

Study of Lactic Acid Level in Cerebro-Spinal Fluid And It's Prognostic Significance in Patients of Cerebral Malaria

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Abstract

Introduction-

Cerebral malaria is defined as a diffuse cerebral encephalopathy, characterized by unarousable coma in the absence of any other attributable cause of unconsciousness (i.e. meningoencephalitis, stroke, head injury, heat stroke, metabolic encephalopathies etc.) in a patient having plasmodium falciparum infection.

Materials and methods

- The present study "study of lactic acid level in cerebro-spinal fluid and its prognostic significance in patients of cerebral malaria" was carried out in the Department of Medicine, Rajendra Institute of Medical Sciences, Ranchi.
- **Study Design:-** Prospective observational study
- **Sample Size:-** 80
- **Study Period:-** Oct. 15 to Oct. 16

Result:- Increased CSF lactic acid was found in 100% cases of cerebral malaria. The mean level of CSF lactic acid at presentation was found to be higher in fatal cases than in the survivors. The mean level in fatal cases was 66.62mg/dl while in survivors, it was 39.17 mg/dl. CSF lactic acid level more than 54mg/dl (double than normal) were associated with higher mortality (80% while 20% patients survived in this group). On the other hand, CSF lactic acid level less than 54 mg/dl were associated with low mortality (13.33%). {P<0.05}

Conclusion:- Cerebral malaria is a medical emergency with very high mortality, 30% mortality in this study. CSF lactic acid generally rises above the normal range in almost all cases of cerebral malaria. Significantly raised CSF lactic acid (>54 mg/dl) is associated with bad prognosis and poor chances of survival, unless energetic and efficient management is done to save the patient. Significantly raised CSF lactic acid (>54mg/dl, double than the normal) level was associated adverse prognostic indicators of cerebral malaria.

Keyword:- Cerebral malaria, CSF Lactic acid, prognostic significance.

I. Introduction

Malaria is one of the most common & oldest recorded parasitic infection known to mankind. It is caused by a protozoan, known as plasmodium & transmitted by bite of infected Anopheles Mosquito. In 2010, there were an estimated 216 million (149-274 million) cases of malaria world wide, of which 91% were *P. falciparum* cases. A vast majority, about 81% were in African region followed by the South-East Asia region (13%) and East Mediterranean (5%). Malaria accounted for 655,000 (537,000-907,000) death of which 91% were in African region, followed by East Mediterranean (3%) and South-East Asia region (6%). Malaria affects mainly poor, underserved and marginalized population in remote rural areas which are characterized by inadequate control measures and limited access to health care. Malaria continues to pose a major public health threat in India, particularly due to *P. falciparum* which is prone to complications. In India about 27% population lives in malaria high transmission (more than 1 cases per 1000 population) areas and about 58% in low transmission areas (0-1 case per 1000 population) areas. About 92% of malaria cases and 97% of deaths due to malaria is reported from North-eastern states, Chhattisgarh, Jharkhand, MP, Orissa, AP, Maharashtra, Gujarat, Rajasthan, WB and Karnataka. Malaria in man is caused by six distinct species of genus Plasmodium-

1) *P. vivax*,

2) *P. falciparum*, 3) *P. malariae*, 4) two morphologically identical sympatric species of *P. ovale*. 5) *P. knowlesi*

Plasmodium falciparum causes the most severe illness.

In person with *P. falciparum* malaria specially with poor immunity, the irregularly or regularly spaced paroxysm are associated with marked prostration and after 7 to 10 days, a rapid deterioration follows in the patient's condition associated with shock and other complications and even death if untreated such malaria (caused by *P. falciparum*) is known as severe falciparum malaria. Death from *P. vivax*, *P. ovale* or *P.*

malaria infection is very rare. The commonly associated complications of severe falciparum malaria are- coma or cerebral malaria, severe anaemia, renal failure, pulmonary edema, or ARDS, hypoglycaemia, circulatory collapse or shock, spontaneous bleeding, repeated generalized convulsions, lactic acidosis.

