

Evaluation of Calcium Levels in Dengue Patient

Meghana Sreenivas¹, Jayapraksh Alva MD²

¹Post Graduate Student, Department of General Medicine, Father Muller Medical College, Kankanady, Mangaluru, Karnataka – 575 002 India
Email: [sreenimegha\[at\]gmail.com](mailto:sreenimegha[at]gmail.com)

²Professor and Dean, Department of General Medicine, Father Muller Medical College, Kankanady, Mangaluru, Karnataka – 575 002 India

Abstract: ***Background and objectives:** Dengue fever (DF) is a major public health problem in India, leading to significant morbidity and mortality. Calcium has been implicated in immunopathogenesis of dengue and is associated with cardiac arrhythmias, myocardial dysfunction. It also plays a role in platelet aggregation. However, there is no evidence that hypocalcaemia is of clinical importance and role of calcium replacement in dengue patients. This study was undertaken to evaluate the relation of serum ionised calcium levels in DF and to correlate with severity. **Methodology:** This descriptive study was undertaken in the Department of General Medicine, Father Muller Medical College, Mangaluru, Karnataka. A total of 43 confirmed cases of DF based WHO criteria were investigated for serum ionized calcium levels and correlated with severity. **Results:** In the present study serum ionized calcium levels ranged between 3.10 to 5.01 mg/dL. The mean and median serum ionized calcium levels were 4.29 ± 0.48 and 4.40 mg/dL. Majority of the patients (79.07%) had lower serum ionized calcium levels. The decrease in platelet count was significantly associated with decrease in serum ionized calcium levels ($p=0.019$). The mean serum ionized calcium levels also decreased significantly with severe DF ($p<0.001$). Majority of the patients were males (81.4%). Most of the patients were aged between 18 to 30 years and the mean age was 34.02 ± 13.85 years. **Conclusion and interpretation:** Hypocalcemia is a common biochemical derangement in DF. Further it is associated with platelet count and severity of the DF.*

Keywords: Dengue fever; Hypocalcemia; Serum ionised calcium levels;

1. Introduction

Dengue virus (DENV) causes a highly infectious illness and is transmitted to humans by mosquitos of the *Aedes* family causing high rates of morbidity and mortality.¹ Worldwide it has been estimated to have affected over 100 countries and 2.5 billion people.² The epidemic was reported from Calcutta, India between July 1963 and March 1964.³

Dengue fever has wide spectrum of clinical manifestations. The clinical features include fever, headache, myalgia, arthralgia and skin rashes. The lab parameters included leucopenia, thrombocytopenia and increased liver function. The complications in dengue are due to severe thrombocytopenia, haemorrhage and plasma leakage leading to third space fluid accumulation and biochemical abnormalities like hypocalcemia.⁴

Evidence with regards to the role of calcium homeostasis in DF is limited. Calcium has been also implicated in the immunopathogenesis of dengue; however, the precise clinical implications of these interactions are yet not clearly defined. Derangements of calcium homeostasis are likely to be associated with myocardial dysfunction and cardiac arrhythmias, platelet aggregation. Studies evaluating the therapeutic use of calcium in dengue have been underpowered and poorly designed to make any firm recommendations.⁵

However, there is no evidence that hypocalcaemia is of clinical importance and role of calcium replacement in dengue patients.⁵ This study was undertaken to evaluate the relation of serum ionised calcium levels in DF and to correlate with severity.

2. Methodology

This hospital based descriptive study was undertaken in the department of General Medicine, Father Muller Medical College Mangalore, Karnataka State, India. A total of 43 confirmed cases of DF based on WHO criteria were investigated for serum ionized calcium levels and was correlated with severity. Patients with oral calcium supplements, malabsorption syndrome, renal dysfunction and with treatment history of drugs causing hypocalcaemia like Rifampicin, Biphosphanates, Phenobarbitone were excluded from the study. Dengue fever was diagnosed by dengue rapid test plus clinical signs according to the World Health Organization (WHO) criteria.^{6,7} The severity of DF was assessed on the basis of WHO criteria as DF without warning signs, DF with warning signs and severe DF. The haemoglobin, platelet count, serum ionised calcium levels were assessed. Hypocalcaemia was defined as the presence of a serum ionised calcium level of < 4.6 mg/dL.

