

Research Article

Clinical and Biological Factors Associated with Treatment Outcome of Cerebral Malaria in Children under Five in Yaounde

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Abstract This is a retrospective study that was carried out in the pediatric unit of the Yaounde Central Hospital from January to August 2008. The aim of the study was to determine the clinical factors associated with the treatment outcome of cerebral malaria in children under five. Included in the study were 77 children with cerebral malaria all of whom received malaria treatment either Quinine or Arteether. They were followed up from admission to discharge. ANOVA and Chi square tests were calculated and the level of significance was 0.05. The mean age of the study population was 29.68 ± 14.20 months, and the sex ratio was 1.85. We noted 22 (29%) deaths during the course of the treatment. Clinical factors associated with death were fever clearance time ($P = .01$) and coma recovery time ($P = .002$). Blood glucose, home treatment and its duration, vomiting and fever at presentation, duration of illness, and parasite clearance time did not influence mortality. As regards biological parameters, the mean hemoglobin level on admission ($P = .004$), high blood urea levels ($P = .01$), and hypoglycemia ($P = .01$) were associated with increased deaths. Health professionals should be sensitized to promptly recognize hypoglycemia, anemia, uremia while checking fever clearance time and coma recovery time in the proper management of cerebral malaria in order to lower mortality in children under five with cerebral malaria.

Keywords cerebral malaria; factors; treatment; outcome; children

1 Introduction

Malaria is an important health and developmental challenge in Africa where young children and pregnant women are particularly vulnerable with approximately 800,000 deaths in children and about 300 million malaria episodes per year [24]. Infection with *Plasmodium falciparum* can be fatal if

prompt diagnosis is not made and adequately managed and if complications such as cerebral malaria occur. According to the World Health Organization, cerebral malaria is present in a patient who cannot localize painful stimulus, has a peripheral asexual falciparum parasitemia, and has no other identified cause of encephalopathy [27].

Cerebral malaria is thought to be caused by the sequestration of infected red blood cells in the deep blood vessels hence blocking the cerebral microcirculation [1]. However, complete obstruction of blood flow is unlikely since survivors rarely have permanent neurological deficits [13]. Sustained lactic acidosis may be the only attributable cause of death in some children [15]. In areas where malaria is endemic, infants are protected from severe malaria during the first 3 to 6 months of life by passive immunity from maternal antibodies, but as this immunity wanes, they become susceptible to cerebral malaria [12]. In Africa, 17 to 50% of hospital admissions for severe malaria are attributable to cerebral malaria with mortality rates averaging 18.6% [11]. The presence of manifestations such as severe anemia, hypoglycemia, lactic acidosis, intractable seizures, and respiratory distress worsen the prognosis [7, 26]. The aim of this study was to determine clinical and biological factors associated with mortality in the course of treatment of cerebral malaria in children under five in the pediatric unit of the Yaounde Central Hospital in Cameroon.

2 Methodology

This longitudinal retrospective study was performed using secondary data source collected between 1995 to 1997 for efficacy and tolerance comparing Arteether and Quinine and whose results have been published elsewhere [18]. It was a multicenter study which did not analyze the clinical and biological risk factors in relation to the outcome. Data was

extracted from patients' records. Children included in this study were those below five years of age consecutively admitted in the hospital and proven to have asexual *Plasmodium falciparum* parasitemia, a Blantyre coma scale of 2 or less with no other obvious cause of the coma. Children known to have chronic diseases such as epilepsy, frank-acquired immunodeficiency syndrome, liver, renal and cardiac illnesses were excluded, as well as those on cardioactive drugs, history of blackwater fever, documented septicaemia, urinary tract infection, and meningitis.

The following parameters were extracted from the patients' files: age, sex, clinical presentation, and history on admission as treatment at home, fever, diarrhea, vomiting at presentation, duration of the illness, and the fasting period. Vital signs, malaria parasitemia, level of blood hemoglobin, blood urea, blood glycemia, blood creatinine were also recorded. We defined coma as a loss of consciousness for at least 30 minutes. The end points of the study were dead or alive. The intermediate outcomes were fever clearance time, parasite clearance time, and coma recovery time. Fever clearance time was defined as the time required to reduce the temperature below 38°C for at least 24 hours. Parasite clearance time was the time needed for the malaria parasites to be completely cleared from the blood. Coma recovery time was the time it took for the child to regain consciousness. Severe anemia was defined as the hemoglobin level below 5 g/dL, hypoglycemia as blood glucose below 40 mg/dL, hyperglycemia as blood glucose above 90 mg/dL, high blood uremia as blood urea above 35 mg/dL and high blood creatinine as blood creatinine above 1.4 mg/dL. Data were analyzed using Epi-Info version 6.1. ANOVA and Chi square tests were calculated and the level of significance was 0.05.

