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Research Paper

Trend of Serum Calcium to Platelet Count: A Prognostic Indicator in Dengue

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ABSTRACT
Background: *There is scarcity of literature documenting serum calcium levels in dengue.*
Methods: *This was a prospective, hospital based, longitudinal, observational study involving children 3 months to 13 years, admitted, with confirmed non-structural protein 1 (NS1) antigen positive for dengue. Outcome measures were serum calcium level and platelet count trends in serologically proven dengue.*
Results: *100 patients of serologically confirmed dengue presented with fever (98%), rash with myalgia (86%), vomiting (72%) abdominal pain (60%) itching (38%) melena (31%) breathlessness (22%) central nervous system (CNS) involvement (16%) epistaxis (12%).*
Conclusion: *Calcium levels and platelet counts during acute phase and recovery were obtained. Normalization of serum calcium along with rise in platelet count is seen in both sexes across all ages in all categories of dengue. Hypocalcemia seen in our study was asymptomatic and recovered without supplementation. Thus, serum calcium can be used as a surrogate marker along with platelet count for recovery in dengue.*
KEY WORDS: *dengue; hypocalcemia; NS1antigen; thrombocytopenia*

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I. INTRODUCTION

Dengue has progressively achieved a global prevalence over the last quarter century with an established endemicity in more than 100 countries. Dengue is a common arboviral disease globally [1]. Population explosion with the need to store water in households and poor solid waste disposal provides the much-needed breeding grounds for *Aedes aegypti*, a daytime biting mosquito of the Stegomyia family, the predominant vector, for all the four strains of dengue virus. Infected humans, enable the female mosquitoes to acquire infection during a blood meal, and following a week-long incubation, the mosquitoes are infective to other humans, to monkeys and also transmit to their offspring by transovarian route.

Epidemics of dengue are associated with attack rates ranging from 50-80%. Worldwide an estimated 500,000 cases of severe dengue infection require hospitalization each year, of which children form a large proportion [2].

Dengue hemorrhagic fever (DHF), characterized by sudden onset high fever often with a biphasic pattern, caused by dengue viruses, is associated with abnormalities in hemostasis and by leakage of fluid and protein from capillaries, which in severe cases results in shock dengue shock syndrome (DSS). It is thought to have an immunopathologic basis [3].

Dengue viral infection is commonly associated with thrombocytopenia, the cause of which is molecular mimicry between dengue virus proteins and endogenous self-proteins. There is generation of antibodies against dengue virus proteins (especially NS1 antigen), which cross-react with platelet surface proteins and thus cause thrombocytopenia [2]. It is known that calcium plays an important role in platelet adhesion [4]. Low blood calcium levels have been demonstrated in dengue infection [5].

There is a scarcity of literature documenting serum calcium levels in dengue infection. Few studies have shown that hypocalcemia occurs in significant number of cases with dengue. Some studies have correlated serum calcium levels with severity of disease.

Hence, we proposed to observe the relation between serum calcium and platelet count in serologically proven dengue.

II. AIMS AND OBJECTIVES

1. To observe the relationship of serum calcium with platelet count in serologically confirmed dengue.
2. To confirm serologically, the clinically suspected cases of dengue.
3. To determine the platelet count and serum calcium level at admission of these serologically proven cases.
4. To determine platelet count and serum calcium of these serologically proven cases at discharge.
5. To determine the relationship between platelet count and serum calcium during acute illness and at recovery.

In light of the above to make recommendations for improving clinical practice.

III. MATERIALS

All children presenting with clinical features of dengue admitted to the pediatric ward and confirmed NS1 antigen positive serologically were the subjects of our study. *Inclusion criteria*: Children of both sex in the age range 3 months to 13 years were included in our study. Only serologically proven dengue NS1 antigen positive cases were included. *Exclusion criteria*: Children who received blood, plasma and/or platelet transfusion (prior to admission) and children who received any calcium oral or intravenous were excluded from our study.

IV. METHODS

We conducted this prospective, longitudinal, observational study between February 2019 and April 2020 on children 3 months to 13 years of age admitted to the Pediatric ward of Rural Medical College and Hospital, Pravara Institute of Medical Sciences, Loni, Ahmednagar, Maharashtra, India. Purposive sampling was followed, using inclusion criteria for children with dengue classified according to new World Health Organization (WHO) guidelines for severity. After obtaining written consent of patient caretakers, we recorded patient details regarding demographic data and clinical examination with special emphasis on presence or absence of warning signs of dengue. Relevant investigations were done with special emphasis on serum calcium level and platelet count for each child, both at admission and at discharge with an interval of 5-7 days. The collected data was entered in the Microsoft Excel Sheet. Descriptive analysis (Frequency distribution) was done using tables and charts with Statistical software SPSS (2015). Correlation between severity of dengue infection as reflected by thrombocytopenia and the serum calcium levels was measured using Spearman's correlation coefficient both in active illness and recovery. Strength of correlation was read as correlation coefficient.

