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Prediction of Malaria Outcome and Its Complication Throught Estimation of Biochemical Marker of Serum Lactate

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Abstract

Introduction: Malaria is a widespread disease in the tropics, including India *Plasmodium vivax is the most prevalent species* and *Plasmodium falciparum is the most virulent one* worldwide. Lactate dehydrogenase (LDH) is an intracellular enzyme which can be elevated in malaria and can be used to know the outcome of severe malaria and its prognosis.

Materials And Method: Optimal test detecting the plasmodium lactate dehydrogenase (rapid diagnosis) was also used in all patients of confirmed cases of malaria, The kit used for estimation of plasma lactate levels was the Randox Kit manufactured by (Randox Laboratories Ltd, 55 Diamond Road, Crumlin, Co. Antrim, United Kingdom, BT29 4, QY). Lactate levels were estimated using biochemistry analyzer TRACE 30 v4.1. Hyperlactatemia was defined as serum lactate levels more than 2 mmol/l.

Results: Out of the 50 patients of malaria, 50% had P.vivax, 35% had P.falciparum, and 15% had mixed infection. Males were 67% of the patients and 33% of patients were females. Increase in level of serum lactate correlated with increase in bloodpressure of patients, decrease in platelets count, bilirubin level, serum creatinine.

Conclusion: Serum lactate levels can be independently used as an indicator of severity of complications and mortality.

Keywords: Malaria, Serum Lactate Dehydrogenase.

Introduction

Malaria is a widespread disease in the tropics, including India *Plasmodium vivax is the most prevalent species* and *Plasmodium falciparum is the most virulent one* worldwide.[1]

The clinical course of *Plasmodium falciparum* malaria may be punctuated by fatal complications. An important challenge for attending physicians in the management of *P. falciparum* malaria is to identify patients who are at high risk of complications and mortality and who may benefit from intensified care and treatment. Parasite count is usually considered the reference standard for this purpose. Although high parasitemia is, in general, more likely to be associated with significant morbidity and mortality than low parasitemia the relationship between the clinical severity of malaria and the density of malaria parasitemia is not straight forward. Since parasites are sequestered in the kidneys, brain, and other organs during

P. falciparum infections, the peripheral parasite count may not accurately reflect the total parasite load.It is well known from the literature that patients with severe *P. falciparum* malaria may present with low peripheral parasitemias.[2]

Lactate dehydrogenase (LDH) is an intracellular enzyme, which catalyses the readily reversible reaction involving the oxidation of lactate to pyruvate with nicotinamide adenine dinucleotide (NAD) serving as coenzyme1. LDH is an enzyme, which is classified as a true intracellular Enzyme2 because of its high degree of tissue specificity where overall tissue concentrations are some 500-fold greater than serum levels under normal circumstances3. LDH have five theoretically possible forms, which are found in human tissues e.g. liver, heart, erythrocytes, skeletal muscles and kidneys. So disease affecting these organs such as renal infarction myocardial infarction and haemolysis have been reported to be associated with significant elevations in total serum LDH activity. Such elevations have been widely applied as diagnostic indices for kidney, liver, heart and red blood cell dysfunction. Additionally, high serum LDH activity has also been reported in small cell carcinoma of the lung, ,nephroblastoma, neuroblastoma and metabolic neuroendocrine tumour8 measles and cervical lymphadenitis, Hodgkin's disease and non-Hodgkin's lymphoma, and in the follow-up of ovarian Dysgerminoma. Plasmodium falciparum malaria infection is a febrile illness accounting for 300-500 million clinical cases annually worldwide. The life cycle of this parasite in the human host includes the developmental cycle in red blood cells, and the cycle taking place in the liver cell parenchyma, includes a series of transformations in the host hepatocytes. Pathophysiological processes usually associated with acute P. falciparum malaria infections, i.e., the hepatic activity of the invading sporozoites leading to centrilobular liver damage and the destruction of the host red blood cells consequent to erythrocytic merogony. Being rich sources of LDH, the acute liver injury and red blood cell destruction will be followed by the release of LDH into the circulation. This finding has important implications because it highlights the potential of using serum LDH activity as an index in the monitoring of acute P. falciparum malaria infection, particularly when all other possible causes of increased serum LDH levels have been eliminated.[3]

Complicated malaria includes cerebral malaria, algid malaria, hematological abnormalities, metabolic acidosis, renal failure, hepatic dysfunction,pulmonary edema, hypoglycemia, and gram negative sepsis[4]The normal blood lactate concentration in unstressed patients is 0.4-1 mmol/l.[5] Hyperlactatemia is defined as a mild-to-moderate (2-5 mmol/L) persistent increase in blood lactate concentration without metabolic acidosis, whereas lactic acidosis is characterized by persistently increased blood lactate levels (usually >5 mmol/L) in association with metabolic acidosis.[6] Malaria can cause lactic acidosis by tissue hypoperfusion and hypoxia, occlusion of microcirculation by parasites, production of lactate by parasite, and decreased hepatic blood flow. Metabolic acidosis is a form of severe malaria according to the World Health Organization (WHO).

