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Childhood Cerebral Malaria in Nigeria: Clinical Features, Treatment and Outcome

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Authors' contributions

This work was carried out in collaboration between all authors. Author SOO did the study design, wrote the protocol and the final copy of the manuscript. Authors PSO and OVK did the statistical analysis, literature searches and drafted the first copy of the manuscript while analyses of the study were by author OAO. All authors read and approved the final manuscript.

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ABSTRACT

Aims: The study aimed at reviewing the clinical features, treatment and outcome of childhood cerebral malaria in a Nigerian health facility, to improve its management and outcome.
Study Design: It is a retrospective study of cerebral malaria patients.
Place and Duration of Study: Department of Paediatrics, Ladoke Akintola University of Technology Teaching Hospital, Osogbo, Nigeria, between September 2011 and August 2012.
Materials and Methods: Hospital records of children managed for cerebral malaria during the study period were retrieved and assessed. Information extracted from the records was: bio-data, anthropometric values, clinical and laboratory findings, treatment modality, outcome and duration of

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hospital stay. SPSS version 19 software was used to analyze the data.
Results: We studied 20 patients. The age range was 7 to 99 months (mean 43.3±25.2), and under-five children accounted for 75% of the patients. Mean admission weight was 12.8±4.0, with percentage weight for age mean of 84.5% ±11.2. More well-nourished (normal weight) patients (12) than underweight (8) were affected, and the difference of their means percentage weight for age was significant (P = .00). The principal complaints were: fever, convulsion and loss of consciousness. The mean packed cell volume at presentation in the hospital was 23.9%±8.0, and nine patients (45%) had blood transfusion. A large proportion of the patients had electrolytes, urea and glucose abnormalities. *Plasmodium falciparum* was the only parasite specie found in the blood films of all the patients, and all cerebrospinal fluid results were normal. Nineteen (95%) patients received parenteral artemisinin derivatives. Five (25%) patients had their antimalarial changed to quinine. Fifty-five percent had a full recovery, 30% were discharged with neurological deficits, 10% discharged against medical advice, and 5% died. Neurological sequelae were found to be more among underweight children and those who were given artemisinin and amodiaquine combination. The outcome appeared to depend on the age of the patient, sex, type of antimalarial given, nutritional status, abnormal laboratory results and illness duration before presentations at the hospital. Mean hospital stay was 10.4±7.9 days.
Conclusion: The use of parenteral artemisinin derivatives or quinine infusion only, rather than artemisinin and amodiaquine combination drugs at the outset of CM management, improvement in children nutrition and regular malaria parasitaemia monitoring during therapy will go a long way to reducing morbidity and mortality among CM patients in Nigeria.

Keywords: Childhood; cerebral malaria; features; treatment; outcome.

1. INTRODUCTION

Malaria continues to be an important global health problem, with over 40% of the world's population - more than 3.3 billion people - at risk of infection of various degrees of severity in countries with on-going transmission [1]. Malaria has an incidence of 1,120/100,000/ year in the endemic areas of Africa [2]. It caused an estimated 655,000 deaths in 2010, mainly among under- 5 children in sub-Saharan Africa [3], although the incidence of the disease declines in older children with increasing immunity [2]. *Plasmodium falciparum* causes the most serious form of illness [4]. Approximately 1% of clinical infections with *Plasmodium falciparum* result in severe disease, of which one of the most severe forms is cerebral malaria (CM) [5]. Cerebral malaria is the most severe neurological manifestation of severe malaria [2], and is the leading cause of death in children, especially under-five [2,6], and non-immune adults [7].

Cerebral malaria (CM) is commonly characterized by fever, seizures, coma and brain stem signs [8]. The recommended treatment for cerebral malaria is parenteral artesunate as first choice, and parenteral quinine by slow intravenous infusion as second line drug [9]. However, despite adequate treatment using current guidelines, the mortality is about 4 - 46% [10], and about 5 – 15% suffered neurological sequelae (hemiplegia, speech problems, cortical blindness, epilepsy) [5]. Earlier studies suggested that surviving CM patients recover fully neurological functions [11], but over the past 15 - 20 years, it has become increasingly clear that many children sustain severe brain injury with CM [2], and 25% have long-term neurological and cognitive deficits or epilepsy [12]. Thus, CM is now considered a leading cause of neuro-disability in sub-Saharan Africa [8].