Statistical analysis

Data was analysed using IBM SPSS Statistics version 20.0 for Windows. For all the continuous variables, the results are either given in Mean \pm SD and/or median and interquartile range (IQR). The normality of the continuous data was assessed by Shapiro Wilk test. The comparison of calcium levels with dengue severity was done by Kruskal-Wallis Test. Chi square test and Fisher's exact test was used to find the association between two categorical variables. All tests were two-tailed and at 95% confidence interval (CI), and a p-value of less than 0.050 was considered significant.

3. Results

In the present study serum ionized calcium levels ranged between 3.10 to 5.01 mg/dL. The mean and median serum ionized calcium levels were 4.29 ± 0.48 and 4.40 mg/dL

respectively. Majority of the patients (79.07%) had lower serum ionized calcium levels (Table 1 and Graph 1). Majority of the patients were males in group A (81.40%). The male to female ratio was 4.37:1. Age ranged from 18 to 67 years. The mean and median age was 34.09 ± 13.76 and 30 years respectively. However 53.49% of the patients were aged from 18 to 30 years. All the patients (100%) presented with fever followed by headache (93.02%) and myalgia (72.09%). Bleeding manifestations were present in 20.93% of the patients. 97.67% of the patients were oriented to time/place/person. Platelet count ranged from 8000 to 200000 per cumm. The mean and median platelet count was 80558.14 ± 48050.72 and 97000 per cumm respectively. Further, 34.88% of the patients had platelet count between 100000 to 149999 per cumm and 11.63% of the patients had <20000 per cumm. With respect severity of dengue, 79.07% of the patients had DF while 18.60% of the patients had DF with warning signs and 2.33% of the patients had severe DF (Table 2).

There was significant association between serum ionized calcium levels and platelet count ($p=0.019$) (Table 3). However no association was found between dengue severity and serum ionized calcium levels ($p=0.342$) (Table 4) but there was significant reduction in mean and median serum ionized calcium levels with the severe disease ($p=0.003$) (Table 5).

4. Discussion

In the present study males outnumbered females with male to female ratio of 4.37:1. A similar study by Mahajan A et al.¹¹ (2019) and Agarwal J et al.⁹ (2010) reported male preponderance with 78% of males. On the contrary, a similar study by Reddy T. et al.¹⁰ (2017) reported almost equal number of males and females (52.7% and 47.3% respectively).

In the present study the mean and median age was (34.09 ± 13.76 and 30 years respectively respectively) and more than half of the study population (53.49%) belonged to the age group between 18 to 30 years suggesting occurrence of DF in younger individuals. It is reported that, dengue affects people of all ages. It was similar to study by Mahajan A et al.¹¹ (2019) where the mean age was 28.7 years and 50% of the patients belonged to age group between 21 to 30 years.

In this study all the patients (100%) presented with fever and second common clinical presentation was headache (93.02%) followed by myalgia (72.09%). However, several Indian studies have reported varied clinical features of dengue fever. These clinical findings were similar to study by Kumar A et al.¹² (2010) where the most common presentation was fever (99.1%), followed by myalgia (64.6%), vomiting (47.6%) and headache (47.6%) and also Sharma S et al.⁸ showed fever (100%) as predominant clinical finding.

According to the WHO,⁶ the severity of dengue infection varies from DF without warning signs, to dengue with warning signs and severe dengue. In the present study, with regard to severity of dengue, majority of the patients

(79.07%) had DF while 18.60% of the patients had DF with warning signs and 2.33% had severe dengue. A recent study by Mahajan A and Shetty IN¹¹ (2019) from Mangalore reported the percentages for patients with severe dengue and dengue with and without WS as 24%, 40% and 36% respectively which was different from the observations of the present study.

In the present study majority of the patients (79.07%) with DF had lower serum ionized calcium levels. The serum ionized calcium levels ranged between 3.10 to 5.01 mg/dL and the mean and median serum ionized calcium levels were 4.29 ± 0.48 and 4.40 mg/dL respectively suggestive of hypocalcaemia in the most of the patients. These observations suggest that, patients with dengue fever are at high risk of hypocalcaemia. This finding corroborated with a recent study by Mahajan A et al.¹¹ (2019) from Mangalore where authors reported hypocalcaemia in 66% of the patients with mean calcium level of the population was 4.42 mg/dL with range being 4.12-4.68 mg/dL.