V. OBSERVATIONS AND RESULTS

In the present study of 100 patients, majority were boys 59 (59%) while 41 (41%) were girls. 17 (17%) patients were in age group of 3 months to 12 months, 36 (36%) patients were in age group of 13 months to 5 years followed by 31 (31%) patients in age group of 5-10 years and 16 (16 %) patients in age group between 10-13 years (**Table 1**).

Table 1. Age and sex wise distribution of dengue cases in our study population

Age (years)	No. of boys (%)	No. of girls (%)	Total (n=100)
3 months -1 year	10	7	17
1 – 5	21	15	36
5– 10	18	13	31
10 -13	10	6	16
Total	59	41	100

The age wise distribution of dengue patients with regard to severity of illness is depicted in **Figure 1**.

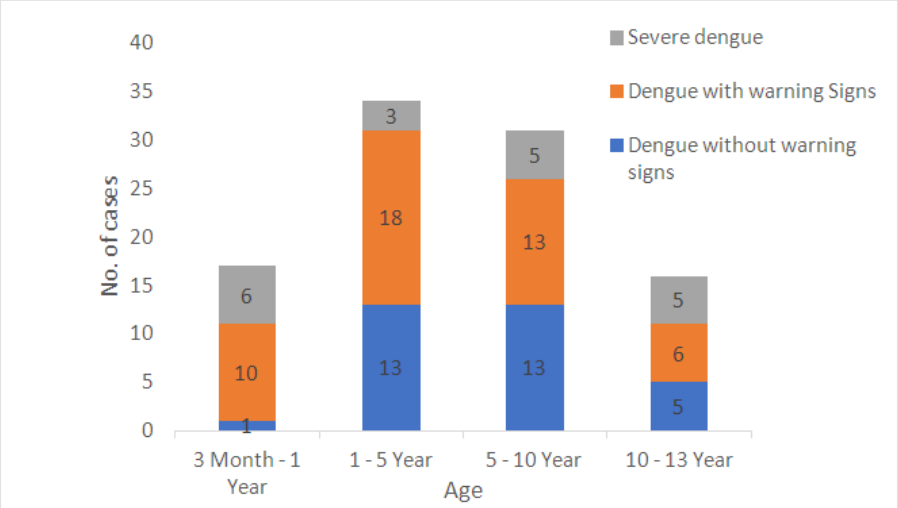

Figure 1. Age wise distribution of dengue severity.

This shows dengue without warning signs is highest in 1- 10 years, dengue with warning sign maximum in 1- 5 years, whereas severe dengue has highest incidence in 3 months to 1year.

Based on the WHO classification of severity of dengue, majority of patients 46% were dengue with warning signs, 34% patients were dengue without warning signs and 20% were severe dengue including DSS, DHF and multi organ dysfunction (**Figure 2**).

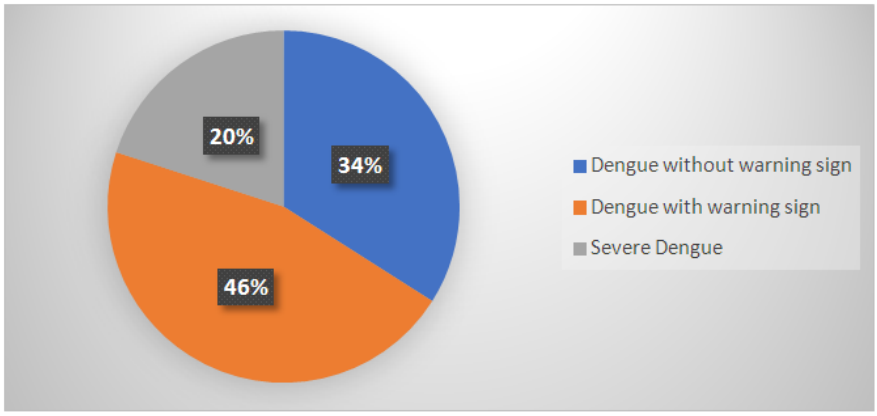

Figure 2. Distribution of Dengue patients according to severity of illness in our study population

In clinical spectrum of dengue, depicted in (**Figure 3**), fever was found to be the most common presentation 98%, followed by rash with myalgia 86%, vomiting 72%, abdominal pain 60%, itching 38%, melena 31% patients, followed by breathlessness 22%, CNS involvement 16% and epistaxis 12%.

