International Journal of Science and Research (IJSR)
ISSN (Online): 2319-7064
Index Copernicus Value (2015): 78.96 | Impact Factor (2015): 6.391

A Clinical Profile of Cerebral Malaria with P. Falciparum Infection

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Abstract: ***Malaria is a protozoan disease transmitted by infected Anopheles mosquito's bite.[1] It is a serious parasitic disease of the entire world affecting 300-500 million people and causing over 1 million deaths each year.[2]Cerebral Malaria (CM), which is the most severe complication of Malaria, is also among the most common causes for non-traumatic, infective encephalopathy in the world.[3] .Right now the most effective way to diagnose cerebral malaria is by a commonly used blood smear by checking for the presence of the parasite and treating with intravenous artemisinin compounds at the earliest[3,4].This study observed that the WHO definition for Cerebral Malaria helps in early identification of high risk cases, so that prompt treatment is instituted early, thereby reducing the mortality rate, the use of GCRBS scoring system helps in determining prognosis and should be used frequently&Intravenous artesunate should become the treatment of choice in adults with severe and cerebral malaria.***

Keywords: Cerebral malaria, P.falciparum, GCRBS scoring

1. Introduction

Malaria is a protozoan disease transmitted by infected Anopheles mosquito's bite.[1] It is a serious parasitic disease of the entire world affecting 300-500 million people and causing over 1 million deaths each year.[2] It is also one of the most common parasitic infections in our country and over 1.1 million cases were reported in 2012. Approximately 2.5 million malaria cases are reported annually from South Asia, of which 76% are reported in India. Malaria is endemic throughout India with 95% of the population at risk of infection.In 2013, 0.1 to 1 confirmed cases per 1000 population were reported in western Maharashtra.[5] The causative organism for malaria is one or more of the five species of *Plasmodium*. These are viz. *Plasmodium vivax*, *Plasmodium falciparum*, *Plasmodium malariae*, *Plasmodium ovale*and *Plasmodium knowlesi*. Most of the cases of Cerebral Malaria (CM) are caused by *P. falciparum*. However, there are increasing reports of Complicated/Severe Malaria by other species as well.[6,7]

Cerebral Malaria (CM), which is the most severe complication of Malaria, is also among the most common causes for non-traumatic, infective encephalopathy in the world.[7] Cerebral Malaria accounts for about 15-20% cases of Severe Malaria/Complicated Malaria. Of the four species of *Plasmodium* causing human malaria, *P.falciparum* has the potential of developing life threatening complications, which may result in fatality. Not surprisingly, malaria may be complicated with neurological manifestations and multiple organ dysfunctions, the cumulative effects of which cause fatality.[8]Cerebral malaria being the most important complication of falciparum malaria is also the leading cause of death in malaria.[5,6] Cerebral malaria is defined as an acute, symmetric encephalopathy associated with sequestration of parasites erythrocytes in the cerebral vessels and capillaries in patients with falciparum malaria.[9]

The World Health Organization (WHO) has laid down definite guideline for diagnosis and management of Cerebral Malaria.[10] This definition requires the presence of unrousable coma using the Glasgow Coma Scale(GCS), exclusion of other encephalitis, especially bacterial meningitis and if possible, locally prevalent encephalitis and the finding of asexual forms of *P. falciparum* in the blood film.Clinically, Cerebral Malaria manifests as diffuse symmetric encephalopathy and focal neurologic signs are unusual. Signs of meningeal irritation are usually absent. There may be Hypotonia or Hypertonia. The deep tendon reflexes are variable, and the plantars may be flexor or extensor; the abdominal and cremasteric reflexes are absent. Flexor or extensor posturing may be seen. Convulsions are usually generalized and repeated.Any patient with asexual forms of *P. falciparum* in the peripheral blood getting altered consciousness not attributable to any other cause should be diagnosed with cerebral malaria.[11]

There is a changing trend in recent times, regarding not only the clinical manifestations, but also the complications and more patients are presenting with severe systemic problems.[12] Recent updates regarding the changing spectrum of severe malaria is precious for early intervention, because it may become fatal if treatment is delayed. Awareness of prevalence of different complications and neurological ones in particular could greatly facilitate the approach towards early diagnosis and prompt treatment.[13]

Neurological sequelae in survivors of Cerebral Malaria have been studied in various studies and are of particular importance because of their reversibility with time.14 Also, various scoring systems have been formulated for establishing prognosis and severity in patients with cerebral malaria.[15,16]

Right now the most effective way to diagnose cerebral malaria is the same as the way to diagnose regular malaria,

with a commonly used blood smear by checking for the presence of the parasite and treating with intravenous artemisinin compounds at the earliest.[3,17]

2. Methodology

The present study is a hospital based Prospective, Observational study. The study included a total of 50 patients who fulfilled the inclusion and exclusion criteria. Once diagnosed to have P. falciparum Cerebral Malaria, they were subjected to a detailed clinical examination and appropriate investigations. Consecutive type of non-probability sampling was employed for selection of study subjects. Final sample size taken 50.

