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Prevalence of Hypocalcemia and Its Potential Value as a Biochemical Marker in Patients with Severe Dengue Infection

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Abstract

Background: Dengue infection is a major public health problem in tropical and subtropical countries including Sri Lanka, leading to significant morbidity and mortality. In severe dengue infection, plasma leakage is observed leading to numerous biochemical derangements including hypocalcemia. We studied the prevalence of hypocalcemia in a population of patients with severe dengue infection.

Methods: A prospective follow up study was conducted in a tertiary care centre in Sri Lanka throughout a one year period. World health organization 2009 criteria were used to diagnose the patients with severe dengue infection. All the patients with severe dengue infection were analyzed with serum ionized calcium during the first 24 hours of onset of the severe dengue clinical criteria.

Results: From the total population of 61 with severe dengue infection, 42(68.8%) were males and 19(31.2%) were females. Mean age of the population was 28.8 years. Among the 61 patients 52(85%) showed hypocalcemia during the first 24 hours of onset of severe dengue infection. Mean ionized calcium level of the population was 0.96 mmol/L, range being 0.53-1.48 mmol/L.

Conclusion: Serum ionized calcium level was significantly reduced in majority of patients with severe dengue infection within the first 24 hours of the onset of severe dengue clinical criteria. Value of serum ionized calcium as a biochemical marker to detect severe dengue infection early should be further explored with large scale studies.

Keywords: Dengue; Hypocalcemia; Sri Lanka; Biochemical marker; Severe dengue

Introduction

Dengue epidemic is one of the most important public health problems in the tropical and subtropical areas of the world [1,2], and it has become a major health issue contributing to significant morbidity and mortality in Sri Lanka [3]. Dengue infection is a systemic and dynamic disease. It has a wide clinical spectrum that includes both severe and non-severe clinical manifestations. After the incubation period, the illness begins abruptly and is followed by the three phases; febrile, critical and recovery. However, during the course of the disease, some patients develop severe manifestations called "severe dengue" which carries a high morbidity and mortality than non-severe dengue cases and warrants intense monitoring and management. According to WHO 2009 classification, severe dengue infection (SDI) is defined by one or more of the following: (i) plasma leakage that may lead to shock (dengue shock) and/or fluid accumulation, with or without respiratory distress, and/or (ii) severe bleeding, and/or (iii) severe organ impairment, of which most occur during the critical phase [1].

In a patient with severe dengue infection numerous serum biochemical parameter changes occur with the onset of plasma leakage, these derangements are not apparent in non-severe dengue patients [4]. Analyzing the correlation between these biochemical parameters and their association with SDI may justify them to be utilized as biochemical markers to differentiate SDI from non-severe cases. Hypocalcemia is known to be associated along with plasma leakage during the critical phase of SDI, but limited data is available about the prevalence and other relevant parameters of hypocalcemia in SDI [1]. However serum calcium levels were studied in abundance with unselected critically ill patients irrespective of the etiology which most of them are patients with sepsis and there is ample evidence that hypocalcemia is a common finding in such unselected critically ill patients especially in intensive care setting [5-7]. Slomp et al. showed that in critically ill patients, albumin adjusted calcium is not a suitable measurement, instead serum ionized calcium is a better indicator in the said patient groups in order to accurately detect hypocalcemia [8]. It is also demonstrated that hypocalcemia is correlated with the disease severity in unselected critically ill patients and place for calcium replacement in such situation is discussed though concrete evidence is lacking [5,7]. In this prospective study serum ionized calcium was studied in a population of patients with SDI admitted to a tertiary care medical unit in Sri Lanka.

Methods

A prospective follow up study was conducted in a general medical unit in Colombo north teaching hospital, Ragama which is a leading tertiary care hospital in Sri Lanka. Study was conducted for one year period from July 2013 to June 2014. According to WHO 209 criteria [1], all the patients admitted to the unit fulfilling the criteria for SDI during the above period were recruited. Prior informed written consent was obtained from the eligible patients. Those who didn't give consent

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were excluded. Ethical approval was obtained from the ethics review committee of the faculty of medicine, University of Kelaniya. A pre-tested interviewer administered questionnaire was used as the data collecting instrument. Patient's clinical, laboratory and imaging data was obtained for the study and kept anonymously and confidentially. None of them were on any form of calcium supplements prior to sample collection. Venepucture was done for serum calcium using standard procedure without applying a tourniquet. Serum ionized calcium levels were measured in patients within the first 24 hours of the critical phase of SDI. Serum ionized calcium was measured instead of serum total calcium [8]. SIEMENS Dimension RxL chemical analyzer was used to measure serum ionized calcium in all recruited patients.

