Original Article

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Analysis of Hypocalcemia in Dengue and Correlation of Serum Calcium Levels with Severity of Dengue Disease

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Abstract

Background: Hypocalcemia has been demonstrated in various tropical diseases, such as leptospirosis, malaria, including dengue. Calcium is believed to play a major role in the immune response in dengue. It has been proposed that the derangements of Calcium levels in the infected myocardial cells may play a major role in development of myocarditis. This study aims to correlate the serum calcium levels with severity of dengue and bradycardia. **Subjects and Methods:** This study was conducted on 100 dengue positive patients, above the age of 18 years, presenting to BMCRI, after obtaining informed consent. Dengue test kit was used for diagnosis which is based on rapid solid phase immunochromatographic test. Physical examination and routine investigations along with serum calcium levels were done and assessed. Radiological imaging was done wherever necessary. They were grouped into one of the three WHO categories based on severity and were correlated with serum calcium levels. **Results:** Out of 100 patients 65 patients had uncomplicated dengue fever while 30 had dengue fever with warning symptoms and 5 has severe dengue/ dengue shock syndrome. Chi-square test showed statistical significant association between severity of dengue and hypocalcemia. (χ^2= 94.08; p=0.00). Statistical analysis revealed significant association between serum calcium levels and pulse rate (χ^2= 16.01; p=0.00). **Conclusion:** Our study and several other studies showed that the presence of hypocalcemia correlates with the severity of Dengue illness and could be considered as one of the predictors of poor outcome. However, further studies are required in these lines that are aimed at understanding if the presence of hypocalcemia can be utilized as a prognostic indicator in dengue infection. The potential role of calcium as a treatment option, to modulate the immune system, in patients with dengue is to be explored.

Keywords: Hypocalcemia, Dengue shock syndrome, Dengue with warning signs, Myocarditis

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Introduction

Dengue is a transmittable vector borne disease caused by member of flavi virus- Dengue virus.[1] Its one of the most important yet neglected tropical illness. They are grouped into four genetically and antigenically related viruses that are known as serotypes 1–4, They are transmitted to humans by the vector mosquito Aedes aegypti or Aedes albopictus.[2] Dengue has caused significant morbidity and mortality in our country and has been implicated as a major a public health problem.

In order to improve and guide better clinical practices, dengue illness is clinically classified into either dengue with or without warning signs and severe dengue. The natural history of Dengue illness progresses through three separate phases: the acute febrile phase, the critical phase with plasma leakage and the convalescent or reabsorption phase.[3,4]

The criteria for dengue with warning signs (DWWS) are as follows:

- Abdominal pain or tenderness
- Persistent vomiting
- Clinical fluid accumulation
- Mucosal bleeding
- Lethargy or restlessness
- Liver enlargement of >2 cm
- An increased haematocrit level that is accompanied by a decreased platelet count.

Severe dengue is characterised by plasma leakage leading to dengue shock syndrome and fluid accumulation with

respiratory distress.

- Severe bleeding as evaluated by a clinician
- Severe organ involvement, including the liver (AST or ALT levels of ≥1,000), the central nervous system (impaired consciousness), the heart and other organs.

Hypocalcemia has been demonstrated in various tropical diseases, such as leptospirosis, malaria including dengue.[5] Various theories for low blood calcium levels have been speculated; reduced Na ± K adenosine triphosphatase (ATPase) activity, reduced Ca^2 ± ATPase activity, acquired parathyroid hormone deficiency, renal 1-alpha hydroxylase insufficiency, reduced intake of dietary vitamin D and reduced intake of calcium.[6]

Calcium is believed to play a major role in the immune response in dengue. It has been proposed that the derangements of calcium levels in the infected myocardial cells may play a major role in the development of myocarditis. In an in-vitro study conducted by Salgado DM et al.[7] they have opined that the increase in diastolic calcium levels in infected myocardium could be causative factor for arrhythmias and altered contractile function.

Aims and Objectives

1. To study the correlation between serum calcium levels and severity of dengue.
2. To correlate Serum calcium levels and bradycardia (heart rate of 60 bpm and less).

Subjects and Methods

This cross sectional study was carried out on patients of Department of general Medicine at Bangalore medical college and research institute (BMCRI) and attached hospitals, Bengaluru, during June 2019 to December 2019. A total 100 adult subjects (both male and females) aged ≥ 18 years were for in this study.