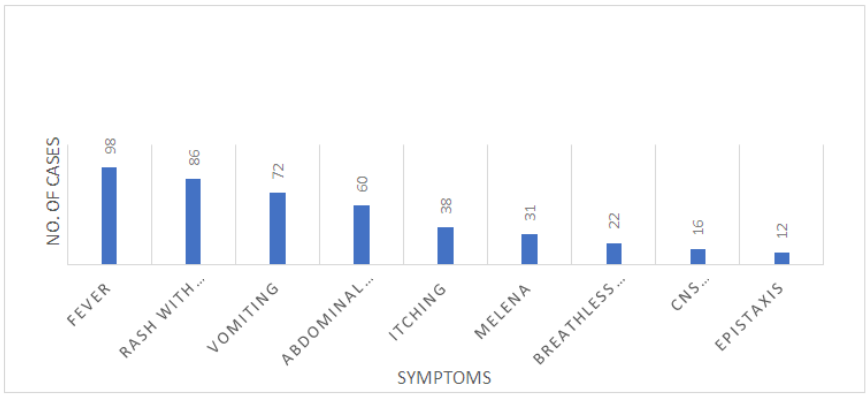

Figure 3. Clinical spectrum of dengue illness in our study population

It is known that, clinical dengue, confirmed serologically is associated with thrombocytopenia soon after its onset. Biochemical hypocalcemia at the onset of clinical dengue illness, that has been observed by us, has been rarely reported or discussed. The fall in serum calcium accompanies the thrombocytopenia which is so characteristic of dengue at its onset. Normalization of serum calcium in these children parallels the rise in platelet count to normal during recovery. This is observed around 5-7 days after onset of dengue illness (**Table 2**).

Table 2. Trend of mean serum calcium and mean platelet count in dengue in our study

Dengue severity groups	No. of cases (N)	Mean serum Ca (mg/dl) ± SD		Mean Platelet count (lac cells/mm3) ± SD	
		Acute phase	Recovery phase	Acute phase	Recovery phase
Dengue without warning sign	34	8.52 ± 0.64	9.154 ± 0.61	1.13 ± 0.57	2.345 ± 1.02
Dengue with warning sign	46	8.13 ± 0.84	8.99 ± 0.83	0.76 ± 0.39	1.92 ± 1.26
Severe dengue	20	7.8 ± 0.47	8.765 ± 0.53	0.29 ± 0.20	1.5 ± 0.67

The observation of this parallel trend of serum calcium with platelet count across all ages (3 months - 13 years) and both sexes can act as a surrogate marker for recovery in dengue and thus an indicator of good prognosis. Hence the present study proves the correlation between total serum calcium levels and platelet counts, both in active disease and on recovery.

This study proves a positive relationship between platelet count and serum calcium during acute illness (r = 0.39) and at recovery (r = 0.49). There was a statistically significant, moderately strong positive correlation between calcium levels and platelet counts in both acute phase and recovery phase. (**Table-3**).

Table 3. Correlation between serum calcium and serum platelet levels in dengue illness in our study.

Correlation	R	p value
Cor (Acute phase)	0.395	<0.001
Cor (Recovery phase)	0.490	<0.001
Cor (Mean)	0.425	<0.001

Applying Linear Regression Model (R^2 = 0.447, ANOVA: F(3,96) = 25.9, MSE = 8.862, p<0.001) it was seen that Severity (beta= -0.471, p<0.001), Calcium level (beta = 0.344, p<0.01) and age (beta = -0.221, p =0.005) were significant predictors of platelet count in the patients **(Figure 4)**.

