

Original Research Article
**Childhood Cerebral Malaria in Nigeria: Clinical
Features, Treatment and Outcome**

ABSTRACT

Aims: The study aimed at reviewing the clinical features, treatment and outcome of childhood cerebral malaria in a Nigerian health facility, in order 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 study period were retrieved and assessed. Information extracted from the records were: bio-data, anthropometric values, clinical and laboratory findings, treatment modality, outcome and duration of hospital stay. Data was analyzed with the SPSS version 19 software.

Results: Twenty out of 24 patients were studied. Age range was 7 to 99 months (mean 43.30 ± 25.24), and under-five children accounted for 75% of the patients. Mean admission weight was 12.78 ± 3.99 , with percentage weight for age mean of $84.5\% \pm 11.18$. More well-nourished patients (12) than underweight (8) were affected, and the difference in 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 was $23.90\% \pm 8.01$, and nine patients (45%) had blood transfusion. A large proportion of the patients had electrolytes, urea and glucose derangements. *Plasmodium falciparum* was the only parasite species found in the blood films of all the patients. Nineteen (95%) patients received parenteral artemisinin derivatives. Five (25%) patients had their antimalarial

changed to quinine. Forty-five percent had full recovery, 40% neurological deficit, 10% discharges against medical advice and 5% died. Mean hospital stay was 10.40 ± 7.90 days.

Conclusion: Fever, multiple convulsions and loss of consciousness were common presentation of CM in Nigeria, with associated neurological sequelae, parasitaemia, anaemia, electrolytes and metabolic derangements, in children that may have normal nutritional status.

Keywords: Childhood, cerebral malaria, presentations, treatment, outcome

1. INTRODUCTION

Malaria continues to be a major 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 the disease [4]. Approximately 1% of clinical infections with *Plasmodium falciparum* result in severe disease, of which one of the most serious forms is cerebral malaria (CM) [5]. Cerebral malaria is the most severe neurological manifestation of severe malaria [2], and is the main cause of death in children, especially under-five [2, 6], and non-immune adults [7].

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 patients fully recover neurologically

[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 presentations, 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, in order to reduce morbidity and mortality in future.

2. MATERIAL AND METHODS

This 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 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 are; presenting complaints, associated symptoms, documented level of consciousness (using Paediatrics Glasgow Coma Scale (PGCS) [13] (at least 1 hour after termination of a seizure or correction of hypoglycemia) [2]), recorded anthropometric values, elicited signs, working and differential diagnoses, laboratory results [full blood counts, blood film for malaria parasites, cerebrospinal fluid and biochemical

parameters (electrolytes, urea, creatinine and glucose levels)]. In this study, blood films for malaria parasites 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]. Also, blood biochemical parameters considered to be normal were: random blood glucose (3.3 – 5.5mmol/L), Sodium (135 – 145mmol/L), Chloride (98 – 106mmol/L), Potassium (3.5 – 5.0mmol/L), Bicarbonate (22 – 29mmol/L) and Urea (1.8 – 6.4mmol/L) [15].

Retrieved from the records of the patients also, were the drugs administered before presentation, during admission, details antimalarial drugs changes if any and duration of unconsciousness. In addition, final diagnosis, date of discharge, duration of hospital stay, mode of discharge, complications observed, and whether patients honoured their follow-up appointment or not, were recorded in the study check lists. All patients who fulfilled WHO criteria for 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 $\pm$ standard deviations ($\bar{x} \pm SD$). 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.

78

79 3. RESULTS

80 During the period covered by the study, 1,022 children, aged 1month to 15years, were
 81 admitted for various diagnoses into our facility. Twenty seven (2.64%) cases of CM were
 82 initially diagnosed, out of which we were able to retrieve 24 case notes. Twenty (83.33%) out
 83 the 24 patients fulfilled WHO criteria for the diagnosis of CM, at one time or the other, while
 84 on admission in the course of their illnesses, were studied. The findings are presented
 85 below.