a) Inclusion criteria : Smear positive cases of P. Falciparum, diagnosed clinically as Cerebral Malaria.
b) Exclusion criteria : Patients with other co-existent causes of unconsciousness like Metabolic causes, Vasculitis, Other Infective causes: Meningitis, Encephalitis, Cerebrovascular accident, Structural lesion

Following investigation findings are noted

- Complete Heamogram: measured by Flow cytometry with 5 part Coulter machine.
- Malarial Parasite Index.
- Blood sugar level - estimated by Glucose Oxidase peroxidase method.
- Serum Creatinine - estimated by Kinetic Jaffey method.
- HIV - status found out by Tridot technique.
- Peripheral Blood Smear (Thick & Thin) for Malarial Parasite
- Falciparum Antigen Test (By MALA SCAN/J. MITRA)
- Renal Function Tests
- LDH (Lactate Dehydrogenase)(UV-Kinetic Method)
- Liver Function Tests
- Electrocardiogram
- Chest X-Ray
- USG Abdomen & Pelvis
- Serum Electrolytes
- Urine: Routine & Microscopy
- Arterial Blood Gases (By Potentiometry Method)

Whenever required:

- CT Scan/ MRI Brain
- Cerebrospinal fluid study
- Blood culture

All Patients were observed till hospital stay and the outcome was studied in terms of Improved Completely, Death, and Neurological Sequelae.

3. Results & Discussion

Results & Observations

Table 1: Age distribution of patients studied

Age in years	*Number of patients*	*Percentage*
14-30	20	40%
31-45	7	14%
45-60	8	16%
>60	15	30%
Total	50	100%

We can see from the above table that the maximum numbers of patients were young (< 30 years). The next commonest were > 60 years (30%) & 45-60 years (16%).

Table 2: Gender distribution of patients studied

Gender	*Number of patients*	*Percentage*
Male	24	48%
Female	26	52%
Total	50	100%

There were more females (52%) than males (48%) in the study.

Table 3: Clinical presentation of patients studied

Symptom	Number of patients	Percentage
Fever	50	100%
Chills & Rigors	45	90%
Convulsion	28	56%
Altered Sensorium	50	100%
Abnormal Behaviour	2	4%
Headache	22	44%
Nausea & Vomiting	32	64%
Breathlessness	24	48%
Cough	25	50%
Abdominal Pain	16	32%
Jaundice	11	22%
Diarrhoea	4	8%
Decreases Urine	8	16%
Bleeding Diathesis	3	6%

Fever and Altered Sensorium was present invariably in all the patients. 90% of fever was associated with chills and rigors. Convulsion occurred in 56% cases with 10% having repeated convulsions. Headache was not a prominent feature and appeared in only 22 of the patients. Schizont rupture has different manifestations and abdominal pain is one of them. Many of the patients presenting with breathlessness and cough, eventually developed ARDS.

Table 4: General physical examination findings

Parameter	No. of patients	Percentage
Glasgow coma scale		
• 3 to 6	14	28%
• 7 to 10	24	48%
• 11 to 15	12	22%
Pulse		
• ≤ 100	22	44%
• > 100	28	56%
Systolic blood pressure		
• ≤ 80	7	14%
• > 80	43	86%
Respiratory Rate		
• ≤ 24	28	56%
• >24	22	44%
Pallor	21	42%
Icterus	14	28%

Glasgow Coma Scale (GCS) was ≤11 in all the patients. Glasgow Coma Scale (Grades: 3-6, 7-10, 101-15), Hypotension (≤ 80 mm Hg) and Respiratory Rate (≤ 24) were defined according to GCRBS Scoring System.[18]

Table 5: Per Abdomen findings

Parameter	No. of patients	Percentage
Hepatomegaly	4	8%
Splenomegaly	7	14%
Ascites	5	10%

Hepatomegaly was seen in 4 patients, while 3 had co-existent Hepato-Splenomegaly

Table 6: CNS findings

Variables	*No of patients*	*Outcome*	
		Full recovery	*Death*
Signs of meningeal irritation/meningism	15	12	3
B/L Deep tendon reflex			
• Normal	22	21	1
• Brisk	21	14	7
• Absent	7	6	1
Decorticate posture	2	0	2
Decerebrate posture	1	0	1
Planter response			
• Flexor	23	23	1
• Extensor	20	11	7
• Equivocal	7	6	1
Focal neurological deficit	5	0	5

As described before, signs of meningeal irritation were not prominent feature and only 12 patients had neck stiffness. Deep Tendon Reflexes were either normal or exaggerated in most of the cases. Abnormal posturing on painful stimuli appeared in 3 of the patients, 2 had Decorticate posture, while 1 had Decerebrate posturing.

Focal signs appeared in 5, and were in the form hemiparesis in 2 patients and focal seizures in 3 of them.

Table 7: Pattern of ophthalmic manifestations

Variables	Total	Outcome	
		Full Recovery	Death
Pupillary size			
• Normal	40	39	1
• Constricted	7	2	5
• Dilated	3	0	3
Corneal reflex			
• Present	42	40	2
• Lost	8	1	7
Fundoscopy			
• Normal	40	39	1
• Exudate	1	1	0
• Haemorrhage	2	1	1
• Papilloedema	7	0	7

7 patients had Papilloedema, while 2 had haemorrhages on Fundoscopy. All the patients with Papilloedema died.