Another study by Adikari M et al.¹⁵ (2016) also concluded that serum ionized calcium level was significantly reduced in majority of patients with severe dengue infection within first 24 hours of onset of severe dengue clinical criteria. This was similar to the results of our study. Reddy T. et al.¹⁰ (2017) from RLJ hospital in Kolar, Karnataka also demonstrated that the severity of dengue infection correlated with the serum ionised calcium levels. Serum ionised calcium was lower than the normal range in severe dengue infection than in the dengue infection with and without warning signs. Uddin KN et al.¹⁴ (2008) studied with 84 dengue patients demonstrated that hypocalcemia is an important biochemical derangement which is correlated with severity of dengue infection and it also revealed that mean serum calcium levels were within the normal range in non-severe dengue patients. Constantine RG et al.¹³ concluded that serum ionised calcium levels were lower in DHF than with DF.

5. Conclusion

Overall, it may be concluded that patients with DF are likely to have lower serum ionised calcium levels. Further, serum ionised calcium levels significantly correlate with the severity of DF and are likely to be significantly low in patients with severe dengue and DF with warning signs than in those with dengue fever. Hence ionised calcium can be used as a prognostic marker for dengue severity but further studies are required to support this hypothesis.

References

- [1] Rice CM. Flaviviridae: The viruses and their replication. In: Virology Fields BN, Knipe DM, Howley PM eds. 3rd ed., Philadelphia: Lippincott-Raven Publishers, 1996. p. 931-59.
- [2] Guzman MG, Kouri G. Dengue: an update. *Lancet Infect Dis* 2002; 2:33-42.
- [3] Jatanasen S, Thongcharoen P. Dengue hemorrhagic fever in South East-Asian countries. Monograph on dengue/dengue haemorrhagic fever. New Delhi: WHO; 1993.

- [4] Senanayake A, Kularatne M. Dengue fever. *BMJ*2015;351:h4661.
- [5] Shivanthan MC, Rajapakse S. Dengue and calcium. *Int J Crit Illn Inj Sci.* 2014 Oct-Dec;4(4):314-6.
- [6] Dengue: Guidelines for Diagnosis, Treatment, Prevention and Control. World Health Organization. Geneva, Switzerland: WHO; 2009.
- [7] Hadinegoro SR. The revised WHO dengue case classification: does the system need to be modified? *Paediatr Int Child Health.* 2012;32 Suppl 1: 33-8.
- [8] Sharma S, Sharma SK, Mohan A, Wadhwa J, Dar L, Thulkar S, et al. Clinical profile of dengue haemorrhagic fever in adults during 1996-outbreak in Delhi, India. *Dengue Bull* 1998;22:20-7.
- [9] Agarwal J, Kapoor G, Srivastava S, Singh KP, Kumar R, Jain A. Unusual clinical profile of Dengue Infection in patients attending a tertiary care teaching hospital in north India. *Int J Infect Dis* 2010;14:174-5.
- [10] Reddy T, Ressay V, Lakshmaiah V, Garlapati R. Hypocalcemia as a prognostic marker for severity in patients with dengue fever. - *Global J Res analysis (GJRA)* 2017;6(11):334-6.
- [11] Mahajan A, Shetty IN. A Study on Correlation between Serum Ionized Calcium and Severity of Dengue Infection. *IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)* e-ISSN: 2279-0853, p-ISSN: 2279-0861. Volume 18, Issue 3 Ser. 2 (March. 2019), PP 44-52.
- [12] Kumar A, Rao CR, Pandit V, Shetty S, Bammigatti C, Samarasinghe CM. Clinical manifestations and trend of dengue cases admitted in a tertiary care hospital, Udupi district, Karnataka. *Indian J Community Med* 2010; 35:386-90.
- [13] Godwin R Constantine et.al, Hypocalcaemia is associated with disease severity in patients with dengue. *J Infect Dev Ctries* 2014; 8(9):1205-1209.
- [14] Uddin KN, Musa AKM, Haque WMM, Sarker RSC, Ahmed AKMS. A follow up on biochemical parameters in dengue patients attending BIRDEM hospital. *Ibrahim Med Coll J* 2008;2 :25-7.
- [15] Adikari M, Perera C. Prevalence of hypocalcemia and its potential value as a biochemical marker in patients with severe dengue infection. *Journal of Tropical Diseases & Public Health.* 2016;4:188.

