

Original Research Article

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Serum ionic calcium levels and hypocalcemia in dengue fever in children and its correlation with its severity: case control study

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ABSTRACT

Background: Dengue fever (DF) is a major health problem, 90% of dengue hemorrhagic fever (DHF) occurring in children <5 years and mortality of 2.5%. Abnormalities like metabolic acidosis, hyponatremia and hypocalcemia can occur in severe dengue especially in dengue shock patients. Alterations in calcium homeostasis, may play a role in the pathogenesis of dengue shock. Objectives is to evaluate serum ionic calcium (Ca^{2+}) levels in children aged 1-18yrs with dengue fever and correlate it with severity and outcome

Methods: The study was prospective hospital based case-control study. Case group had 75 children with dengue fever with equal number of controls. Cases were classified according to WHO classification. Serum Ca^{2+} levels were estimated within 24 hours of admission.

Results: Majority of children with dengue were in the age-group of 6-15 years (71.4%). Out of 75 cases, 16% were dengue without warning signs, 54.7% dengue with warning signs and 29.3% were severe dengue cases. Mean Ca^{2+} level (in mmol/l) was 1.2009 (± 0.09) among controls and 1.0911 (± 0.10) in dengue cases ($p=0.0001$). Mean Ca^{2+} level in dengue without warning signs was 1.0950 mmol/l, dengue with warning signs was 1.1088 mmol/l and severe dengue was 1.0559 mmol/l. Mean Ca^{2+} level in severe dengue was significantly lower compared to dengue with warning signs ($p=0.04$). Hypocalcemia was seen in 56% of dengue cases but only 14% among controls. Seven children with severe dengue who died had hypocalcemia.

Conclusions: Hypocalcemia is common in dengue fever. Lower levels of ionic calcium correlate with severity of dengue illness and may be considered as a prognostic indicator of poor outcome.

Keywords: Calcium, Dengue fever, Hypocalcemia, Mortality, Severity

INTRODUCTION

Dengue fever is a major public health problem in more than 100 tropical and sub-tropical countries in South-East Asia, the Western Pacific and South and Central America¹. Throughout the world it is estimated that 50 million cases of dengue fever occur annually.¹ Each year around 500 000 people with Dengue haemorrhagic fever (DHF) require hospitalization and approximately 90% of them

are children aged less than five years.¹ Among them about 2.5% die.¹ Critical condition caused by any medical or surgical illness may trigger an acute phase response which in turn is associated with several metabolic derangements.² Several biochemical abnormalities like metabolic acidosis, hyponatremia and hypocalcemia can occur in severe dengue especially in dengue shock patients.³ Among these the detection of hypocalcemia demands special consideration.⁴ Calcium plays a key role

in platelet aggregation, immune response in dengue infection.⁵ Known cardiovascular manifestations of hypocalcemia include hypotension, reduced myocardial function, electrocardiogram (ECG) abnormalities, and heart failure.⁶ Therefore, alterations in calcium homeostasis, may play a role in the pathogenesis of dengue shock also.⁷ There is a scarcity of literature documenting serum calcium levels in dengue infection.^{7,8} These few studies have shown that hypocalcaemia occurs in significant number of cases with dengue and some studies correlated serum calcium levels with the severity of dengue.^{7,9} However, these few studies are in adult dengue patients and have measured total serum calcium levels not ionic calcium levels.^{4,7,10} Numerous studies have clearly demonstrated that the measurement of ionized (free) calcium is the test of choice in nearly all diagnostic and treatment situations.¹¹ Therefore, we have undertaken case control study where we have measured ionic calcium levels in children with dengue fever and correlated their levels with the dengue fever severity using new WHO classification.¹²

METHODS

This hospital based prospective case-control study was conducted in the Department of Pediatrics, JSS Medical College Hospital from October 2014 to March 2016.

Inclusion criteria

Children between 1 to 18 years with clinical features of Dengue fever were enrolled in this study based on revised WHO criteria.¹²

Exclusion criteria

Children who received blood transfusion and calcium (oral or intravenous) before admission.

