Original Article

Pattern of Clinical and Laboratory Presentation of Cerebral Malaria among Children in Nigeria

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Abstract

Introduction: Cerebral malaria (CM) is the most lethal form of severe malaria with high case fatality rates. Overtime, there is an inherent risk in changing pattern of presentation of CM which, if the diagnosis is missed due to these changing factors, may portend a poor outcome. Variations in the pattern of clinic-laboratory presentations also make generalization difficult. This study was, therefore, set out to report the pattern of clinical and laboratory presentation of CM. **Methods:** This was a cross-sectional study among children aged 6 months to 14 years admitted with a diagnosis of CM as defined by the World Health Organization criteria. A pretested pro forma was filled, and detailed neurological examination and laboratory (biochemical, microbiology, and hematology) investigations were done. P <5% was considered statistically significant. **Results:** Sixty-four children were recruited with a mean age of 34.9 ± 24.9 months and a male-to-female ratio of 1.9:1. There were 87.5% of under-five children. Fever (96.9%) was the major presenting feature closely followed by convulsions (92.2%). Convulsions were mainly generalized (94.9%) and multiple (76.5%). Profound coma (Blantyre coma score of 0) was present in 12.5% of cases, and the leading features on examination were fever (84.4%) and pallor (75.0%). Retinal vessel whitening (48.4%) was the most common funduscopic abnormality. Metabolic acidosis (47.9%), severe anemia (14.1%), hyperglycemia (17.2%), and hypoglycemia (7.8%) were seen among the children. Few (1.6%) had hyperparasitemia and bacteremia (3.2%). **Conclusion:** Early recognition of the clinical presentation and prompt management may improve the outcome of cerebral malaria.

Keywords: Cerebral malaria, clinical features, coma, hyperparasitemia, Nigeria

Introduction

Malaria constitutes a public health burden in over 84 countries, affecting about 40% of the world population.[1-3] The World Health Organization (WHO) reported that there were 245 million cases of malaria globally, causing 619,000 deaths out of which 76% occurred in under-five children.[1,3] Four countries account for half of the global burden – Nigeria contributing the highest (27%).[3,4] In Nigeria, malaria is responsible for 60% of outpatient clinic visits, 50 million cases, and 100,000 deaths.[4-6]

Cerebral malaria (CM) constitutes about 20%–30% of severe malaria with case fatality rates of 5%–50%.[1,7] CM is an acute febrile, rapidly progressive, diffuse encephalopathy accompanied by altered consciousness in the absence of other causes.[1,2,8] There have been some studies[5-7,9-11] on the clinical presentation of CM in different parts of the world including Nigeria with varying results, especially concerning neurologic manifestations such as hyperreflexia, hypertonia, transient hemiparesis, abnormal posturing which may be decerebrate or decorticate or opisthotonus, and retinal hemorrhages.[5,6,10]

Furthermore, most of the studies were conducted over decades ago, after which there have been various intensified efforts in malaria control such as widespread use of insecticide-treated bed nets, indoor residual spraying, intermittent preventive

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therapy for pregnant women, and use of artemisinin-based therapy among others. These interventions interrupt the time of exposure and consequently interfere with the acquisition of partial immunity against malaria and thus may change the outlook of the pattern of presentation and neurologic manifestations of CM compared to what was obtained previously.

Thus, this study aimed to observe the pattern of clinical and laboratory presentation in CM and to identify the neurological manifestations.

Methods

Study design

This was a prospective cross-sectional study.

Study location

The study was carried out at the Children's Emergency Ward (CEW) of the Wesley Guild Hospital, Ilesa. The hospital is a tertiary health institution which is one of the units of the Obafemi Awolowo University Teaching Hospitals Complex. Ilesa is a semi-urban town located in the rainforest belt of Nigeria.

Study population

All children aged 6 months to 14 years admitted into the CEW during the study period with a diagnosis of CM as defined by the WHO criteria:[8] unarousable coma (Blantyre score ≤2) for more than 30 min, asexual forms of *Plasmodium falciparum* parasitemia, and exclusion of other common causes of loss of consciousness were recruited while children with history suggestive of neurological abnormalities such as cerebral palsy, seizure disorder, or delayed neurodevelopment were excluded.

Study duration

The study duration was November 2021–April 2022.