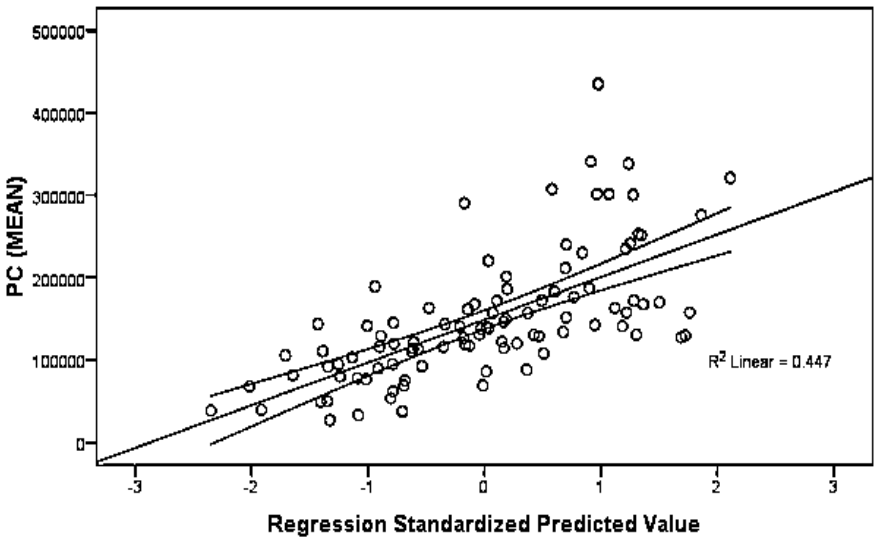

Figure 4. Scatter plot depicting Linear Regression Model in our study population

VI. DISCUSSION

The phases of dengue, both, the acute phase and the recovery phase, together usually last for about 5-7 days. There should be a high index of suspicion for dengue if a patient presents with an abrupt onset of high fever, flushing, headache, abdominal pain, vomiting, melena, petechiae which may be associated with body ache, hypotension and in a few cases CNS involvement. Dengue infection is potentially a fatal illness. Fluid management, supportive care and correction of metabolic derangements is the mainstay of treatment.

Calcium plays an important role in platelet adhesion is well known [4]. Also, calcium appears to play a role in the induction of dengue specific T-helper cells. Dengue antigen has been shown to increase the influx of calcium into T cells. The proliferation of dengue specific T-helper cells appears to be dependent on calcium. This role of calcium in the immunopathogenesis of dengue results in a fall of serum calcium level in active disease [5].

Baton S M, Oncog A (2014), in a study among dengue children revealed that there is a significant decrease in serum calcium in dengue shock syndrome compared to dengue fever. They concluded that this may imply calcium replacement as part of the management of DSS [6].

Studies from Thailand by Bunnag T, Kalayanarooj S (2011), also concluded that while managing DSS in children with proper intravenous fluids, correction of common laboratory abnormalities like hyponatremia, hypocalcemia and acidosis is important, also reported hypocalcemia in 68.3% children among 41 with DSS [7].

Cabrera-Cortina JI, Sanchez-Valdez E, De Lezama D et al (2008), reported overall improvement of 10 dengue fever patients following oral calcium carbonate when compared with control group. However, therapeutic implications of calcium supplements in these studies are not statistically empowered [8].

Hypocalcemic tetany is an infrequently recognized association with acute dengue infection and has been reported in 2 children. Though there is evidence that hypocalcemia maybe more pronounced in severe dengue, lower calcium levels have not shown a causative association with mortality as reported by Kapoor S, Singh A (2012) [9].

Sanchez-Valdez, E, Delgado-Aradillas M, Torres-Martinez JA et al (2009), reported overall improvement of clinical condition of 5 DF patients who received oral calcium carbonate and Vitamin D_3 [10].

Arun Gogna, Sitla Pathak, Kamakshi Dhamiji quoted that level of mean sodium and potassium were significantly reduced among cases with severe dengue who presented with warning signs [11].

Bandaru AK, Vanumu CS stated that the prevalence of deranged severe electrolytes was more common among severe cases of DHF [12].

Jirapinyo PI, Treetrakaran AR, Vjaradul CH et al from Thailand reported that significant hypocalcemia is seen in complicated DHF [13].

WHO protocol (2009) includes calcium replacement along with correction of glucose and acidosis in dengue with fluid resistant shock. Routine use of calcium in patients with dengue fever cannot be recommended. Maintenance of calcium homeostasis in critical dengue patients should be decided on a case-to-case basis by experienced clinician [http//www.who.int/tdr/publication/documents/dengue diagnosis.pdf] [14]. The hypocalcemia observed in our study is asymptomatic and hence needs no treatment.

VII. CONCLUSION

Due to known risk of fatality, diagnosis of dengue comes as a bombshell, creating anxiety in the parents of children suffering dengue. Besides clinical recovery, an objective laboratory test i.e., normalization of serum calcium level along with the rise in platelet count to normal, can act as a marker of recovery, thus allaying their anxiety.

VIII. RECOMMENDATION

In light of the above, it is hereby recommended to use serum calcium as a surrogate marker along with platelet count, for recovery in dengue. Larger studies including adolescents are also suggested. Future research studies may focus on low ionic calcium associated myocardial dysfunction and the need for calcium supplementation, in symptomatic hypocalcemia or otherwise. The hypocalcemia observed in our study was asymptomatic and showed recovery without supplementation, oral or otherwise. Studies with larger sample size should be conducted to ensure generalizability.

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Ethical approval: This study was approved by the Institutional Ethical Committee of Pravara Institute of Medical Sciences- Deemed University, Loni, Maharashtra, India. (approval number PIMS/DR/RMC/2019/318). Due informed written consent was taken from parents for the study.

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