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Clinical and haematological determinants of outcome among children with cerebral malaria in a tertiary centre in Nigeria

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Abstract: *Background:* Many clinicaland haematological changes occur as a result of severe malaria, of which cerebral malaria (CM) is a common entity. These changes affect virtually all organs and systems of the body. We identify various clinical and haematological determinants of outcome in CM so as to institute proactive management of such children.

Methods: All children who met World Health Organization (WHO) diagnostic criteria for CM over 8 month-period were prospectively studied. The presenting symptoms and its duration, detailed physical examination and laboratory parameters were obtained. Logistic regression was employed to determine the prognostic significance of various clinical and laboratory parameters. Outcome indicators were full recovery, alive with neurological sequelae or death of the children.

Results: Of the 892 children admitted into the Children Emergency Unit (CEU) over the study period, 50 (5.6%) had CM with M: F ratio of 1:1 and age range of 6 months to 12 years. Sixty percent were aged less than 5 years. The defining symptoms were fever (100%), coma (100%) and convulsion (98%).

Forty-one (82%) patients survived, while nine (18%) died. Of the 41 survivors, 30 (73.2%) recovered fully, while 11 (26.8%) had neurological deficits at discharge. Identified clinical and laboratory predictors of mortality and neurological sequelae in CM included Blantyre coma score of 0-2($p = 0.018$) prolonged coma recovery time > 26 hours ($p = 0.026$), abnormal breathing pattern ($p = 0.0124$), absent corneal reflex ($p = 0.012$), absent pupillary reflex ($p = 0.012$), depressed tendon reflex ($p = 0.028$), hyperreflexia ($p = 0.014$), retinal haemorrhage ($p = 0.001$), duration of admission ($p= 0.000$), hyper parasitaemia ($p = 0.001$), hypoglycemia ($p= 0.014$) and leucocytosis ($p = 0.008$). Independent determinants of immediate post-recovery neurological deficits and death were hyper-parasitaemia (OR = 8.657, $p = 0.017$.) and leucocytosis(OR = 1.090; $p = 0.035$

Conclusion: CM is a potentially reversible encephalopathy associated with high mortality and sequelae. Affected children with the above listed clinical / haematological parameters especially hyperparasitemia and leucocytosis should be given proactive management to improve the outcome.

Key words: cerebral malaria, clinical and haematologic parameters, outcome

Introduction

Cerebral malaria (CM) in children is the most severe neurological complication of infection with *Plasmodium falciparum*, and is a clinical syndrome whose hallmark is impaired consciousness, with coma being the most severe manifestation.[1] Multiple complications following P. falciparum infection in children can occur with cerebral malaria (CM) causing some of the highest mortalityrates.[2,3]It is a major cause of acute non-traumatic encephalopathy necessitating admission in children emergency room.[4] Globally, up to 1 million people are affected yearly and the largest proportion is accounted for by children below the age of 5 years living in sub-Saharan Africa (SSA).[5]The period 2000 to 2015 witnessed remarkable reductions in the estimated rate of malaria deaths in almost all countries in Africa.[6] There was an estimated overall decrease of 57% in the malaria death rate over this period, from 12.5 deaths per 10,000 population per year in 2000 to 5.4 in 2015. However, in

a recent World malaria report, there were 229 million cases of malaria in 2019 compared to 228 million cases in 2018. The estimated number of malaria deaths stood at 409 000 in 2019, compared with 411 000 deaths in 2018.[7] Also, Children under 5 years of age remained the most vulnerable group affected by malaria; in 2019 they accounted for 67% (274 000) of all malaria deaths worldwide.[7] The trend of the malaria burden still shows that African countries continue to carry a disproportionately high share of the global malaria burden accounting for 94% of all malaria cases and deaths. In 2019 World Health Organisation (WHO) reports, Nigeria led other 5 African countries to contribute to approximately half of all malaria deaths worldwide. In general, between 17% and 50% of hospital admissions for severe malaria are attributed to CM across African cities.[8,9]Furthermore, children that survive CM can remain with life-long post CM sequelae, especially neurological deficits, affecting quality of life.[2]

Cerebral malaria in children carries a poor prognosis with a high mortality, especially if not treated promptly, the assessment of clinical and laboratory manifestations and the subsequent interventions instituted determine the clinical outcome in such children.[5,10] The morbidity and mortality from CM remain a call for concern in Nigeria and globally considering the awareness and control measures/programmes; mounted against malaria by different policy makers.[8,11]

The clinical manifestations of cerebral malaria (CM) are non-specific and varied across studies.[9,12,13]Some authors have reported some of the clinical features that predict death in severe malaria among African children.[14–16] Such factors include severe anaemia, altered consciousness, depth of coma, hypoglycaemia, respiratory distress and features of severe sepsis.[12,17] However, there have been few attempts to assess clinical and laboratory factors that determine the outcome of cerebral malaria in children and particularly which combinations of factor(s) best predict clinical outcomes.[17,18]
In view of high burden of childhood CM with its attendant potential fatal outcome, efforts toward prompt identification of factors that will determine this outcome is vital in its management. The aim of this study was therefore to identify clinical and haematological determinants of outcome in children with CM so as to institute anticipatory management for such children to prevent orlimitpotential fatal outcome.

