



ORIGINAL RESEARCH PAPER

General Medicine

A STUDY ON HYPOCALCEMIA IN PATIENTS WITH ACUTE MALARIA

KEY WORDS: Malaria, Hypocalcemia, Vivax Malaria, Falciparum

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ABSTRACT

AIMS AND OBJECTIVES

1. To assess the presence and severity of hypocalcemia in different types of malaria.

METHODS

A total of 200 subjects who attended Out Patient Department and who got admitted in Yenepoya Medical College Hospital, Of these 200 subjects, 100 were cases and 100 were controls.

MATERIALS AND METHODS

Patients were selected according to the inclusion criteria. After selecting the patients, a detailed history was taken which includes age, presenting complaints, history of other comorbid conditions. A thorough physical examination and systemic examination was done for all patients. The patients were admitted and was subjected to treatment. Follow up of patients were done during the hospital stay regarding the development of complications. Informed consent was taken and the necessary blood investigations was carried out. Measurement of serum calcium levels, collected without tourniquet under aseptic precautions in container.

CONCLUSION

This study was done to find serum calcium levels in different types of malaria and to compare with non malarial subject and to determine whether there is presence of hypocalcemia according to severity of malaria
Total of 200 patients who comes to the op or got admitted in yenepoya medical college hospital were studied during the period of January 2015 to January 2016. 100 patients were case subjects and 100 patients were control.
Complete history and physical examination were done followed by laboratory investigation to find out presence of malaria and to determine serum calcium and corrected calcium levels in all patients.
Majority of patients are between age group of 20 to 30 and majority are males.
The serum calcium levels and corrected calcium levels are significantly lower in malarial subject when comparing to control group. Among the types of malaria, lower values of calcium were observed in complicated malaria
Hence result of our study are in close agreement that with other similar studies showing that hypocalcemia is prevalent in patients with malaria and severity of hypocalcemia is related with severity of malaria.

INTRODUCTION

Malaria has been noted for more than 4,000 years. The term malaria was derived from the Italian word mal'aria which means "bad air". The classical malaria attack lasts for about 6-10 hours. It comprises of following events: Cold stage (chills and rigors), Hot stage (fever, headaches, vomiting; seizures in children), Sweating stage (sweating, returns to normal body temperature, tiredness). Typically the attacks occur every second day with the "tertian" parasites such as *P. falciparum*, *P. vivax*, and *P. Ovale* and every third day with the plasmodium malariae which is a "quartan" parasite.

Most of the patient presents with a combination of the following symptoms: Fever with chills and rigors, Increased Sweating, Headache, Nausea and vomiting, Multiple site pain, and Malaise. Signs of malaria include: Fever, Tachypnea, Icterus, Splenomegaly, Hepatomegaly

INCIDENCE OF MALARIA IN KARNATAKA STATE AND DAKSHINA KANNADA DISTRICT

In 1994 total cases of malaria in Karnataka state was 266682 and among that 4744 people of dakshina Kannada district was affected. In 2000 total number of malaria cases in Karnataka was 107999 and among those 2653 cases was from Dakshina Kannada. In 2014 total cases of malaria was declined to 12335 in Karnataka, but incidence of malaria cases was more in Dakshina Kannada 8240. It may be due to sudden spurt in industrialization and constructional activities²¹.

CALCIUM

The Ca ions play an important role in maintaining some important body functions. They are controls nerve excitability. This effect is mainly seen on the peripheral neuromuscular mechanism. Fibrillary twitching of a muscle can be produced by perfusing that muscle with Ca free fluid. It produces hyper irritability of automatic ganglia. Maintains the integrity of the skeletal muscles. An increase in the ionized Ca results in an increase in muscle contractility and vice versa. Maintains the tone and contractility of

heart. Ca acts as an antidote to the depressant action of potassium on the heart.

It is necessary for the clotting of blood. Ca decreases cellular permeability. Therefore it is used in allergic conditions to reduce exudation which produces wheals and rushes. Ca serves as a constituent of the intercellular cement.

Ca plays an important role in the formation of certain tissue and bones. Normally 25 – 35% is excreted in the urine and the remaining in the stools

HYPOCALCEMIA IN MALARIA

Parasite metabolism

Calcium plays a very important role in normal development of various stages of malarial parasite. Especially in asexual cycle.

All three forms of calcium- total, free and exchangeable calcium is found to be higher in RBCs infected with malarial parasites. It increases with the maturation of parasite up to trophozoite stage and declines after that.

Ca²⁺ is exclusively located in the parasite compartment in the infected erythrocytes and changes but little in the cytosol of host cell.