Permission for conducting the study was taken from the JSS Institutional Ethical Committee and a written consent was taken from the parents. Dengue infection was confirmed by NS1 antigen detection by ELISA or IgM ELISA (Mac ELISA). For the total number of dengue cases, equal number of age and gender matched children with non-dengue febrile illness (NS1 antigen negative) in whom where an alternate diagnosis was already reached were taken randomly as controls. To assess the correlation between the severity of the dengue illness and the calcium levels, we used the Spearman correlation coefficient. For that, the assumption made were alpha of 0.05, power of 80% and minimal correlation beyond chance expected was 25%. This returned the value of 123. Another 10 to 15% for any technical issues was added and rounded it off to 150.

A detailed history, clinical examination findings were entered in a prewritten proforma. Three ml blood was collected, and ionized calcium estimation done by ion selective electrode method using an auto analyser within

24 hours of admission. Children were classified according to new WHO guidelines for the severity and ionic calcium levels were correlated with severity of dengue.

Statistical analysis

Data collected was analysed using the EpiData, Epiinfo and SPSS 15.0 for windows software. Appropriate statistical tests like Descriptive statistics, Frequencies/percentages, Chi-square test, ANOVA test and T-test for independent samples were applied.

RESULTS

Majority (37.33%) of children with dengue fever were in the age group of 11-15 years, followed by 33.3% in the age group of 6-10 years, 28% in the age group 1-5 years and only 1.3% of were in age group 16-18 years. The mean age (\pm SD) of case group is 8.453 ± 4.354 and that of control group is 8.653 ± 4.273 ($P > 0.05$). The distribution of children in different age groups is similar in cases and control groups as they were matched age wise. Equal number of male (39) and female children (36) were taken in both cases and control groups ($P > 0.05$) (Table 1). The mean duration of fever in cases is $4.27 (\pm 1.68)$ and that of controls is $4.59 (\pm 1.03)$, both ranging between 1 to 12 days.

Table 1: Demographic details and ionic calcium levels of cases and controls.

Variables	Cases n=75 (%)	Control n=75 (%)	'P' value
Age groups			
1-5 years	21 (28)	20 (26.66)	
6-10 years	25 (33.33)	21 (28)	
11-15 years	28 (37.33)	33 (44)	0.839
16-18 years	1 (1.3)	1 (1.3)	
Years	8.453	8.653	
Mean (SD)	(4.35)	(4.23)	
Gender			
Males	39 (52)	39 (52)	1.0
Females	36 (48)	36 (48)	
Ionic calcium levels			
Mean ionic calcium Mean (SD) [mmol/l]	1.0911 (0.102)	1.2009 (0.099)	0.0001
Hypocalcemia (Ionic calcium <1.10mmol/l)	42 (56)	11 (14.7)	0.0001

Based on the WHO severity criteria of dengue, 12 (16%) were classified as “dengue without warning signs” group, 41 (54.7%) dengue with warning signs” and 22 (29.3%) as “severe dengue” group at admission. Out of 12 dengue without warning signs cases, 4 progressed to dengue with warning signs and none to severe dengue. Out of 41

dengue with warning signs 9 children progressed to severe dengue.

Table 2: Mean calcium levels and proportion of hypocalcemia among cases and controls.

Parameter	Dengue (n=75)	Controls (n=75)	P value
Mean ionic calcium	1.0911	1.2009	
Mean (SD) [mmol/l]	(0.102)	(0.099)	0.0001
Hypocalcemia n (%) (Ionic calcium < 1.10mmol/l)	42 (56)	11 (14.7)	0.0001

Table 3: Mean ionic calcium levels in dengue fever according to severity.

Dengue severity groups	N	Mean ionic calcium (mmol/l)	Std. deviation
Dengue without warning signs	12	1.0950	0.11310
Dengue with warning signs	41	1.1088	0.09003
Severe dengue	22	1.0559	0.11134

Table 4: Comparison of Mean ionic calcium levels in sub groups based on severity and outcome.

