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STUDY OF LIVER FUNCTIONS TEST IN SEVERE FALCIPARUM MALARIA IN NORTHEASTERN REGION OF RAJASTHAN

Physiology

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ABSTRACT

Background: Severe falciparum malaria with liver function abnormalities is more vulnerable to the development of dreaded complications in Northeastern state of India. Objective: Therefore present study was designed to explore the liver Functions variables in severe falciparum malaria in Northeastern region of Rajasthan.

Methods: This observational study was performed at the R N T Medical College Udaipur, India. Total 60 malarial patients who tested positive for plasmodium falciparum were enrolled in present study. Severity of falciparum was diagnosed by clinical and laboratory biomarkers as given by working group of World Health Organization and subsequently all 60 patients were divided into severe malaria (Group-I) which comprised of 20 patients and simple falciparum malaria (Group-II) it include 40 patients. A comprehensive clinical history, socio-demographic information and liver function variables were examined. SPSS-16 software was used for statistical analysis.

Results: Males with falciparum malaria were significantly ($p<0.01$) higher as compared to females and significantly ($p<0.01$) higher numbers of patients died in severe malaria as compared to simple falciparum malaria. The liver function variables, Aspartate amino-Transferase (AST), Alanine amino-Transferase (ALT), serum total bilirubin and blood urea were significantly ($p<0.001$) higher in patients with severe malaria as compared to simple falciparum malaria while random blood glucose, serum albumin and prothrombin time were significantly ($p<0.001$) lower in patients with severe malaria.

Conclusion: It concluded that a high incidence of severe P. falciparum malaria was significantly associated with high mortality rate and declined lung functions.

KEYWORDS

Severe Falciparum Malaria, Uncomplicated malaria, Mortality, Liver function, Prothrombin Time.

Introduction:

Malaria is a main parasitic disease of mankind recognized to survive in India for many of years. In malice of extraordinary growth in medical science in latter half of the century, malaria still persists to be a foremost assassin of mankind particularly in developing countries. Malaria was almost eradicated from India in the early 1960s but the disease has reemerged as a major communal health problem. Malaria has returned in the 1990s with new features not witnessed during the pre-eradication days and malaria control has become a complex endeavor[1]. According to world malaria statement 2013 there were 207 million cases of malaria in 2012 consequential in 627000 deaths. Thirteen percent of these cases were accounted from South East Asia, 52% of which were reported from India. India contributed 1.04 million of malaria cases leading to 504 deaths [2]. Areas of Rajasthan, particularly the North eastern region have been endemic for malaria. The prevalence of malaria is rising in other areas and the malaria at one time a rural disease has diversified into different types like urban malaria. Most of the malarial deaths are due to Plasmodium falcipharum as of its severe and complicated clinical presentation. It presents in complicated forms such as cerebral malaria, acute renal failure, jaundice, anemia, hypoglycemia, haematuria, shock, disseminated intravascular coagulation (DIC), hyperpyrexia, non-cardiogenic pulmonary edema, adult respiratory distress syndrome (ARDS), adrenal insufficiency-like syndrome, hyper-parasitemia, black-water fever, cardiac arrhythmias, and gastrointestinal syndromes [3]. Jaundice is frequent in adults with malaria and there is other confirmation of liver dysfunction with raise in serum total bilirubin, serum transaminases, and prothrombin time and decrease serum albumin [4]. Jaundice in malaria is caused by hemolysis of red blood cells, inflammation in liver and cholestasis. Liver manifestation contributes to hypoglycemia, lactic acidosis and impaired drug metabolism. With the increasing incidence of Plasmodium falciparum infection therefore several cases of severe malarial are presenting with un-classical fever and jaundice pretentiousness diagnostic conundrum with acute viral hepatitis on one hand and therapeutic challenge on the other [5,6]. It is noticed that the patients of falciparum malaria with liver function abnormalities is more vulnerable to the development of dreaded complications. Hence, the present study was undertaken to liver function test in severe falciparum malaria in North-eastern region of Rajasthan.

Material and Methods:

This observational study was performed at the department of general Medicine; R N T Medical College and associated Maharana Bhupal hospital, Udaipur, India. All *falciparum* malarial patients, both sex, aged between 10-70 years, were selected from the patients admitted in Department of general Medicine, R N T Medical College, Udaipur. Total 60 *falciparum* malarial patients mean age 42.33±5.10, who tested positive for plasmodium *falciparum* (peripheral blood smear positive and rapid diagnostic antigen detection test positive) were included in the our study. Patients with history of alcoholics, malignancy pregnant women and liver disease were expelled from present study. After establishing the diagnosis of *falciparum* malaria, a comprehensive clinical history was taken in reference to the existence of fever, vomiting, pain abdomen, nausea, diarrhea, delirium, convulsion, unconsciousness, aphasia, headache any neurological manifestation , yellow urine, anorexia and jaundice. Moreover, an absolute clinical examination with particular emphasis on fever, jaundice, and presence of hepatomegaly and splenomegaly, postural hypotension and complete neurological assessment were done using appropriate tool and technique. Informed written consent was obtained from all the patients or relative (guardian) prior to start the study. The study protocol was approved by institutional ethics committee.