As there is high mortality due to malaria and a high prevalence of complicated malaria in India, there is an acute need to identify patients at risk of developing complications and to intensify care given to those patients, so that the mortality burden is reduced.

In the study, serum lactate levels in all patients of P. Vivax and P. falciparum malaria were correlated with various clinical and biochemical parameters and with severity and prognosis of malaria.

Aim and Objectives

Aim

To estimate serum lactate level in patients with plasmodium vivax, plasmodium falciparum, and mixed malarial infection and correlate it with biochemical parameters and with outcome of disease.

Objectives

1) To know whether serum lactate dehydrogenase can be use as predictor marker in severity of malarial.

2) To know the outcome of malaria by biochemical marker like serum lactate level.

Materials and Method

Place of study: Department of Pathology and Department of Medicine,AVBRH, JNMC, DMIMS (DU), Sawangi (Meghe),Wardha.

Study design : Cross-sectional, analytical, prospective, and observational study.

Study duration: 2 years (January 2017 to 2019)

Sample size: 50 patients

Method: A fifty patients older than 14 years old who were admitted to intensive care unit and general medicine wards with a diagnosis of malaria made by standard method of peripheral blood smear examination demonstrating the parasite, were selected for the study. Patients having a past history of systemic illnesses like hypertension, diabetes, chronic renal failure, tuberculosis, nephritic syndrome, acute or chronic viral hepatitis and chronic liver disease, and those taking medication that was likely to affect liver and renal function tests, were excluded from this study. Patients who fulfilled inclusion criteria were thoroughly interrogated with regards to presenting complaints like fever, chills, jaundice, oliguria, hematuria, swelling over body, breathlessness, bleeding tendencies, altered sensorium, convulsions etc. On admission, vital parameters like temperature, pulse rate, blood pressure, and respiratory rate were recorded. Signs such as pallor, icterus, edema, bleeding were noted. Systemic examination was done. Investigations including peripheral smears, complete blood counts, platelet count, urea and creatinine, bilirubin, liver enzymes, and blood sugar tests were done.

The diagnosis of malaria was made by the gold standard method of peripheral blood smear examination by demonstration of asexual form of plasmodium. The thin smear was prepared from a finger prick, methanol fixed, and stained with diluted Giemsa using buffered water at pH 7.2 seen under oil immersion, and a minimum of hundred fields were examined before declaring the slides negative. Optimal test detecting the plasmodium lactate dehydrogenase (rapid diagnosis) was also used in all patients. Parasite density index was calculated for all patients being included. A blood sample for plasma lactate level on admission was collected from a stasis free vein, without using a tourniquet. The sample was collected in a fluoride ethylene diamine tetra acetic acid (EDTA) bulb and was immediately sent for processing on an ice pack for estimation of plasma lactate levels.

Plasma was separated by centrifugation within 30 min. The kit used for estimation of plasma lactate levels was the Randox Kit manufactured by (Randox Laboratories Ltd, 55 Diamond Road, Crumlin, Co. Antrim, United Kingdom, BT29 4, QY). Lactate levels were estimated using biochemistry analyzer TRACE 30 v4.1. Hyperlactatemia was defined as serum lactate levels more than 2 mmol/l.

Inclusion Criteria

(1) Malaria positive patients by peripheral smear and paracheck.

Exclusion Criteria

(1) Patients who were having fever with or without rigors but were negative for malaria parasite by Peripheral smear and paracheck.

(2) Acquired Immune Deficiency Syndrome

(3) Liver Cirrhosis

(4) Hepatitis

(5) Alcoholism

(6) Kidney Disorders

(7) Patients on self medication with any antimalarial drugs prior to presentation.

(8) Pregnant Woman

(9) Malignancy.

Demographic details

Clinical Proforma: Age, Sex, MRD, ward, bed, clinical examination, clinical diagnosis were taken.

Investigations: Peripheral smear for malarial parasite, complete blood count, urea and creatinine, bilirubin, liver enzymes and blood sugar test, serum lactate dehydrogenase.

