2 Determinants Of Poor Prognosis In Children With Cerebral Malaria In An Urban City Of Nigeria

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Abstract

Cerebral malaria is a leading cause of morbidity and mortality in childhood and the incidence has increased with the emergence of chloroquine resistant *P. falciparum.* This study intends to determine factors responsible for poor prognosis of cerebral malaria in children.

This is a prospective study carried out at the University of Ilorin Teaching Hospital over a one year period between December 1998 and November 1999. The clinical features and laboratory parameters were correlated with outcome in the patients

There was an inverse relationship between age and the development of cerebral malaria and poor outcome. Children less than 3 years of age have a high morbidity and mortality compared to the older children. A coma score of = 2 has an unfavourable outcome ($\chi 2 = 3.95$, $p = 0.049$, Odds ratio "OR" 2.63, Relative risk "RR" 2.49). Deep breathing ($\chi 2 = 17.15$, $p = 0.0003$, OR 46, RR 23.5), absent corneal reflex ($\chi 2 = 16.93$, $p = 0.00003$, OR 34, RR 17.5), retinal haemorrhage ($\chi 2 = 11.96$, $p = 0.0005$, OR 31.3, RR 19.2), hypoglycaemia ($\chi 2 = 12.49$, $p = 0.0003$, OR 22.5, RR 11.75), and severe anaemia (pcv = 15) are associated with a poor outcome.

Decerebration and the level of parasitaemia are not statistically significant in determining outcome.

In conclusion, age less than 3 years, a coma score of = 2, deep breathing, absent corneal reflex, retinal haemorhage, hypoglycaemia and elevated blood urea occurring singly or in combination portend a poor prognosis in patients with cerebral malaria. The observation of any of these signs calls for a more intensive care of the patient.

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Introduction

In sub-Saharan Africa, malaria is one of the leading causes of morbidity and mortality in children aged 1-5 years[1-2].

Cerebral malaria is the most serious complication of severe malaria and a significant cause of neurologic sequelae and death[3-6]. Incidence of neurologic sequelae has been reported to vary between 8% and 28% and death between 5% and 50%[3-7]. At the University of Ilorin Teaching Hospital (UITH) in Nigeria, unpublished hospital data from 1990 to 1998 show a rising incidence of severe malaria including cerebral malaria and consequent rise in mortality/neurologic sequelae (Ojuawo A, personal communications). This trend has been observed in other studies[8], and has been largely attributed possibly due to emergence of chloroquine (CQ) and sulfadoxine-pyrimethamine (S-P) resistance to *P.falciparum* malaria[9-10] and delay in substituting effective chemotherapy.

This study aims at determining the prognostic factors and outcome determinants in children with cerebral malaria in an urban city of Nigeria.

Patients and Methods

The study was carried out at the Emergency Paediatric Unit (EPU) of UITH, Ilorin. The Teaching hospital is located in a state capital in the middle belt zone of Nigeria. The topography of the state is mainly Guinea savannah and the climatic conditions have been fully described elsewhere[11]. Malaria is endemic and perennial, and there is a high prevalence of chloroquine resistant P falciparum (CRPF) malaria[12] in the locality. The study was conducted between 1st December 1998 and 30th November 1999. Consecutive patients admitted at the EPU within the time frame of the study who were aged between 6 months and 15 years, and whose parents gave informed consent were recruited if they met our research definition of cerebral malaria[13]. Children with cerebro-spinal fluid (CSF) results suggestive of intracranial infection and those with previous neurological deficits were excluded from the study.

Table I: The observed symptoms and signs in the 53 children with cerebral malaria studied.

Symptoms and signs	**Number**	**Percentage (%)**
Altered consciousness	53	100%
Fever	51	96.2%
Convulsion	41	77.4%
Vomiting	25	47.2%
Anorexia	17	32.1%
Dark colored urine	7	13.2%
Diarrhoea	5	9.4%
Coma score ? 2	30	56.6%
Pallor	35	66%
Dehydration	8	15.1%
Deep breathing	6	11.3%
Jaundice	15	28.3%
Hepatomegaly	36	67.9%
Splenomegaly	13	24.5%
Decorticate posture	3	5.7%
Decerebrate posture	7	13.2%
Absent corneal reflex	18	34%
Retinal haemorrhage	5	9.4%
Drug before admission(**n=44**)		
Paracetamol	21	39.6%
Chloroquine	20	37.7%
Native medicine	13	24.5%
Alive	**44**	**83%**
Died	**9**	**17%**

Ethical clearance was obtained from the ethical committee of the Teaching hospital.