Dengue severity [WHO classification]	Mean ionic calcium[mmol/l]±SD	P value
Dengue survived cases	1.1082±0.08830	
Dengue expired cases	0.9243±0.06876	0.00083
Dengue +warning signs	1.1088±0.0900	0.04532
Severe dengue	1.0559±0.1113	
In severe dengue cases		
Discharged	1.094±0.0687	
Expired	0.9743±0.1448	0.01472

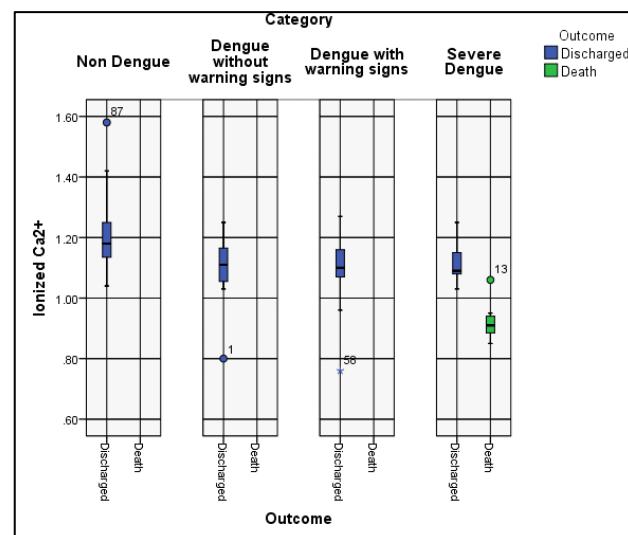
The mean ionized calcium levels in control group is 1.2009 (± 0.099) mmol/l and that of dengue cases is 1.0911 (± 0.102) mmol/l ($p=0.0001$) (Table 2). Comparison of Mean ionic calcium levels in various groups is shown in the Table 3 and 4. Serum ionic calcium levels were significantly low in severe dengue and expired dengue cases (Table 3).

Out of 75 dengue cases, hypocalcemia was observed in 42 (56%) cases and while only in 11 (14%) of cases in the control group ($p=0.0001$) (Table 2). Hypocalcaemia was observed in 50% of “Dengue without warning signs” group, 52.5% of “dengue with warning signs” group and 68.2% of “Severe dengue” Group. Out of 75 dengue

cases seven children expired. No deaths were reported in controls, dengue without warning signs and dengue with warning signs groups. The median ionized calcium of all the discharged subjects in control group is 1.18 mmol/l, dengue without warning signs” group is 1.11 mmol/l, “dengue with warning signs” group is 1.10 mmol/l, discharged cases (n=15) in “severe dengue” group is 1.08 mmol/l (Figure 1). All children with severe dengue who died had hypocalcemia on admission and in six of them ionized calcium levels were below 1mmol/L (Table 5).

Table 5: Ionic calcium levels and hypocalcemia in fatal dengue cases.

Case No.	Age (years)	Ionic calcium levels (mmol/l)
Case 1	7	1.06
Case 2	12	0.90
Case 3	13	0.87
Case 4	1	0.91
Case 5	8	0.93
Case 6	14	0.85
Case 7	12	0.95



Box plot graph also suggests that ionized calcium levels in those expired was significantly lower

Figure 1: Box plot of ionized calcium levels in different dengue severity groups with respect to the final outcome.