Study Design: cross sectional study

Study Location: This was a tertiary care teaching hospital based study done in Department of General Medicine, at BMCRI and attached hospitals.

Study Duration: June 2019 to December 2019

Sample size: 100 patients

Subjects & selection method: The study population was drawn from patients presenting to BMCRI and attached hospitals who tested positive for dengue.

Inclusion criteria

- Tested positive for dengue
- Age ≥ 18 years
- Both sex

Exclusion criteria

- Pre-existing renal or hepatic dysfunction
- Known endocrine diseases causing hypocalcemia
- Unwilling to give informed consent

Methodology

100 dengue positive patients were divided into three groups based on the severity as per the WHO criteria, and were correlated with serum calcium levels.

Statistical Analysis

Appropriate statistical tests like Descriptive statistics, Frequencies/percentages, Chi-square test, ANOVA test and T-test for independent samples were applied.

Results

A total of 100 dengue positive patients were included in the study. Age distribution of the study population revealed the data as in [Table 1].

Table 1: Age distribution of the study population

Age (Years)	Frequency	Percent
18 to 25	46	46.0
26 to 35	33	33.0
36 to 45	13	13.0
Above 45	8	8.0
Total	100	100.0

72% of the study population were male as compared to 28% females. Among the study population, more than half of the subjects had dengue fever (65 patients) whereas 30 subjects had Dengue with warning Signs and only 5 subjects had Dengue Shock Syndrome.

Table 2: Distribution of severity of dengue based on the WHO criteria

Dengue Severity	Frequency	Percent
Dengue Shock Syndrome	5	5.0
Dengue with warning Signs	30	30.0
Dengue Fever	65	65.0
Total	100	100.0

[Table 2] shows distribution of severity of dengue based on the WHO criteria.

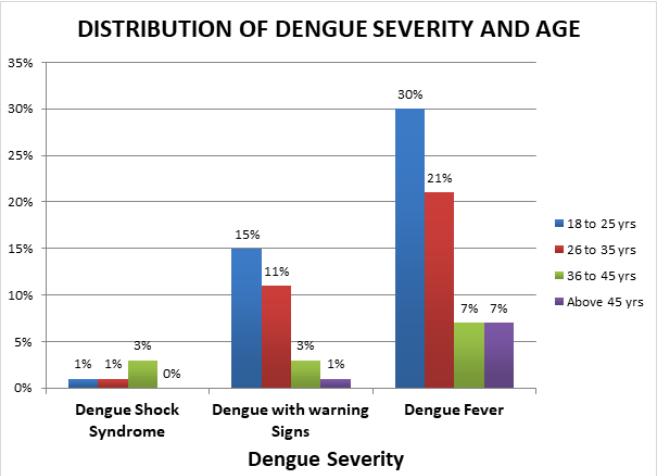

Figure 1: Distribution of dengue severity and age

Chi- square test was applied to check the association between dengue severity and age. Chi-square test showed no statistical significant association between dengue severity and age (χ^2= 12.02; p=0.062).

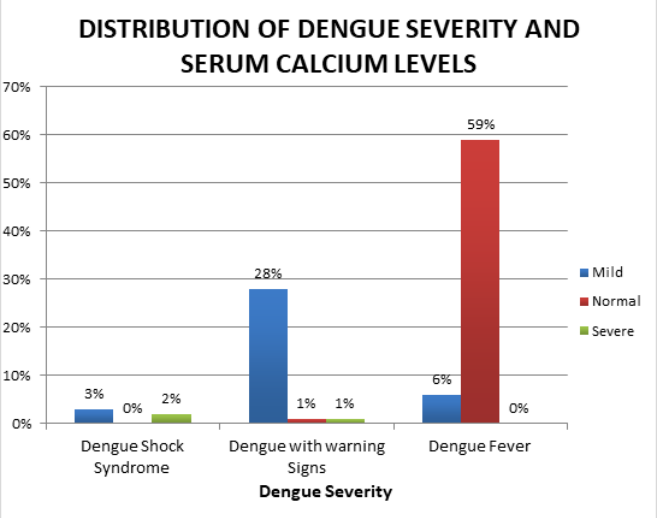

Figure 2: Distribution of dengue severity and serum calcium levels

Chi- square test was applied to check the association between dengue severity and serum calcium levels. Chi-square test showed statistically significant association between dengue severity and hypocalcemia. (χ^2= 94.08; p=0.00).