Materials and Methods

The study was conducted at the Children Emergency Unit (CEU) of the LAUTECH Teaching Hospital (LTH), Ogbomoso, Nigeria. Ogbomoso is an urban centre in Oyo State of the Southwestern Nigeria, a malaria region lying on latitude $8^0071N - 8^0161N$ of the equator and longitude $4^0161E - 4^0301E$ of Greenwich meridian time.[19]

This was a prospective study conducted between February and September 2018 involving children admitted consecutively into the CEU of LTH, Ogbomoso. CM in this study was defined according to the World Health Organization (WHO) as a patient who had altered sensorium lasting more than 30 minutes; with peripheral asexual P. falciparum parasitaemia and had no other identified causes of an encephalopathy.[14] The Ethical and Research Committee of LTH, Ogbomoso approved the study and consent from the parents/caregivers were obtained. Information on the parents' occupation and level of education was also obtained in order to determine their social class using the Oyedeji's classification system.[20]
Information was obtained through self-designed proforma for this study with respect to the details of cerebral malaria including bio-data of the children, duration of presenting symptoms. These were followed by detailed clinical examination which included anthropometry, general and systemic examinations involving the pulmonary and cardiovascular systems, abdominal, central nervous system and fundoscopy. Level of consciousness was assessed using Blantyre's coma scale for children with maximum score being 5; score of 0-2 was defined as deep coma and score 3-4 as light coma.[18]

At presentation blood was taken from each patient for random blood sugar, complete blood count, blood film for malaria parasites, and serum electrolytes, urea and creatinine. Cerebrospinal fluid (CSF) was also obtained for chemistry and microbiology laboratory examinations. The blood films for malaria parasites were examined and reported for specie type and parasite density. Blood film for malaria parasites was monitored daily while other investigations such as blood culture, urinalysis and urine culture were carried out based on need. Further tests were based on when the previous results were abnormal or when the patients' clinical condition dictated a need for repeat. All patients were treated with intravenous artesunate in line with treatment guidelines on malaria by WHO.[10] Adjunct treatment were informed based on the associated complications, and in addition to other supportive therapy like oxygen therapy, airway management, fluid therapy and nutrition. The clinical outcome was determined at discharge or when patient died. The outcome of each patient was assessed as either full recovery, alive with neurological sequelae, or dead.

Data Analysis

Data were analysed using Statistical Package for Social Sciences (SPSS) version 21. Patients were classified using the presence or absence of some selected clinical and laboratory parameters. Test of association between variables was by Chi-square. Student t-test was used to compare means of normally distributed continuous variables. Stepwise multiple logistic regression analysis was employed to determine the prognostic significance of various clinical and laboratory parameters. In the analy-

sis, confidence level was set at 95% with level of significance of $p < 0.05$.

Results

General characteristics

Of the total number of 892 patients that were admitted into CEU during the study period, 50 met the criteria for CM accounting for 5.6% of all children admitted during the period. The male-to-female ratio was 1:1. The mean age was 4.86 ± 3.16 years (range between 6 months and 12 years) with 60% aged less than five years.

Table I shows clinical presentation in relation to the outcome in children with CM. Up to 48.7% of children died or had immediate post-recovery neurological abnormalities among the population who convulsed. Of the children with difficulty in breathing, 75% either died or survived with immediate post-recovery neurological abnormalities which was significantly higher than 29% among those who recovered fully. In all, convulsion ($\chi 2+ = 4.084$, $p = 0.043$) and difficulty in breathing ($\chi 2+ = 4.084$, $p = 0.012$) were the presenting complaints significantly associated with poor outcome.