86 Males (10) and females (10) were equally affected given ratio 1:1. The ages of the patients
 87 studied ranged from 7 to 99 months (mean 43.30 ± 25.24), and under-five accounted for 75%
 88 of the patients. The occurrence of CM among children of different age groups is shown in
 89 Table 1. Patients in our series weighed between 7.4 and 23.0Kg on admission (mean 12.78
 90 ± 3.99). The lowest percentage weight for age of the expected was 68.3% and the highest
 91 105.6% (mean $84.5\% \pm 11.18$). Out of the 20 patients studied, 12 (60%) had normal weight
 92 for age and 8 (40%) were found to be underweight. The mean percentage weight for age for
 93 well-nourished was 91.78 ± 7.81 , and that of mal-nourished (underweight) was 73.45 ± 3.95 .
 94 The difference is statistically significant ($t = 6.10091$ df 18 $P = .00$).

95 Eighteen out of the 20 patients (90%) presented with complaints of fever, convulsion and
 96 loss of consciousness, while 1 (5%) had fever and loss of consciousness and another one
 97 (5%) fever only. All the 20 patients presented with fever, 75% (15/20) were intermittent, and
 98 5(25%) continuous. All the 20 patients convulsed at one time or the other in the course of
 99 their illnesses, 9 (45%) convulsed before admission only, while another 9 (45%) patients had
 100 convulsions both before and during admission, with 2 (10%) convulsed during admission
 101 only. The episodes of convulsion among the patients ranged from 1 to 30 (mean 6.90 ± 8.09 ,
 102 median and mode were 4). Well-nourished patients (12) had average of 8.58 episodes of
 103 convulsion, whilst mal-nourished (underweight) patients (8) had average of 4.38 episodes.

104 The difference was not statistically significant ($t = 1.14718$ df 18 $P = .26$). Eighteen (90%)
 105 patients had generalized convulsion and 2 (10%) had partial but one became secondarily
 106 generalized.

107

108 **Table 1: Occurrence of cerebral malaria among children age groups**

109

Ages in Months	Number of Patients	Percentages (%)
1-12	3	15.0
13-36	5	25.0
37-60	7	35.0
>60	5	25.0
Total	20	100

110

111 Eighteen out of 20 patients presented with complaint of unconsciousness, the duration of
 112 their unconsciousness before presentation ranged between 3 and 144 hours (mean 18
 113 ± 33.54 , median 6 and mode 3), the PGCS of these 18 patients at presentation was found to
 114 range between 2 and 13 (mean of 7.5 ± 2.55 , median 8 and mode 9). The remaining 2
 115 patients were found to be unconscious with PGCS of 8 and 10 respectively during
 116 examination at presentation. The average time of full recovery of consciousness after the
 117 commencement of antimalarial drugs was 138.2 hours ± 167.2 , median 61 hours and mode
 118 24 hours (range: 9 – 528 hours). The total period of unconsciousness (before presentation
 119 plus during admission) in these patients ranged between 13 to 600 hours (mean 150.20
 120 ± 191.75 , median 65.50, mode 55). Other symptoms documented were: vomiting (5 patients),
 121 difficulty with breathing (4), cough (3), dark-brown urine (2), pallor (2) and generalized body
 122 weakness (1). Duration of illness before presentation ranged between 2 and 14 days (mean
 123 4.10 ± 2.75). Before presentation, drugs given to the patients were: quinine (3 patients),

124 chloroquine (4), arthemeter (5), artemether/lumefantrine (1), ceftriazone (1) and
125 ampicillin/cloxacillin (1).

126 CM was the initial diagnosis in 60% (12/20) of the patients, followed by meningitis 25%
127 (5/20) and other diagnoses (septicaemia and other forms of severe malaria) accounted for
128 15%. Ten (50%) of our patients were admitted during night shift, whilst 9 (45%) and 1 (5%)
129 were admitted during the morning and afternoon shifts, respectively.