It is said that plasmodium falciparum alters the permeability of RBC membrane to calcium ions and therefore it causes 30 fold increase in calcium intake¹³. Irreversible morphological and functional abnormalities of infected RBCs are caused by increased intracellular calcium and decreased efflux of calcium from infected RBCs¹³. Increased calcium levels affect the potassium loss in infected RBCs which increases water loss, a pre hemolytic effect.

Concentration of free calcium in the intact parasite is maintained at a predetermined level, regardless of the free calcium in the surrounding milieu, probably by means of calcium-pump ATPase.

Hypocalcaemia is more prevalent in falciparum and complicated malaria. Low serum concentrations of calcium, phosphate, glucose and sodium bicarbonate can be seen in severe malaria, with increase in – lactate, blood urea nitrogen, creatinine, urate, muscle and liver enzymes, conjugated and unconjugated bilirubin^{6,7}.

Mild hypocalcaemia is commonly seen in severely ill, especially in patients who were given blood and glucose infusion in malaria.

Various mechanism associated with hypocalcaemia in malaria are Garcia GR et al¹⁹ found that Plasmodium uses Ca⁺⁺ based signaling pathway, this results in reduced calcium status, especially intracellular calcium but not usually millimolar concentration of Ca⁺⁺ found in body fluids. This disturbed the environment of the host cell cytoplasm. But how the protozoa achieved the calcium homeostasis – was unanswered Moises wasserman et al²⁷, observed Increase in calcium dependent Transglutaminase activity is found as a cause of decreased level of calcium. This decrease is found simultaneous with maturation of the parasite. The effect was found maximum when the trophozoites were 48 hrs old and at that time most of the calcium was shown to be located in the parasite.

Petithory-JC et al⁸, in his study of severe malaria contracted after laboratory contamination, noticed a severe hypocalcemia of 6.7mg/dl. They found further that hypocalcemia was connected with hypoalbuminemia, in ten other patients who was severely infected with plasmodium falciparum. But they could not establish the relation between hypocalcemia and hypoalbuminemia. They did not mention the clinical and therapeutic indication of hypocalcemia in their study.

Davis-TM et al⁷, 1991, observed 172 Thai adults infected with acute falciparum malaria with 10 severely ill patients and found 35.5% among them had mild asymptomatic hypocalcemia (1.79-2.11 mmol/l = 7.28-8.63 mg/dl) with no difference between uncomplicated and complicated malaria. Six prospectively studied patients showed hypocalcemia during treatment, with inappropriately low serum intact PTH concentrations, but increased in 3 patients to high levels on the fifth day. Plasma phosphate concentration was low in 43% of patients and high in 8.7% on the day of admission, severe depletion was seen in 14 subjects of whom 11 patients were severely infected. This study showed that mild hypocalcemia is common in malaria regardless of the severity, with depressed PTH response as a contributing factor.

Davis TM et al⁹, 1991 in another study investigated serum ionized calcium and intracellular phosphates in 18 subjects, 10 infected with falciparum malaria and 8 with vivax malaria, with 10 healthy subjects (controls) according to the information from previous studies, that the hypocalcemia is a common metabolic abnormality in acute falciparum malaria and malaria associated with hypocalcemia is mild and asymptomatic with equal frequency in uncomplicated and severe cases, and a relationship between low serum phosphate concentration and disease severity with marked hypophosphatemia occurring 3-4 times more often in patients with severe P.falciparum infection than in uncomplicated cases. they found that patients with plasmodium falciparum malaria had lower serum ionized calcium and parathormone concentrations and significantly much lower serum parathormone concentration than controls. And they concluded that almost 13/3 of patients with acute malaria will show hypocalcemia and equal propotion of patients will develop a similar degree of hypocalcemia during initial treatment.

They also found that decreased serum ionized calcium were similar in patients with both vivax and falciparum malaria at presentation or developed during treatment and usually mild and asymptomatic, except in severe anemic patients receiving citrated blood products where a falling serum ionized calcium could not stimulate a counter regulatory response. The inappropriate low parathormone response most clearly seen in the Falciparum group suggest that a "euparathyroid syndrome" is an important

contributory factor. Though most of patients with plasmodium falciparum malaria and half of the patients with plasmodium vivax malaria had hypophosphatemia, it was not in the range of causing neuro-encephalopathic symptoms, coagulopathy and haemolysis but it contributes to haemolysis.

Both the results supported and extend the findings of their previous studies which had examined mineral homeostasis on the infected human and malarial parasite, either alone or in concert with both cellular and extracellular phosphate concentrations remains to be elucidated from further studies.