Table 1: Clinical outcome and presenting complaints in children with cerebral malaria

Presenting complaints	Clinical outcomes (A) Full recovery n (%)	(B) Alive with sequelae and Death n (%)	χ^{2+}	A vs B P
Fever				
Yes	30 (60.0)	20 (40.0)	NA	NA
No	0 (0.0)	0 (0.0)		
Convulsion				
Yes	20 (51.3)	19 (48.7)	4.084	*0.043
No	10(90.9)	1 (9.1.0)		
Loss of consciousness				
Yes	30 (60.0)	20 (40.0)	NA	NA
No	0 (0.0)	0 (0.0)		
Pallor				
Yes	8 (50.0)	8 (50.0)	0.9803	0.3221
No	22 (64.7)	12 (35.3)		
Jaundice				
Yes	3 (50.0)	3 (50.0)	0.007	0.9292
No	27 (61.4)	17 (38.6)		
Dark brown urine				
Yes	9 (64.3)	5 (35.7)	0.077	0.7809
No	21 (58.3)	15 (41.7)		
Reduction in urine output				
Yes	2 (33.3)	4(66.7)	0.955	0.3285
No	28 (63.6)	16 (36.4)		
Difficulty Breathing				
Yes	3 (25.0)	9 (75.0)	6.255	*0.0124
No	27 (71.1)	11(28.9)		

χ^{2+}: Chi square with Yates's correction, $p < 0.05$ indicates significance, NA: Not Applicable

Table 2 shows neurological examination findings at presentation in relation to outcome in children with CM. Low Blantyre coma score (score of 0-2), absent corneal reflex, absent pupillary reflex, and papilloedema/retinal hemorrhages, abnormal posturing, hyporeflexia and hyperreflexia were significantly associated with poor outcome ($p < 0.05$). Mortality increased with decreasing coma scores, children with deep coma have a 2.25 risk of dying or developing immediate post- recovery neurological abnormalitiesand it is statistically significant (RR = 2.25, p = 0.018). All the children who died had sluggish or no pupillary reaction and there is a significantly increased risk of poor outcome among them (RR = 2.92, p = 0.021). Children with abnormal fundoscopic findings (papilloedema / retinal haemorrhage) have a 3-fold relative risk of mortality (RR = 3.14, p = 0.001). Also, subjects with decorticate or decerebrate posture have 2.85 relative risk of dying or developing neurological abnormalities (RR = 2.85, p-value = 0.002.)

Laboratory findings among children with cerebral malaria

All the subjects had asexual forms of *Plasmodium falciparum*parasitaemia on admission with degree of parasitaemia ranging from 44,861 to 576,662 parasites per µl of blood and a mean of 324,006 parasites/µl. Hyperparasitaemia (parasite density > 250,000/µl) was observed in 70% of the children. Subjects with hypoglycaemia were significantly associated with mortality and risk of developing neurological abnormalities ($\chi^2 = 6.601$, RR= 3.65 p=0.014). Mean PCV was 23.98 ± 7.70, 72% of the children had anaemia with severe anaemia seen in 8%.Mean platelet count was 179.1 ±45.8 and thrombocytopenia (< 150,000/mm^3)recorded in 24% of the children. Total white blood cell count (WBC) ranged from 4.8 to 58.0 X 10^9/L with a mean of 15.0 ±10.4 X 10^9/L. Leucocytosis (WBC count > 12.0 X 10^9/L) was observed in 62% of the subjects.

Table 2: Relationship between clinical outcome and neurological findings of 50 children with cerebral malaria

Neurological parameters	Clinical outcome (A) Full recovery n (%)	(B) Alive with sequelae n (%)	(C) Death n (%)	RR	X^2	A*(B+C) p
Blantyre coma score			-			
0-2	8 (40.0)	3 (15.0)	9 (45.0)			
3-4	22 (73.3)	8 (26.7)	0 (0.0)	2.25 (1.1- 4.5)		
					5.556	*0.018
Doll's eye reflex						
Negative/Equivocal	6 (50.0)	2 (16.7)	4 (33.3)			
Positive	24 (63.2)	9 (23.7)	5 (13.2)	1.36 (0.67 – 2.74)		
					0.658	0.417
Pupillary Light reflexes						
Sluggish/no reaction	16 (48.5)	8 (24.2)	9 (27.3)			
Normal reaction	14 (82.4)	3 (17.6)	0 (0.0)	2.92 (1.1- 8.59)		
					5.362	*0.021
Fundoscopy						
Papilloedema/Haemorrhage	3 (21.4)	4 (28.6)	7 (50.0)	3.14 (1.68- 5.89)		
Normal	27 (75.0)	7 (19.4)	2 (5.6)		12.054	*<0.001
Corneal reflexes						
Absent	3 (27.3)	3 (27.3)	5 (45.5)			
Present	27 (69.2)	8 (20.5)	4 (10.3)	2.36 (1.31- 4.28)	6.294	*0.012
Posturing						
*Abnormal	3 (23.1)	4 (30.8)	6 (46.2)			
Normal	27 (73.0)	7 (18.9)	3 (8.1)	2.85 (1.55 – 5.22)	9.979	*0.002
Tone						
Normal	7 (87.5)	0 (0.0)	1 (12.5)			
Hypotonia	17 (58.6)	5 (17.2)	7 (24.1)	3.31 (0.50 – 21.78)		
Hypertonia	6 (46.2)	6 (46.2)	1 (7.7)	4.31 (0.64 – 28.84)	2.295	0.129
					3.590	0.058
Tendon reflexes						
Normal	13 (86.7)	2 (13.3)	0 (0.0)	3.59 (0.92 – 13.96)		
Depressed	12 (52.2)	3 (13.0)	8 (34.8)	4.38 (1.11 – 17.32	4.799	*0.028
Hyperreflexia	5 (41.7)	6 (50.0)	1 (8.3)		6.075	*0.014

