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Original Research Article

A CROSS SECTIONAL STUDY ON THE ASSOCIATION BETWEEN SERUM IONIZED CALCIUM LEVEL AND SEVERITY OF DENGUE FEVER

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ABSTRACT

Background: Aim: To study the association between serum ionized calcium level and severity of dengue fever.
Materials and Methods: A hospital-based cross-sectional study was conducted at T.S. Misra Medical College, Lucknow. One hundred serologically confirmed adult dengue patients (NS1/IgM positive) were enrolled. Patients were classified according to WHO 2009 criteria into dengue without warning signs, dengue with warning signs, and severe dengue. Serum ionized calcium was measured using an ion-selective electrode method. Hematological and biochemical parameters were recorded, and associations were analyzed using Chi-square and descriptive statistics.
Results: The mean age was 35.1 years, with male predominance (68%). Severe dengue was observed in 22% of cases, dengue with warning signs in 42%, and dengue without warning signs in 36%. These were corelated with serum ionized calcium levels. Hypocalcemia was a prominent finding (< 0.001). Patients with hypocalcemia had higher hematocrit (48.8 ± 3.9%) and lower platelet counts (49,000 ± 21,000/µL) compared to patients having normal ionic calcium levels.
Conclusion: Hypocalcemia is significantly associated with severe dengue and correlates with hematocrit rise and thrombocytopenia. Routine monitoring of ionized calcium may serve as a simple, cost-effective prognostic marker for identifying patients at risk of complications. Larger multicentric studies are warranted to validate its role in clinical management.
Keywords: Dengue fever, Ionized calcium, Hypocalcemia, Disease severity, Prognostic marker.

INTRODUCTION

Dengue is a disease spread by the Aedes mosquito, and it is an entity known to mankind since 1780.[1] After 1960, the incidence of dengue has shown an exponential increase, with several recent outbreaks reported mainly from South Asian countries.[2] Dengue infection and dengue hemorrhagic fever (DHF) are major causes of morbidity and mortality in the tropical regions of the world. It is estimated that 390 million become infected with dengue per year, of which 96 million manifest apparently.[3]

The dengue virus is a single-stranded RNA virus of the genus Flavivirus, comprising four distinct serotypes (DEN-1 to DEN-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.[4]

In India, in recent years dengue has been a major health issue contributing to significant mortality and morbidity. The year 2022 saw an unprecedented increase in vector Borne diseases, primarily dengue and malaria. The major factors contributing to this mortality are a severe form of dengue infection and its complications like shock syndrome, hemorrhagic manifestations, and severe thrombocytopenia. So, we need to identify the patients who are all going through these complications.[5] The probability of DENV

transmission increased with increasing temperature and absolute humidity. An increase in built up area, a proxy for urbanization, was discovered to be another predictor of increasing dengue incidence.

Various biochemical markers have been measured to identify the severe form of dengue infection, like AST, ALT, platelet count, PCV, and electrolytes, especially calcium levels.[6] Calcium plays a key role in platelet aggregation, immune response in dengue infection. Known cardiovascular manifestations of hypocalcemia include hypotension, reduced myocardial function, electrocardiogram (ECG) abnormalities, and heart failure. Therefore, alterations in calcium homeostasis may play a role in the pathogenesis of dengue shock also. Serum calcium is known to be important in cardiac and circulatory function. The administration of intravenous calcium has been a routine practice in resuscitation protocols for traumatic, hemorrhagic and cardiogenic shock, a practice supported by the presence of hypocalcemia and the observed beneficial effects of calcium therapy in these conditions.[7] Uddin et al. reported that the mean total calcium levels were significantly lower in patients with DHF than in patients with uncomplicated dengue fever (DF). However, free calcium is a more useful index than total calcium and provides a better indication of calcium status.[8]

There is a scarcity of literature documenting serum calcium levels in dengue infection. These few studies have shown that hypocalcemia occurs in a significant number of cases with dengue and some studies correlated serum calcium levels with the severity of dengue. Numerous studies have clearly demonstrated that the measurement of ionized (free) calcium is the test of choice in nearly all diagnostic and treatment situations.[9,10]

Therefore we aimed to study the association between serum ionized calcium level and severity of dengue fever.

MATERIALS AND METHODS

After obtaining approval from Institutional Ethics Committee of T.S. Misra Medical College and Hospital, this hospital-based observational cross-sectional study was conducted in the department of general medicine and department of biochemistry, in T.S. Misra medical college and hospital, Lucknow, Uttar Pradesh, India, over a period of 18 months. All the confirmed 100 dengue patients coming in the OPD/IPD of department of general medicine in the hospital and fulfilling the inclusion criteria during the duration of the study, were enrolled for the study.