DISCUSSION

Dengue infection is potentially a fatal illness. Fluid management, support of the involved organs and correction of metabolic derangement is the mainstay of treatment.⁵ Calcium plays a role in the platelet aggregation and in the functioning of myocardial tissue.⁵ Calcium homeostasis derangements are probably associated with cardiac arrhythmias and myocardial dysfunction.^{2,5} Calcium homeostasis derangements are observed in dengue as documented by in vitro studies.⁵

Intravenous calcium has been a routine practice in the resuscitation protocols for the management of dengue shock.¹² Therefore, probably alterations in calcium homeostasis may play a role in the pathogenesis of dengue shock also.⁷ Jirapinyo et al, from Thailand reported protracted hypocalcemia in a complicated dengue haemorrhagic fever.¹³ Hypocalcemic tetany in association with dengue infection has been reported in 2 children.¹⁴

Over all authors observed hypocalcaemia in 56% of dengue children vs. 14% of control group ($p=0.000$) and the prevalence of hypocalcaemia increased as the severity of dengue increased. Similar to present study observation Constantine et al also reported that 86.9% of DHF had hypocalcemia vs 29.7% in DF ($p <0.05$).⁷ However we utilised new dengue classification to assess the severity of dengue. Bunnag et al, also reported hypocalcaemia in 68.3% among 41 Dengue Shock Syndrome (DSS) children.³ Similar observation was made in children with dengue from Philippines also.¹⁵ Nguyen et al, reported hypocalcemia in 14.2% of infants with DHF from Vietnam.¹⁶ Uddin et al, noted significantly lower mean total calcium levels in DHF patients than with uncomplicated dengue fever patients.⁴ The serum total calcium levels of dengue patients decreased significantly ($P = 0.000$) as compared to that of healthy control group in a study from Pakistan which involved only 15 cases and controls.¹⁰

In a Sri Lankan study out of 61 cases with severe dengue infection, ionised hypocalcaemia was noted in 85% of cases where as it is 68.2% in severe dengue group in our study.⁸ They observed mean ionized calcium level of 0.96 mmol/L in their cases with severe dengue, whereas it was 1.05 mmol/L in our severe dengue study group.⁸ However, there were no control group in their study. Authors also observed that the mean ionic calcium values were lower in children with severe dengue when compared to dengue with or without warning signs. In the current study serum ionic calcium levels significantly correlated with dengue severity. Similarly, Constantine et al, also showed that mean ionized calcium levels were lower in DHF (1.02 mmol/l than in those with DF [1.09]) $p<0.05$.⁷

Authors observed that the mean ionised calcium levels were lower in seven children with dengue who died when compared with children with severe dengue (0.88 mmol/l vs 1.09 mmol/l) and all seven of them had hypocalcaemia. The case fatality rate in our study was 9.3%. Out of seven who died three were referred to us with fluid resistant shock and one had massive gastrointestinal bleeding along with severe hepatitis. In six of them ionized calcium levels were below 1 mmol/l. In 4 infants with fatal DSS, 3 of them had hypocalcemia in a study by Nguyen et al.¹⁶

Baton et al, in a study among dengue children revealed that there is a significant decrease in serum calcium in

dengue shock syndrome compared to dengue fever and they concluded that this finding may imply calcium replacement as part of the management of dengue shock syndrome.¹⁵ Study from Thailand also concluded that while managing DSS with proper intravenous fluids; correction of the common laboratory abnormalities like acidosis, hyponatremia and hypocalcemia is important.³ WHO protocol also includes calcium replacement along with correction of abnormalities of glucose and acidosis in fluid resistant shock.¹² Sánchez-Valdés et al, reported overall improvement of clinical condition of 5 DF patients who received oral calcium carbonate and Vitamin D3.¹⁷ Cabrera-Cortina et al, reported a significant increase ($p <0.05$) in the platelet counts and clinical improvement of 10 DF patients following oral calcium carbonate when compared with control group¹⁸. However, therapeutic implications of calcium supplements in dengue in these studies are not statistically empowered.

Limitation of the study include; no serial estimation of ionised calcium levels was done during the course of hospital stay.

CONCLUSION

The presence of hypocalcemia correlates with the severity of dengue illness and may be considered as one of the predictors of poor outcome. However, further well-designed studies are needed which are aimed at understanding whether the presence of hypocalcemia can be utilized as a prognostic indicator in dengue infection.

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Ethical approval: The study was approved by the JSS Institutional Ethical Committee

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