Sample size estimation

The minimum sample size was estimated using the formula:[12]

$n = (z^2pq)/d^2$

"z" is the standard normal deviate, usually set at 1.96 (95% level of significance).

"p" is the proportion of CM. A 3.9% prevalence of CM reported[13] was used.

"q" is 1−p

"d" is the tolerable absolute sampling error: 5% was used for this study.

$n = (1.96^2 \times 0.039 \times [1-0.039])/0.05^2$

≈58.

Allowing 10% attrition, the sample size = 64 children with CM.

Study procedure

All consecutive subjects who fulfilled the inclusion criteria were recruited. A pretested pro forma was used for data collection. At presentation, the history obtained included demographic characteristics such as age, sex, parental occupation, and educational attainment. Duration of the loss of consciousness and details of other symptoms such as fever and convulsions were obtained.

Each participant was examined at presentation, and a detailed neurological examination was also done. The level of consciousness was assessed using the Blantyre coma score (BCS) (patients with a score of two or less were recruited).[1] The BCS assesses the best motor response to call or pain with a score of 0–2, best verbal response to call or pain with a score of 0–2, and eye movement with or without ability to follow object with a score of 0–1. From the three criteria, a total score was calculated (minimum = 0, maximum = 5).[6] A state of unarousable coma is reached with a score <3 while a BCS of 0 was profound coma. Pupil size on first exposure to light source (i.e., before response to the light) was observed and recorded as either wide/dilated if it covers more than about two-thirds of the iris diameter, mid-size if it is about half the iris diameter, constricted if it is less than half but more than a third of iris diameter, and pinpoint if it is barely perceptible. Pupillary reaction/response to light was also noted and recorded as either normal, slow, or none. Funduscopic examinations were done using a handheld Gowllands United Kingdom ophthalmoscope after dilating the pupils with 1% tropicamide, and the findings were categorized as retinal whitening, vessel changes, retinal hemorrhage, and papilledema.

Investigations

At admission, 8 mL of venous blood was obtained using standard procedure. The sample was used for complete blood count, random blood glucose, blood culture, electrolyte, urea, and creatinine estimation. Malaria parasite identification and count were done on admission. A drop of blood each was placed on two slides to make thin and thick blood smears for species identification and parasite density, respectively. The thick film was air-dried and buffered distilled water (pH 7.2) was added to lyse the cells while the thin film was fixed with methanol for 2 min and then air-dried. Both were stained with Giemsa stain and observed under the microscope. The number of asexual forms of the parasite counted against 200 white blood cells (WBCs) on the thick film will be used to determine parasite density thus:

$$\text{Parasite density } (\text{per } \mu\text{L}) = \frac{\text{Number of parasite counted} \times \text{Patient's total WBC}}{\text{Number of WBC counted } (200)}$$

The malaria parasite count was done daily for all the patients for the first 3 days of admission except in those who died within this period.

Lumbar puncture was done under aseptic conditions. Three milliliters of cerebrospinal fluid (CSF) was collected and analysed for glucose and protein estimation as well as for microscopy, culture and sensitivity. No patient had abnormally

high CSF protein/low CSF glucose, and the total CSF white cell count was <5/mm^3 in all of the patients. Urinalysis was also done.

Treatment

Convulsions were aborted with intravenous diazepam 0.3 mg/kg, and where intravenous access was yet to be secured, intramuscular paraldehyde 0.1 mg/kg or 1 mL/year of life (to a maximum of 5 mL) was given or rectal diazepam (0.5 mg/kg) given. Intramuscular phenobarbitone 20 mg/kg loading dose was given to those who had repeated convulsions despite the above measures, and the maintenance dose of 5 mg/kg of phenobarbitone in two divided doses every 12 h was given.

Hypoglycemia (defined as random whole blood glucose below 2.2 mmol/L) was corrected with 0.5–1 g/kg (equivalent to 1–2 mL/kg) of 50% dextrose water diluted with sterile water to 10%–20% given intravenously. Continuous glucose supply was ensured via 10% dextrose water infusion at maintenance rate as well as nasogastric tube feeding. Random blood glucose was assessed initially every half hour until normal values were obtained on two consecutive occasions, thereafter the glucose estimation using standardized glucometer with Dextrostix was done every hour for two occasions, then every 2 h, and then 4 h till two consecutive normal values were obtained.