130 Packed cell volume (PCV) at presentation ranged between 8 to 37% (mean 23.90% $\pm$ 8.01).
131 Seven (35%) patients had normal PCV ($\geq$ 30%), whilst 10%, 25% and 30% had mild (25-
132 29%), moderate (20-24%) and severe ($\leq$ 19%) anaemia, respectively. Nine out of the 13
133 anaemic patients were transfused with blood during the course of their illnesses.
134 *Plasmodium falciparum* was the only malaria parasite specie found in the blood films of all
135 the patients, and the counts were: one plus (+) in 7 (35%) patients, two pluses (++) in 9
136 (45%), 3 (15%) had three pluses (+++), and one (5%) patient had four pluses (++++). The
137 cerebrospinal fluid (CSF) results of all the 20 patients were within normal limit. We were able
138 to retrieve 11 electrolytes, 10 urea and 13 random blood glucose results out of the 20
139 patients. Out of the 11 electrolytes results, 10 (90.9%) patients had one or more electrolytes
140 derangements. The details of biochemical parameters seen in the patients are shown in
141 Table 2.

142 During admission, six (30%) patients received intravenous artesunate only, 9 (45%) had
143 intravenous artesunate and amodiaquine via nasogastric tube, 1 (5%) had intravenous
144 quinine infusion, and 4 (20%) were given intramuscular Arteether combined with
145 amodiaquine via nasogastric tube. Five (25%) patients had their antimalarial changed to
146 quinine infusion and one to artemether/lumefantrine combination because of poor response.
147 In addition to the antimalarial, 17 patients were initially given antibiotics, 15 received
148 phenobarbitone and 2 mannitol. Others drugs given to some of the patients were diazepam,
149 paraldehyde and paracetamol.

150 **Table 2: Available biochemical parameters with number of abnormalities**
151

Parameters (mmol/L)	HCO ₃	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 (±2.28)	132.9 (±6.85)	4.2 (±0.80)	102.1 (±8.6)	9.92 (±5.52)	5.29 (±1.42)
Values median	19	131	4.3	101	9.2	5.4
Values mode	18	131	3.6	101	4.1	6.5
Abnormal results	8	7	4	6	7	8
Elevated values	Nil	1	2	4	7	6
Depressed values	8	6	2	2	Nil	2

152 Eight (40%) patients had neurological deficits. One patient had 3 neurological sequelae,
153 whilst 4 patients had 2 each and 3 patients had one each. These were: motor deficit (2),
154 cortical blindness (2), aphasia (5), hearing impairment (1) and loss of developmental
155 milestone (4). Table 3 shows neurological deficits in relation to age group, while Table 4
156 shows neurological deficits in relation to the type of antimalarial drug used. Other
157 complications observed in these patients were anaemia, anaemic heart failure,
158 hypoglycaemia, electrolyte derangements, and acute kidney injury.

159 **Table 3: Neurological deficits in relation to age groups**
160

Neurological	Age group in month
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deficit						
	1 -12 n (%)	13-36 n(%)	37-60 n (%)	>60 n (%)	Total n (%)	
Yes	1 (33.3%)	3 (60%)	2 (28.6%0	2 (40%)	8 (40%)	
No	2 (66.7%)	2 (40%)	5 (71.4%)	3 (60%)	12 (60%)	
Total	3 (100%)	5 (100%)	7 (100%)	5 (100%)	20 (100%)	
161	χ^2 =1.270 df 3 P = .74					
162						
163						

164 **Table 4: Neurological deficits in relation to the type of antimalarial used**
165

Antimalarial given	Neurological Deficits		
	Yes n (%)	No n (%)	Total n (%)
I.V Artesunate	1 (12.5)	5 (41.7)	6 (30)
I.V Artesunate and amodiaquine	6 (75)	3 (25)	9 (45)
IV Quinine	0 (0)	1 (8.3)	1 (5)
IM Arteether + Amodiaquine	1 (12.5)	3 (25)	4 (20)
Total	8 (100)	12 (100)	20 (100)
$\chi^2 = 5.07$ df 3 P = .17			

167

168 Nine (45%) patients were discharged with full recovery, 8 (40%) with various neurological
169 deficits, 2 (10%) discharged against medical advice (DAMA) and 1 (5%) died. The duration
170 of hospital stay of the patients ranged between 3 to 30 days (mean 10.40 $\pm$ 7.90, mode 6
171 days). Only 8 (47.05%) out the 17 discharged patients honoured their follow up appointment,
172 including 4 out 8 patients with neurological deficits.