At admission in the emergency room, detailed history (including the age, sex, duration of illness, presenting clinical features, drug taken before presentation) was taken from the parent or guardian. The patients were examined for palor, jaundice, level of hydration, blood pressure, signs of meningeal irritation, power, tone, and reflexes in the limbs, and fundoscopy.

Coma was graded using the Blantyre coma scale[14] and the grading was done on admission and repeated every 4 hours until the child was awake or dead.

Parasitological diagnosis was made from examination of a thin and thick film of blood obtained by finger prick and stained with Giemsa stain. The level of parasitemia was determined by counting the number of asexual parasites relative to 200 leucocytes in each thick blood film. Baseline complete blood count, cerebro-spinal fluid (CSF) and blood cultures, along with plasma and CSF biochemistry were determined. Blood glucose was determined on admission using the "one-touch" electronic glucometer.

After the commencement of treatment, physical examination and assessment of coma score were repeated every 4 hours until patient recovered or died.

In survivors, assessment was continued every 12 hours until discharge. Hematocrit and parasite densities were repeated every 12 hours after the commencement of treatment. Parasite counts were discontinued when 2 consecutive films were negative. Blood sugar was determined hourly for the first six hours and at 12 hours. Further sampling was discontinued if hypoglycaemia was not detected at 12 hours.

Treatment: All the patients were treated with intravenous quinine except those with haematuria before or during therapy, whose treatments were changed to intramuscular (IM) artemether. Quinine was given as a loading dose of 20mg/kg salt in 10mls/kg of 10% dextrose water (D10) over 3 hours. This was followed every 8 hours thereafter by a 10mg/kg salt in D10 over 2 hours until the child regained consciousness and could swallow. Quinine was subsequently changed to oral to complete seven days of therapy. Patients with quinine treatment failure were treated with IM artemether. Artemether was administered as a dose of 3.2mg/kg start dose, followed after 12 hours by 1.6mg/kg. The dose was continued as 1.6mg/kg everyday thereafter for 4 days to complete a total dose of 9.6mg/kg course. Seizures

Seizures were treated with 0.15ml/kg of paraldehyde followed by IM Phenobarbitone (10mg/kg loading dose and 5mg/kg maintenance dose twelve-hourly as required).

Children diagnosed to have cerebral edema were treated with 10% intravenous mannitol solution. This was infused rapidly over 30 minutes and followed after one hour by a 1mg/kg dose of IV frusemide. Three doses of Mannitol were given every 4 hours.

General nursing care of the unconscious patient was undertaken and included turning of patient every 2 hours, half-hourly monitoring of pulse, respiration, and temperature with strict fluid intake/output and assessment of renal status. All survivors had a full neurologic assessment done before discharge and were followed up in the neurology clinic for 6 months for features of gross or subtle neurologic sequelae.

Statistical Analysis

Proportions were compared by Chi square tests with a p value < 0.05 being significant. The risk factors associated with the clinical and laboratory parameters were determined from the Odds ratio "OR" and the Relative risk "RR".

Results

One thousand, three hundred and fifty six children were admitted during the study period, of which 53 (3.9%) had cerebral malaria. Twenty (37.7%) were males and 33 (62.3%) were females giving a male : female ratio of **1:1.6**. The mean age at presentation was 3.9 years (range 10months 14years). The highest number of cases was recorded between the months of June and November. Seventy percent of the cases were referred from private health institutions, 30.2% were direct admissions from home and 1.9% was referred from public health institution.

Table I shows that the clinical features at presentation include altered consciousness (100%), fever (96.2%) and convulsions (77.4%). Thirty (56.6%) of the children had coma score of = 2 (unarousable).

Common pre-admission medications included Paracetamol, chloroquine and Native medications in 39.6%, 37.7% and 24.5% of the patients respectively.

Forty-four (83%) of the patients survived whilst 9 (17%) died. Of the survivors, 34 (77.3%) made full recovery, while 10 (22.7%) had neurological sequelae. Coma resolution time (CRT) among survivors ranged between 6-990 hours with thirty (68.2%) of the survivors recovering from coma within 48 hours. Five cases with CRT > 96 hours had complications like aspiration pneumonia (60%) and sepsis (40%).