Cerebral malaria manifests as diffuse symmetric encephalopathy, focal neurological signs are unusual. Although some passive resistance to head flexion may be detected, signs of meningeal irritation are lacking. Muscle tone may be either increased or decreased. The tendon reflexes are variable, and the plantar reflexes may be flexor or extensor. Flexor or extensor posturing may be seen. Approximately 15% of patients have retinal haemorrhages. Convulsions, usually generalized and often repeated, occur in up to 50% of children with cerebral malaria. More covert seizure activity is also common particularly among children, and may manifest as repetitive tonic-clonic eye movements or even hypersalivation.

Hypoxia & ischemia of brain has been described as the major possible cause, which can occur due to interference to the micro-circulatory flow to the brain. Besides coma may be compounded by hypoglycaemia, lactic acidosis & shock if present. Intravascular sequestration of the parasitized red cells due to cyto-adherence & rosette formation leads to interference in the micro-circulatory blood flow to the brain, obstruction mainly taking place in the cerebral capillaries & post capillary venules. This interference leads to cerebral anoxia and ischemia causing altered sensorium, obtundation & coma. The anoxia & ischemia of brain leads to cerebral anaerobic glycolysis, resulting in formation of lactic acid in excess amounts, which are reflected in to CNS as raised lactic acid level.

II. Material And Method

The present study was carried out in the Department of Medicine, Rajendra Institute of Medical Sciences, Ranchi.

Inclusion criteria:

- 1) Primary pool- patients hospitalized with complain of fever with clinical diagnosis of malaria.
- 2) Secondary pool- the cases from primary pool with definite diagnosis of cases of P. falciparum malaria along with features suggestive of cerebral malaria.

Exclusion criteria:

- 1) Pre-existing neurological disorders
- 2) Patients with pre-existing convulsive disorder

80 cases of different age and sex of fever with coma without any other attributable cause of unconsciousness, the presence of positive blood smear or positive rapid test (kit test) for plasmodium falciparum were selected with the clinical diagnosis of cerebral malaria.

The following investigations have been done in cases under study:

- 1) Blood for TC & DC of WBCs, Hb% estimation.
- 2) Peripheral blood smear both thick and thin for the presence of pla.falciparum.
- 3) Rapid diagnostic kit test for Pla.falciparum.
- 4) RBS
- 5) Examination of CSF for protein, sugar, cells, and lactic acid.

The study of lactic acid level in CSF was done with the help of semiautolyzer test.

III. Statistical Analysis

Chi-square test was used to find the significance of frequency distribution of study parameters between group CSF lactic acid more than 54 mg/dl and less than 54 mg/dl. Student t test was used to find the significance of mean values of study parameters between both the groups. Microsoft Excel and Word were used to prepare the tables and graphs.

IV. Result

The total no of cases studied (n= 80). 50 (62.5%) were male while 30(37.5 %) were female. The age of cases under varied 17 years to 55 years. Mean age of patients under study 34.41. The maximum incidence of the disease was observed in 21 – 40 years age – group (61.5%). Number of case was from rural area 63 (78.75%) and from urban area 17 (21.25%). 57 (71.25 %) of cases under study were from tribal community and 23 (28.75%) are non-tribal. (table 1)

The age group less than 20 yrs the observed mortality was 16.67% while in the age group 21-40 years the observed mortality was 34.61 % .In the age group of 41-60 years mortality was found to be 25%.

History of fever with rigor, (100%), headache (100%), unconsciousness (100%) & absent neck stiffness (100%) were present in all cases of cerebral malaria at the time of presentation. Convulsion was present in 30% cases.

Vomiting was present in 12.5% cases while dehydration was present in 35% of cases, corneal reflex was absent in 27.5%.Jaundice was present in 12.5% of cases. Hepatomegaly was found in 27% cases while splenomegaly was present in 37.5%. Both hepato-splenomegaly were found together in 25% cases, Acute renal failure was present in 7.5% cases.Hence a history of fever with rigor, headache, altersensorium, absent neck rigidity, anaemia was the most common presentation.Dehydration, convulsion, hepatomegaly, splenomegaly , acute renal failure , jaundice and decerebrate rigidity were sometimes present.