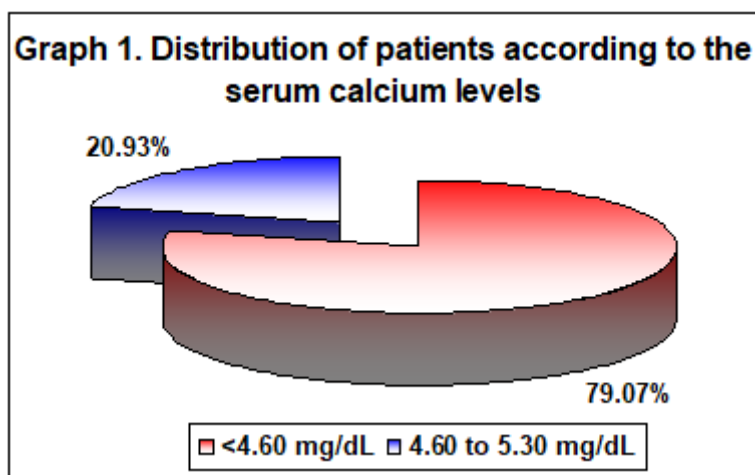


Table 1: Clinical profile of the patients

Parameters	Mean		Median	IQR	Range	
	Mean	SD			Min	Max
Age (Years)	34.09	13.76	30.00	25.75	18.00	67.00
Pulse rate (per minute)	60.53	7.04	60.00	12.00	45.00	77.00
Respiratory rate (per minute)	22.42	1.61	22.00	0.50	20.00	28.00
Temperature (°C)	99.39	0.73	99.00	1.20	98.60	102.00
Systolic blood pressure (mm Hg)	101.86	10.97	100.00	20.00	80.00	130.00
Diastolic blood pressure (mm Hg)	69.30	11.00	70.00	20.00	50.00	90.00
Haemoglobin (gm%)	15.07	1.81	15.20	2.10	9.30	18.50
Platelet count (lakhs per cumm)	80558.14	48050.72	97000.00	81500.00	8000.00	200000.00
Serum ionized calcium levels	4.29	0.48	4.40	0.59	3.10	5.01

Table 2: Distribution of patients according to the sex, age, clinical presentation, platelet count and dengue severity

Parameters	Categories	Distribution (n=43)	
		Number	Percentage
Sex	Male	35	81.40
	Female	8	18.60
Age group (Years)	18 to 30	23	53.49
	31 to 40	7	16.28
	41 to 50	6	13.95
	51 to 60	6	13.95
	61 to 70	1	2.33
Clinical presentation	Fever	43	100.00
	Headache	40	93.02
	Myalgia	31	72.09
	Bleeding manifestations	9	20.93
Orientation to time/place/person	Oriented	42	97.67
	Disoriented	1	2.33
Platelet count (per cumm)	<20000	5	11.63
	20000 to 49999	10	23.26
	50000 to 99999	10	23.26
	100000 to 149999	15	34.88
	>150000	3	6.98
Dengue severity	DF	34	79.07
	DF with warning signs	8	18.60
	Severe DF	1	2.33

Table 3: Association of calcium levels with platelet count

Platelet count (per cumm)	Calcium levels (mg/dL)				Total	
	<4.6 (n=34)		4.6 to 5.3 (n=9)		Number	Percentage
	Number	Percentage	Number	Percentage		
<20000	5	100.00	0	0.00	5	11.63
20000 to 49999	10	66.67	0	0.00	10	23.26
50000 to 99999	9	90.00	1	11.11	10	23.26
100000 to 149999	9	300.00	6	66.67	15	34.88
>150000	1	20.00	2	22.22	3	6.98

p=0.019

Table 4: Association of calcium levels with dengue severity

Dengue severity	Calcium levels (mg/dL)			
	<4.6		4.6 to 5.3	
	Number	Percentage	Number	Percentage
DF	25	73.53	9	100.00
DF with warning signs	8	23.53	0	0.00
Severe DF	1	2.94	0	0.00
Total	34	100.00	9	100.00

p=0.342

Table 5: Comparison of mean median calcium levels with severity of DF

Dengue severity	n	Calcium levels (mg/dL)			
		Mean	SD	Median	IQR
DF	34	4.43	0.37	4.48	0.51
DF with warning signs	8	3.85	0.46	3.77	0.45
Severe DF	1	3.10	-	3.10	-
p value		0.003			