Definition of terms

- Acidosis: Serum bicarbonate level <15 mmol/L
- Multiple convulsions: More than two episodes of generalized convulsions in 24 h
- Severe anemia: Venous hematocrit below 15%
- Hyperpyrexia: Axillary temperature ≥40°C
- Hyperglycemia: Fasting whole blood glucose above 7.8 mmol/L
- Hypoglycemia: Whole blood glucose below 2.2 mmol/L
- Hypokalemia: Serum potassium level <3.5 mmol/L
- Hyponatremia: Serum sodium level <135 mmol/L
- Hypernatremia: Serum sodium level >150 mmol/L
- Leucocytosis: WBC count of more than 11,000/μL
- Low bicarbonate: Serum bicarbonate level <20 mmol/L
- Low creatinine: Serum creatinine level <50 μmol/L
- Elevated creatinine: Serum creatinine level >132 μmol/L
- Renal insufficiency/impairment: Serum creatinine >265 μmol/L
- Thrombocytopenia: Platelet count <90 × 10^3/μL
- Thrombocytosis: Platelet count >400 × 10^3/μL
- Mild parasitemia: Malaria parasite counts below 1000 cells/μL
- Moderate parasitemia: Malaria parasite counts from 1000 to 9999 cells/μL
- Severe parasitemia: Malaria parasite counts from 10,000 cells/μL and above. Hyperparasitemia: Malaria parasite counts above 250,000 cells/μL or more than 5% red cells parasitized.

Data analysis

Data were analyzed using SPSS for Windows software version 22 (SPSS Inc., Chicago, IL, USA). Means and standard deviations, proportions, and percentages were determined as appropriate. Test of associations between categorical variables was done using the Chi-squared test and 95% confidence intervals (CI) documented. The association between two continuous variables was determined using the correlation test. Probability (P) = 0.05 was considered statistically significant.

Results

During the study period, a total of 664 children were admitted into the CEW, out of which 257 (38.7%) had severe malaria and 79 (11.9%) were managed for CM.

Sociodemographic characteristics

The age range of recruited children was 6 to 120 months with a mean age of 34.9 ± 24.9 months. Fifty-six (87.5%) were under-five children. Children aged 13–24 months constitute the predominant age group (37.5%). Forty-two (65.6%) were males giving a male-to-female ratio of 1.9:1. The difference in the proportion of males and females was not statistically significant ($\chi^2 = 0.671$, $P = 0.413$). The age and sex distributions of the children are shown in Table 1.

Clinical presentation

The frequency distribution of symptoms before presentation is shown in Table 2. Fever (96.9%) and convulsions (92.2%) were the other most common presenting symptoms. Fever was the first symptom to occur except two who had convulsions first. The duration of symptoms before presentation was shortest for loss of consciousness with a range of 1–20 h and a mean of 5.4 ± 5.4 h and longest for fever with a duration ranging from 24 to 192 h with a mean of 75.5 ± 41.1 h.

The mean duration of illness before presentation was 74.0 ± 41.5 h and range of 12–192 h. The majority (65.6%) presented within 72 h of the occurrence of the first symptom while 30 (46.9%) presented within 48 h. Sixteen (25.0%) presented by 120 h, while 5 (7.8%) presented by 168 h. Only 1 (1.6%) presented at 192 h.

Table 3 shows the clinical signs at presentation. In addition to the loss of consciousness, the other most common signs were fever (84.4%) and pallor (75.0%). The mean temperature at admission was 38.3°C ± 0.9°C with a range of 35.6°C–40.9°C. Fifty-four (84.4%) had fever out of whom 4 (6.3%) had hyperpyrexia. The temperature was significantly positively correlated with the number of convulsions (r = 0.285, P = 0.029).

Fifty-nine (92.2%) convulsed before presentation and the mean age of those who convulsed (35.6 ± 24.4 months) was higher than those who did not (27.4 ± 31.8 months) and the difference was not statistically significant (t = 0.702, P = 0.485). The types and patterns of convulsions are shown in Figure 1. Generalized convulsion (72.9%) was predominant while tonic-clonic (42.4%) pattern was majorly observed.