CLINICAL IMPLICATIONS OF HYPOCALCEMIA IN MALARIA

Adovalande et al, in their study show that serum calcium is utilized by the parasite and this creates drug resistance in parasites. Sometimes there is Chloroquine resistance seen in Plasmodium Falciparum because of intracellular calcium utilization. This results in decreased calcium status in patients as well as drug resistance. When the channels of calcium were blocked with Verapamil & Fantofarone, then the Chloroquine resistance is totally reversed. Verapamil appeared 2 to 3 times more potent than Fantofarone in reversing the drug resistance.

Sheibel et al designed the calcium channel blockers as therapy in malaria due to the established fact, that calcium and calmodulin antagonists inhibit human malaria parasites.

But Kalra-A et al¹⁵ in her study in mice found the disturbance of the calcium regulating mechanisms by nifedipine treatment which resulted in subnormal phagocytic cell responses that lead to severe and rapidly fatal P.berghei infection in mice. These observation reveal the disadvantages of using CCB to reverse the chloroquine resistance in malaria.

Hypocalcemia in ARF may lead to myocardial dysfunction. In patients receiving drugs such as quinine and quinidine, which prolongs the QT interval, hypocalcemia could also predispose to arrhythmias and even death.

AIMS AND OBJECTIVES

To assess the presence and severity of hypocalcemia in different types of malaria.

METHODOLOGY

A total of 200 subjects who attended Out Patient Department and who got admitted in Yenepoya Medical College Hospital, Of these 200 subjects, 100 were cases and 100 were controls.

Materials and methods

Patients were selected according to the inclusion criteria. After selecting the patients, a detailed history was taken which includes age, presenting complaints, history of other comorbid conditions. A thorough physical examination and systemic examination was done for all patients. The patients were admitted and was subjected to treatment. Follow up of patients were done during the hospital stay regarding the development of complications. Informed consent was taken and the necessary blood investigations was carried out. Measurement of serum calcium levels, collected without tourniquet under aseptic precautions in container.

Following investigations were done in all patients: Serum calcium levels Malaria smear or MPFT CBC (Complete Blood Count)

ESR (Erythrocyte sedimentation Rate)
LFT(Liver Function Tests RFT(Renal Function Tests)
ECG (Electrocardiography)

statistical analysis

Prevalence of hypocalcaemia in different types of malaria were compared by ANOVA and inter group comparison was done by using 't' test

Ethics

The study was conducted after ethical clearance from the ethics

committee and university as per standard protocols and guidelines.

RESULTS

The study comprised of 200 subjects out of which 100 were malaria patients and 100 were healthy controls. All case study patients were diagnosed to have acute malaria. The control group consisted of non malarial healthy individual with acute self limiting illness aging between 18 to 60. serum calcium level and MPFT were done for all the patients and corrected calcium was calculated according to the serum albumin levels measured in the patients.

Out of 100 cases 79 were males and 21 were females. In the control group 78 were male and 22 were females. In our study majority of patients are construction workers by occupation.

Majority of patients(45.5%) studied in both case and control groups were between age group of 21-30 years of age. Even though malarial infection could occur at any age ,but there was preponderance among the younger subject and males. The control group were sex matched to case group. Majority of patients were found to have uncomplicated plasmodium vivax malaria(62%) followed by plasmodium falciparum(14%), mixed malaria(14%) and complicated malaria(10%).

The serum calcium level in uncomplicated vivax malaria group was of 8.35 mg/dl ± 0.52, in plasmodium falciparum were with a mean of 8.34mg/dl ± 0.55, mixed malaria were with a mean of 8.48 mg/dl ± 0.57, and were significantly lower in complicated malaria with a mean of 7.98 ± 0.75 (p value of 0.16). The serum calcium studied in overall case group were highly significant with a mean of 8.33mg/dl ± 0.56 when compared to serum calcium level of control group were with a mean value of 8.95 mg/dl ± 0.43 (p value of less than 0.01)

The serum albumin value in plasmodium vivax malaria group were with a mean value of 3.96 mg/dl ± 0.42 , in plasmodium falciparum with a mean of 3.95 mg/dl ± 0.35 , mixed malaria with a mean of 3.90 mg/dl ± 0.12 and lower in complicated malaria with a mean of 3.80 mg/dl ± 0.35 (p value of 0.595). There is no significant difference between serum albumin among case and control with a mean value of 3.93 mg/dl ± 0.37 and 3.93 mg/dl ± 0.33 respectively (p value of 0.47)

The corrected calcium levels in plasmodium vivax were with a mean value of 8.32 mg/dl ± 0.76, in plasmodium falciparum with a mean of 8.38 mg/dl ± 0.50, mixed malaria with a mean of 8.56 mg/dl ± 0.63 and significantly lower in complicated malaria with a mean of 8.15 mg/dl ± 0.86 (p value of 0.55) There is a significant difference in corrected calcium among case and control with a mean value of 8.34 mg/dl ± 0.72 and 8.99 mg/dl ± 0.48 respectively(p value of less than 0.01).