Neurological sequelae seen among survivors include hemiparesis (18.2%), cortical blindness (9.1%), aphasia (6.8%), and recurrent seizures (4.5%). Others include deafness, ataxia, bruxism and facial nerve palsy in 2.3% each (**Table II**)

Fifty seven percent of the survivors were followed up after discharge from hospital.

At 3 months follow up, 70% of the survivors who had paraparesis regained full power in the limbs, whilst 75% of those with cortical blindness regained full vision. Recurrent convulsions, hemiplegia and deafness persisted beyond three months post-discharge.

Relationship between presenting clinical features and outcome

Age: There was a strong inverse relationship between age and development of cerebral malaria (**fig. 1**), and also between age and prognosis. **Table III** shows that children aged < 3 years are more likely to develop cerebral malaria and are also more likely to die from the disease than the older children ($\chi 2 = 1.63$, $p = 0.2017$, OR 2.92, RR 2.48).

Coma score: Seven (23%) of the 30 patients with admission coma score = 2 died compared to 1 (4.4%) of 23 patients with coma score >2 on admission. Low admission coma score carries a significantly higher

Table II: The neurological sequelae seen amongst the 44 survivors with cerebral malaria in this study.

Neurological sequelae	Number	Percentage
Hemiparesis	8	18.2%
Cortical blindness	4	9.1%
Aphasia	3	6.8%
Hyperactivity	2	6.8%
Irrational behaviour	2	6.8%
Recurrent seizures	2	4.5%
Deafness	1	2.3%
Ataxia	1	2.3%
Bruxism	1	2.3%
Facial nerve Palsy	1	2.3%

Table III: The association between neurological sequelae, the observed clinical features and outcome in the 53 children with cerebral malaria.

Features	Total	Neurological Sequelae		Died	$\chi 2$	p
		NO	YES			
Convulsions post treatment*	**25**	**12**	**7**	**6**	**12.5**	**0.003**
Jaundice	15	10	3	2	0.01	0.937
Dehydration	8	4	2	2	0.26	0.436
Deep breathing**	**6**	**1**	**1**	**4**	**8.21**	**0.005**
Hepatomegaly	36	23	6	7	0.30	0.517
Splenomegaly	13	8	3	2	0.46	0.456
Absent corneal reflex**	**18**	**4**	**5**	**9**	**21.8**	**0.0002**
Retinal haemorrhage**	**5**	**1**	**2**	**2**	**2.80**	**0.049**
Cerebral oedema	15	12	1	2	0.27	0.442
Decerebration	14	8	4	2	1.86	0.475
Coma score ? 2**	**30**	**15**	**7**	**8**	**2.82**	**0.035**
Pcv ? 15	19	11	5	3	0.45	0.243
Hypoglycaemia**	**6**	**3**	**0**	**3**	**12.33**	**0.003**
High Urea level	**3**	-	-	**2**	-	-

**significant association between clinical features and poor outcome

risk of death or neurological sequele ($\chi 2 = 3.59$, p = 0.0581, OR 6.7, RR 5.37).

Convulsions: Of the study population, 41 (77.4%) presented with history of convulsions or convulsions before commencement of therapy. This was not a determinant of eventual outcome. However 25 (47%) patients convulsed after commencement of therapy, out of which 6 (24%) died while 7 (28%) developed neurological sequele compared to 3 (10.7%) deaths and 3 (10.7%) neurological sequele in 28 patients who did not convulse during the course of therapy. Convulsions after commencement of therapy were strongly associated with poor outcome ($\chi 2 = 1.65$, p = 0.199, OR 2.63, RR 2.24).

Deep breathing: Six subjects had features of deep breathing, 3 of these died while one had neurological sequelae. Compared to children without this feature, these subjects have a highly significantly higher risk of death or neurological sequele ($\chi 2 = 17.15$, p = 0.0003, OR 46, RR 23.5).

Absent corneal reflexes: This feature was associated with poor outcome as 78% of the children with this feature either died or developed neurological sequelae ($\chi 2 = 16.93$, p = 0.00003, OR 34, RR 17.5).

Retinal Hemorrhages: This was observed in 5 (9.43%) of the 53 children. Only one (20%) of the 5 survived without any sequelae, 2 (40%) died while the remaining 2 survived with sequelae. Retinal hemorrhages carry significant risks of poor outcome compared to those without this sign ($\chi 2 = 11.96$, p = 0.0005, OR 31.3, RR 19.2).