The objective of this study was to review the clinical features, laboratory findings, treatment and outcome of cerebral malaria among children admitted into Ladoke Akintola University of Technology (LAUTECH) Teaching Hospital {LTH}, Osogbo, Nigeria. To the best of our knowledge, this had not been done since the inception of the hospital in 1998. The outcome may serve as a guide to effectively manage cerebral malaria, to reduce morbidity and mortality in future.

2. MATERIALS AND METHODS

The study is a descriptive cross-sectional retrospective study of children diagnosed and treated for CM between September 1, 2011, and August 31, 2012, in LTH, Osogbo, Osun State, Nigeria. The hospital is the Teaching Hospital of Ladoke Akintola University of Technology

(LAUTECH), Ogbomoso, and a referral centre for general and district hospitals in Osun State, and the surrounding States - Ondo, Ekiti, Oyo and Kwara. Osogbo is the State Capital of Osun State, located in the south –western Nigeria.

The case-notes of children diagnosed as CM between September 1, 2011, and August 31, 2012, were retrieved and examined, and necessary information extracted. The information extracted from the records included: date of admission, date of birth, age, gender, parents educational level and occupation. Others were; presenting complaints, associated symptoms, documented level of consciousness (using Paediatrics Glasgow Coma Scale (PGCS) [13] (at least 1 hour after termination of seizure or correction of hypoglycemia) [2]), recorded anthropometric values and elicited signs. Furthermore, information extracted from case-notes were: initial clinical and differential diagnoses, laboratory results [full blood counts, blood film for malaria parasites, cerebrospinal fluid and biochemical parameters (electrolytes, urea, creatinine and glucose levels)] and final diagnosis. The result of blood films for malaria parasites and counts were recorded as: one plus (+) when 1-10 parasites per 100 thick film fields were seen, two pluses (++) for 11-100 parasites per 100 thick film fields, three pluses (+++) for 1-10 parasites per single thick film fields and four pluses (++++) for >10 parasites per single thick film fields [14]. The thick and thin blood films for the malaria parasites were stained with Giemsa stain and repeated for the patients, especially when patients did not respond to treatment as expected. Also, blood biochemical parameters considered to be normal were: random blood glucose (3.3 – 5.5 mmol/L), Sodium (135 – 145 mmol/L), Chloride (98 – 106 mmol/L), Potassium (3.5 – 5.0 mmol/L), Bicarbonate (22 – 29 mmol/L) and Urea (1.8 – 6.4 mmol/L) [15].

Retrieved from the records of the patients also, were the drugs administered to the patients before the presentation to the hospital, during admission, details of antimalarial drugs changes if any and duration of unconsciousness. Also, the length of hospital stay, mode of discharge, date of discharge, complications observed, and whether patients honoured their follow-up appointment or not, were also recorded in the study checklists. All patients who fulfilled WHO criteria for the diagnosis of CM were included in the study. According to the World Health Organization (WHO) definition, CM is present in a patient who: 1) Cannot localize a painful stimulus; 2) Has peripheral asexual *Plasmodium falciparum* parasitemia; 3) Has no other identified causes of an encephalopathy [10].

Statistical analyses were performed using version 19.0 of the IBM SPSS software package (SPSS Inc, Chicago, IL, USA). The package was used to determine the frequencies, means and to construct cross-tabulations. Data was presented as frequency tables and mean ± standard deviations (x ± SD). Means were compared using Student's t-test. Association between cerebral malaria and values of determined parameters were assessed using chi-square. A P-value equal or less than .05 was considered indicative of a statistically significant difference.

3. RESULTS

During the period covered by the study, 1,022 children, aged 1month to 15years, were admitted for various diagnoses into our facility. Twenty-seven (2.64%) cases of CM were initially diagnosed, out of which we were able to retrieve 24 case notes. Twenty (83.33%) out the 24 patients, whose final diagnosis was cerebral malaria (fulfilled WHO criteria for the diagnosis of CM), were included in the study. We present the findings as below:

Males and females were equally affected (ratio 1:1). The ages of the patients studied ranged from 7 to 99 months (mean 43.3±25.2), and under-five accounted for 75% of the patients. Shown in Table 1 below is the occurrence of CM among children of different age groups and gender. Patients in our series weighed between 7.4 and 23.0 Kg on admission (mean 12.8±4.0). The lowest percentage weight for age of the expected was 68.3% and the highest 105.6% (mean 84.5% ±11.2). Out of the 20 patients, 12 (60%) had normal weight for age and 8 (40%) were found to be underweight. The mean percentage weight for age for well-nourished was 91.8±7.8, and that of malnourished (underweight) was 73.5±4.0. The difference was statistically significant (t = 6.10091 df 18 P = .00).