Severity of falciparum (Severe malaria) was diagnosed by clinical and laboratory biomarkers as given by working group of World Health Organization [7-8] and subsequently all 60 patients were divided into severe malaria (Group-I) which comprised of 20 patients and simple or uncomplicated falciparum malaria (Group-II) it include 40 patients.

Plasmodium falciparum malaria was diagnosed using a peripheral blood film examination and further conformed by commercially available rapid diagnostic malaria antigen test which detect *P. falciparum* histidine rich protein 2 (HRP2) or *plasmodium* specific lactate dehydrogenase (pLDH). (Combo Malaria Ag-pLDH/HRP2, PMC, Ltd Mumbai, India; was used for differential diagnosis of plasmodium species.)

Blood samples were achieved from all malarial patients by veni-puncture at the time of conscription and before the anti-malarial treatment. Samples were collected into 3.8% sodium citrate and clean

plain test tubes were analyzed for prothrombin time and biochemical parameters, respectively. After clot formation, all samples were instantly centrifuged (3000 rpm) for 8-10 minute; the sera were separated and frozen at 4.6º C until analysis. Prothrombin time was measured using commercial available diagnostic kit by tissue thromboplastin method.

Sera were used for measurement of biochemical variable, at room temperature by enzymatic process using marketable offered diagnostic kit on semi-automated biochemical analyzer (Transasia Erba Chem 5 plus). The liver function variables and the respectively methods applied are the followings: aspartate amino-transferase (AST) and alanine amino-transferase (ALT) - Henry method (Modified IFCC); random blood glucose-GOD/POD method; total serum bilirunin-Diazo method; serum alkaline phosphates (ALP): beckmam unicel method, Albumin: Bromocresol Green (BCG) method.

Statistical Analysis

The data were statistically analyzed and baseline characteristics of the malaria patients were expressed in percentages and mean ± SD. Chi-square test was used for the relationship of qualitative data and Independent Student "t" test was used to compare difference liver functions variables between severe and simple falciparum malaria groups. P< 0.05 was considered statistically significant. Statistical analysis was done using SPSS windows version 20.0 software (SPSS Inc., Chicago, Illinois).

Results:

This study was conducted on 60 P. *falciparum malaria* patients or cases in Department of general Medicine, R N T Medical College associated Maharana Bhupal hospital, Udaipur (India) and the following results were drawn from the present study. This study was performed on population over 10 year's age group. Total 60 blood smear positives patients of falciparum malaria were observed out of these 36 had males (60 %) and 24 (40 %) had females age ranging from 10 to 70 years.

Table no-1: Incidence of severe and simple falciparum malaria (As per WHO)

Type of Malaria	Total Cases			Survived			Died		
	Male	female	Total	Male	female	Total	Male	female	Total
Severe (n=20)	11 (55 %)	9 (45%)	20 (33.33 %)	6 (60%)	4 (40%)	10 (50%)	5 (50%)	5 (50%)	10 (50%)
Simple (n=40)	25 (62.5 %)	15 (37.5 %)	40 (66.66 %)	25 (62.5 %)	15 (37.5 %)	40 (100%)	0	0	0
χ^2 (Chi square) =5.35. df=1 , p=0.001 considered significant. The row and column association is statistically significant. (Severe malaria > Simple malaria P<0.01, In case severe malaria Male> female P<0.05, significant, died malaria cases significantly higher in severe malaria (P<0.05) as compared to simple malaria.									

Out of 60 patients, 20 (33.3%) patients were presented as severe malaria as defined by World health organization. Among these 11 (55%) had male and 9 (33.33%) had female. Amongst severe malaria 10 (50%) patients were survived and 10 (50%) were died. Moreover, 40 (66.66%) patients showed as simple falciparum malaria amongst these 25 (62.5 %) had male and 15 (37.5 %) had female amongst this group all has been survived and no death has been reported. As per chi-square test males with falciparum malaria were significantly (p<0.01) higher as compared to females and significantly (p<0.01) higher numbers of patients died in severe malaria as compared to simple falciparum malaria. It implies that severe falciparum malaria significantly associated with high mortality (Table-1).

Table: 2. Comparison of liver function variables between severe and simple falciparum malaria.