Inclusion Criteria

1. All patients with serologically confirmed dengue fever (dengue NS1/ IgM ELISA positive) in the age group 18-60 years.
2. Those patients who gave written informed consent for the study.

Exclusion Criteria

1. Patients on oral supplemental calcium or vitamin D intake.
2. Patients on the drugs known to alter serum calcium levels e.g. rifampicin, bisphosphonates, phenobarbitone, phenytoin, steroids, chloroquine, calcitonin, etc.
3. Patients below 18 years and above 60 years.
4. Patients with co-morbidities known to alter serum calcium levels like chronic liver disease, chronic kidney disease.
5. Pregnant patients.
6. Those who did not give consent.

Methodology

After obtaining written informed consent, a structured proforma was used to record demographic data, clinical history, examination findings, and laboratory results. Patients were classified into three groups—dengue without warning signs, dengue with warning signs, and severe dengue—according to WHO 2009 criteria. Blood samples were collected within 24 hours of diagnosis to measure serum ionized calcium using a calibrated automated blood gas analyzer. Additional tests, including complete blood count, liver and renal function tests, were performed to aid classification and exclude comorbidities.

Laboratory Methodology

Serum ionized calcium was measured using an ion-selective electrode method on a calibrated blood gas analyzer (Radiometer ABL800 Basic). Samples were collected in heparinized tubes and processed within 30 minutes to ensure accuracy. Standard operating procedures and regular quality control were followed. Additional biochemical and hematological tests were performed using automated analyzers to support dengue severity classification.

Validity and Reliability

Internal validity was ensured by using WHO 2009 criteria and validated laboratory methods. External validity was supported by enrolling a representative sample of adult dengue patients from a tertiary care hospital. Reliability was maintained through concurrent data entry with 10% cross-checked. A pilot study validated tools and protocols, and inter-rater reliability showed excellent agreement (Cohen's kappa = 0.85).

Quality Assurance

Quality control included daily calibration of equipment, standardized training of data collectors, and regular data audits. Ten percent of proforma entries were independently verified, with discrepancies resolved by consensus. Data were double-entered to reduce errors, and Good Clinical Practice guidelines were followed to ensure data quality.

Statistical Analysis

Data were entered into a Microsoft Excel spreadsheet and analyzed using SPSS version 29.0. Descriptive statistics, including means, standard deviations, frequencies, and percentages, were used to summarize demographic and clinical characteristics.

The Chi-square test was applied to assess associations between categorical variables. A p-value <0.05 was considered statistically significant.

RESULTS

The majority were young adults, with 44% belonging to the 18–30 years age group, followed by 32% in the 31–40 years range. Middle-aged individuals (41–50 years) accounted for 14%, while older adults (50–60 years) comprised only 10% of cases. The mean age of presentation was 35.16 ± 12.2 years. Of the total cases, 68.0% patients were male while, 32.0% patients were female. The majority (68%) had no associated comorbidities, indicating that most cases occurred in otherwise healthy individuals. Among those with comorbid conditions, diabetes mellitus was the most frequent (18%), followed by hypertension (12.0%), and thyroid dysfunction (8.0%). Also, 6.0% of the cases were smokers and 9.0% were alcoholics. [Table 1]

Out of total 100 patients, 57 patients (57.0%) had fever duration 4-6 days, followed by 32 patients (32.0%) who had fever for 3 days or less. Only 11 patients (11.0%) reported fever persisting beyond 6 days. The mean duration of fever in the study population was 4.9 ± 2.6 days. [Table 2]

Among 100 confirmed dengue patients, the mean hemoglobin level was 12.72 ± 1.21 g/dL (range: 8.90–14.50 g/dL). The mean packed cell volume (PCV) was 42.80 ± 3.12% (range: 38.0–55.0%). The total leukocyte count showed a mean of 6018.45 ± 2675.13 cells/µL (range: 1306.0–12400.0). Platelet count was markedly reduced with a mean of 82154.0 ± 49865.5 per µL (range: 9000–189000). The mean serum albumin level was 3.89 ± 0.62 mg/dL (range: 2.80–5.20). Finally, the mean total calcium level was 3.94 ± 0.49 mg/dL (range: 2.88–5.7). [Table 3]