Table 2 shows the presenting symptoms of the patients. Fever was intermittent in 75% (15/20) of patients and continuous in 5 (25%). The lowest body temperature recorded for the patients ranged between 35.5 and 37℃ (mean 35.98±0.47, mode and median were 36).

Table 1. Occurrence of cerebral malaria among children of different age groups and gender

Age group in months	Gender		
	Female n (%)	Male n (%)	Total n (%)
1-12	1 (10)	2 (20)	3 (15)
13-36	2 (20)	3 (30)	5 (25)
37-60	5 (50)	2 (20)	7 (35)
>60	2 (20)	3 (30)	5 (25)
Total	10 (100)	10 (100)	20 (100)

$\chi^2 = 2.019$, $df = 3$ $P = .57$

Table 2. Presenting symptoms of children with cerebral malaria

♦Sym-ptoms	Patients																				
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	(%)
Fever	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	100
Convul	x	x	x	x	-	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	95
LOC	x	x	x	x	-	x	x	x	x	x	x	-	x	x	x	x	x	x	x	x	90
Vomit	x	-	x	-	x	x	-	-	-	-	-	-	-	-	-	x	-	-	-	-	25
DB	-	x	-	-	-	-	x	-	-	-	-	x	x	-	-	-	-	-	-	-	20
Pallor	-	x	x	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	10
DBU	x	-	-	x	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	10
GBW	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	x	-	-	-	5
Cough	-	-	-	-	-	-	-	-	-	-	-	-	x	-	-	x	-	x	-	-	15
HA	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	x	-	-	5

♦*Convul = Convulsion, LOC = loss of consciousness, Vomit = Vomiting, DB = Difficulty with breathing, DBU = Dark brown urine, GBW = General body weakness, HA = Headache*

x*Signs and symptoms registered during clinical examination at the emergency ward*

Also, the highest temperature ranged between 38 and 41℃ (mean 39.41±0.86, mode 39.5, 40 and median 39.5). All the 20 patients convulsed at one time or another in the course of their illnesses, 10 (50%) convulsed before admission only, while 9 (45%) patients had convulsions both before and after admission, and one (5%) convulsed during admission only. The episodes of convulsion among the patients ranged from 1 to 30 (mean 6.9±8.1), median and mode were 4). Well-nourished patients (12) had an average of 8.6 episodes of convulsion while malnourished (underweight) patients (8) had an average of 4.4 episodes. The difference was not statistically significant (t = 1.14718 df 18 P = .26). Eighteen (90%) patients had generalized convulsion, and 2 (10%) had partial, but one became secondarily generalized.

Before presentation at the hospital, the duration of illness ranged between 2 and 14 days (mean 4.10±2.75); duration of unconsciousness in 18 patients ranged between 3 and 144 hours (mean 18±33.54, median 6 and mode 3), while the total period of unconsciousness (before presentation plus during admission) in these patients ranged between 13 to 600 hours (mean 150.2±191.8, median 65.5, mode 55). Patients had been treated at home or referral centre with: quinine (3 patients), chloroquine (4), artemether (5), artemether/lumefantrine (1), ceftriaxone (1) and ampicillin/cloxacillin (1). The average time all the patients (20) recovered full consciousness after the commencement of antimalarial drugs was 138.2 hours ±167.2, median 61 hours and mode 24 hours (range: 9 – 528 hours).

The initial clinical diagnoses in the patients were: cerebral malaria (CM) 60% (12/20), meningitis 25% (5/20) and other diagnoses (septicaemia and other forms of severe malaria) 15%. However, when the patients were reviewed with the laboratory results, CM was the final diagnosis made in all the 20 patients. Ten (50%) of our patients were admitted during the night shift, while 9 (45%) and 1 (5%) were admitted during the morning and afternoon shifts, respectively.