Cerebral malaria patients, presenting with random blood sugar (RBS) less than 70mg/dl were 18 in number with the percentage of fatality was 55.56%. While 62 patients were found RBS more than 70 mg/dl ,77.42 % cases survived and only 22.58% cases were fatal (P<0.05).Severe anemia (Hb<=7gm/dl) was found in 20 cases with mortality of 70 % while only 30% patients survived with severe anemia. Lesser degree of anemia (Hb> 7gm/dl) was found in 60 cases with mortality of 83% of patients(P<0.05). In the fatal cases of cerebral malaria, the mean CSF lactic acid level was found 66.26 mg/dl with standard deviation of 16.91 while in the survivors; the mean CSF lactic acid was 39.17mg/dl with standard deviation of 7.66.

The actual difference between the mean is 27.45(66.62-39.17).Unpaired t test (student t test) is applied and p valve is found significant (P<0.05). (Table 2) CSF lactic acid levels more than 54 mg/dl (double than normal) were associated with a mortality of 80% while 20% patient survived in this group. On the other hand, CSF lactic acid level less than 54 mg/dl were associated with a mortality of 13.33%, while 86.67 % patients survived in the group.Chi square test is applied- The observed difference between the mortality (or survivor) figures of the two groups is significant (p< 0.05). So lactic acid > 54mg/dl was associated with very high mortality. CSF lactic acid <54mg/dl was associated with better survivor.(Table 3)

Table 1-Age distribution of cases under study

Age group (Years)	No. of cases (n =80)	% of cases in given age group	No. of male cases	% of male patient	No. of female cases	% of female patient
<20 yrs	12	15%	6	50%	6	50%
21-40 yrs	52	65%	32	61.5%	20	38.5%
41-60 yrs	16	20%	12	75%	4	25
Total cases	80	100	50	62.5%	30	37.5%

Table 2- Showing mean level of CSF lactic acid level and standard deviation in fatal and survived cases of cerebral malaria.

	NO. OF CASES	MEAN CSF LACTATE (Mg/Dl)	STANDARD DEVIATION
FATAL CASES OF CEREBRAL MALARIA	24	66.62	16.91
SURVIVORS OF CEREBRAL MALARIA	56	39.17	7.66

Table 3showing elation ship between CSF lactic acid level and prognosis in patients of cerebral malaria

	n	fatal case	survivors cases	% mortality	% survival
Patients of cerebral malaria with CSF lactic acidlevel> 54mg/dl malaria	20	16	4	80	20
Patients of cerebral malaria with CSF lactic acidlevel<54mg/dl malaria	60	8	52	13.33	86.67

Figure 1 - Showing Age & Sex Distribution Of Patients

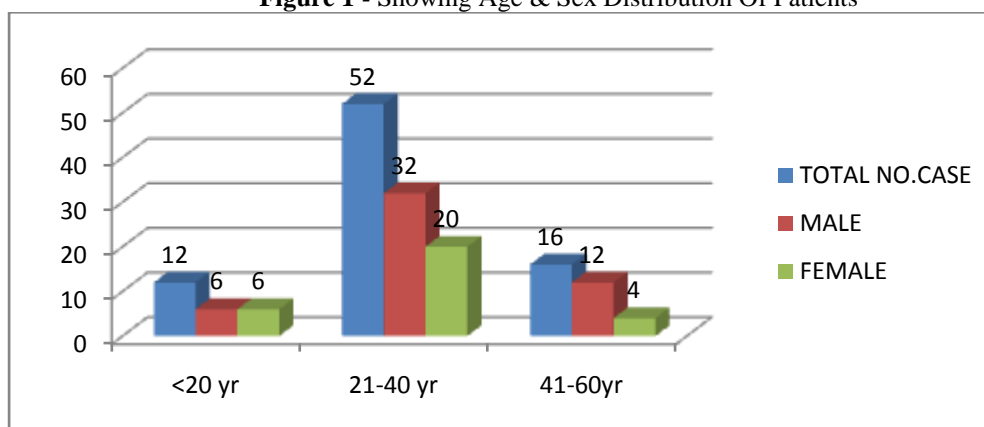


Figure 2- showing means CSF lactic acid level in fatal & surviving cases of cerebral malaria