Table 8: Blood Investigations

Blood investigations	Criteria	Number of patients
Haemoglobin (gm/dl)	<6	3
	6-7.9	9
	8-10	20
	>10	18
Platelet count (lakh)	>1.5	23
	< 1.5	27
Sr Creatinine (mg/dl)	≤ 1.50	30
	1.50-3.0	13
	3.0-4.50	6
	> 4.5	1
Blood urea (mg/dl)	<45	23
	45-99	24
	>100	3
Total bilirubin (mg/dl) (Indirect Bilirubin)	≤ 3.0	36 (46)
	3.0-5.9	11 (3)
	>6.0	3 (1)
Serum Bicarbonate Levels (mEq/L)	< 15	10
	15-24	22
	> 24	18

Severe anaemia (< 6 mg/dl) was present in 3 of our patients. This probably would be due to haemolysis and co-existent nutritional factors. 7 patients had AKI (Sr Creatinine > 3 mg/dl) and 27 had raised Blood Urea Levels. Indirect Bilirubin was more than 3 mg/dl in 4 of the patients, out of which 3 died. Sr Lactate Dehydrogenase could be done in 40 of our patients and was found to be raised in 32. Serum Bicarbonate levels were decreased in 32 of the patients, 25 of which had pure metabolic acidosis and 7 had mixed metabolic and respiratory acidosis. All were treated with intravenous Sodium Bicarbonate.

Table 9: Treatment received by the patients

Treatment	Route of administration	No. of patients	Percentage	Deaths
Artesunate + Quinine	Intravenous	7	14%	4
Artesunate	Intravenous	43	86%	5

According to the WHO guidelines, patients received IV Artesunate. IV Quinine was given in patients who did not respond to Artesunate.

Table 10: Other Complications in Cerebral Malaria

Parameter	No. of Patient	Percentage
AKI	8	16%
ARDS	10	20%
Hypotension	7	14%
Hypoglycaemia	4	8%
Metabolic acidosis	16	32%
Multi organ failure	13	26%

AKI (Sr Creatinine > 3 mg/dl) was seen in 8 of our patients, out which 4 died. Multiple Organ Failure occurred in 13 patients, out of which 9 died. In short all those who died had Multiple Organ Failure. Hypoglycaemia also proved deleterious as all4 patients with blood sugar levels below 40 mg/dl died.

Table 11: GCRBS Scoring

GCRBS Score	No of Patients
< 5	37
≥ 5	13

Patients were graded according to the new GCRBS Scoring system and it was found to be reliable.

These newly introduced scoring system for malaria proved to be helpful in prognosticating patients. All the patients who died had GCRBS Scores 0f ≥ 5,which has a poor

outcome. None of the patients with favourable score of < 5 suffer fatal outcome.

Table 12: GCRBS Scoring and Outcome

GCRBS Score	No of Patients	Death
< 5	37	0
≥ 5	13	9

9 out of 50 patients in our study were discharged against medical advice. Out of those 9, 3 died later on and 6 recovered completely.

13 patients had scores ≥ 5. Out of these 9 died. Out of the surviving 4, three did not have ARDS and Hypoglycaemia.

37 patients had favourable score of < 5. All of them survived. Amongst these patients with favourable scores, 4 had Multiple Organ Failure but, none of these 4 had ARDS and/or Hypoglycaemia.

So, ARDS and Hypoglycaemia appeared to be deleterious in the study.

Table 13: Outcome

Parameter	No of Patients	Percentage
Deaths	9	18%
Completely recovered	39	78%
Neurological Sequel	2	4%

Neurological sequelae were present in 2(4%) of our patients, one had psychosis and the other had cerebellar ataxia. 30 (78%) recovered completely while 9 (18%) died. Duration of recovery was approximately 1 month in both cases.

4. Conclusion

The WHO definition for Cerebral Malaria helps in early identification of high risk cases, so that prompt treatment is instituted early, thereby reducing the mortality rate. The pathogenesis of coma remains obscure. Reduced microcirculatory flow caused by sequestration of parasitized erythrocytes and rigid erythrocytes is central in the pathophysiology of severe disease. Fever & altered sensorium are invariably present in all patients of cerebral malaria. Multiple Organ Failure and Hypoglycaemia were the most deleterious complications, which is comparable to other studies.Patients with Glasgow Coma Scale > 6, GCRBS Score < 5 and Haemoglobin levels > 9 mg/dl had good prognosis. Patients with Focal Neurological Deficit, Absent Corneal Reflexes, Papilloedema, Dilated Pupils and Severe Anaemia had poor prognosis. The use of GCRBS scoring system helps in determining prognosis and should be used frequently. Out of the 5 parameters only two (Creatinine and bilirubin) are laboratory parameters and the rest three are clinical parameters which can be easily determined at the bedside. The Cut-off score of 5 was useful in grading patients. Prevention strategies and early diagnosis and treatment with effective antimalarial drugs in the public health sector are equally important.

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