control (3.97 mmol/l) differed significantly (P. value 0.01) from test (3.30 mmol/l). Mean calcium and phosphorus (8.80 and 3.50 mg/dl) in the control were also differed from test (8.51 and 3.30), (P.

values 0.02 and 0.004, respectively). In contrast, serum magnesium (mg/dl) in the control group (1.96) showed no significant difference from that of test group (1.90) (P. value 0.08). The biochemical parameters studied were neither affected by age nor by gender of the patient group. Clinically, fever was present in 97.5% of patient, headache in 95.5%, joints pain in 71%, lethargy 67%, vomiting in 49%, skin rash in 40%, abdominal pain 24% and bleeding in 17.5%. **Conclusion:** We strongly conclude that electrolyte evaluation should be considered in the counseling of DENV infected patients. Patients need to be subjected to necessary laboratory investigations including serum electrolyte levels to decrease the rate of morbidity and mortality associated with the disease.

Keywords

Dengue Virus, Hemorrhagic Fever, Dengue Shock Syndrome, Electrolytes, Eastern Sudan

1. Introduction

Dengue is a mosquito borne viral infection found in tropical and sub-tropical regions of the world, an increase in infection has been seen in recent years due to many factors including urbanization and air travel. Over 2.5 billion people of the world's population are now at risk for Dengue. The consequences of Dengue Virus (DENV) infection range from asymptomatic condition, Dengue fever (DF), or severe forms, such as Dengue hemorrhagic fever (DHF) and Dengue shock syndrome (DSS). Severe Dengue is characterized either by plasma leakage, fluid accumulation, respiratory distress, severe bleeding, or organ impairment. Clinical manifestations offer the earliest markers in predicting severe Dengue disease [1]. Signs and symptoms of Dengue fever range from mild asymptomatic to warning signs including abdominal pain, mucosal bleeding and liver enlargement that warrant ICU admission. Yet approved vaccines for immunization are commercialized. An ideal biomarker should be able to identify individuals who are at risk of developing severe Dengue [2]. The mechanism by which only a few DENVs infected individuals' progress to severe Dengue disease is poorly understood [2]. Dengue infection has been associated with a variety of renal disorders but in the vast majority of cases, both are self-limited [3]. Dengue virus (DENV) is one of the most wide spread flaviviruses that re-emerged throughout recent decades, as it has made a global public health concern and is no longer related to tropical and subtropical countries only. Approximately 2.5 billion individuals from more than 110 countries are at danger of DENV infection each year due to the lack of an efficient vaccine and a specific treatment [4]. Dengue fever (DF) is a mosquito-borne viral disease caused by one of four closely-related Dengue virus serotypes (DENV1-4) of the genus Flavivirus and family Flaviviridae and it is mainly transmitted by *Aedes aegypti* with other species of Aedes

mosquito involved [5]. There are 4 serotypes of dengue viruses known as DENV-1, DENV-2, DENV-3, and DENV-4 where the infection of any serotype of DENV yields a wide range of symptoms ranging from mild Dengue fever to severe Dengue (SD) with complications such as plasma leakage and severe bleeding. Clinically, the features of acute DENV infection are rather nonspecific, as the symptoms such as high fever, arthralgia, headache, myalgia, and rash [6]. The geographical distribution of Dengue is pan tropical, and in some African regions. It is endemic in tropical and subtropical countries included between 25 degrees north latitude and 25 degrees south latitude, particularly in south East Asia and epidemic in the Caribbean, West Africa, tropical America and pacific islands. Further spread will be depending on the *Aedes Aegypti* into new areas in South America. Maintenance of Dengue is supported by an increasing demography, in controlled urbanization and climatic condition favorable to the vectors. Spread of Dengue is primarily caused by modem transportation, especially air craft. Dengue is, obviously, an important risk for travelers going to endemic areas [7]. In 1779-1780, the first reported outbreak of Dengue fever (DF) occurred almost simultaneously in Asia, North America, and Africa. This indicates that the virus and its vector have a worldwide distribution especially in the tropical regions of the world [8]. Although it is present in 19 countries on Africa continent, with the fact that all 4 Dengue serotypes circulate in the continent, still the epidemiology of Dengue fever in Africa is more poorly characterized [9]. In the US Centers for Disease Control and Prevention (CDC) the Dengue and/or DHF reports approximately 100 - 200 suspected cases of Dengue infection per year [10]. Dengue fever typically is a self-limiting disease with a mortality rate of less than I %. When treated, DHF has a mortality rate of 5%. Untreated DHF has a mortality rate as high as 50%. The disease is distributed worldwide in tropical areas and the incidence is equal in males and females. In Southeast Asia, DHF is primarily an illness of children and is the leading cause of death and hospitalization in that population [11]. An estimated 2.5 billion people are at risk of Dengue Infection, and of the 100 million cases of Dengue fever per year, up to 500,000 develop hemorrhagic fever (DHF) or Dengue shock syndrome (DSS), the life threatening forms of the infection [12]. The critical feature of DHF is plasma leakage. This results from endothelial gaps in the peripheral vascular bed without necrotic or inflammatory changes in the endothelium. DHF typically begins with the initial manifestations of DF [13].

