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HYPOCALCEMIA AS A PROGNOSTIC MARKER FOR SEVERITY IN PATIENTS WITH DENGUE FEVER

Dr Thanuj Reddy	Post Graduate, Department of General Medicine.
Dr Vishwanath Reddy	Assistant Professor, Department of General Medicine.
Dr Lakshmaiah V	Professor, Department of General Medicine.
Dr Rakesh Garlapati	Post Graduate, Department of General Medicine.

ABSTRACT

INTRODUCTION: Dengue fever is a major cause of morbidity and mortality. Serum free calcium (Ca2+) plays an important role in cardiac and circulatory function.

METHODOLOGY: This cross-sectional study was done at RLJ hospital in Kolar, Karnataka. All probable cases of dengue were diagnosed and classified according to World Health Organization criteria.

RESULTS: The mean age was 40.8 years, and the majority were males (n = 79, 52.6%). Mean serum Ca2+ was significantly lower in patients with severe dengue (4.16mg/dl) than in those with dengue fever without warning signs and with warning signs (4.66mg/dl,4.36mg/dl) ($p < 0.001$).

CONCLUSIONS: Serum Ca2+ levels significantly correlated with dengue severity. Hypocalcaemia is significantly prevalent in patients with severe form than in patients of Dengue with and without warning signs.

KEYWORDS : serum calcium, Dengue haemorrhagic fever, dengue

INTRODUCTION

Dengue is a disease spread by the *Aedes* mosquito, and it is an entity known to mankind since 1780[1]. Dengue infection is the most rapidly emerging vector-borne viral disease with a 30-fold increase in global incidence over the last five decades[2]. It is a major public health concern throughout tropical and subtropical regions of the world. In India, every year cases are spreading to newer geographical areas[2]. The origin of word "dengue" is derived from the Swahili phrase ka-dinga pepo which describes the disease is being caused by an evil spirit. In India, the first outbreak was in Kolkata followed by a major outbreak in Delhi[3]. Dengue is believed to infect 50 to 100 million people worldwide every year. Dengue virus is an RNA virus of the family flaviviridae; they are otherwise called arboviruses[3]. Four dengue virus serotypes have been identified till now-DENV-1, DENV-2, DENV-3 and DENV-4. These serotypes may be in circulation either singly, or more than one can be in circulation in any area at the same time.[4] Recurring outbreaks of dengue fever have been reported from various states/union territories—Andhra Pradesh, Chandigarh, Delhi, Goa, Haryana, Gujarat, Karnataka, Kerala, Maharashtra, Rajasthan, Uttar Pradesh, Puducherry, Punjab, Tamil Nadu, and West Bengal. Every year, during the period July–November, an upsurge of dengue cases has been observed. The disease has a seasonal pattern; the cases peak after the monsoons and are not uniformly distributed throughout the year[3].The exact pathogenetic mechanism for different clinical manifestations of dengue fever is still not clearly understood. Various mechanisms are proposed to explain signs and symptoms such as complex immune mechanism, T-cell mediated antibodies cross reactivity with vascular endothelium, enhancing antibodies, complement and its products and various soluble mediators including cytokines and chemokines. The most favoured are virus strains enhancing antibodies and memory T-cells in a secondary infection resulting in "Cytokine Tsunami"[4]. Currently, the most accepted theory is that of an abnormal or amplified immunological response occurring in a secondary infection with a different serotype than in the primary infection. This results in an antibody-dependent enhancement of immunological reaction, resulting in endothelial injury, plasma leakage, reduced intravascular volume, and circulatory collapse[1].Numerous studies have proved that measurement of serum free calcium is used as test of choice for many diagnostic situations. Our study evaluates the association between severity of dengue infection with serum free calcium levels.

METHODOLOGY:

Study population and sampling

A cross-sectional study was performed at RLJ hospital in Kolar, India, over a period of six months in 2017. A blood sample of inpatients with confirmed dengue infection was collected for the study, after written informed consent was obtained. Patients with comorbidities like hypertension, diabetes, and cardiac diseases and those on anti-hypertensive/anti-arrhythmic medications, calcium supplements, or any other drugs affecting calcium homeostasis were excluded, as these would alter the blood pressure, serum calcium levels, and ECG findings.

Definitions

All probable cases of dengue were diagnosed according to the World Health Organization (WHO) criteria. Confirmation of diagnosis was done with one of the following laboratory tests: IgM antibody, IgG antibody and NS1Ag Positive.

- **CRITERIA FOR DENGUE WITHOUT WARNING SIGNS**: Living in/travel to dengue endemic area. Fever and 2 of the following criteria: Nausea, vomiting, Rash Aches and pains, Tourniquet test positive, Leukopenia, any warning sign, Laboratory confirmed dengue (when warning signs are absent).
- **CRITERIA FOR DENGUE WITH WARNING SIGNS:** Warning signs**:** Abdominal pain or tenderness**,** Persistent vomiting**,** clinical fluid accumulation**,** mucosal bleed**,** lethargy; restlessness**,** liver enlargement >2cm**,** Laboratory: Increase in haematocrit concurrent with rapid decrease in platelet count.
- **CRITERIA FOR SEVERE DENGUE:**

1. Severe plasma leakage leading to: Shock (DSS)**,** Fluid accumulation with respiratory distress
2. Severe bleeding as evaluated by clinician
3. Severe organ involvement**:** Liver: AST or ALT>=1000**;** CNS: Impaired Consciousness; Heart; and other organs

Data collection and analysis

The clinical parameters recorded were presence of suggestive symptoms (fever, headache, retro-orbital pain, arthralgia, myalgia, rash, and bleeding manifestations), evidence of fluid leakage (pleural effusion and ascites), pulse rate, and systolic and diastolic blood pressure. In addition, the following investigations were performed: white cell count, platelet count, packed cell volume,

serum free calcium level, ECG, chest x ray, ultrasound abdomen. Blood samples for the estimation of serum free calcium were drawn on the day of admission. Hypocalcaemia was defined as the presence of a serum free calcium level of <4.64 mg/dl. All data were double-entered and cross-checked for consistency.