Packed cell volume (PCV) at presentation in the hospital ranged between 8 to 37% (mean 23.9% ±8.0). Seven (35%) patients had normal PCV (≥30%), whilst 10%, 25% and 30% had mild (25-29%), moderate (20-24%) and severe (≤19%) anaemia, respectively. Nine out of the 13 anaemic patients were transfused with blood during their illnesses. *Plasmodium falciparum* was the only malaria parasite specie found in the blood films of all the patients. The counts were:

one plus (+) in 7 (35%) patients, two pluses (++) in 9 (45%), 3 (15%) had three pluses (+++), and one (5%) patient had four pluses (++++). A repeat blood films were done for malaria parasite, especially when the patient did not respond to the treatment as expected. The cerebrospinal fluid (CSF) results in all the 20 patients were within normal limit. We were able to retrieve 11 electrolytes, 10 urea and 13 random blood glucose results out of the 20 patients. Out of the 11 electrolytes results, 10 (90.9%) patients had one or more abnormal results. Table 3 shows the details of the biochemical parameters found in the patients.

Table 4 shows the types of antimalarial drugs given to the patients and pattern of changes. In addition to the antimalarial, 17 patients were initially given antibiotics, 15 received phenobarbitone and two mannitol. Others drugs given to some of the patients were diazepam, paraldehyde and paracetamol.

Neurological deficits were observed in eight (40%) patients while on admission, 1 died and another one was discharged against medical advice by the parent. One patient had three neurological sequelae while four patients had two each and three patients had one each. These sequelae were: motor deficit (2), cortical blindness (2), aphasia (5), hearing impairment (1) and loss of developmental milestone (4). Table 5 shows observed neurological deficits in relation to age groups. Other complications seen in these patients were anaemic heart failure (5 patients), and acute kidney injury (1).

Table 3. Available biochemical parameters with number of abnormalities

Parameters (mmol/L)	HCO3	Na	K	Cl	Urea	Glucose
Results available (n)	11	11	11	11	10	13
Obtained values range	16 - 23	120 - 147	2.8 – 5.2	84 - 118	4.1 - 22	2.3 – 7.6
Values mean (±SD)	19.7 (±2.3)	132.9 (±6.9)	4.2 (±0. 8)	102.1 (±8.6)	9.92 (±5.5)	5.3 (±1.4)
Values median	19	131	4.3	101	9.2	5.4
Values mode	18	131	3.6	101	4.1	6.5
Abnormal results (n%)*	8 (72.7)	7 (63.6)	4 36.4)	6 (54.6)	7 (70)	8 (61.5)
Elevated values (n%)*	♦None	1 (9.1)	2 (18.8)	4 (36.4)	7 (70)	6 (46.2)
Depressed values (n%)*	8 (72.7)	6 (54.6)	2 (18.8)	2 (18.8)	♦None	2 (15.4)

*♦No patient had abnormally high or low value; *The percentage is in relation to the available results*

Table 4. Types of antimalarial given and pattern of changes

Antimalarial given	Antimalarial Change		
	YES n (%)	NO n (%)	Total n (%)
♦I.V Artesunate	2 (33.3)	4 (28.6)	6 (30)
♦I.V Artesunate and amodiaquine	3 (50.0)	6 (42.9)	9 (45)
♦IV Quinine	0 (0)	1 (7.1)	1 (5)
*IM Arteether + Amodiaquine	1 (16.7)	3 (21.4)	4 (20)
Total	‡6 (100)	14 (100)	20(100)

$\chi^2 = 0.556$ df 3 P = .91

*‡Five (25%) patients had their antimalarial changed to quinine infusion and one to artemether/lumefantrine combination because of poor response; ♦I.V: Intravenous Infusion, *IM: Intramuscular Injection*

Table 5. Observed neurological deficits in relation to age groups

Age group in month	Neurological deficits		
	Yes n (%)	No n (%)	Total n (%)
1-12	1 (33.3)	2 (66.7)	3 (100)
13-36	3 (60.0)	2 (40.0)	5 (100)
37-60	2 (28.6)	5 (71.4)	7 (100)
>60	2 (40.0)	3 (60.0)	5 (100)
Total	8 (40.0)	12 (60.0)	20 (100%)

χ^2 =1.270 df 3 P = .74

The outcome of cerebral malaria in the patients in relation to antimalarial drugs given is shown in Table 6, to gender in Table 7, to nutritional status in Table 8 and duration of illness before presentation in the hospital in Table 9. Only 7 (41.2%) out of the 17 discharges, including 4 out of 6 patients discharged with neurological deficits honoured their follow-up appointments, and also one out of 2 patients who discharged against medical advice (DAMA) came back for a follow-up. The duration of hospital stay of the patients ranged between 3 to 30 days (mean 10.4±7.9, mode six days), and its relationship to antimalarial given is shown in Table 11.