Observation and Results

Table 1- Association of systolic blood pressure in malaria patients with lactate level

Malarial species	Lactate level (mmol/lt)	Systolic B. P.(≤90 mm of Hg	Systolic B. P. (>90 mm of Hg)
P. vivax (P.V)	<2	1	4
	>2	6	13
P.falciparum (P.F)	<2	1	2
	>2	2	14
Mixed (P.V./P.F.)	<2	0	0
	>2	1	6
Total		11	39

Table 2- Association of platelet count of malaria patients with lactate level

Malarial species	Lactate level (mmol/lt)	Platelet count (<50000/μl)	Platelet count (50000-150000/μl)	Platelet count (>150000/μl)
P. vivax (P.V)	<2	2	2	1
	>2	17	3	0
P.falciparum (P.F)	<2	1	1	0
	>2	12	3	0
Mixed (P.V./P.F.)	<2	0	0	0
	>2	7	0	1
Total		39	9	2

Table 3- Association of serum bilirubin of malaria patients with lactate level

Malarial species	Lactate level (mmol/lt)	S.bilirubin (<1.2 mg/dl)	S. bilirubin (1.3-3.0 mg/dl)	S. bilirubin (>3 mg/dl)
P. vivax (P.V)	<2	4	1	0
	>2	8	9	3
P.falciparum (P.F)	<2	1	1	1
	>2	5	3	7
Mixed (P.V./P.F.)	<2	0	0	0
	>2	1	1	5
Total		19	15	16

Table 4- Association of serum creatinine of malaria patients with lactate level

Malarial species	Lactate level (mmol/lt)	S.creatinine (≤1.6 mg/dl)	S.creatinine (1.7-3 mg/dl)	S. creatinine (>3 mg/dl)
P. vivax (P.V)	<2	5	0	0
	>2	11	8	1
P.falciparum (P.F)	<2	2	0	0
	>2	6	5	5
Mixed (P.V./P.F.)	<2	0	0	0
	>2	2	2	3
Total		26	15	9

Out of the 50 patients of malaria, 50% had P.vivax, 35% had P.falciparum, and 15% had mixed infection. The majority, 33%, of patients were 21-30 years old. Males were 67% of the patients and 33% of patients were females.It was observed that higher the serum lactate levels, more was the duration of stay of the patient in hospital. In this study, 90% of patients survived and 10% of patients succumbed. Out of the 45 survivors, 21 patients (47.7%) had some form of complicated malaria, whereas all patients who succumbed (5) had complicated malaria.

Out of the total 50 study subjects, 53% had complicated malaria while 47% were uncomplicated cases. Twenty six percent of patients of P. vivax malaria, having hypotension had hyperlactatemia. 14% of P.falciparum patients and 20% of mixed malaria patients with hypotension had hyperlactatemia [Table 1].

The majority (91.3%) of patients of all types of malarias having hypotension had hyperlactatemia versus 8.7% who had normal lactate levels. Out of the 78 patients who had severe thrombocytopenia, 10 succumbed. 76% of patients with P. vivax and severe thrombocytopenia (<50000) and 88% of P. falciparum patients with same range of platelets had hyperlactatemia. All of the patients with mixed malaria and severe thrombocytopenia had hyperlactatemia. In all, 89.7% of patients of all types of malarias who had severe thrombocytopenia had hyperlactatemia versus 10% having normal lactate levels. The patients with mild thrombocytopenia and normal platelet count had mostly normal serum lactate levels. Hence, this difference was statistically significant (P = 0.001) [Table 2].

Hemoglobin levels less than 5 gm/dl were found in 10% of patients, all of them had hyperlactatemia. Fifty percent of patients of P. vivax malaria having jaundice had hyperlactatemia, while the values for P. falciparum and mixed malarias were 60% and 86%, respectively. 95.16% of patients of all types of malarias having serum bilirubin >1.3 mg/dl had hyperlactatemia versus 4.8% having normal lactate levels [Table 3]. 42% of P. vivax patients having alanine transaminase (ALT) >40 had hyperlactatemia while the values for falciparum and mixed malaria patients were 54% and 73%, respectively.

Those having normal liver functions mostly had normal serum lactate values and hence this difference was statistically significant (P 0.018). All patients (of all types of malaria) with serum creatinine >1.6 mg/dl had hyperlactatemia. Patients with abnormal serum creatinine mostly had normal values of serum lactate and the difference in the two groups was statistically significant (P = 0.00736) [Table 4].

Hyperlactatemia was present in 56% of patients with P. vivax positive malaria who had blood urea level of >40 mg/dl while 68% of P. falciparum positive and 86% of mixed malaria patients had an elevated urea level. Hence, most patients who had complications of malaria had lactate levels >2 mmol/l; in most cases it was statistically significant. All patients who died had a serum lactate level of >2 mmol/l. All 10 patients (100%) had platelet counts of <50000/µl. Blood urea was >40 mg/dl in 8 patients (80%) and creatinine was >3 mg/dl in 4 patients (40%).

Hypotension and jaundice were present in 6 patients (60%). Severe anemia was observed in 2 patients out of 5 (40%).