The number of convulsions before presentation ranged from one to 12 with a mode of two. Nine (14.1%) had one episode

Table 1: Age and sex distribution of the 64 children with cerebral malaria

Age groups (months)	Sex		Male-female ratio	Total	Cumulative total	Cumulative (%)
	Male	Female				
≤12	4 (57.1)	3 (42.9)	1.3:1	7	7	10.9
13–24	14 (58.3)	10 (41.7)	1.4:1	24	31	48.4
25–36	9 (69.2)	4 (30.8)	2.3:1	13	44	68.8
37–48	6 (85.7)	1 (14.3)	6:1	7	51	79.7
49–60	4 (80.0)	1 (20.0)	4:1	5	56	87.5
>60	5 (62.5)	3 (37.5)	1.7:1	8	64	100
Total	42 (65.6)	22 (34.4)	1.9:1	64		

Figures in parentheses represent percentages of row total

Table 2: Frequency distribution of clinical symptoms at presentation

Symptoms*	Frequency (*n*=64), *n* (%)	Duration before presentation (h)	
		Range	Mean±SD
Loss of consciousness	64 (100.0)	1–20	5.4±5.4
Fever	62 (96.9)	24–192	75.5±41.1
Convulsions	59 (92.2)	0.75–95	13.2±18.7
Pallor	34 (53.1)	1–96	24.7±21.9
Vomiting	27 (42.2)	1–144	42.8±32.3
Difficulty with breathing	20 (31.3)	1–24	9.1±9.1
Passage of dark urine	16 (25.4)	2–96	24.9±24.3
Diarrhea	7 (10.9)	1–144	56.0±44.7
Headache	7 (10.9)	10–48	21.7±13.4
Jaundice	7 (10.9)	1–24	6.2±10.0
Gastrointestinal bleeding	1 (1.6)		4.0

*All of the children had more than one symptom at presentation. SD: Standard deviation

Table 3: Frequency distribution of clinical signs at presentation

Clinical signs	Frequency* (*n*=64), *n* (%)
Unconsciousness	64 (100.0)
Fever	54 (84.4)
Pallor	48 (75.0)
Deep rapid breathing	19 (29.7)
Jaundice	10 (15.6)
Cold extremities	8 (12.5)
Dehydration	5 (7.8)
Hyperpyrexia (T°>40.0°C)	4 (6.3)
Subnormal temperature (T°<36.5°C)	1 (1.6)

*All of the children had more than one sign at presentation

of convulsion, 17 (26.6%) had two episodes, while 33 (51.6%) had more than two episodes including one child who had 12 episodes. The number of convulsions increased significantly with increasing duration of unconsciousness (r = 0.324, P = 0.012). The duration of loss of consciousness before presentation ranged from 1 to 20 h with a mean of 5.4 ± 5.4 h.

Convulsions lasted between 2 and 50 min with a mean of 13.4 ± 11.5 min. Of those that convulsed, 23 (29.0%) had episodes lasting up to 5 min, 14 (23.7%) had episodes lasting between 6 and 10 min, and 16 (27.1%) had episodes lasting 15–30 min. The remaining 6 (10.2%) had episodes lasting more than 30 min.