The fatal case was 54-month-old female patient admitted during the night shift. She presented with fever, convulsion and loss of consciousness, and she had multiple convulsions (10) during admission, with some neurological deficits. She weighed 12 Kg (69.4% of the expected), had hyponatremia, hypokalemia, hypochloremia, hyperglycaemia, and anaemia (PCV 25%). Blood film revealed two pluses (++) of *P. falciparum*, and she was placed on intravenous artesunate and the electrolytes imbalance was addressed. Despite all these, there was no significant response and a repeat blood film still showed trophozoites of the malaria parasite and quinine infusion was introduced without success.

Table 6. Outcome of cerebral malaria in relation to antimalarial given

Antimalarial given	Outcome				
	Death n (%)	‡DAMA n (%)	♦Neuro deficit n (%)	Full recovery n (%)	Total n (%)
♠I.V Artesunate	1 (16.7)	1 (16.7)	-	4 (66.6)	6 (100)
♠I.V Artesunate + Amodiaquine	-	1 (11.1)	5 (66.7)	3 (22.2)	9 (100)
♠IV Quinine	-	-	-	1 (100)	1 (100)
*IM Arteether + Amodiaquine	-	-	1 (25)	3 (75)	4 (100)
Total	1 (5)	2 (10)	6 (30)	11 (55)	20 (100)

χ^2 = 13 df = 12 P = .37

*‡DAMA: Discharged against medical advice. ♦Neuro deficit: Discharged with neurological deficits. ♠I.V: Intravenous Infusion, *IM: Intramuscular Injection*

Table 7. Outcome in relation to gender

Gender	Outcome				
	Full recovery	‡Neurol deficit	♦DAMA	Death	Total
Male	5 (50)	4 (40)	1 (10)	0 (0)	10 (100)
Female	6 (60)	2 (20)	1 (10)	1 (10)	10 (100)
Total	11(55)	6 (30)	2 (10)	1 (5)	20 (100)

χ^2 =1.76 df 3 P = .62; ‡DAMA: Discharged against medical advice. ♦Neuro deficit: Discharged with neurological deficits.

Table 8. Outcome in relation to nutritional status

Nutritional status	Outcome				
	Full recovery	‡Neurol deficit	♦DAMA	Death	Total
Normal weight	8 (66.6)	2 (16.7)	2 (16.7)	0 (0)	12 (100)
Underweight	3 (37.5)	4 (50)	0 (0)	1 (12.5)	8 (100)
Total	11(55)	6 (30)	2 (10)	1 (5)	20 (100)

χ^2 =5.36 df 3 P = .17; ‡DAMA: Discharged against medical advice. ♦Neuro deficit: Discharged with neurological deficits.

Table 9. Outcome in relation to the duration of illness before presentation

Duration in days	Outcome				
	Full recovery	‡Neurol deficit	♦DAMA	Death	Total
≤ 3	8 (66.6)	4 (33.4)	0 (0)	0 (0)	12 (100)
> 3	3 (37.5)	2 (25)	2 (25)	1 (12.5)	8 (100)
Total	11(55)	6 (30)	2 (10)	1 (5)	20 (100)

χ^2 =5.35 df 3 P = .15

‡DAMA: Discharged against medical advice. ♦Neuro deficit: Discharged with neurological deficits.

Table 10. Duration of hospital in relation to antimalarial given

Antimalarial given	Duration of hospital stays in days				
	1 – 5 n (%)	6 –10 n (%)	11-15 n(%)	>15 n (%)	Total n(%)
♠I.V Artesunate	2 (33.3)	2 (33.3)	1 (16.7)	1 (16.7)	6 (100)
♠I.V Artesunate + Amodiaquine	1 (11.1)	5 (55.6)	0 (0.0)	3 (33.3)	9 (100)
♠IV Quinine	0 (0.0)	1 (100)	0 (0.0)	0 (0.0)	1 (100)
*IM Arteether + Amodiaquine	1 (25.0)	2 (50.0)	0 (0.0)	1 (25.0)	4 (100)
Total	4 (20.0)	10 (50.0)	1 (5.0)	5 (25.0)	20 (100)

$\chi^2 = 5.03$ df = 9 P = .83

*♠I.V: Intravenous Infusion, *IM: Intramuscular Injection*

4. DISCUSSION

The finding of 27 (2.64%) cases of CM out of 1,022 admissions was similar to 2.7% and 2.8% found in Yaounde, Cameroun [16] and Ile-Ife, Nigeria [17], respectively. However, the prevalence of CM in this study is less than 5.5% found in Ado-Ekiti, Nigeria [18]. The prevalence of CM may depend on the geographic area, the season of the year and health institution in which the study was carried out and, also, the type and design of the study. In the malaria endemic region, the incidence of CM is more than that of the non-endemic region because malaria transmission is throughout the year in the former, with peaks during the rainy season. Also, the disease is a severe one, and referral centres (tertiary and secondary health facilities) manage most of them leading to high prevalence in such hospitals. The prospective study usually records higher prevalence than retrospective because of the limitation (missing records) in the latter.