Among the survivors, the mean lactate level in those cases without any complications was 3.16 ± 1.41 mmol/l but that in survivors who had complications was 4.63 ± 1.3 mmol/l. The mean serum lactate level in survivors was 3.86 ± 1.54 mmol/l, while the same in non-survivor group was 6.72 ± 0.39 mmol/l, which was statistically significant (*P* = 0.0319). Hence, raised serum lactate.

Discussion

Maegraith postulated that the factors involved in hepatic dysfunction in acute P. falciparum malaria infection involve a synergy between local circulatory failure and centrilobular cellular damage. Since LDH is found in clinically-significant amounts in both the liver and red blood cells, the observed increase in serum LDH activity during acute P. falciparum malaria infection in this study can be accounted for by a synergy between the two pathophysiological processes usually associated with acute P. falciparum malaria infections, i.e., the hepatic activity of the invading sporozoites leading to centrilobular liver damage and the destruction of the host red blood cells consequent to erythrocytic merogony. Being rich sources of LDH, the acute liver injury and red

blood cell destruction will be followed by the release of LDH into the circulation. This finding has important implications because it highlights the potential of using serum LDH activity as an index in the monitoring of acute P. falciparum malaria infection, particularly when all other possible causes of increased serum LDH levels have been eliminated.

Grover et al reported a serum LDH level of 432 IU in hospitalised acquired immune deficiency syndrome (AIDS) patients with Pneumocystis carinii pneumonia. Similarly, Cassidy and Reynolds showed that patients with acute viral hepatitis A and B, ischaemic hepatitis and acetaminophen-induced injury are all associated with increases of up to five times the upper limit of normal LDH activity. These variations in the relative magnitudes of serum LDH activities place the P. falciparum-induced increase in serum LDH in between the values reported in the studies by Grover et al and Cassidy and Reynolds.This is a reflection of the differences in the aetiology and pathogenesis of these varied conditions. Ischaemic hepatitis, viral hepatitis and acetaminophen-induced injury are much more severe manifestations of a progressive and irreversible liver damage, sometimes involving other organs like the kidney and brain as seen in viral hepatitis, while the picture in AIDS is a consequence of the onset of a multisystem disease whose progression has been slowed down by anti-retroviral drug therapy. In addition, the magnitude of changes in serum LDH activity during acute P. falciparum malaria infection and other diseases/conditions like Pneumocystis carinii pneumonia, hepatitis and drug-induced liver injury can also potentially be used in distinguishing the aetiology and pathogenic outcomes of these conditions.[7]

The prevalence of complicated malaria has significantly increased in the last decade. Due to this increase, a reliable indicator of the severity of malaria is needed so that efficient intensive care can be provided to severely affected patients. The most common etiology of hyperlactatemia in severe malaria is probably the increased anaerobic glucose metabolism due to generalized microvascular sequestration of parasitized red blood cells (RBCs) that decreases blood flow to tissues.[8] Not many studies have been conducted from this part of India to correlate hyperlactatemia as an indicator of severity of malaria. In the present study, a significant number of patients of complicated and severe P. vivax, falciparum, and mixed malaria had hyperlactatemia. The serum lactate levels showed a significant association with most of the complications of malaria like anemia, thrombocytopenia,jaundice, and renal failure. Raised serum lactate levels were significantly associated with mortality ($P < 0.05$).

In a study by Waller et al., hyperlactatemia was shown to be an independent indicator of a fatal outcome of severe malaria in African children.[9] In a study by Day et al., hyperlactatemia was present in 35% of patients and was associated significantly with metabolic acidosis.[10] Acidosis in turn was significantly associated with a fatal outcome. In a study by English et al. on children, patients having complications, like coma and respiratory distress, had a higher serum lactate level.[11] In a study by van Genderen et al., admission plasma lactate levels were significantly higher in travelers with severe falciparum malaria than in those with uncomplicated malaria. That study suggested that a timely determination of plasma lactate levels on admission may provide the clinician with a useful tool for estimating disease severity.[12] In a study by Krishna et al., mean venous blood lactate

concentrations were almost twice as high in fatal cases as in survivors (7.1 mmol/L vs. 3.6 mmol) and were correlated with levels of tumor necrosis factor and interleukin 1-alpha.[13] In this study, the serum lactate levels showed a signifi cant

association with most of the complications of malaria like anemia, thrombocytopenia, jaundice, and renal failure. Raised serum lactate levels were significantly associated with mortality ($P < 0.05$).

Conclusion

Serum lactate levels can be independently used as an indicator of severity of complications and mortality.

Those having hyperlactatemia can be observed more carefully for complications and care can be intensified in these patients so that morbidity and mortality is effectively reduced.

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