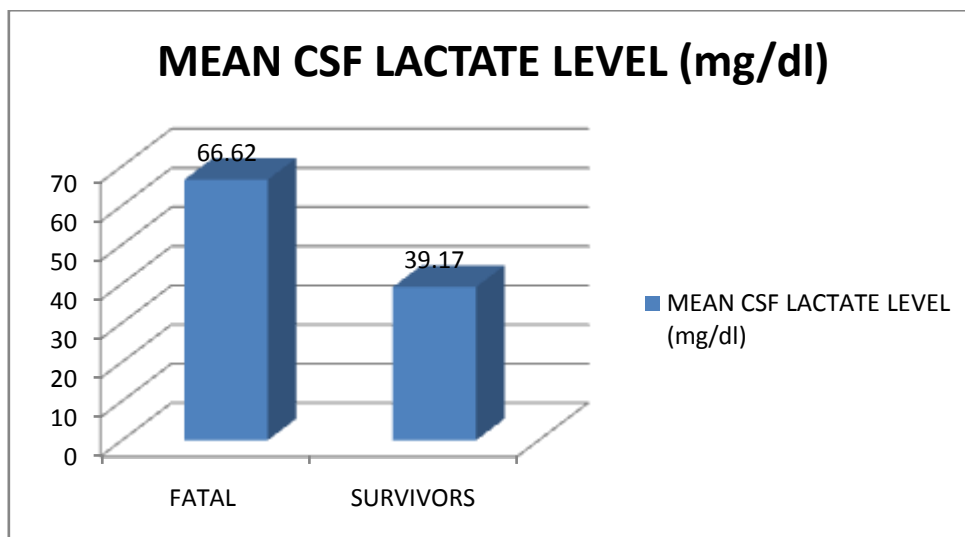
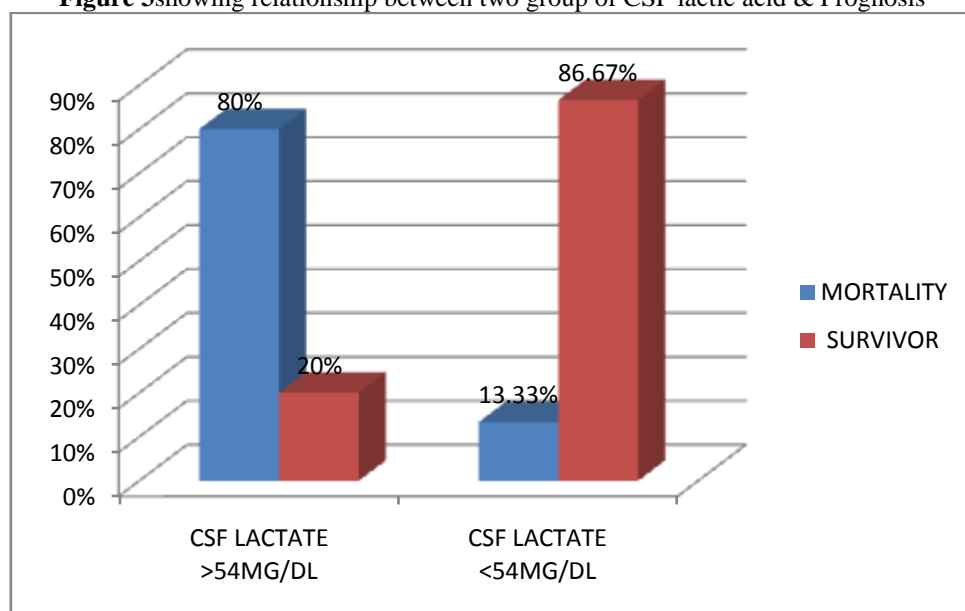


Figure 3 showing relationship between two group of CSF lactic acid & Prognosis



V. Discussion

In a study carried out by white and warrel et.al.in (1985)⁵ forty five patients had been studied. Out of this 64% were male and 36% were female with the mean age of patient being 23 years. In another study carried out by Turner ,Morrison et.al.(1994)¹⁶ the age varied from 19-67 years and the mean age of occurrence was 35 year. In present study mean age of patient is 34 year.62.5% were male and 37.5% were female which is compatible with previous study.In a study carried out by Phillips and Gilles (1988)¹⁷ they found mortality rate ranging from 20-25%. In present study mortality is 30%. The clinical sign which were associated with mortality in this study were deep unconsciousness with Glasgow coma scale score 7 or less (69% mortality, n=26,18 died, 4 survived) , absent corneal reflex (82% mortality, n=22,18 died 4 survived), severe anaemia with haemoglobin equal to 7 gm/dl or less (70% mortality, n= 20,14 died ,6 survived) , occurrence of convulsion (58.33% mortality, n= 24, 14 died ,10 survived). In a study carried out by Molyneux, Taylor et.al.(1988)¹⁸ on the clinical features and prognosis indicators in cerebral malaria, 131 patients were studied. Mortality was 15% .The clinical sign which were associated with adverse prognosis were profound coma (65% mortality), absent corneal reflex (55% adverse prognosis) and convulsions (38% mortality). These finding are in consistence with but on the lower side than the finding of the present study. History of high fever with rigor, headache, anaemia, altered sensorium or unconsciousness with absent neck stiffness was the most comman (100%) mode of presentation. Convulsions were found in 30% of cases. These finding are in consistence with other studies.