RESULTS

The sample size was 150. The mean age of patients was 40.8 years, and the majority were males (n = 79, 52.6%). Mean serum Ca2+ was significantly lower in patients with severe dengue (4.16mg/dl) than in those with dengue fever without warning signs and with warning signs (4.66mg/dl,4.36mg/dl) ($p < 0.001$). A significant difference was observed between mean serum calcium levels of severe dengue and dengue with and without warning signs. (TABLE 3). There was no statistically significant difference found between the age group among the groups (TABLE 1). There was no statistically significant difference found between sex among the groups. (TABLE 2)

Table 1: - Distribution of subjects according Age group among the groups

AGE GROUP	DENGUE			Total
	Without WS	With WS	Severe	
20yrs& below	0	5	6	11
	.0%	10.0%	12.0%	7.3%
21-40yrs	29	22	20	71
	58.0%	44.0%	40.0%	47.3%
41-60yrs	12	14	16	42
	24.0%	28.0%	32.0%	28.0%
>60yrs	9	9	8	26
	18.0%	18.0%	16.0%	17.3%
Total	50	50	50	150
	100.0%	100.0%	100.0%	100.0%

P Value = 0.226, there was no statistically significant difference found between the age group among the groups

Figure 1: - Graph showing Distribution of subjects according Age group among the groups

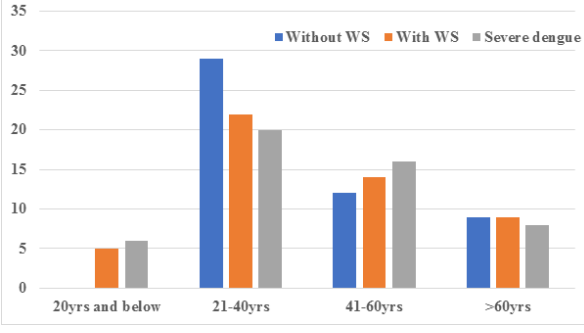

Table 2:- Distribution of subjects according Sex among the groups

SEX	DENGUE			Total
	Without WS	With WS	Severe	
Female	29	18	24	71
	58.0%	36.0%	48.0%	47.3%
Male	21	32	26	79
	42.0%	64.0%	52.0%	52.7%
Total	50	50	50	150
	100.0%	100.0%	100.0%	100.0%

P Value = 0.088, there was no statistically significant difference found between sex among the groups

Figure 2:- Graph showing Distribution of subjects according Sex among the groups

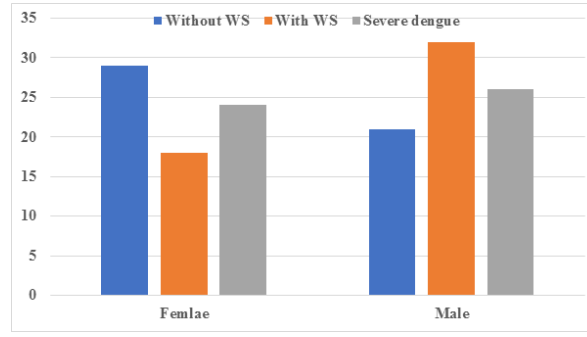

Table 3: - Comparison of mean serum calcium levels among the Groups

Serum calcium	DENGUE			P value
	Without WS	With WS	Severe	
Mean + SD	4.66+0.191	4.36+ 0.46	4.16 + 0.40	<0.001

DISCUSSION

Dengue is the most common mosquito-borne viral infection in the world. In severe dengue infection numerous serum biochemical parameter changes occur with the onset of plasma leakage[1]. Analysing the relation between serum free calcium and its association with severe dengue infection may justify it to be utilized as a biochemical marker to differentiate severe dengue from non-severe cases. Hypocalcaemia is known to be associated with plasma leakage during the critical phase of severe dengue, but limited studies are available about the presence of hypocalcaemia in severe dengue. However, irrespective of the aetiology of sepsis in few unselected critically ill patients, serum calcium were estimated. There is ample evidence that hypocalcaemia is a common finding in such unselected critically ill patients especially in intensive care setting[2].

We demonstrated serum free calcium as biomarker for severity in dengue patients similar to the results of a limited number of studies. It was interesting to note that the severity of dengue infection correlated with the serum free calcium levels. Serum free calcium was lower than the normal range in severe dengue infection than in the dengue infection with and without warning signs.

Uddin et al. demonstrated that hypocalcaemia is the important biochemical derangement which is correlated with severity of dengue infection and revealed that mean serum calcium levels were within the normal range in non-severe dengue patients. Considering above facts, it is clear that serum ionized calcium could be a potential biochemical marker in order to identify severe dengue patients and plan appropriate management in the clinical setting. The pattern and trend of serum calcium in dengue patients can be revealed by further research and monitoring. It is also important to study the clinical significance of hypocalcaemia in severe dengue and value of calcium supplementation in such patients with severe hypocalcaemia[8]

The current study has shown a relationship between serum free calcium and severe dengue infection. Nevertheless, further studies with larger cohorts are needed to further evaluate the relationship between serum free calcium and severe dengue infection and can be used as a prognostic marker for dengue infection.

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