In Sudan, Dengue fever (DF) is considered a major public health issue in the eastern region of the country, where it has been reported since 1908 with endemicity and frequent outbreaks in the coastal and sub-coastal areas of the Red Sea and Kassala states. Dengue fever has serious presentations like Dengue hemorrhagic fever (DHF) and Dengue shock syndrome (DSS) among Sudanese population especially in Red Sea state with increased morbidity and mortality rates.

Although researchers tried to study valuable issues concerning DENV infection in Eastern Sudan, this is the first study to focus the determination of elec-

trolytes in these patients. The pattern of studied electrolytes included Calcium, Magnesium, Phosphate, Sodium, and Potassium. Effective vaccination and treatment are not yet proved for Dengue infection, however, medications are based on the treatment of underlying symptoms, rehydration and patient relax.

2. Methods

The study was a retrospective observational cross-sectional study carried out in the Eastern Sudan College of Medical Science and Technology and Port Sudan Teaching Hospital. Ethical approval was obtained from the research committee in the Ministry of Health, Red Sea state.

This study was performed in the period from June 2018 to September 2021 and included 200 confirmed Dengue fever patients from whom written consent was obtained and 200 healthy appearing adults as a control group. Patients with a past history of renal or liver disease and patients with lupus erythromatosis were excluded.

Interview with the patient were done to explain the objective of the study and to obtain data to fill questionnaire which specifically designed to obtain information which help in either including or excluding certain individuals in or from the study which contain demographic details (Name, age, gender and address) and history of disease. Two samples of blood (3 ml for each) were collected from each participant, one in heparinized containers and another in plain containers and preserved at 2˚C - 8˚C refrigerator till analyzed. All samples were subjected to the determination of plasma levels of Total Calcium, Magnesium and Phosphate using a PT350 Bio system spectrophotometer (Germany) and reagent kits of Bio System companies and plasma levels of Sodium, Potassium using ROCHE iron selective electrode (Germany). For Dengue fever diagnosis, serum IgM and IgG antibodies were estimated using ELISA technique. Statistical analysis was done by the SPSS software and descriptive statistics were obtained in terms of actual numbers and percentages.

3. Results

The higher percentage of patients of DENV infection was from individuals of middle age (40 - 49 years old) representing 29% of cases (**Figure 1**).

Clinical presentation of DENV infection in this study varied significantly amongst patients. The highest frequency was associated with Dengue fever followed by Dengue hemorrhagic fever then Dengue shock syndrome (**Table 1**).

Biochemical findings for sodium, potassium, calcium, magnesium and phosphorous were significantly lower (P. value less than 0.05) in Dengue virus infected patients than in the control group. Exception is the serum concentration of magnesium (**Table 2**).

Interestingly, the biochemical findings in different categories of Dengue virus infection were statistically different. The studied parameters were significantly higher in Dengue fever than in Dengue hemorrhagic fever patients (**Table 3**).

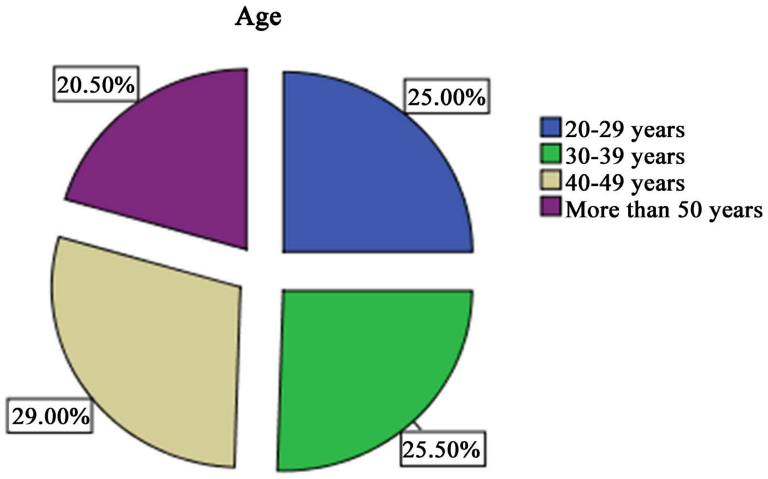

Figure 1. Age distribution (in years) in patients.

