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Clinical Presentation, Haematological Indices and Management of Children with Severe and Uncomplicated Malaria in Douala, Cameroon

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Abstract: This study carried out from January to June 2007, was undertaken to describe the clinical presentation of childhood malaria in Douala, a meso-endemic area as far as malaria transmission is concerned. One hundred and seventy eight children were enrolled after informed consent of their parents. The sample characteristics were recorded and clinical as well as preliminary laboratory investigations were performed. Thirty eight children coming for vaccination and counselling was targeted to serve as control. According to the results obtained, cerebral malaria (CM) seems to be associated with young age, whilst Malaria anaemia (MA) was predominant among older children. Hyperpyrexia and hyperparasitaemia were high among CM patients and 11.1% of them died, however, no neurological sequel was noticed immediately after discharge on those who survived. Haemoglobin and glycaemia were low on MA and CM patients; these groups had low percentage in bed nets utilization as well. These results suggest that the clinical presentation of the disease differ with the geographic location and malaria disease features varies according to the severity. Such studies could contribute to the management of the disease.

Key words: Uncomplicated, cerebral, anaemia, malaria, children, Douala

INTRODUCTION

Because its roots lie deep within human communities, malaria is a unique disease. It remains a major threat to human health, despite considerable national and international control efforts. Malaria annually causes at least one million deaths, most of which occur in African children. Continued progress in understanding this scourge is required (Snow *et al.*, 2004). Even though several studies on childhood malaria have been undertaken in sub-Saharan Africa (Modiano *et al.*, 1998; Biemba *et al.*, 2000; Idro *et al.*, 2006; Guiyedi *et al.*, 2007), the fact is that its presentation varies with the setting, showing that there is still a remarkable shortage of clinical description of the disease in different endemic regions, particularly as far as the severity is concerned. Severe malaria anaemia and cerebral malaria are considered among the major clinical manifestations in severe childhood malaria. Their pathogenesis are multi-factorial and are not fully understood; there is then the need to address their complex aetiology (Mockenhaupt *et al.*, 2004).

The disease pattern and the relative contribution of individual symptoms to poor prognosis and mortality

differ with endemicity, geographic location, access to health services and age, among other factors. As severe malaria results largely from late recognition and subsequently late intervention, clinical research is needed on how to improve or accelerate the recognition of severe malaria, how to accelerate referral and how to ensure that adequate intervention is taken as early as possible (Mishra *et al.*, 2006). The clinical spectrum of severe malaria and its epidemiology were described in different settings in Cameroon (Chiabi *et al.*, 2004; Akenji *et al.*, 2005).

The results of a study on childhood malaria are reported in the most populous city of Cameroon: Douala town. It was taken up in order to describe the clinical spectrum and haematological characteristics, as well as to understand the trend in pattern of morbidity of the disease in our setting, particularly to look for variations in different disease severity groups: Uncomplicated Malaria (UCM), Malaria Anaemia (MA), Cerebral Malaria (CM) and the combine symptoms of MA and CM. We cannot assume that lessons learnt in some observational studies in other part of Africa will automatically apply to a different epidemiological, genetic, cultural and healthcare setting.

MATERIALS AND METHODS

Study area: Malaria continues to be the major cause of morbidity and mortality in Cameroon. The overall level of the disease is mesoendemic. Douala is the most populous city, situated near the Atlantic Ocean, in the south-western part of the country. The major epidemiological feature of malaria in this area is its perennial transmission throughout the year. This study took place from January to June 2007 at 4 hospital centres scattered in Douala town: Laquintinie Hospital, Deido District Hospital, Palmier District Hospital and Emilie Saker Paediatric centre. The study protocol was reviewed and approved by Cameroon Bioethics Committee and by the Provincial Delegation of Public Health covering the town of Douala.

Study population: All children less than 15 years old, who presented to the participating health institution for health problem were screened for the study. Children with diarrhoea, non malaria infections and those with a positive HIV status were excluded. Finally, 178 eligible ones with different disease severity were enrolled. To recruit controls, we had 2 possibilities: either to go to a primary school in order to recruit healthy subjects (this would mean others procedures), or to do it in hospitals where we already have permission to carry out this research. We chose the 2nd option and 38 children coming to hospital for nutritional counselling and for vaccination were targeted to serve as control, provided they were malaria free after thin blood film examination and HRP2 test. After informed consent, 3 mL of blood was collected by venipuncture from arm. Blood was then stored in 2 kinds of sample tubes: one with 0.124 M trisodium citrate in it (2 mL) and one EDTA tube (1 mL). Furthermore, one drop of blood was used for malaria diagnosis. Lumbar puncture was performed in children with history of coma, if clinically indicated and Cerebrospinal fluid examined in order to assess the cause, either cerebral malaria or Non Malaria Encephalopathy (NME). Patients were assigned to the various groups on the basis of World Health Organisation guidelines for the definition of uncomplicated and severe malaria (Imbert, 2003). Children with a positive HIV status were excluded from the study.