The lowest value of calcium were found in complicated case

Complications seen in our study are acute renal failure and MODS (In compli complicated malaria cases)

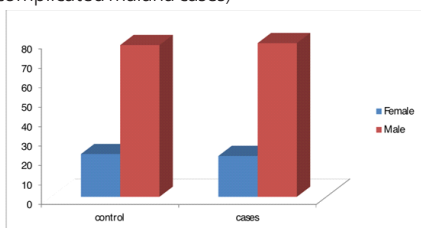


Figure 1 : Majority of patients are males in both case and control groups

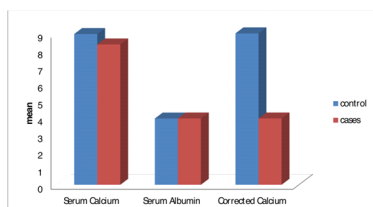


Figure No:3 Comparison of mean calcium level among case and control

Table 5 : showing comparison of Mean and standard deviation of calcium levels, serum albumin, corrected calcium among cases and controls

T-Test

Group Statistics

	Group	N	Mean	Std. Deviation	P VALUE
Serum Calcium	Control	100	8.95	.43	<0.01
	Cases	100	8.33	.56	
Serum Albumin	Control	100	3.93	.33	0.47
	Cases	100	3.93	.37	
Corrected Calcium	Control	100	8.99	.48	<0.01
	Cases	100	8.34	.71	

Calcium and corrected calcium were significantly lower in malarial group.

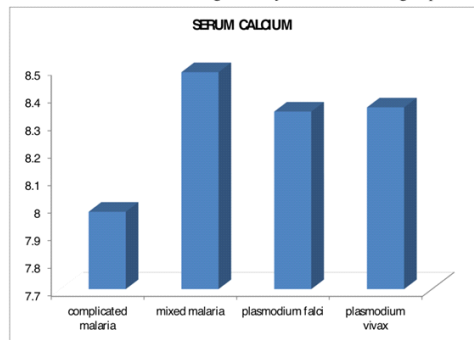


Figure 4 : Showing mean value of serum calcium in different types of malaria

DISCUSSION

In our study we observed that hypocalcemia is a complication of malaria. Prevalance of hypocalcemia is more in complicated malaria, followed by uncomplicated falciparum, vivax and mixed malaria infections. The cause of hypocalcemia could not be assessed from the study.

Several authors reported hypocalcemia in all types of malaria. Davis et al, in 1991 studied 172 adults with acute falciparum malaria and 10 critically ill patients. His team observed that 35.5 % patients had mild hypocalcemia(asymptomatic) and also observed that there is no significant difference in critically ill patients. In their study they also found low parathormone and phosphate levels in 43 % of cases. They concluded that hypocalcemia is common in malaria regardless of severity of disease. The cause for hypocalcemia may be decreased parathormone levels.

Davis et al, 1991 , in another study of 18 malaria patients observed hypocalcemia in 33.3 % of cases during acute presentation and another 33.3 % developed the same during the therapy. The lowest values were observed in falciparum malaria. They observed decreased phosphate level in falciparum malaria

Prabha et al in 1998 ,studied 60 patients and found hypocalcemia in 45% of patients. They also observed significantly lower calcium level in complicated malaria. They also found association between hypocalcemia and parasite load .the.Q- Tc prolongation also observed and reported cardiac death on quinine therapy in 3 patients with prolonged Q-Tc. 50

Hypocalcemia in malaria may be due to various mechanism explained in previous studies like

- 1) use of calcium based signaling pathway by plasmodium which causes disturbance of environment of the host cell cytoplasm.
- 2) PI falciparum infected red blood cells have increased permeability for calcium
- 3) Increased calcium dependent transglutaminase activity may be a cause of hypocalcemia
- 4) Utilization of serum calcium by parasites leads to drug resistance in parasites

- 5) Disturbed parathyroid hormone profile may also leads to hypocalcemia
- 6) Renal dysfunctioning in malaria causes more urinary excretion of calcium

Other features which may contribute to hypocalcemia are hypomagnesemia, hypoalbuminemia, parasite load etc

Hypocalcemia in malaria may leads to prolonged Q-Tc interval which can leads to hypotension, cardiac block especially after quinine therapy.

SUMMARY AND CONCLUSION

This study was done to find serum calcium levels in different types of malaria and to compare with non malarial subject and to determine whether there is presence of hypocalcemia according to severity of malaria Total of 200 patients who comes to the op or got admitted in yenepeya medical college hospital were studied during the period of January 2015 to January 2016. 100 patients were case subjects and 100 patients were control.

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