Table 1. Clinical conditions exhibited by patients of the study.

No.	Condition	Number of patients	Percentage
1	Dengue fever	160	80%
2	Dengue hemorrhagic fever	35	17%
3	Dengue shock syndrome	5	3%
	Total	200	100%

Table 2. Biochemical Findings in Dengue Virus Infected patients as compared to the control group.

Parameter	Reference Range	Control group N = 200	Patient group N = 200	P. value
Sodium (mmol/l)	135 - 145	138.2 ± 3.3	132.5 ± 4.1	0.020
Potassium (mmol/l)	3.5 - 5.1	3.97 ± 0.51	3.30 ± 0.4	0.010
Calcium (mg/dl)	8.4 - 10.4	8.8 ± 0.6	8.51 ± 0.76	0.020
Magnesium (mg/dl)	1.7 - 2.4	1.96 ± 0.29	1.90 ± 0.36	0.080
Phosphate (mg/dl)	2.5 - 4.5	3.5 ± 0.69	3.30 ± 0.80	0.004

Table 3. Biochemical Findings in Dengue fever patients as compared to Dengue hemorrhagic fever patients.

Parameter	Dengue Fever (M ± SD) N = 160	Dengue Hemorrhagic Fever (M ± SD) N = 35	P. Value
Sodium (mmol/l)	133.1 ± 3.9	131.20 ± 2.20	0.050
Potassium (mmol/l)	3.4 ± 0.36	3.03 ± 0.20	0.000
Calcium (mg/dl)	8.74 ± 0.57	7.72 ± 0.62	0.000
Magnesium (mg/dl)	2.01 ± 0.28	1.47 ± 0.33	0.000
Phosphate (mg/dl)	3.5 ± 0.67	2.29 ± 0.54	0.000

Furthermore, statistically significant differences were detected in biochemical findings of Dengue fever and Dengue shock syndrome patients all being significantly lower in Dengue shock syndrome than in Dengue fever patients (Table 4).

On the other hand, insignificant difference in biochemical findings was detected between Dengue hemorrhagic fever and Dengue shock syndrome patients except for Calcium and sodium which were both higher in Dengue hemorrhagic fever than in Dengue shock syndrome (Table 5).

Finally, all categories of DENV infection were neither affected by gender nor by age of the patients. (Table 6) shows the frequency of clinical presentations exhibited by our patients.

Table 4. Biochemical Findings in Dengue fever patients as compared to Dengue shock syndrome patients.

Parameter	Dengue Fever (M ± SD) N=160	Dengue Shock Syndrome (M ± SD) N= 5	P. Value
Sodium (mmol/l)	133.1 ± 3.9	121.30 ± 2.1	0.000
Potassium (mmol/l)	3.40 ± 0.36	2.90 ± 0.50	0.020
Calcium (mg/dl)	8.74 ± 0.57	6.60 ± 0.54	0.000
Magnesium (mg/dl)	2.01 ± 0.28	1.50 ± 0.28	0.020
Phosphate (mg/dl)	3.50 ± 0.67	2.22 ± 0.15	0.000

Table 5. Biochemical Findings in Dengue hemorrhagic fever patients as compared to Dengue shock syndrome patients.

Parameter	Dengue Hemorrhagic Fever (M± SD) N = 160	Dengue Shock Syndrome (M ± SD) N = 35	P. Value
Sodium (mmol/l)	131.2 ± 2.2	121.3 ± 2.1	0.000
Potassium (mmol/l)	3.03 ± 0.20	2.9 ± 0.50	0.500
Calcium (mg/dl)	7.72 ± 0.62	6.60 ± 0.54	0.000
Magnesium (mg/dl)	1.47 ± 0.33	1.50 ± 0.28	0.800
Phosphate (mg/dl)	2.29 ± 0.54	2.22 ± 0.15	0.500

Table 6. Clinical symptoms exhibited by patients of the study.

No.	Symptoms	Frequency (N = 200)
1	Fever	97.5%
2	Headache	85.5%
3	Joints pain	71%
4	Lethargy	67%
5	Vomiting	59%
6	Skin rash	40%
7	Abdominal pain	24%
8	Bleeding	17.5%

4. Discussion

Dengue fever can be presented with a variety of clinical presentations with unpredictable progression and outcomes. Its presentation ranges from asymptomatic forms to sever shocks, eventually resulting in death [14]. Dengue is considered a major health threat by the World Health Organization. An increase in the infection has been seen in recent years due to many factors including urbanization and air travel. Over 2.5 billion people of the world population are now at risk of Dengue [15]. The mechanism by which only a few DENV diseases had associated with dangerous presentation is poorly understood. The host immune response has been considered as the major factor responsible for Dengue pathogenesis [16]. Viral infection has been implicated in autoimmunity and SLE [17]. Several hypotheses on the pathogenesis of the DENV have been proposed. Viruses can induce autoimmunity through several mechanisms including mimicry activation of Tells by super antigens and dissemination of T cells previously activated in a site of inflammation. It could be apotheosized that after an infection by DENV, the antibodies react, and due to an alteration in the FC receptor, there is an adequate elimination of immune complexes which leads to synthesis of inflammatory cells [17].