Overdiagnosis of CM in the resource-poor environment is common and challenging, partly because CM is considered in all children having fever with altered consciousness in Nigeria. [9] Also, partly because the further investigations needed to differentiate it from other causes of encephalopathy may be delayed or not available. We demonstrated overdiagnosis in our study, as 20 patients out 24 fulfilled WHO criteria for the diagnosis CM. In this study, 75% of children affected with CM were under-fives in agreement with the earlier study, [16] with pre-school children (37 - 60-month-old) bearing the brunt [2] (see Table 1). The waning or even disappearance of maternal antibodies against malaria parasites in the children when they are yet to acquire enough and potent immunity against malaria [10], may account for this. Also, increase outdoor activities (day care and schooling) of this group of children could expose them to mosquito bites, and subsequently malaria infection.

Continuous fever in malaria infection usually occurs when complications like hyperparasitemia, severe anaemia, fluid, electrolytes and other metabolic derangements set in [19-21]. When the complications occur, affected patient goes into hyperdynamic circulation [22], with increased metabolic rate (catabolic state) [23]. It is, therefore, imperative for the attending physician to do a comprehensive evaluation of patients as clinical findings may point to early complications, and prompt and appropriate remedy instituted.

Convulsion is a common clinical finding in CM [24]. It could be the reason for seeking medical help in the hospital as it is usually sudden and dramatic, and parents fear that the child may die. Commonly, convulsions in CM are generalized, and multiple [5,24] and can occur before or after admission, or both. Convulsion in CM is usually due encephalopathy. Various hypotheses have been postulated as the causes of encephalopathy, but the most popular being the sequestration theory [5]. Efforts should be made to prevent further convulsion during admission to prevent further neuronal damage [5]. Further convulsions during admission could be as a result of misdiagnosis or worsening of the disease condition caused by delay in instituting appropriate and effective treatment. Also, complications – hypoglycaemia, severe anaemia causing hypoxic encephalopathy, intracranial hypertension [23], acute kidney injury (AKI) (hypertension), electrolyte derangements and home remedy, especially homemade concoctions made from cow urine and onion [25], may further cause seizures. The affectation of the brain in CM is usually global with cerebral oedema predominating. Hence convulsion usually generalizes as seen in 90% of our patients.

The relationship between malnutrition and cerebral malaria is controversial, with conflicting reports from studies on their relationship [26].

More well-nourished (normal weight) patients (12) than underweight (8) were affected, with statistically significant difference (P = .00) between their means percentage weight for age. The finding alluded the believing or assertion that CM is more prevalent among well-nourished (normal weight) than malnourished [27], especially underweight children [28]. Reasons adduced are that well-nourished children have not been exposed to malaria as frequently as malnourished, and therefore, are not able to develop the same degree of immunity as the malnourished children [29]. Furthermore, well-nourished children with higher haematocrit and plasma protein levels are more vulnerable to stagnant *anoxaemia* in *falciparum* malaria infection [29].

Malnourished children were less susceptible to malaria and, even CM when compared to well-nourished [18,30]. However, the outcome of CM in the malnourished children is very poor, as observed in this study, that only death recorded was a malnourished child. Among other reasons why malnourished succumb to severe malaria are: coexisting bacterial infections, electrolytes and fluid derangements, hypoglycaemia, hypocalcaemia, hypothermia, congestive cardiac failure and overwhelming sepsis [30]. These conditions should be painstakingly sought for and treated. Furthermore, as nutritional status of malnourished children improves during therapeutic feeding or treatment, the incidence of malaria and even CM increased in them [31]. Therefore, as part of the management of under-nutrition in malaria endemic area, all malnourished children should have access and use Insecticide Treated Nets (ITN) and malaria chemoprophylaxis [31].