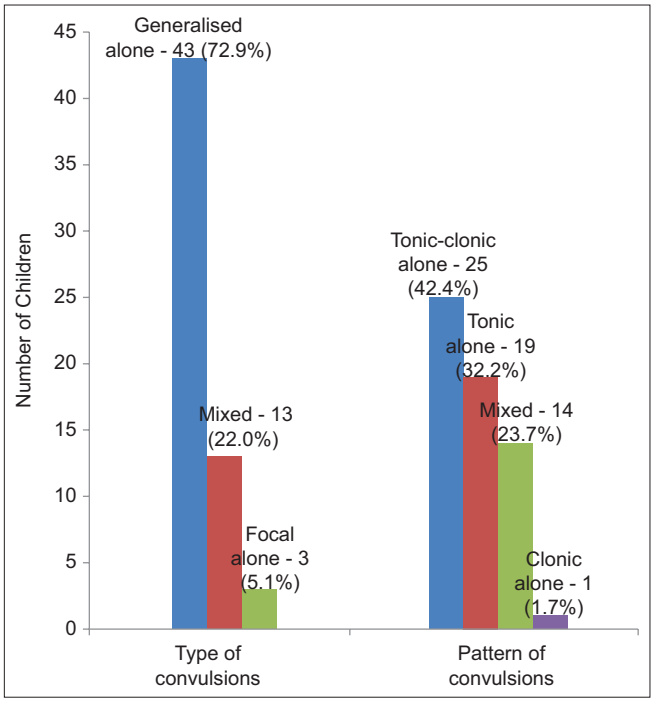

Figure 1: Types and patterns of convulsions recorded among the children

Thirty-two (50.0%) had a BCS of two while 8 (12.5%) had profound coma (BCS of 0). There was a significant negative correlation between the coma score and the duration of unconsciousness (r = −0.323, P = 0.009). The mean duration of unconsciousness before presentation was significantly longer in those with profound coma than without profound coma (10.1 ± 5.8 h vs. 4.7 ± 5.1 h, t = −2.793, P = 0.007, 95% CI = −9.39 – [−1.56]). Similarly, prolonged convulsion (>30 min) occurred significantly more among those who had profound coma (3 of 7, 42.9%) compared with 3 (5.8%) of 52 children without profound coma (χ^2 = 9.289, P = 0.018, RR = 7.43, 95% CI = 1.85–29.89).

Neurological presentation

Table 4 shows the frequency distribution of the abnormal neurologic findings. The majority had abnormal tone (71.9%)

and abnormal reflexes (70.3%), with the major abnormalities being hypertonia (43.8%) and hyperreflexia (42.2%).

Eleven (17.0%) of the 64 children had lateralizing signs. Of those, unilateral hypertonia/hyperreflexia was most common and was identified in 8 (73% of those with lateralizing signs). Two (18.2%) had hypotonia on one side while 1 (9.1%) had a deviation of angle of the mouth. This mouth finding may be a subtle sign of status epilepticus in children with CM, but electroencephalography was not performed in this study.

Twenty-four (37.5%) of the 64 children had abnormal posturing. Of those, decerebrate, opisthotonos, and decorticate posturing in 14 (58.3%), 9 (37.5%), and 1 (4.2%) subjects, respectively, were identified among those with abnormal posture. Abnormal posturing occurred significantly more among children with low BCS ($\chi^2 = 10.124$, $P = 0.005$).

The most common abnormal funduscopic finding was vessel whitening (48.4%) while retinal hemorrhage (17.2%) was the least common. Although abnormal fundoscopic finding was observed in a higher proportion of those with profound coma (7 out of 8; 87.5%) compared with 30 (53.6%) out of 56 without profound coma, this difference was not statistically significant ($\chi^2 = 3.304$, $P = 0.124$).

Sixteen (25.0%) of the 64 children had abnormal pupillary size. Of those, 14 (87.5%) had dilated pupil and 2 (12.5%) had pinpoint pupil of those with abnormal pupillary size. Seven (87.5%) of the eight children who had profound coma as against 9 (16.1%) of the 56 without profound coma had abnormal pupillary size. This difference was statistically significant ($\chi^2 = 19.048$, $P = 0.0001$, RR = 5.44, 95% CI = 2.83–1046). Similarly, abnormal pupillary response was present in all of those who had profound coma as against 25 (44.6%) without profound coma. This was statistically significant ($\chi^2 = 8.589$, $P = 0.005$, RR = 2.24, 95% CI = 1.40–3.09).

Laboratory investigations

The means and ranges of the laboratory parameters are shown in Table 5 while Table 6 shows the frequency distribution of the abnormal laboratory findings. Electrolytes and urea as well as full blood count could not be done in one child, hence the child was excluded from analysis involving those tests.

The mean hematocrit was 22.2% ± 7.0%. Severe anemia was present in 9 (14.1%) children. The mean WBC count was 11.0 ± 6.3 × 10^3 cells/μL. Nineteen (30.2%) had leukocytosis, and the total white cell count had a significant negative correlation with the BCS ($r = -0.340$, $P = 0.006$) while a significantly higher proportion (50.0%) of those who had profound coma had WBC count >15,000 cells/μL compared with the 14.5% without profound coma ($\chi^2 = 5.694$, $P = 0.037$, RR = 3.45, 95% CI = 1.34–8.83). The absolute neutrophil count showed a significant negative correlation with the coma scores ($r = -0.340$, $P = 0.006$); however, this correlation was not observed with the percentage of neutrophils ($r = -0.108$, $P = 0.398$).