*Abnormal posturing includes decorticate/decerebrate, p<0.005

Table 3 shows that mean PCV and platelet count were lower among children who died as compared to those who recovered and they show no significant association with clinical outcome. The mean WBC count is significantly associated with mortality and post-recovery neurological abnormalities, (t = -2.769, p-value = 0.008). Children who died or had immediate post-recovery neurological abnormalities, significantly had a higher mean parasite density than survivors who recovered fully (t = -2.614, p = 0.001.) The Log (parasite density) correlates to the parasite count as follows: 12.42 ± 0.606 = 246175 parasite/µl (alive without sequelae); 12.78 ± 0.582 = 353,557 parasite/µl (alive with neurological abnormalities) and 12.93 ± 0.417= 410,692 parasite/µl (died).

Clinical outcome in children with cerebral malaria

The duration of the children on admission differs significantly across clinical outcomes (F = 27.50, p = 0.000). The median coma recovery time (CRT) was 26 hours. The mean CRT was significantly lower in children who recovered fully compared to children who recovered with immediate post-recovery neurological abnormalities (t = 2.308, p = 0.026) (Table 3). Also, the longer the CRT the longer the length of hospital stay (r =.4.81, p= 0.001). The case fatality rate (CFR) was 18.0%, with 22.0% having one or more immediate post-recovery neurological abnormalities and 60.0% recovered fully. The predominant neurological abnormalities observed were regression of attained developmental milestone seen in 10% of the children, and 8% each for facial paresis and hypertonia/rigidity.

Determinants of poor outcome in children with cerebral malaria

Following a step wise logistic regression analysis of all factors that were significant at bivariate level, the independent predictors of mortality or recovery with sequelae were hyperparasitaemia (OR = 8.657**,** p- 0.017**;** Coefficient (β)=2.158, Confidence interval =1.46-51.0**)** and leucocytosis (OR = 1.090,p- 0.035, Coefficient (β) = 0.086; Confidence interval =1.006-1.181). The selected model was significant as revealed by Omnibus test χ^2 = 18.911, p <0.001and had a sensitivity of 84.2% and a positive predictive value of 80.6%.

Table 3: Mean haematological parameters, mean coma recovery time and duration of admission across the clinical outcome in the study population

Laboratory parameters	Clinical outcomes A Full Recovery Mean ± SD	B Alive with sequelae Mean ± SD	C Death Mean ± SD	t/F	A vs (B+C) p-value
PCV	24.37 ± 8.34	24.64 ± 5.52	20.00 ± 9.41	0.220	0.982
WBC (cells/mm^3)	11.07 ± 5.23	18.75 ± 8.52	20.39 ± 8.99	-2.769	*0.008
Platelet count	186.7 ± 50.57	186.54 ± 23.3	145.11 ± 36.4	1.433	0.158
log (Parasite density)	12.42 ± 0.606	12.78 ± 0.582	12.93 ± 0.417	-2.614	*0.001
Coma recovery time (hours)	26.77±13.81	41.9 ± 28.25	-	2.308	*0.026
Duration of admission	150.1 ± 33.2	178.2 ± 30.5	40.3 ± 20.2	F = 27.50	*0.000

t = t statistic, p- < 0.05 indicates significance, F = F statistic

Table 4: Predictors of clinical outcome among children with cerebral malaria

Variables	Coefficient (B)	Odds ratio	95% CI for Odds ratio		*p*
Chloride	0.758	2.135	0.013	4.321	0.197
Log10 parasitemia	2.158	8.657	1.467	51.09	*0.017
WBC count	0.086	1.090	1.006	1.181	* 0.035
Omnibus test, χ^2 = 18.911, p <0.001					
Sensitivity; 84.2%					
Positive Predictive value; 80.6%					

Discussion

The prevalence of cerebral malaria in this study was 5.6%. This is similar to the report by Oluwayemi et al[9] in a similar prospective study within the same South-western Nigeria. This is significantly higher than values of 2.8%[21] and 2.64%[22] reported in retrospective studies in Ile Ife and Osogbo respectively. The differences in the prevalence rates may be explained by the seasonal variation in the study area, the possibilities of missing data in retrospective study, duration of the research as well as the study design.