Cerebral Oedema: 15 (28.3%) of the subjects were diagnosed as having cerebral oedema. Two of these (13.3%) died and one (6.6%) survived with sequele. None of the 38 patients without cerebral oedema died, though, 16 (42%) had neurological sequelae ($\chi 2 = 5.17$, p = 0.023).

Decerebration: Features of decerebrate/decorticate posturing were noticed intermittently during the course of illness in all patients. The more profoundly depressed patients however had decorticate/decerebrate posturing at the time of admission (18.9%) and stayed in this position longer. There was however no significant relationship to outcome between this group and those without features of decerebration at admission ($\chi 2 = 0.58$, p = 0.445).

Relationship between some laboratory features and outcome

Hypoglycemia: Hypoglycemia was significantly commoner among children admitted directly from home compared to those admitted from other hospitals (5/16 Vs 1/37, RR = 11.56, p = 0.007). Hypoglycemia was also related to poor outcome irrespective of whether the child was referred from a hospital or direct from home. Three of the 6 patients with hypoglycemia died compared to 2 of 47 patients without hypoglycemia ($\chi 2 = 12.49$, p = 0.0003, OR 22.5, RR 11.75). The mean serum glucose was also lower in children who developed neurologic sequelae compared to those who survived and were discharged

without any sequelae.

Parasitemia: There was no significant difference in level of parasitemia between those patients who recovered fully without sequelae compared to those with sequelae or death. However the mean level of parasitemia was higher among patients with coma grade =2 although this also did not reach statistical significance.

Anaemia: There was no significant difference in mean hematocrit levels between patients who recovered uneventfully and those with unfavorable outcome (p=0.16). However patients with PCV < 15 requiring blood transfusion had a higher risk of poor outcome ($\chi 2 = 1.29$, $p = 0.256$, OR 3.89, RR 3.58).

Others: Only 3 children presented with raised blood urea on admission, 2 of them died. The number was too small for any meaningful statistical insinuations.

Discussion

Cerebral malaria has remained a significant cause of neurologic disability and death in children living in sub-saharan Africa[5-7,10]. Usual estimates of CFR range between 5 and 50%[6-7,14-16] and neurologic disability between 8 and 28%[3-7]. In our study, we found 17% fatality, with 22% of the survivors developing neurological deficits. Despite the recent upsurge in chloroquine-resistant parasites in Nigeria, our fatality rate was similar to that reported by Bondi[3] ten years earlier in Nigeria when CQ resistance was not a significant consideration in malaria morbidity and mortality. Our fatality rate was however higher than that reported by Meremikwu et al[3]. The difference in fatality rates between these two studies may be related to differences in management protocols (quinine vs CQ) and the effect of drug resistance.

The consistently high mortality rate for cerebral malaria in many studies has prompted the need to develop a protocol for early identification of risk factors for poor outcome in order to improve case management. In the African setting where resources are either not available or scanty, identifying patients at risk on time will allow for quick decisions for referral of very sick children to higher centers and also allow decisions to be taken on resource sharing among very sick children. Some bed-side clinical and laboratory risk factors have been identified as prognostic determinants of outcome in several studies. These include deep coma, hypoglycemia, respiratory distress, "deep breathing", lactic acidosis, ocular lesions, jaundice and hyperparasitemia[3,13,14,16].

In this study we identified "deep breathing", coma score = 2, retinal haemorrhages, absent corneal reflexes and hypoglycemia as significant determinants of poor prognosis.

Almost 70% of the cases were referred from private health institutions. In contrast only one child (2%) was referred from government hospital.

In our study those children with features of deep breathing had a significantly higher risk of death or sequele. Respiratory distress is known to be an important prognostic marker in children with *P.falciparum* infection[17,18]. In majority of cases, it reflects an underlying metabolic acidosis, usually associated with acidemia[18]. In these patients, hyperventilation to compensate for metabolic acidosis appears to be the most important cause of deep breathing[16].

In most African setting where even basic laboratory investigations cannot be carried out, deep breathing is an important bedside indicator of severe metabolic acidosis[19].

Ocular lesions are fairly common findings in childhood cerebral malaria[20-24]. In this study, we found absent corneal reflexes and retinal hemorrhages to be associated with poor prognosis. The association between retinal hemorrhages and poor prognosis has been observed in other studies[20,22], however some workers did not find such association but found papilloedema, which occur in 8% of children with cerebral malaria to carry the worst prognosis[21].