Liver function variables	Severe F. malaria (n=20) (Mean ±S D)	Simple F. malaria (n=40) (Mean ± SD)	p-Value
Age (ranging 10-70 years)	41.63±4.10	43.48±4.96	0.563
Aspartate amino-Transferase (AST) (IU/L)	95.54±10.65	42.86±5.45	0.001
Alanine amino-Transferase (ALT) (IU/L)	140.30±15.90	62.65±9.75	0.001
Blood glucose (RBS) (mg/dl)	55.42±5.66	70.89±4.78	0.001
Serum Total Bilirunin (mg/dl)	6.45±1.23	1.5±0.85	0.001
Serum alkaline phosphates (ALP) (IU/L)	75.69±16.45	68.24±15.65	0.092
Serum Albumin (gm/dl)	3.54±1.27	5.24±2.45	0.005
Prothrombin Time (PT in sec)	12.18± 2.84	14.86±2.36	0.003
Blood Urea (mg/dl)	47.53±5.96	32.68±4.69	0.001

The levels and comparison of mean of liver function variables between severe and simple falciparum malaria are shown in table-2. The liver function variables Aspartate amino-Transferase (AST), Alanine amino-Transferase (ALT), serum total bilirubin and blood urea were significantly (p<0.001) higher in patients with severe malaria as compared to simple falciparum malaria while random blood glucose, serum albumin and prothrombin time were significantly (p<0.001) lower in patients with severe malaria. Moreover, there were no significantly (p>0.05) difference observed in age and serum alkaline phosphates (ALP) between severe and simple malaria. It implies that severe falciparum malaria significantly associated with decline liver functions.

Discussion:

The incidence of *P. falciparum* in India is increasing. The entire population of India (99.5 %) is nowadays deemed to be under malaria risk (9). Although in majority of patients, malaria shows as a straightforward fever with punctual recovery, it may existence in severe form with systemic complications mainly renal and hepatic failure, leading to high morbidity and mortality. More recently, *Plasmodium falciparum* accounts for nearly 50% of reported malaria cases in India [2,10].

In our study 60 blood smear and rapid diagnostic test positive patients were assessment, among males with falciparum malaria were significantly (p<0.01) higher as compared to females and significantly (p<0.01) higher numbers of patients died in severe malaria as compared to simple falciparum malaria which is agreement with previous report [11]. The most important characteristic of severe malaria is intense parasite sequestration within cerebral blood vessels, cyto-adherence of parasitised red blood cells to endothelial cells [12] to non infected erythrocytes may help to pathogenesis of cerebral malaria by compromising the cerebral circulation [13].

In present study, liver function variables Aspartate amino-Transferase (AST), Alanine amino-Transferase (ALT), serum total bilirubin and blood urea were significantly (p<0.001) higher in patients with severe malaria as compared to simple falciparum malaria while random blood glucose, serum albumin and prothrombin time were significantly (p<0.001) lower in patients with severe malaria. This findings accordance with several earlier studies [14-18]. A case control study was done by Abro et al, [14] reported that hepatic dysfunction in *P. falciparum malaria* ranged from mild elevation of liver enzymes to acute hepatitis (ALT>10 times of normal level). It indicates severe illness with high frequency of complication and mortality rates. Another study noticed that a significant percentage of patients having falciparum malaria with jaundice fulfill the criteria for malarial hepatic dysfunction. It should be considered in patients presenting with acute febrile illness with jaundice so that specific treatment can be given [15]. In addition, Indian study was performed by Mishra et al,[16] reported that hepatomegaly and mild elevation of enzymes can be observed in a significant proportion of patients, involvement of liver leading to acute hepatitis or liver cell necrosis is a relatively uncommon complication in *P. falciparum malaria.* Similarly, Elbadawil NE et al, suggested that the mean level of most of the biochemical liver function test parameters, were below the normal reference ranges, and a highly significant difference was observed between pregnant women with malaria, and their controls, in the level of AST, ALT, total protein, albumin and globulin, but not in the level of total bilirubin, direct bilirubin and indirect Bilirubin [17]. Moreover, positive correlation of liver enzymes and bilirubin shows that liver function tests should be

performed along with early diagnosis of *Plasmodium falciparum malarial* infections in order to prevent complications and to reduce mortality [18]. Results of aforementioned several studies are harmony with present finding.

Limitation of present study is that laboratory indices of poor prognosis and clinical presentation of *falciparum malaria* were not measured in this study therefore further cohort or clinical studies with huge sample and longer duration are required to investigate cause of liver function manifestation in severe malaria and mortality rate.

Conclusion:

It concluded that a high incidence of severe malaria and mortality rate in *P. falciparum* and severe malaria had significantly associated with high mortality rate and declined lung functions.

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