Chi- square test was applied to check the association between serum calcium levels and pulse rate. Chi-square test showed statistical significant association between serum calcium levels and pulse rate (χ^2= 16.01; p=0.00).

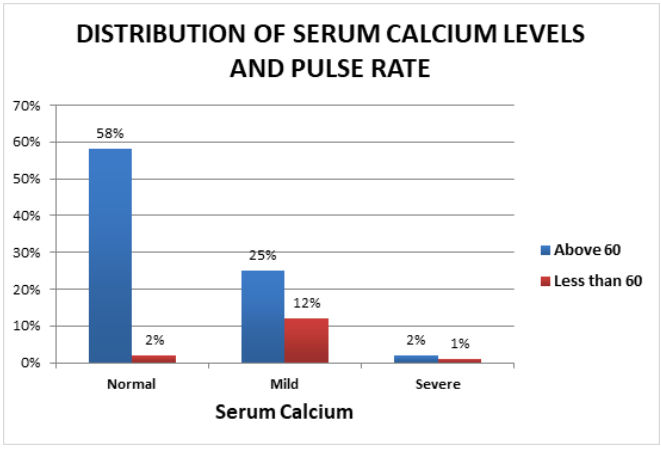

Figure 3: Distribution of serum calcium levels and pulse rate

Discussion

In our study we had wide range of age difference ranging from18 years to 60 years. Mean age of the subjects was 29.08 ± 9.422 years. Out of 100 subjects, 46% of the subjects were in the age range of 18 to 25 years followed by 33 subjects belonging to 26 to 35 years. 3 out of 5 subjects who had Dengue Shock Syndrome, were aged between 36 to 45 years.

Our study population was male predominant, 72% of the study population being males as compared to 28% females. This could be due to small sample size and selection bias. Among the study population, more than half of the subjects had uncomplicated dengue fever (65 patients), whereas 30 subjects had Dengue with warning Signs and only 5 subjects had Dengue Shock Syndrome.

Mean serum calcium levels on admission were 9.036 ± 0.9227 mg/dl. The admission serum calcium values revealed more than half of the subjects had normal serum calcium levels- 60 patients, followed by 37 subjects had mild serum hypocalcimia, and 3 subjects had severe hypocalcemia (<7.6mg/dl). Out of 3 subjects who had severe calcium deficiency, 2 had Dengue Shock Syndrome and 1 subject had Dengue with warning Signs. Chi-square test showed statistically significant association between dengue severity and hypocalcemia. (χ^2= 94.08; p=0.00).

Our study results are in line with the study by Kavita et al where they observed that low serum calcium levels correlated significantly with: 1. severity of dengue illness 2. increased risk of bleeding manifestations.[8] Another study conducted by Kesavan at Selam showed high statistical significance (p=0.0005) in serum calcium level between

dengue without warning signs(Mean serum calcium level =9.27meq/l) and dengue with warning signs (Mean serum calcium level =7.95mq/l) /severe dengue (Mean serum calcium level =7.60meq/l).[9]

85% of the subjects had normal pulse rate while 15 subjects had bradycardia. Out of 3 subjects having severe hypocalcemia, 2 subjects had pulse rate above 60bpm whereas out of 60 subjects having normal serum calcium levels, only 2 had bradycardia (PR< 60bpm). Chi-square test showed statistical significant association between serum calcium levels and pulse rate (χ^2= 16.01; p=0.00).

Drawbacks

The study conducted had small sample size with very less number of severe cases. Using ionised calcium instead of serum calcium levels would have given better insights.

Inference

In our study, we observed that there was significant association between dengue severity and hypocalcemia. Out of 3 subjects who had severe hypocalcemia, 2 had Dengue Shock Syndrome and 1 subject had Dengue with warning Signs. The presence of hypocalcemia correlates with the severity of dengue illness and could be considered as one of the predictors of poor outcome. However, further studies are required in these lines that are aimed at understanding if the presence of hypocalcemia can be utilized as a prognostic indicator in dengue infection. The potential role of calcium as a treatment option, to modulate the immune system, in either hypocalcemic or normocalcemic patients with dengue is to be explored.

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