3 Results

Out of the 80 children aged 0 to 5 years enrolled, 3 were excluded because they had other infections (two were infected with *Salmonella spp* and one with *Citrobacter freundii*). The age range of the 77 patients included was 6–58 months with a mean age of 29.68 ± 14.20 months. There were 50 (65%) males and 27 (35%) females giving a sex ratio of 1.85. Children in the age range of 6–24 months were 38 (49.3%), while 39 (50.7%) were in the range of 25–58 months. The age group of 19–24 months was most represented with 20 (26%) patients.

Outcome of the children enrolled in the study

There were 22 (29%) deaths within the course of the treatment, while 55 (71%) remained alive. Out of the 22 deaths, 6 (27%) were females and 16 (73%) were males ($P = .5$). Concerning the outcome in relation to sex, there was no

statistical difference between those who died and those who remained alive ($OR = 0.60$, $P = .36$).

Clinical history

Of the 77 children studied, Table 1 shows that there was no statistical difference between children who died compared to those alive as regards home treatment ($P = .81$), fever ($P = .65$), diarrhea ($P = .38$), and vomiting ($P = .06$) on admission. The fasting period varied from 4 to 96 hours. There was no statistically significant difference between those who died compared to those who survived in the duration of the fasting period ($P = .06$), mean duration of illness ($P = .73$), mean duration of home treatment ($P = .87$). Chloroquine was the drug of choice used by 69 children before admission. The duration of admission of the children ranged from 1 to 28 days. For those who died, the mean length of stay in the hospital was 1.42 ± 1.56 days, while that of those who survived was 8.50 ± 3.85 days ($P < .01$).

Physical signs on admission

There was no statistically significant difference between the group of dead children and those who survived as regards rectal temperature ($P = .72$), weight ($P = .47$), height ($P = .81$), pulse rate ($P = .26$), respiratory rate ($P = .45$), and the systolic blood pressure ($P = .78$). Biological parameters. Table 2 shows biological parameters of the children with respect to the outcome. As concerns the mean hemoglobin level on admission, there was a statistically significant difference ($P = .04$) in the group that died (9.6 ± 2.4 g/dL) compared to those who survived (8.1 ± 2.4 g/dL), and the mean blood urea ($P = .00$). Conversely, there was no statistical difference in the two groups for the mean level of glycemia ($P = .14$), hyperglycemia ($P = .58$) and the mean level of blood creatinine ($P = .63$). Hypoglycemia ($P = .01$) and high blood urea level ($P = .01$) were risk factors associated with death in the study. The mean parasite load was 75589.1 ± 84800.49 trophozoites/ μ L of blood in the children who died, and 106447.7 ± 191723.6 in those who survived, but there was no statistically significant difference in the two groups ($P = .52$).

Response to treatment

There was no statistically significant difference in outcome in the children treated with either Quinine or Arteether. These drugs were both protective ($OR = 0.36$, $P = .05$). There was a statistically significant difference in the two groups for fever clearance time ($P = .01$) and coma recovery time ($P = .002$) but not for the parasite clearance time ($P = .42$).

	Dead <i>n</i> = 22	Alive <i>n</i> = 55	OR	<i>P</i> -value
Clinical history				
Treatment at home	20 (91)	49 (89)	1.22	.81
Fever at presentation	20 (91)	50 (91)	1.00	.65
Diarrhea at presentation	5 (22)	8 (14)	1.72	.38
Vomiting at presentation	14 (39)	22 (40)	2.62	.06
Fasting period (hours)	24.5 ± 25	16.6 ± 12		0.06
Mean duration of illness (days)	3.59 ± 2	3.76 ± 1.98		.73
Mean duration of home treatment (hours)	44.15 ± 34.59	45.54 ± 31.46		.87
Mean duration of hospitalization (hours)	1.42 ± 1.56	8.50 ± 3.85		.0000
Physical examination				
Temperature (°C)	38.9 ± 0.8	39 ± 1.1		.72
Respiratory rate (cycles/min)	48.9 ± 15.22	46.2 ± 13.3		.45
Pulse (beats/min)	153.7 ± 21.9	147.3 ± 22.5		.26
Blood pressure (mmHg)	59.0 ± 11.5	59.8 ± 9.4		.78
Weight (kg)	11.9 ± 2.7	12.0 ± 3.0		.47
Height (cm)	87.5 ± 11.2	88.3 ± 11.9		.81
Response to treatment				
Quinine	16 (72.7)	27 (49)	0.36	.05
Arteether	6 (27)	28 (53.8)	0.36	.05
Fever clearance time (hours)	108 ± 79.9	46.3 ± 40.5		.01
Parasite clearance time (hours)	31.0 ± 1.4	44.6 ± 23.6		0.42
Coma recovery time (hours)	80.0 ± 0.0	29.6 ± 15.7		.002

P-value < .05 is significant. OR = odds ratio

Table 1: Clinical assessment of children studied in relation to the outcome.