Absent corneal reflex is an indicator of severity of depression of consciousness[14], a prognostic indicator of poor outcome[13-14], a finding that was confirmed in this study.

There was no association between level of parasitemia and prognosis in this study, a finding that is similar to other studies[25]. Some studies however found hyperparasitemia to be a significant indicator of poor prognosis[13-14]. A number of possible explanations have been suggested for the apparent lack of association between parasite density and risk of dying[25]. Prior home treatment with CQ in areas of drug resistance (as in our locality) may reduce parasite densities without fundamentally altering the course of disease. Alternatively, severe malaria cases may have sequestered parasites in vital organs, reducing peripheral parasitemia at the same time worsening the prognosis[25].

Hypoglycemia on admission is a common finding in children with cerebral malaria. In this study however, hypoglycaemia was observed in 11 percent of the cases, a finding that is similar to that of other workers[26] . This could be as a result of a large proportion of the patients coming from private hospitals where glucose would have been infused as part of the management. Despite the low prevalence

l Features	Present		Absent			χ2	p value	Odds
	No	*Death*	*No*	*Death*		ratio	"RR"	
3 years	31	7	12	2	1.63	0.2017 2.92	2.48	
sions	25	6	28	3	1.65	0.199 2.63	2.24	
:e		15	1	38	1	0.47 0.491	2.64	2.53
ation	8	1	45	1	1.94	0.163 6.29	5.63	
reathing		**6**	**3**	**47**	**1**	**17.15 0.0003**	**46**	**23.5**
megaly	36	6	17	1	1.15	0.283 3.20	2.83	
megaly	13	1	40	1	0.71	0.397 3.25	3.08	
: corneal reflex		**18**	**9**	**35**	**1**	**16.93 0.00003**	**34**	**17.5**
l haemorrhages		**5**	**2**	**48**	**1**	**11.96 0.0005**	**31.3**	**19.2**
l oedema		15	2	38	0	5.17 0.023	-	-
bration	14	1	39	1	0.58	0.445 2.92	2.79	
score ? 2		**30**	**7**	**23**	**1**	**3.59 0.0581**	**6.7**	**5.37**
cell volume ?	15	19	2	34	1	1.29 0.2563	3.89	3.58
lycaemia		**6**	**3**	**47**	**2**	**12.79 0.0003**	**22.5**	**11.75**

**significant association between clinical features and death

of hypoglycemia in our study, the few patients with this feature either died or recovered with sequelae.

Anemia was not associated with poor prognosis in this study as 76% of the children who were anemic received blood transfusion and this intervention is likely to have modified the eventual outcome.

Fifty eight percent of the children were less than 3 years of age, a finding consistent with that of other studies[3,13-14]. This reflects immune status in the younger age groups, as in this population incidence of cerebral malaria is higher on account of a fall in protective maternal antibodies and increasing exposure to mosquito bites. Immunity is expected to build up in the child with advancing age and thus a fall in incidence of disease is expected.

Convulsion after commencement treatment was associated with poor outcome in this and other studies[13,14]. Hypoglycaemia, hyponatraemia or intracranial sequestration of metabolically active parasites may cause convulsion. Its occurrence despite the institution of therapy is an indication of severity of disease, and it may be recurrent or persistent despite the use of anticonvulsant drugs. It aggravates intracranical hypertension; causes death of neurons and it may also precipitate aspiration. Repeated episodes may result in the production of a large net lactate load in muscle tissue, which cannot be cleared rapidly in cerebral malaria[27], leading to deterioration of the clinical state.

Acute renal failure is not uncommon in severe malaria[28-30]. The main pathophysiologic mechanism involves obstruction of the capillaries and post capillary venules by infected red blood cells and activation of monocytes that release cytokines and tumor necrosis factor[29]. Other factors include volume depletion, intravascular hemolysis and hypotension[31]. Acute tubular necrosis is the main renal complication of falciparum malaria but latent forms of acute glomerulonephritis have also been documented[29]. There was no child with frank renal failure in this study but there was evidence of impaired renal function (high serum urea and creatinine) in 3 children who eventually suffered an unfavorable outcome.

In conclusion, age less than 3 years, a coma score of 2, deep breathing, absent corneal reflex, retinal haemorhage, hypoglycaemia and elevated blood urea occurring singly or in combination portend a poor prognosis in patients with cerebral malaria. The observation of any of these signs calls for a more intensive care of the patient.

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