Table 4: Abnormal neurological findings at presentation

Abnormal neurologic sign*	Frequency* (*n*=64), *n* (%)
BCS	64 (100.0)
0	8 (12.5)
1	24 (37.5)
2	32 (50.0)
Abnormal tone	46 (71.9)
Hypertonia	28 (43.8)
Hypotonia	18 (28.1)
Abnormal tendon reflexes	45 (70.3)
Hyperreflexia	27 (42.2)
Hyporeflexia	18 (28.1)
Abnormal funduscopic finding	37 (57.8)
Vessel whitening	31 (48.4)
Retinal whitening	29 (45.3)
Retina hemorrhage	11 (17.2)
Abnormal pupillary response	33 (51.6)
Slow/sluggish	23 (35.9)
No response	10 (15.7)
Absent cornea reflex	29 (45.3)
Abnormal pupil size	16 (25.0)
Dilated/wide	14 (21.9)
Pin-point	2 (3.1)
Babinski response	19 (29.7)
Lateralizing signs	11 (17.2)
Signs of meningeal irritation	4 (6.3)

*Most children had more than one feature. BCS: Blantyre coma score

Table 5: Laboratory findings in children with cerebral malaria

Laboratory parameter	Range	Mean±SD
Biochemical		
Random blood sugar (mmol/L)	0.8–12.6	5.0±2.5
Creatinine (μmol/L)	29–600	74.2±75.3
Serum sodium (mmol/L)	114.0–144.0	130.1±7.0
Serum potassium (mmol/L)	1.6–5.4	3.9±0.7
Serum bicarbonate (mmol/L)	17.0–26.0	21.0±2.4
Urea (mmol/L)	2.1–34.0	6.9±4.9
CSF protein (g/dL)	6.0–55.0	19.6±13.5
CSF glucose (mg/dL)	0.6–7.2	3.6±1.6
Hematological		
Packed cell volume (%)	7.0–37.0	22.2±7.0
WBC (×10^3 cells/μL)	3.0–32.0	11.0±6.3
Neutrophil (%)	20–80	53.8±16.2
Absolute neutrophil count (×10^3 cells/μL)	1.3–21.1	6.0±4.4
Lymphocyte (%)	18–80	46.3±16.6
Eosinophil (%)	0–3	0.4±0.7
Platelet count (×10^3 cells/μL)	43.0–398.0	135.3±58.2
Microbiological		
Parasite density (×10^3 parasites/μL)	0.4–396.4	39.1±64.8

CSF: Cerebrospinal fluid, WBC: White blood cell, SD: Standard deviation

Thirty-five (55.6%) children had hyponatremia with the majority (39.7%) having mild hyponatremia. There was no significant association between the serum sodium and the

Table 6: Abnormal laboratory findings in children with cerebral malaria

Abnormal laboratory parameter	Frequency (n=64), n (%)
Anemia (%)	
PCV <30	50 (78.1)
PCV <20	28 (43.8)
PCV <15	9 (14.1)
Leucocytosis	
WBC >11,000/μL	19 (30.2)
WBC >15,000/μL	12 (19.0)
Thrombocytopenia (<90,000/μL)	14 (22.2)
Hypoglycemia	5 (7.8)
Hyperglycemia	11 (17.3)
Low bicarbonate (15–20 mmol/L)	30 (47.6)
Low creatinine (<50 μmol/L)	21 (33.3)
Elevated creatinine (>132 μmol/L)	4 (6.3)
Hyponatremia	35 (55.6)
Mild (125–135 mmol/L)	25 (39.7)
Severe (<125 mmol/L)	10 (15.8)
Hypokalemia (<3.5 mmol/L)	15 (23.8)
Mild parasitemia (1–999/μL)	11 (17.2)
Moderate parasitemia (1000–9999/μL)	21 (32.8)
Severe parasitemia (≥10,000/μL)	31 (48.4)
Hyperparasitemia (>250,000/μL)	1 (1.6)
Bacteremia	2 (3.2)

Most patients had more than one feature. PCV: Packed cell volume, WBC: White blood cell

duration of illness (r = −0.100, P = 0.435), the duration of unconsciousness (r = 0.141, P = 0.271), or the number of convulsions (r = 0.027, P = 0.840). Hypokalemia was present in 15 (23.8%) children. There was a significant negative correlation between the serum potassium and the coma score (r = −0.277, P = 0.028).

Hypoglycemia was present in 5 (7.8%) children, with 2 (3.1%) having intractable hypoglycemia. There was no significant correlation between the random blood sugar and the duration of coma (r = 0.056, P = 0.658) or depth of coma (F = 0.170, P = 0.834).