173 The fatal case was 54 month old female patient admitted during night shift. She presented
174 with fever, convulsion and loss of consciousness, and she had multiple convulsions (10)
175 during admission, with some neurological deficits. She weighed 12Kg (69.4% of the
176 expected), had hyponatremia, hypokalaemia, hypochloraeaemia, hyperglycaemia, and
177 anaemia (PCV 25%). Blood film revealed 2 pluses (++) of *P. falciparum*, and quinine
178 infusion was introduced after completion of intravenous artesunate without improvement.

179 **4.DISCUSSION**

180 The finding of 27 (2.64%) cases of CM out of 1,022 admissions was similar to 2.7% and
 181 2.8% found in Yaounde, Cameroun [16] and Ile-Ife, Nigeria [17], respectively. However, the
 182 prevalence of CM in this study is less than 5.5% found in Ado-Ekiti, Nigeria [18]. The
 183 prevalence of CM may depend on the geographic area, the season of the year and health
 184 institution in which the study was carried out and, also, the type and design of the study.
 185 Over diagnosis of CM in resource poor environment is common and challenging. This is
 186 because CM is expected to be considered in all children having fever with altered
 187 consciousness in Nigeria until further investigations, which may be delayed or not available,
 188 proved negative [9]. This was demonstrated in our study as 20 patients out 24 fulfilled WHO
 189 criteria for the diagnosis CM.

190 In this study, 75% of children affected with CM were under-fives as documented previously
 191 [16], with pre-school children (37 - 60 month old) bore the brunt [2] (see Table 1). This could
 192 due to the waning or even disappearance of maternal antibodies against malaria parasites,
 193 when the children are yet to acquire enough and potent immunity against malaria [10]. Also,
 194 these group of children are getting involved in outdoor activities (day care and schooling),
 195 thereby exposing them to mosquito bites.

196 All our patients presented with fever, 75% intermittent and 25% continuous. Continuous
 197 fever usually occurs in malaria when complications like hyperparasitaemia, severe anaemia,
 198 fluid, electrolytes and other metabolic derangements set in [19, 20, 21]. When complication
 199 occurred, affected patient goes into hyperdynamic circulation [22], with increase metabolic
 200 rate (catabolic state) [23]. It is therefore imperative for the attending physician to do a detail
 201 and comprehensive evaluation of patients as clinical findings may point to early
 202 complications, so that prompt and appropriate remedy can be instituted.

203 Convulsion is a common clinical finding in CM [24]. It could be the reason for seeking
 204 medical help in the hospital as it is usually sudden and dramatic, and parents fear that the

205 children may die. Commonly, convulsions in CM are generalized and multiple [5, 24] and can
 206 occur before or during admission, or both. Convulsion in CM is usually due encephalopathy.
 207 Various hypotheses have been postulated as the causes of encephalopathy but the most
 208 popular being the sequestration theory [5]. All efforts should be made by the attending
 209 physician to prevent further convulsion during admission as this may prevent further
 210 neuronal damage [5]. Causes of convulsion during admission may include the following:
 211 worsening of the disease condition caused by delay in instituting appropriate and effective
 212 drugs, complications – hypoglycaemia, severe anaemia causing hypoxic encephalopathy,
 213 intracranial hypertension [23], acute kidney injury (AKI) (hypertension), electrolytes
 214 derangement and drugs earlier given by the parents, especially native concoctions made of
 215 cow urine and onion [25]. The affectation of the brain in CM is usually global with cerebral
 216 oedema predominating, hence convulsion usually generalize as seen in 90% of our patients.