CSF lactic acid level was increased in all 80 cases. In the fatal cases, the CSF lactic acid ranged from 41.44mg/dl to 93.36 mg/dl. If CSF lactic acid was very high (>54 mg/dl) , patients generally had high mortality (n=20, 16 died, 4 survived) . In the study carried out by White N.J. Warrel D. A. Et.al (1985)⁵, CSF lactic acid was found to be raised in 44 patient's of cerebral malaria out of 45 cases with a percentage of 98%. Another study carried out by Molyneux ,Taylor et. Al. (1989)¹⁸, CSF Lactic acid was raised in 93 patients out of 131 cases (71%). These results are in consistence with the results obtained in this study but higher side.

Mean level of CSF lactic acid in fatal cases was 66.62 mg/dl,(S.D.= 16.91,S.E.=3.6) while in survivors , it was 39.17 mg/dl (S.D.=7.66,S.E.=3.6)and P value <0.05. So the mean level of CF lactic acid at presentation was found to be higher in fatal cases than in the survivors. These results are significant and are in consistence with the wok of White N.J. Warrel D. A. Et.al (1985)⁵ they found CSF lactic acid in fatal cases mean + standard deviation = 9.0+- 5.3 m mol/L vs CSF lactic acid in survivors (3.4+-1.1 mmol/L), P= 0.0002 and Taylor, wirima, Molyneux (1989)¹⁸[CSF lactic acid in fatal cases =5.3+-3.3 mmol/L vs CSF lactic acid in survivors = 3.68+-1.6 mmol/L] (1 mmol lactic acid = 9 mg/dl).

In our study it was found that if CSF lactic acid level more than 54 mg/dl than mortality was 80 % (n=20, 16 died, 4 survived), while if it was less than 54mg/dl than mortality was 13.33% (n=60, 8 died, 52 survived). In study carried out by White N.J. Warrel DA (1985)⁵, all patients with CSF lactate level above 6mmol/L (=54mg/dl) had died (100% mortality). Hence these finding are in consistence with the finding obtained in the present study.

In our study patients, presenting with random blood sugar (RBS) less than 70mg/dl were 18 in number with the percentage of fatality was 55.56%. While 62 patients were found RBS more than 70 mg/dl ,77.42 % cases survived and only 22.58% cases were fatal (P<0.05).In a study carried by Marsh, Foster, et. al. (1995)²⁰ found hypoglycaemia to be a risk factor for adverse prognosis in patients of cerebral malaria(relativerisk3.3,95%c.i.=1.6to6.7)in addition to other factor. Waller , Krishna , crawley ey.al.(1986)²¹ , while studying the clinical feature and outcome of sever malaria in Gambian children, found hypoglycaemia to be independent indicator of poor prognosis beside other factor .

VI. Conclusion

On the basis of above results obtained in the present study, the following conclusions have been drawn:-

Cerebral malaria is a medical emergency with very high mortality ranging from 25-50% (30% mortality in this study).It predominantly affects non-immune and partially immune persons.CSF lactic acid generally rises above the normal range in almost all cases of cerebral malaria.Significantly raised CSF lactic acid (>54 mg/dl) is associated with bad prognosis and poor chances of survival, unless energetic and efficient management is done to save the patient. Significantly raised CSF lactic acid (>54mg/dl, double than the normal) level was also associated with the presence of other established adverse prognostic indicators of cerebral malaria like absent corneal reflex , decerebrate posturing , GCS score < 7, severe anemia etc.

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