Serum creatinine was normal in 38 (60.3%), 21 had low values (<50 μmol/L), while 4 had elevated levels (above 132 μmol/L). One of the four who had high creatinine levels had a value of 600 μmol/L (renal insufficiency). Although mean serum creatinine was higher among those who passed coke-colored urine (76.1 ± 53.5 vs. 73.5 ± 81.9 μmol/L), this was not statistically significant (t = −0.119, P = 0.906).

The CSF-to-blood glucose ratio was normal for all patients (range was 0.5–0.9). The total CSF white cell count was <5/mm^3 in all of the patients. No patient had abnormally high CSF protein/low CSF glucose. No organism was identified either by Gram staining or culture in the CSF of all of the patients.

Sixteen (25.0%) of the 64 children passed coke-colored urine. Hemoglobinuria was supported by urinalysis in 12 (75.0%) of the 16 who passed coke-colored urine. Ten (62.5%) of the 16 had trace proteinuria while the others had no proteinuria. Urine culture was positive for *Staphylococcus aureus* in one child who also had prolonged fever and the child was given appropriate antibiotics.

Severe parasitemia was present in 31 (48.4%) children while hyperparasitemia occurred in only 1 (1.6%). There was no significant correlation between the parasite density and the duration of illness (r = 0.097, P = 0.446), the duration of unconsciousness (r = −0.031, P = 0.808), and the depth of coma (F = 1.405, P = 0.253).

Only 2 (3.2%) of the 63 in whom blood culture was done had organisms isolated. The organisms isolated were alpha-hemolytic *Streptococcus* and *Klebsiella* species.

Discussion

CM was responsible for 11.9% of admissions. The incidence of CM in this study was higher than incidence reported from a study in Ile-Ife[14] and Ilorin[13] both in Nigeria. The retrospective nature of the study in Ile-Ife makes it liable to missing records and consequently low incidence. Furthermore, the centers referred to in the two previous studies may take only referred cases, the present study center provides primary and secondary health-care services additionally, and so the 11.9% obtained in this study may be more reflective of the situation in the community. Furthermore, because this study was done during the rainy season when malaria incidence is higher, there was likely to be a higher concentration of severe malaria, including CM in this study more than in the two earlier mentioned studies which were done all year round.

As in other studies,[15,16] majority of the children in this study presented within 72 h of the first symptom. The most common reason for the presentation was loss of consciousness being the one with the shortest mean duration before a presentation. This was shorter than the study from Malawi.[15] The shortness of duration of coma before presentation in this study may be related to the admission policy of the hospital of study which allowed direct presentation without a formal referral, despite being a tertiary center. Similarly, the long duration of fever prior to presentation (mean 74 h) highlights an area for public health/access improvement. If parents can access local care to diagnose malaria at the onset of fever, severe disease may be prevented.

Apart from fever, convulsion was the next most common symptom. This is similar to previous observations of preadmission convulsions.[15] Occurrence of convulsions in this study, like in the previous one,[15] had no significant association with age or temperature, hence making them unlikely to be febrile seizures. Although the presence of convulsion is not included in the WHO diagnostic criteria for CM, researchers[8,17] suggested that convulsions in severe malaria, rather than being viewed only as febrile seizures, may be indicative of direct cerebral involvement. Hypoxic injury to the brain caused by

disruption of microcirculatory blood flow due to sludging of parasitized cells within the brain capillaries, as well as direct axonal injury by malaria pigments and neurotoxic cytokines with resultant neurological dysfunction, may be responsible for both the seizures as well as other neurologic features in CM.[2]

Although generalized convulsions were still more common in this study like in other studies,[8,14,15] focal convulsions were observed more during this study than previously reported values.[7] The reasons for the higher incidence of focal convulsions among children in this study are not immediately clear. Although CM has been described as a diffuse encephalopathy in which focal neurological signs are relatively unusual, focal brain ischemic lesions in area distal to a microcirculatory obstruction in the brain have however been documented in some Kenyan children.[18] However, the lack of brain imaging in this study has made it impossible to determine if focal brain lesions were present in some of the children.