217 The relationship between malnutrition and cerebral malaria is controversial, with conflicting
 218 reports from studies on their relationship [26]. More well-nourished patients (12) than
 219 underweight (8) were affected, with statistically significant difference ($P = .00$) between their
 220 means percentage weight for age. This is in keeping with believe or assertion that CM is
 221 more common in well-nourished than mal-nourished [27], especially underweight children
 222 [28]. Reasons adduced were that well-nourished children have not been exposed to malaria
 223 as frequently, and therefore, were not able to develop the same degree of immunity as the
 224 malnourished children [29]. Furthermore, well-nourished children with higher haematocrit
 225 and plasma protein levels are more vulnerable to stagnant anoxaemia in *falciparum* malaria
 226 infection [29].

227 It had been shown in some previous studies that malnourished children were less
 228 susceptible to malaria and, even CM when compared to well-nourished [18, 30]. However,
 229 the outcome of CM in the malnourished children was very poor. This was seen in our study
 230 that only death recorded was a 54 month old malnourished child who weighed 12Kg (69.4%

231 of the expected weight for age). Among other reasons why malnourished succumb to severe
 232 malaria are: coexisting bacterial infections, electrolytes and fluid derangements,
 233 hypoglycaemia, hypocalcaemia, hypothermia, congestive cardiac failure and overwhelming
 234 sepsis [30]. These conditions should be painstakingly sought for and treated by attending
 235 physician. Furthermore, as nutritional status of malnourished children improves during
 236 therapeutic feeding or treatment, the incidence of malaria and even CM increased in them
 237 [31]. Therefore, as part of management of under-nutrition in malaria endemic area, all
 238 malnourished children should have access and use Insecticide Treated Nets (ITN) and
 239 malaria chemoprophylaxis [31].

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

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

257 The patients in our series had various electrolytes abnormalities (see Table 2). Severe
 258 hyponatraemia, hypokalaemia and low bicarbonate levels are common in *Plasmodium*
 259 *falciparum* infection [19]. The attending physician should bear this in mind, and investigate
 260 and correct them because this may determine the outcome. From the clinical point of view,
 261 hyponatraemia, hypokalaemia and metabolic acidosis are indicators of severity and
 262 determinant of outcome in CM [19, 33]. However, the use of Ringer's lactate as fluid of
 263 resuscitation in CM may be unsafe as a good number of patients may have hyperkalaemia
 264 and hypercalcaemia at presentation [20]. It was observed in the present study that 18% (2
 265 out of 11) of the patients studied had hyperkalaemia. Also, Enwere et al [21] and Oguiche et al
 266 [33] argued that the administration of hypotonic saline and isotonic glucose solutions to
 267 resuscitate cerebral malaria patients is questionable in the view of the fact that majority of
 268 the children in their studies suffered hyponatraemia, and about 54.6% (6 out of 11) and 70%
 269 (7 out of 10) of patients in this study had hyponatraemia and azotaemia, respectively.

270 It is intriguing to note that most patients (6 out of 8) with blood glucose abnormalities had
 271 hyperglycaemia rather than the usual hypoglycaemia (see Table 2). The reason could be
 272 that the attending physician obtained the blood samples for glucose estimate after the
 273 commencement of dextrose infusion, an act that needs to be discouraged. However, other
 274 possible reasons could be that since most patients were referred from other health facilities,
 275 they could have already been infused with dextrose water from the referral centres.
 276 Furthermore, we operate in a society in which mothers make every effort to ensure that their
 277 children feed, especially when ill. They force feed the children with fluid diet oblivious of the
 278 inherent dangers (choke and aspiration). The act should be discouraged, and its contribution
 279 to the low prevalence of hypoglycaemia will need to be evaluated in another study. On the
 280 contrary, it could have been stress induced hyperglycaemia, as any illness in a child is
 281 stressful to him/her, more so with multiple convulsions in CM. Response to stress due to any
 282 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 in 2001 reported the association between hyperglycaemia and severe malaria, and that CM stimulates glucose production to a greater extent than other forms of malaria [35].