Results

A total of 61 patients with SDI were analyzed. Forty two (68.8%) patients were males and 19 (31.2%) patients were females. Initially dengue infection was diagnosed and confirmed by NS1 antigen detection or Dengue IgM antibody detection. All patients were above 12 years, age range being 12 - 67, while mean age of the population was 28.8 years. All patients were subsequently recovered and no deaths were reported among the study population. Majority (n=59, 96.7%) of patients were without a previous history of dengue infections, while only 2 patients had a previous documented history of dengue infection. Serum ionized calcium level was measured during the first 24 hours since the onset of the SDI category according to WHO 2009 criteria.

Among the 61 patients, 52 (85%) showed hypocalcemia i.e. serum ionized calcium level was below 1.11 mmol/L considered as hypocalcemia. Mean calcium level of the population was 0.96 mmol/L, range being 0.53-1.48 mmol/L.

Discussion

Above results revealed that hypocalcemia is commonly associated with SDI. Among 61 patients with severe dengue, 52 (85%) showed hypocalcemia during the first 24 hours of the onset of the critical phase of SDI (Table 1). Mean calcium level of the above study population was 0.96 mmol/L significantly below the cut off mark for hypocalcemia 1.11 mmol/L. These findings were consistent with the association of hypocalcemia in unselected critically ill patients other than severe dengue although the mechanisms and clinical sequel of hypocalcemia may differ from other non-dengue patients with critical illness. Though theoretically postulated scientific evidence are limited in current literature with regard to prevalence of hypocalcemia among dengue patients, thus its value as a biochemical marker. Studies done among unselected patients with critical illness have also shown that ionized hypocalcemia is associated with increased mortality hence its value as a prognostic marker [5,7]. Malavige et al. studied serum Interleukin-10 (IL-10) as a marker of SDI but concluded as unsuitable to be used as a robust biomarker because of its poor discriminatory value between SDI and non-severe dengue patients [9]. However Uddin et al. 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 [4]. Another review endorsed the relationship between hypocalcemia and SDI, however monitoring serum calcium or calcium supplementation is not recommended in the current dengue management guidelines [1,10]. Considering above facts it is apparent that serum ionized calcium could be a potential biochemical marker in order to differentiate SDI from other dengue patients and plan out appropriate management in the clinical setting. We suggest further research to evaluate this association

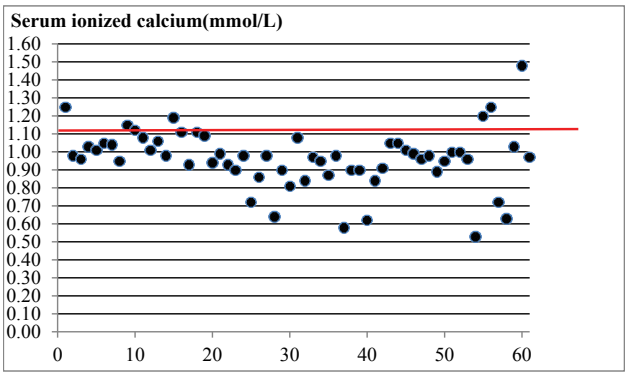

Figure 1: Among 61 patients with severe dengue, 52(85 %) showed hypocalcemia during the first 24 hours of the onset of the critical phase of SDI.

more extensively among dengue patients in order to determine the sensitivity and other relevant parameters. Research involving serial monitoring of serum calcium in diagnosed dengue infection will also reveal important information regarding the pattern and the trend of serum calcium in those patients. This will be of greater importance considering the fact that the relatively lower cost of the serum calcium test and less operator or interpreter dependant than other imaging modalities used to diagnose severe dengue cases such as ultrasound scan [1]. It will also be important to study the clinical significance of hypocalcemia in SDI and value of calcium supplementation in such patients with severe hypocalcemia.

Conclusion

Our study illustrates that hypocalcemia is a common biochemical derangement in SDI, when measured within first 24 hours of the onset of the critical phase of SDI in majority of patients. This infers serum hypocalcemia as a potential biochemical marker to detect severe dengue infection early. Development of such low cost, less operator dependant and readily available markers may greatly improve the clinical decision making and clinical outcome of SDI and its complications especially in resource poor settings. We call for further research to evaluate the above association and determine its clinical relevance in large scale studies and potential value of calcium supplement in SDI patients with hypocalcemia.

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