Malaria diagnosis: Blood was spotted on the slide and thick films were prepared in duplicate. The slides were labelled, allowed to dry, stored in a slide rack and transported to the laboratory of health and nutrition of the University of Douala. The thick film was then stained in 10% Giemsa solution for 20 min and then allowed to dry.

The parasites were counted with a microscope (Motic) using the thick film on the basis of number of parasites per 200 white blood cells; this was converted to the number of parasites per μL of blood. For control subjects, in addition to the thick film, we carried out the more sensitive antigenic test to detect PfHRP2 (*P. falciparum* specific Histidin Rich Protein 2) using ParaHit dipstick (Span Diagnostics Ltd., India).

Definition of categories: Malaria anaemia was taken to be a haemoglobin concentration of $<8.0 \text{ g dL}^{-1}$ or a PCV <18 . Malaria anaemia was defined as a haemoglobin concentration of this level in a patient who had a positive malaria smear. Cerebral malaria was diagnosed if a patient with a positive smear for malaria presented with impaired consciousness as measured by a Blantyre coma score of ≤ 2 (range: 0-5) and had a normal cerebro-spinal fluid. The coma score was determined as described by Molyneux *et al.* (1989) for all comatose patients. Children without any of the above mentioned symptoms, but presenting with usual malaria symptoms and a positive malaria smear were classified as UCM patients.

Clinical care of subjects

Baseline evaluation: Demographic data, information on the use of impregnated bed net to prevent malaria (whether or not bed net was used to cover the bed when resting or sleeping) or on recent drugs use and significant medical history were obtained. A complete physical examination, including neurological status according to the Blantyre coma scale (Molyneux *et al.*, 1989) and prostration assessment (define as inability to sit unassisted in a child who can normally do so, or inability to drink in a child who cannot normally sit up) were performed.

Inpatient care: Clinical monitoring of patients included measurement of axillary's or rectal temperature, neurological and prostration status every 6 h. A physician evaluation was performed every 24 h or more frequently if clinically indicated. In addition, standard nursing care was provided. For example, paracetamol was administered for temperatures $>38^\circ\text{C}$ at a dose of 10 to 17 mg kg^{-1} every 8 h.

Antimalarial therapy: Cameroon national treatment guidelines for malaria management were used for treatment. Children with UCM were given Quinine base (25 mg kg^{-1} 24 h in 500 mL of glucose solution 5%) for 3 days and after that were discharged; Those with SMA (Haemoglobin level $<5 \text{ g dL}^{-1}$) were given blood followed by Quinine base (25 mg kg^{-1} 24 h in 250 mL of glucose

solution 5%) for 3 days and an Iron supplementation (6 to 10 mg kg⁻¹ 24 h); They were discharged at least 7 days after admission; CM patients were given Quinine base (25 mg kg⁻¹ 24 h in 500 mL of glucose solution 5%) for 3 days followed by an Artemisinin combination therapy and an Iron supplementation; They were discharged at least 7 days after admission as well. Some antibiotics like Dexametazone or Ceftriaxone was given as clinically indicated in order to treat non-detected infections following paediatrician's recommendations.

Laboratory evaluation: Malaria diagnosis was performed as previously describe. Haematological parameters (including: White and Red blood cells, platelets counts, as well as Haemoglobin level and Hematocrit) were determined using an automated coulter (Celly 70, France) with the blood collected on EDTA tube. The plasma obtained after centrifugation of the blood collected on citrated tube was used for glycaemia determination by a colorimetric enzymatic method using Glucose oxidase and peroxidase (SGM, Italy); the optical density was read at 510 nm using a spectrophotometer (Helios β, Thermospectronic UVB 102615).

Quality control: As stated earlier, slides for malaria diagnosis were prepared in duplicate. One slide was read by a hospital labs technician, who was not involved in the research work and the other was read by one member of our research team. The two results were confronted and a consensus was found in term of parasitaemia. The haematological measurements were made at Deido district hospital using the same model of machine (coulter) and the same technique. Glycaemia for all recruitment sites was measured using the same spectrophotometer and the same method at the laboratory of Health and Nutrition of the University of Douala. All these measurements were blinded, with the technician unaware of the background of the sample.

Statistical analysis: Data was analysed using GraphPad Prism version 4.00 for Windows, GraphPad Software, San Diego California USA, www.graphpad.com. Categorical variables were compared using Fisher's exact test and continuous variables with Student's t-test. p-values were used as measure of significance, a p<0.05 was considered significant.