On the average, our patients were anaemic. Anaemia is a common complication of malaria. Malaria parasites lyse red blood cells, and it could be severe enough to cause anaemia, anaemic heart failure, and even jaundice in the patients. Malaria parasites could thrive better in a relative hypoxic state, which promotes their growth and maturation [22]. Blood transfusion is a common phenomenon in Children Emergency Units in malaria endemic area. The intriguing thing we observed about blood transfusion in some of these patients with malaria anaemia is convulsion after transfusion. The convulsion might result from disequilibrium of patients' internal milieu, and/ or encephalopathy caused by sequestrations of parasitized red blood cells (from transfusion) in cerebral vessels.

The number of malaria parasites in the blood films could vary as the yield depends on when the sample is taken and who is looking at the blood film. There could be deep tissue sequestrations leaving the peripheral blood few or no malaria parasite. The presence of malarial pigment in monocytes is a useful indicator for diagnosing malaria, especially in anaemic children and in patients with severe malaria associated with absent or low parasitaemia [32]. In non-immune persons, like younger children, even low-level parasitemia may be accompanied by severe illness [10].

Our patients had various electrolytes abnormalities (Table 3). Severe hyponatraemia, hypokalemia and low bicarbonate levels are common in *Plasmodium falciparum* infection [19]. From the clinical point of view, hyponatraemia, hypokalemia and metabolic acidosis are indicators of severity and determinant of outcome in CM [19,33]. However, the use of Ringer's lactate as fluid of resuscitation in CM may be unsafe as a good number of patients may have hyperkalaemia and hypercalcaemia at presentation [20]. We observed in the present study that 18% (2 out 11) of the patients had hyperkalaemia. Also, Enwere et al. [21] and Oguche et al [33] argued that the administration of hypotonic saline and isotonic glucose solutions to resuscitate cerebral malaria patients is questionable. The researchers hinged on the fact that majority of the children in their studies suffered hyponatraemia, and this study alluded to their stand as about 54.6% (6 out of 11) and 70% (7 out of 10) of our patients had hyponatraemia and azotaemia, respectively.

It is intriguing to note that most patients (6 out 8) with blood glucose abnormalities had hyperglycaemia rather than hypoglycaemia (Table 3). The reason could be that the attending physician obtained the blood samples for glucose estimate after the commencement of dextrose infusion, an act that needs to be discouraged. However, other possible reasons could be that since most patients were referred from other health facilities, they could have already been infused with dextrose water from the referral centres. Furthermore, we operate in a society in which mothers make every effort to ensure that their children feed, especially when ill. The mothers force feed their children with fluid diet when they refuse to eat, oblivious of the inherent dangers (choke and aspiration). The act should be discouraged, and its contribution to the low incidence of hypoglycaemia needs to be

evaluated in another study. On the contrary, it could have been stress induced hyperglycaemia, as any illness in a child is stressful to him/her, more so with multiple convulsions in CM. Response to stress due to any acute illness tends to provoke the release of counter-regulatory hormones such as cortisol, catecholamines, and glucagons that favour elevation of glucose levels [34]. Van Thien et al [35], in reported the association between hyperglycaemia and severe malaria, and that CM stimulates glucose production to a greater extent than other forms of malaria.

Anecdotal evidence showed that physicians, including paediatricians, are frowning at the use of artemisinin alone to treat cerebral malaria in our environment, especially when artemisinin combination therapy (ACT) has been recommended to treat uncomplicated malaria. The act seems to negate the objectives of ACT usage – prevention of resistance, recrudescence and promotion of efficacy. Considering the half-life of artemisinin derivatives, 10 - 60 minutes [36] and severity of cerebral malaria, patients would be left without adequate anti-malaria concentration in their systems for as long as 11 – 23 hours, because parenteral artemisinin derivatives are given 12 to 24 hours interval [9]. At times, artemisinin derivatives would have to be changed to quinine infusion after days on artemisinin derivatives without expected improvement (Table 4). This further predisposes patients to complications and prolonged hospital stay. Hence, physicians use ACT, especially artemisinin and amodiaquine combination from the outset to manage cerebral malaria.

However, the finding of this study showed that children who were given artesunate and amodiaquine combination appeared to develop neurological sequelae (Table 6) and have prolonged hospital stay (Table 10). Although, there was no statistically significant difference (P = .37 and P = .83), it will be proper to avoid the use artesunate and amodiaquine combination to treat CM from the outset until the findings from other studies could invalidate or confirm these findings. ACT can be used to further treat malaria in CM patients when they are fully conscious and eating. Our sample size was small to make a categorical statement, but it is food for thought for physicians and health policy makers. Therefore, there is a need to investigate further these findings using a larger sample size in this environment.