Dengue infection is associated with multiple organ dysfunction involving Liver, muscles, heart, brain and kidney [18]. Dengue fever has been associated with various types of renal disorders such as proteinuria, hematuria, glomerulonephritis and acute kidney injury [19]. The renal manifestations may lead to changes in the concentration of electrolytes in Dengue fever patients. These include salt depletion, excess water from increased metabolism, decreased renal excretion, transient inappropriate antidiuretic hormone secretion or the influx of sodium into the cells as a result of dysfunction of sodium potassium pump.

In our study, the mean serum sodium concentration was (132.5 mmol/L). This is similar to the results obtained by three other studies; namely, Poornimashankar *et al.* [20] (133.7 mmol/L), Mekmullica *et al.* [21], 2005 (132 mmol/L) and Lumpapong *et al.*, [22] (133 mmol/L). The (mean ± 1SD) sodium levels in Dengue fever, Dengue hemorrhagic fever and Dengue shock syndrome were (133.1 ± 3.0), (131.2 ± 2.2) and (121.3 ± 2.1), respectively. Mekmullica *et al.* [21] cited that hypernatremia was 9.7 times more common in Dengue patients. This was different from our findings where hyponatraemia was detected in 43.5% of patients. This may be due to our relatively smaller sample size. The mean serum sodium level was significantly lower in shock patients compared to non-shock patients (P. value 0.003). In our study the (mean ± 1SD) potassium levels in the above mentioned categories (3.4 ± 0.36 mmol/L), (3.03 ± 0.20 mmol/L) and (2.9 ± 0.50 mmol/L), respectively, were similar to the findings of Widodo D. [23] and Kalitaj *et al.* [24] who have both reported hypokalaemia in the three categories of the disease. Similarly, the (mean ± 1SD) of calcium levels of the various categories (8.74 ± 0.74 mmol/L), (7.72 ± 0.62 mg/dl) and (6.60 ± 0.54 mg/dl), respectively, were similar to the findings of Gissel G. *et al.* [25]. The present study

found that the (mean ± 1SD) of magnesium levels in Dengue fever, Dengue hemorrhagic fever and Dengue shock syndrome were (2.01 ± 0.28 mg/dl), (1.47 ± 0.33 mg/dl) and (1.50 ± 0.28 mg/dl), respectively, which were concordant to the findings of the above mentioned study. The (mean ± 1SD) of serum phosphorus level in Dengue fever patients of this study was (3.5 ± 0.67 mg/dl), in Dengue hemorrhagic fever patients was (2.29 ± 0.54 mg/dl) and in Dengue shock syndrome was (2.22 ± 0.15 mg/dl).

In our study, the prevalence of DF in males was higher than in females, and fever was detected in (97.5%) of patients which was similar to a study done by Relwani P. R. *et al.*, who reported that fever is one of the common features associated with Dengue fever (98.66%) [26]. In the present study headache was observed in 85.5% disagreeing with a study done by Narayana M. *et al.* [27] who found that headache was seen in around (18.9%) of patients but similar with a study done by Relwani P. R. *et al.* where headache was reported in (86.6%) [26] of patients. Joint pain found in 71% of our patients is similar to a study done by Relwani P. R. *et al.* who found Joint pain in around (69.00%) [26]. Vomiting was seen in 59% of our patients which slightly higher compared to study conducted by Voung N. L. *et al.* who found that vomiting was seen in 44.00% of patients. Lethargy found in 67% of our patients was slightly less than that found by Relwani P. R. *et al.* (70.6%) [26]. In the present study skin rash was associated with 40% of patients similar to a study done by Poornimashankar *et al.* who found that skin rash was present in (43.06%) [20] of patients. Abdominal pain was reported in 24% of our patients but a lower number was observed by Relwani P. R. *et al.* who found that Abdominal pain was seen in around (18%) [26]. Bleeding was found in 17.5% of our patients but a study done by Unniklishnar R. and Faizal B. P. found that bleeding was evident in 7.5% [28] of the patients.

5. Conclusion

Electrolyte disturbances are common in Dengue fever patients mainly those exhibiting complications of the disease. Routine assessment of these patients should include the determination of blood electrolytes as a check for the prediction of these disturbances.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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