Hypocalcemia was a prominent finding, with 63% showing ionic calcium levels below 4.5 mg/dL (<1.12 mmol/L). A further 31% had values within the intermediate range of 4.5–5.6 mg/dL (1.12–1.40 mmol/L), while only 6% demonstrated levels ≥5.6 mg/dL (>1.40 mmol/L), which are closer to or above the normal physiological range. 1mg/dL calcium = 0.2495 mmol/L. [Table 4]

Patients classified as having Dengue Fever without warning signs exhibited the highest mean ionized calcium level of 4.63 ± 0.24 mg/dL, followed by those with Dengue Fever with warning signs, who had a mean level of 4.28 ± 0.33 mg/dL. Patients with Severe Dengue showed the lowest mean ionized calcium level of 3.76 ± 0.18 mg/dL. A statistically significant association was observed between serum ionized calcium levels and the severity of dengue infection (p-value < 0.001). [Table 5]

Table 1: Distribution of the studied cases based on their age, gender and comorbidty

Age in years	No. of cases (n=100)	Percentage
18-30	44	44.0
31-40	32	32.0
41-50	14	14.0
50-60	10	10.0
Mean age in years	35.16±12.2 years.	
Gender		
Male	68	68.0
Female	32	32.0
Comorbidities		
None	68	68.0
Diabetes Mellitus	18	18.0
Hypertension	12	12.0
Thyroid dysfunction	8	8.0
Cardiovascular disease	5	5.0

Table 2: Distribution of the studied cases based on duration of fever

Duration of fever in days	No. of cases (n=100)	Percentage
≤3	32	32.0
4-6	57	57.0
>6	11	11.0
Mean Duration of Fever	4.9±2.6 days	

Table 3: Biochemical parameters

Parameters	Mean±SD (min-max)
Hemoglobin g/dL	12.72±1.21 (8.90-14.50)
Packed Cell Volume (PCV)	42.80±3.12 (38.0-55.0)
Total Leucocyte Count (TLC)	6018.45±2675.13 (1306.0-12400.0)
Platelets	82154.0±49865.5 (9000-189000)
Albumin mg/dL	3.89±0.62 (2.80-5.20)
Calcium	3.94±0.49 (2.8-5.7)
SGPT (U/L)	60.8±27.1 (30-120)
SGOT (U/L)	74.7±31.8 (40-150)
Serum Creatinine (mg/dL)	1.2 ± 0.3 (0.6-1.8)

Table 4: Distribution of cases according to Ionic Calcium

Ionic calcium (mg/dL)	Ionic Calcium (mmol/L)	No. of cases (n=100)	Percentage
<4.5 (Hypocalcaemia)	<1.12	63	63.0
4.5 to 5.6 (Normal)	1.12 to 1.40	31	31.0
≥5.6 (Hypercalcaemia)	>1.40	6	6.0

Table 5: The association between serum ionized calcium levels and the severity of dengue infection

Severity of dengue	Serum Ionized Calcium (mg/dl)	Serum Ionized Calcium (mmol/L)	p-value
Dengue Fever without warning signs	4.63±0.24	1.16 ± 0.06	**<0.001**
Dengue Fever with warning signs	4.28±0.33	1.07 ± 0.08	
Severe Dengue fever	3.76±0.18	0.94 ± 0.04	

DISCUSSION

Dengue fever remains a major public health challenge in tropical and subtropical regions, with India bearing a significant burden of morbidity and mortality. Identifying early prognostic markers is crucial for timely intervention and improved outcomes. Among the biochemical parameters studied, serum ionized calcium levels have gained attention as a potential indicator of disease severity. Thus, analyzing the relationship between serum-free calcium and its association with severe dengue infection may prove helpful in improving treatment outcomes.[11]

In the present study, the majority were young adults, with 44% belonging to the 18–30 years age group, followed by 32% in the 31–40 years range. Our findings were comparable to the findings of Suresh SR et al,[12] who reported that the majority of the patients were males (n= 68, 68%) and females (n= 32, 32%). Most of the cases were in the age range from 20 to 29 years (37.0%) followed by 30 to 39 years (23.0%) and 40 to 49 years (17.0%). According to Mahajan A et al,[13] the mean age of the study participants is 28.7 years (range 6-56 years). The minimum age is 6 years and the maximum age is 56 years. Majority, 25 (50%) of the study subjects were in the age group of 21-30 years. Majority of the individuals in the study were males (78%).