The observed neurological deficits were more among the Toddlers (Table 5). It could be presumed to result from the fact that the brains of children in this age group are more vulnerable to CM probably due to its immaturity, coupled with rapid acquisition of new skills. Prolonged exposure to high doses of lipid-soluble analogues of artesunate can cause neurological damage in animal experiments [37]. Could this be the case in this study (Table 6); in a society where any drug could be purchased across the counter without doctors' prescription or equipment to monitor serum levels? Therefore, the contributions of artesunate to severe and persistent neurological sequelae need further assessment.

The outcome of cerebral malaria in this study is similar to earlier studies. [16-18] Documented case fatality rate (CFR) range between 4 to 46%, [10] and our 5% CFR falls within this range. The CFR in this study is comparable to 5.2% and 5.6% in Nigeria [17] and Cameroun [16], respectively. However, our CFR is less than 13.3% [38] and 13.6% [18] in some previous studies. Thirty percent (30%) of our patients were discharged with neurological sequelae. It was similar to 28.2% and 38.6% found in studies in Ado-Ekiti [18] and Calabar [38] Nigeria, respectively, but higher than 10.3% and 16.7% found in Ile-Ife, Nigeria, [17] and Yaounde, Cameroun, [16] respectively. These variations might due to a different time at which the researchers assesses the patients for neurological sequelae; whether it was done while the patient was still on admission or at discharge or in follow-up clinic. Fifty-five percent (55%) of our patients had a full recovery, while Oluwayemi et al [18] recorded 35% and Zaroog et al. [6] 84%. Although they were not statistically significant in this study, the outcome of this study appeared to depend on the age of the patient (Table 5), sex (Table 7), type of antimalarial given (Table 6), nutritional status (Table 8), early presentations to the hospital (Table 9), electrolytes derangements and hyperglycaemia. Also, the outcome could depend on early diagnosis, the severity of the disease, and the promptness, adequacy and effectiveness of the intervention.

One phenomenon we found in our study that was not reported in other similar studies is discharged against medical advice by the parents. The reasons given among others were a slow paste of full recovery, and financial constraint. This behavior by the relatives is not surprising as we

operate in an environment where any time or money spent on health is considered a waste. To buttress this fact, only 7 out of 17 discharges and 4 out of 6 patients discharged with neurological deficits came back for follow-up appointments. This unacceptable behavior of the parents could jeopardize the health of their wards. In order to stop this trend, the public should be educated through various mass media to have attitudinal change towards their health, the health institutions and its workers.

5. CONCLUSION

Our study revealed that fever, multiple convulsions, loss of consciousness and normal weight were the principal clinical features, and low haematocrit, *P. falciparum parasitaemia* and electrolytes and metabolic derangements were common laboratory findings in CM. The common drugs used were artemisinin derivatives singly or in combination with amodiaquine. The percentage of children who suffered neurological sequelae was high, especially among children given artemisinin and amodiaquine combination and those had poor nutritional status. The outcome appeared to depend on the age of the patient, sex, type of antimalarial given, nutritional status, electrolytes derangements, hyperglycaemia and early hospital presentations.

The objective of this study was to review the clinical features, laboratory findings, treatment and outcome of cerebral malaria among children. The outcome of this study may serve as a guide to correctly and effectively manage CM, so as to reduce morbidity and mortality in future. With the finding that neurological sequelae tends to associate with the use of artemisinin and amodiaquine combination in the management of CM, amodiaquine should be avoided from the outset of CM management till the patient is conscious and eating. Parenteral artemisinin derivatives or quinine infusion only should be used as recommended. [1,9] Also, parents should be encouraged to feed their children well and come early to the hospital whenever their children become ill. As far resource can accommodate, blood films for malaria parasite should be done at a regular interval for all severe malaria patients to monitor responses to therapy and to detect drug failure early, so that second line drugs could be used promptly. With the above suggestions followed, the morbidity and mortality of CM could be reduced appreciably.

ETHICAL APPROVAL

In a retrospective study, individual consent is not required provided the article will be free of any personal identifiable information. To ensure this, patients' names, initials, hospital numbers and photograph were excluded from the manuscript. The Ethical Committee of Ladoke Akintola University of Technology (LAUTECH) Teaching Hospital, Osogbo is vested with authority to give approval to any research study involving human subject(s) or records, and its publication. The Ethical Committee approved this study.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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