Anecdotal evidences showed that physicians, including paediatricians frown at the use of arterminisin alone to treat cerebral malaria in this environment, especially when arterminisin combination therapy (ACT) has been recommended to treat simple malaria. The act seems to negate the objectives of ACT usage – prevention of resistance, recrudescence and promotion of efficacy. Considering the half -life of arterminisin derivatives which is less than 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 - 23hours. This is because parenteral arterminisin derivatives are given 12 to 24 hours interval [9]. At times, arterminisin derivatives had to be changed to quinine infusion after days on arterminisin derivatives, which further predispose patients to complications and prolonged hospital stay. Our sample size was small to make a categorical statement, but it is a food for thought for health policy makers. Therefore, there is a need to further investigate these findings using a larger sample size in this environment.

Eight patients (40%) had neurological deficit, which occurred more among the Toddlers (see Table 3). This may result from the fact that the brains of children in this age group are more vulnerable to CM because of immaturity, couple with rapid acquisition of new skills. Concerning the relationship between neurological deficit and antimalarial usage shown in Table 4, it has been documented that protracted exposure to high doses of lipid-soluble analogues of artesunate can cause neurological damage in animal experiments [37]. Could this be the case; 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 in this environment.

309 Outcome of cerebral malaria in this study was not too different from what was previously
 310 found. It had been documented that case fatality rate (CFR) range between 4 to 46%, [10]
 311 and our 5% CFR falls within this range. The CFR in this study is comparable to 5.2% and
 312 5.6% in Nigeria [17] and Cameroun [16], respectively. However, our CFR is less than 13.3%
 313 [38] and 13.6% [18] in some previous studies. The higher case fatality rate might have
 314 resulted from the study design, delayed diagnosis, severity of the disease, and promptness
 315 and effectiveness of intervention. Forty percent (40%) neurological sequelae in this study is
 316 similar to 38.6% found in a study in Ado-Ekiti, Nigeria [18] but higher than 10.3%, 16.7% and
 317 28.2% found in Ile-Ife, Nigeria [17], Yaounde, Cameroun [16] and Calabar, Nigeria [38],
 318 respectively. These variations might due to different time at which the neurological sequelae
 319 assessments were done; whether it was done while patient was still on admission or at
 320 discharge or in follow-up clinic. Forty five percent (45%) of our patients had full recovery,
 321 whilst Oluwayemi et al recorded 35% [18] and Zaroog et al, 84% [6]. Full recovery may
 322 depend on early presentations and diagnosis of the patient illness, severity of the disease,
 323 age of the patient and the promptness and adequacy of the intervention.

324 One phenomenon we found in our study that was not reported in other similar studies is
 325 discharge against medical advice. Ten percent (10%) of the patients studied were
 326 discharged by their parents against medical advice. The reasons given among others were
 327 slow pace of full recovery and financial constrain. This behavior by the relatives is not
 328 surprising as we operate in environment where any time or money spent on health is
 329 considered a waste. To buttress this fact, only 8 out of 17 discharges and 4 out of 8
 330 neurological deficit patients came back for follow-up appointment. This unsatisfactory
 331 behavior of the parents could jeopardize the health of their wards. To stop this trend, public
 332 should be educated through various mass media to have attitudinal change towards their
 333 health, the health institutions and its workers.

334

335 5. CONCLUSION

336 Cerebral malaria still remains a big challenge to children and care givers in malaria endemic
337 areas. It is a serious acute medical emergency, which commonly presents with fever,
338 multiple convulsions, loss of consciousness, with associated neurological sequelae,
339 parasitaemia, anaemia, electrolytes and metabolic derangements, and high mortality rate, in
340 children that may have normal nutritional status.

341

342 ETHICAL APPROVAL (WHERE EVER APPLICABLE)

343

344 The study protocols were in accordance with the ethical standards of the Helsinki
345 Declaration of the World Medical Association. Ethical approval was obtained for the study
346 from the Ethical Committee of Ladoke Akintola University of Technology (LAUTECH)
347 Teaching Hospital, Osogbo.

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459

460 **DEFINITIONS, ACRONYMS, ABBREVIATIONS**

461 There is no new term to define.

462

463 **APPENDIX**

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