In the present study, 57 patients (57.0%) had fever duration 4-6 days, followed by 32 patients (32.0%) who had fever for 3 days or less. Only 11 patients (11.0%) reported fever persisting beyond 6 days. The mean duration of fever in the study population was 4.9 ± 2.6 days. Our findings were consistent with the findings of Suresh SR et al,[12] who reported that the average duration of fever was 4.6 days. 35 (35%) patients had mucosal bleeding manifestations (8.0% had Haematuria, 9.0% had melena, 11.0% had oral bleed and 7.0% hade petechiae). Also, Kesavan S et al,[14] reported that 7(41.17%) cases presented with various bleeding manifestations, rest 4(23.52%) cases manifested with both plasma leakage and profound shock.

In the present study, among 100 confirmed dengue patients classified according to the WHO 2009 Dengue Guidelines, the largest proportion of 42 patients (42.0%) were categorised as having Dengue Fever with warning signs, followed by 36 patients (36.0%) who had Dengue Fever without warning signs. Severe Dengue was observed in 22 patients (22.0%). Suresh SR et al,[12] reported that 37 (37%), 54 (54%) and 9 (9%) patients were classified as Dengue Fever (DF), Dengue Fever with Warning Signs (DF + WS) and Severe Dengue (SD), respectively. Pramiladevi R et al,[15] had 35% without warning signs, 17.1% with warning signs and 47.9% with severe dengue.

In the present study, Hypocalcemia was a prominent finding, with 63% showing ionic calcium levels below 4.5 mg/dL (<1.12 mmol/L). Our findings were similar to the findings of Suresh SR et al,[12] who reported that the mean serum calcium in the study was 3.92 ± 0.50 mg/dL, which is low. A study conducted in Mexico by Sanchez-Valdez E et al,[16] on five patients with dengue infection demonstrated that oral calcium carbonate and vitamin D3 supplementation significantly increased the number of platelets in patients with dengue infection when compared with a control group. Uddin KN et al,[8] 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. Saini CK et al,[17] results demonstrate that the serum free calcium levels significantly correlated with the severity of dengue. The mean serum free calcium was significantly lower in patients with DHF than in those with uncomplicated DF, and the prevalence of hypocalcemia was higher in patients with DHF than in patients with DF.

In the present study, patients with hypocalcaemia had a significantly higher mean haematocrit of 48.8 ± 3.9% compared to 37.7 ± 2.8% in patients with normal calcium levels. Similarly, platelet count was markedly lower in patients with hypocalcaemia, with a mean of 49,000.0 ± 21,000.5 per µL, compared to 105,000.0 ± 15,000.2 per µL in those with normal calcium levels. A statistically significant difference was observed in key blood parameters between those with hypocalcaemia (ionized calcium <4.5 mg/dL, n=63) and those with normal ionized calcium levels (≥4.5 mg/dL, n=37) (p-value <0.001 for both parameters). Our findings were comparable to the findings of Mahajan A et al,[13] who reported that an association was also found between free calcium and individual parameters like platelet count, ALT and

haematocrit. Deshwal R et al,[18] observed that patients with severe dengue had significantly lower corrected serum calcium levels (7.8 ± 0.6 mg/dL) compared to non-severe cases (8.6 ± 0.5 mg/dL). They also noted that hypocalcemia correlated with higher hematocrit and lower platelet counts, supporting its role as an early prognostic marker. Indraja S et al,[19] in a prospective observational study of 120 patients, reported mean hematocrit values of 39.2 ± 4.1% and platelet counts of 92,000 ± 25,000/µL in severe dengue cases, compared to 28.5 ± 3.2% hematocrit and 158,000 ± 18,000/µL platelets in non-severe cases. Their findings closely mirror the present study, reinforcing the predictive value of these parameters.

Serum ionized calcium may serve as a useful, low-cost biochemical marker for identifying severe dengue and guiding management. Further research is needed to understand its trends and clinical significance, including the role of hypocalcaemia and potential benefits of calcium supplementation.

Limitations

Although the findings were statistically significant, the sample size (n=100) may not adequately represent variability across different age groups, comorbid conditions, or dengue serotypes. Additionally, as this was not a follow-up study, it does not allow for assessment of disease progression or prediction of patient outcomes.

CONCLUSION

The study demonstrates a significant association between hypocalcemia and dengue severity, with lower ionized calcium levels linked to higher hematocrit and lower platelet counts. This suggests a role of calcium imbalance in the pathophysiology of severe dengue. Clinically, monitoring ionized calcium may help identify high-risk patients, though its therapeutic role requires further research. Overall, serum ionized calcium correlates with dengue severity and may serve as a prognostic marker, but larger studies are needed for confirmation.

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