The majority of children in this study had a BCS of 2. Only 12.5% had profound coma. This proportion of patients with profound coma is just about half of the 24% reported in Malawi.[15] The cause of impaired consciousness in CM is unclear but is thought to be due to several interacting mechanisms which include but are not limited to anemia and hypoglycemia. The lower proportions of children with severe anemia and hypoglycemia in this study compared to the study from Malawi may explain the lower number of children with profound coma obtained. In addition, the shorter mean duration of coma before presentation in this study compared to the observation from Malawi which implies a reduced exposure to the damaging effect of hypoxia, anemia, and hypoglycemia on the brain was also in keeping with fewer children with profound coma observed in this study. The contributions of factors other than hypoglycemia and anemia to neuro-depression could be responsible for this.

About 57% of the children had one retinal abnormality or the other. These findings conformed to what was described as malaria retinopathy.[19] These retinal changes were found to be more discriminatory for CM[20] and were thought to be an extension of the pathologic changes occurring in the brain. Vessel whitening is thought to be caused by sequestration of parasitized red cells whose hemoglobin has been consumed by the parasite, thereby altering the normal red color seen in retinal vessels containing red cells with intact hemoglobin. Retinal whitening was attributed to retinal ischemia[21] while the hemorrhage is an extension of the ring hemorrhage that occurs in the brain.[20] The presence of these changes may therefore be an indicator of the severity of the pathologic changes that have occurred in the brain. From these observations, including the high prevalence of focal neurologic features seen in this study, it could therefore be deduced that sequestration of parasitized cells with subsequent localized microcirculatory obstruction, hypoxia, and other perivascular responses was more likely to be responsible for the neurologic features seen in this environment rather than diffuse brain swelling in which generalized neurological manifestations would be expected.

The frequency of retinal hemorrhages in this study was lower than what was reported in Malawi by Beare *et al*.[19] In the Malawi study, the coma duration criterion for the subject recruitment was 4 h unlike in this current study which was 30 min. This implies that the pathologic processes in the brain and the retina would have gone on for much longer, hence more of the subjects would be identified with retina hemorrhage. Furthermore, with the use of indirect ophthalmoscopy in that study, which gives a wider view of the retina, more peripheral hemorrhages would be identified than in the current study where direct ophthalmoscopy was used.

The spectrum of laboratory findings in this study was similar to another study.[22] However, the prevalence of hypoglycemia in this study is lower than the study in Lagos.[23] The factors identified to be risk factors for hypoglycemia from the study in Lagos were present only in a few children in this study which may explain the low rate of hypoglycemia observed in this study. These factors include hyperparasitemia, loss of consciousness for longer than 8 h before presentation, and low admission coma score. Similarly, the duration of the fast before the presentation was also a factor that contributed to hypoglycemia. In large cities like Lagos, the duration of unconsciousness and hence the duration of fast are likely to be prolonged, thereby predisposing the child to hypoglycemia. This is due to the delays occasioned by contact with numerous mid-level health-care providers following the outset of patients' symptoms before they arrived at the high-level referral centers where CM will eventually be treated.

The present study showed that children with deeper coma had elevated white cell count, this was similar to a study in Kenya[24] where leukocytosis was predominant among children with severe malaria, though the elevated white cell count was significant in severe malaria anemia. This could mean that there are alternate cause of coma and particularly anemia in children with severe malaria.

The presence of bacteremia in severe malaria has been well documented in other studies[24,25] although it is still unclear whether this association is mere co-incidence or one predisposing to the other. However, previous studies are in agreement on the fact that the prevalence of bacteremia in CM is significantly lower than in severe malarial anemia and that nontyphoidal *Salmonella* which is the major organism implicated in malaria-associated bacteremia is not of much significance as an etiology of bacteremia in CM as it is in severe malarial anemia. Findings in this study also conform to these positions. The prevalence of bacteremia in this study was similar to the findings in Kenya and Malawi.[24,25]

The strengths of this study include the use of standard WHO criteria in subject recruitment and that all subjects had funduscopy and detailed investigations. It is however limited by the inability to perform postmortem among children who died which was the confirmation of the diagnosis of CM.

Conclusion

This study had characterized the clinical and laboratory features of children admitted with WHO-defined CM at the Wesley Guild Hospital, Ilesa, Nigeria, and has documented the clinical course of CM among the subjects.

Research quality and ethics statement

This study was approved by the Institutional Review Board/ Ethics Committee (Ethics and Research Committee of Obafemi Awolowo University Teaching Hospital Complex, Ile-Ife, Osun state IRB/IEC/0004553). The authors followed applicable EQUATOR Network guidelines during the conduct of this research project.

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Conflicts of interest

There are no conflicts of interest.

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