	Dead <i>n</i> = 22	Alive <i>n</i> = 55	OR	<i>P</i> -value
Hypoglycemia	8 (36.3)	9 (16.3)	2.90	.01
Hyperglycemia	6 (27)	17 (31)	1.05	.58
Severe anemia	0	4 (7.3)	0.00	.29
High blood urea	5 (22)	5 (10)	2.64	.01
High blood creatinine	5 (22)	18 (32.7)	0.60	.63

P-value < .05 is significant

Table 2: Biological characteristics with respect to children's outcome.

4 Discussion

This longitudinal retrospective study was derived from a secondary data source on the efficacy and tolerance comparing Arteether and Quinine in the treatment of cerebral malaria. Data were extracted in order to determine factors associated with death as concerns the history of the illness, physical signs, and the treatment response. The results showed that cerebral malaria occurred in 49.3% of the children of 6–24 months and in 50.7% of children 25–59 months. This is contrary to the findings of Oduro et al. [20], who reported a prevalence of 4.4% and 8.7%, respectively, in these age groups and Chiabi et al., who noted a prevalence of 38.8% of cerebral malaria in children

aged 2 months to 15 years [3]. Children less than 6 months had the lowest frequency of cerebral malaria. This might be explained by the fact that in endemic areas, infants are protected by passive immunity from maternal malaria antibodies [3, 14]. This immunity wanes as the infant gets older and consequently the susceptibility to cerebral malaria increases [12, 14]. There were more males with cerebral malaria than females in this study, with a sex ratio of 1.85. This is similar to findings of other studies on severe malaria in children less than five [3, 6].

The fatality rate of cerebral malaria varies with the health facility and geographic area. Rates of 4% to 46% have been reported in the past decades [11], and less than 10% of children who survived cerebral malaria may develop neurological sequelae [7, 11, 17, 25]. Concerning the outcome of the children in our study, the lethality rate was 28.6%. This is moderately higher than the 15.7–27.4% noted by Moyou-Somo et al. [18]. This difference could be explained by the upper age limit of children in that study which was 10 years. This was also higher than the 22.2% noted by Idro et al., in Kenyan children [8], and the 14% and 21.5% noted, respectively, by Brewster et al. and Jaffar et al., in Gambian children [2, 10], 17.8% observed by Lesi et al. in Nigerian children [16], and 19% noted by Murphy et al. in children in the sub-Saharan Africa region [19]. The mortality rate was

lower than the 57.7% reported by Endeshaw et al. [4] and the 37% of Taylor et al. [22]. This can be explained by the fact that before the past decade, the management of patients with severe malaria and more precisely cerebral malaria was not well codified and implemented by malaria programs. The mean weight of the children, although not the best parameter to evaluate protein-energy malnutrition, did not show a statistically significant difference between the groups of dead children and survivors, even though it is known that protein-energy malnutrition is associated with greater malaria morbidity and mortality in humans [21]. Convulsions and coma preceded by fever were found to be present in more than 90% of children with cerebral malaria [23]. Fever was not associated with death in this study and the administration of specific medications before arrival in the hospital could be the explanation, whereas some authors found that fever associated with neurological involvement is highly associated with death [8]. Presenting clinical symptoms as vomiting, diarrhea, duration of fasting, and the duration of illness were not independent factors associated with death. Fasting can cause hypoglycemia and deprive the child of energy, hence increasing the chances of death. Hypoglycemia, shown previously to be a predicting factor of neurological involvement and death [8,2], was associated with death in our study. The lack of statistical significance of fasting in this study ($P = .06$) might be explained by the effect of the sample size. The level of parasitemia even though high in this study, was not associated with death. This high parasitemia was found in children with uncomplicated malaria in Cameroon [9] and may be one of the reasons why most of the children studied had anemia at entry. Severe anemia was not associated with death as reported by others [20]. Hyperparasitemia with levels greater than 500,000 trophozoites/ μL was found by Ikome et al. in children with cerebral malaria [9]. Although Arteether and Quinine were both therapeutically effective as revealed in the previous study [7], fever clearance time and coma recovery time were significantly associated with mortality. This is plausible because fever spikes have been correlated with incremental rise in serum levels of tumor necrosis factor- α , responsible for severe malaria [5], which in the end of course is associated with mortality [11]. The length of hospital stay was significantly associated with death; the shorter the length of stay, the higher the probability of dying. These findings should be interpreted in the context from limitations of the study; first from the small sample size because of recall bias in the history and secondly because it was a hospital-based study and cannot be generalized to the whole community.

5 Conclusion

This study showed in a univariate analysis that clinical factors associated with mortality in the course of treatment

of cerebral malaria were fever clearance time, coma recovery time, while the biological factors were mean level of hemoglobin, uremia, and hypoglycemia. We thus conclude that there is a need to sensitize health professionals to promptly recognize hypoglycemia, anemia, uremia while addressing fever clearance time and coma recovery time in the proper treatment of comatose children with cerebral malaria in order to reduce mortality in children less than five.

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