The prevailing clinical presentation of CM in this study were fever, altered sensorium, and convulsion, this is in conformity with clinical features that have been documented in other studies.[4,9,17]Impaired consciousness has been described as the hallmark of CM, with coma being the most predominant presentation.[2,4] The median duration of fever and unconsciousness prior to presentation was 66 hours and 5 hours respectively, which suggest that an uncomplicated malaria can progress rapidly to CM, this supported the findings reported by other researchers.[12,18] It is essential that health workers be vigilant and prompt in their approach to the management of uncomplicated malaria to prevent such rapid progression to CM. The variation in the pattern of clinical findings may be explained by different age range of the patient across studies, severity and duration of symptoms at presentation, associated co-morbidities and complications.

The mean *P*. falciparum count of 324,000/µlin this study is significantly higher than reports from many studies in Nigeria.[4,17,23] but similar to the mean parasitaemia reported by Molyneux et al.[18] Hyper parasitaemia in 70% of the children with CM in this study is also far higher than 4.5% reported in a similar prospective study.[9] The malaria parasite count yield is a function of timing of sample collection with respect to merozoites release at the peak of fever. There could also be deep tissue sequestrations leaving the peripheral blood with few or no malaria parasites thus affecting the parasite count.[22,24] Proportion of subjects with anaemia (72%) leukocytosis (62%) and thrombocytopaenia (24%) observed in this study is within the range of what has been documented.[4,22]

Regarding the outcome of children with CM, the high CFR of 18% in this study showed that CM remains a major contributor to childhood mortality in keeping with previous reports.[12,21,25]The wide variation in fatality rate across the different studies may be explained based on the study design; durations of the studies or management modalities. The common immediate post-recovery neurological deficits recorded in this study were regression of developmental milestone, facial paresis, hypertonia and abnormal gait. These were similar to earlier reports by other researchers.[9,18,22] There were only very few cases of hemiparesis, urinary incontinency and cortical blindness in contrast to what has been described in some earlier studies.[9,25] The prevalence of 22% neurological deficit as at the time of discharge in this study was lower than 28.2% and 38.6% found in studies in Ado-Ekiti.[9] However, this proportion of neurological deficits is higher than reports of 10.3% found in Ile-Ife.[21] The variations observed across studies might be due to timing of assessment for neurological sequelae; either on discharge or during clinic follow-up.

Clinical and laboratory findings with statistically significant association with mortality and development of neurological deficit were similar to those identified by some authors.[2,4,17] Convulsion and difficulty in breathing were the only presenting symptoms identified in this study to be associated with poor outcome of death and post-recovery neurological deficits. This is in keeping with

finding by other authors.[9,18] In severe malaria, respiratory distress has been reported as a relatively common finding and is a well-established predictor of mortality among children with severe malaria, up to fourfold increased risk of death.[16,26] In contrast, difficulty in breathing was not found to be an independent predictor of mortality in our study. The findings of absent corneal and pupillary reflexes, retinal haemorrhages, papilloedema, etc. as clinical features predictive of poor outcome are consistent with the findings in other studies.[14,17,18] Other clinical features in the study which were associated with but not independently predictive of mortality or development of neurological deficits in CM are deep coma (Blantyre's score 0-2), depressed tendon reflexes and abnormal posturing.

Hyperparasitemia and leucocytosis were the laboratory factors identified as independent predictors of death and development of neurological deficits. Hyperparasitemia has been reported as an independent predictor of mortality in children with CM, [18,27]similar to findings in this study. However, parasite density unexpectedly correlates poorly with disease severity as identified by some authors.[4,12] Leucocytosis was also found to be an independent determinant of poor outcome of death/neurological deficit in this study alongside hyperparasitemia. This has also been documented as independent predictor of poor outcome by Molyneux et al.[18] The leucocytosis observed in this study may further suggest a comorbid illness of septicemia but blood culture was only done as occasion demanded among the studied population.

Conclusion

In conclusion, the identified clinical and haematological determinants of outcome of CM in children should be properly monitored to help to stem down mortality and morbidity associated with cerebral malaria.

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