RESULTS

Figure 1 is an overview of patient's recruitments profile. Table 1 shows that the medium age of CM patients was significantly lower than the one of MA patients (27.48±25.59 and 47.84±39.33 months respectively,

p = 0.0107) and Table 3 confirm that bed nets uses decrease with disease severity, being lower in CM patients than in MA patients.

Clinical data on admission: On admission, temperature was significantly higher in CM patients than MA and UCM patients (39.64±0.98°C, 38.99±0.85°C and 38.58±0.94°C, respectively; p<0.0001). However when we observed our population, hyperpyrexia (T°≥40°C) was more prevalent in children with CM and MA than in children with CM alone (54.54 and 36%, respectively). All children with CM, CM and MA were prostrated on admission, while we had only 74.51 and 45.88%, respectively with MA and UCM patients. It is noteworthy that 49.02 and 16.47% of children who were finally classified, respectively as MA and UCM patients had Blantyre Coma Score (BCS) between 2 and 4, signalling an impaired consciousness.

Clinical outcome: Four children (3 males and 1 female) in the CM group died. These were the only fatal cases reported (median age: 17.75±5.74 months). Two of them were coming from small private health centres and had severe parasitaemia (≥250000 parasites μL⁻¹), whilst the 2 other had high parasitaemia (between 50000 and 250000 parasites μL⁻¹). However no neurological sequelae were observed immediately after discharge among those who survived. According to Table 2, fever resolution time (FRT) seems to last longer in children with CM and MA than CM alone (81.6±30.36, 66±37.44, 45.14±28.46, 33.9±22.88 h in children with CM and MA, CM alone, MA, UCM, respectively; p<0.0001). Coma Resolution Time (CRT) seems to be almost the same in CM and MA and CM alone (16.2±8.02 and 16.3±10.04 h in children with CM and MA and MA alone, respectively; p = 0.9716). Prostration resolution time (PRT) increased with disease severity (28.70±19.19, 45.45±23.91, 56.25±26.55, 59.4±36.93 h in children with UCM, MA, CM alone and CM and MA respectively; p = 0.0002).

Laboratory data: Parasitaemia increase from UCM to CM, as the log transformed Parasitaemia shows (3.65±0.73, 4.36±0.74, 4.72±0.79, 5.04±0.43 for UCM, MA, CM only and CM and MA, respectively; p<0.0001), however hyperparasitaemia seems to be more prevalent among CM patients than children with SMA (32 and 5.88%, respectively). White blood cell (WBC) counts and hyperleucocytosis (WBC≥10000 μL⁻¹) have the same trend than parasitaemia and hyperparasitaemia in our population (80.95 and 53.49% for hyperleucocytosis in children with CM alone and SMA, respectively). As expected, haemoglobin (Hgb) level is very low in children

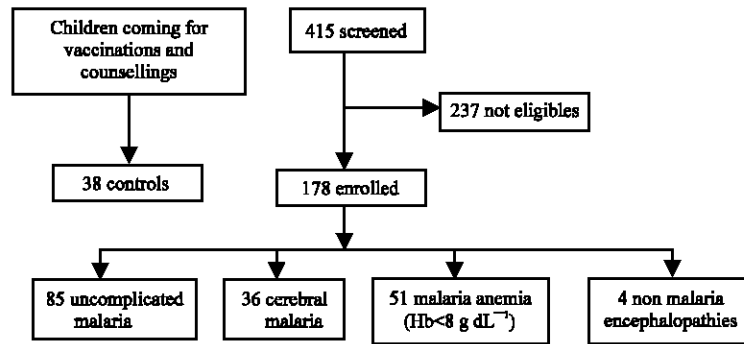


Fig. 1: Study profile of patient

Table 1: Baseline characteristics of malarial patients (according to disease severity) and controls

Parameters	Control (n = 38)	UCM (n = 85)	MA (n = 51)	CM only (n = 25)	CM and MA (n = 11)
Population characteristics					
Age (months)	53.71±45.51a	41.51±41.11	47.84±39.33	27.48±25.59	31.91±27.98
Male, n (%)	12 (31.58)	52 (61.18)	30 (58.82)	12 (48)	6 (54.55)
Weight (kg)	18.06±7.99	15.94±8.75	15.02±7.95	11.66±4.52	12.32±3.80
Temperature (°C)	37.20±0.28	38.58±0.94	38.99±0.85	39.67±0.95	39.56±1.10
Laboratory data					
Log 10 parasitemia	NR	3.65±0.73	4.36±0.74	4.72±0.79	5.04±0.43
Hyperparasitemia (%)	NR	0 (0)	3 (5.88)	8 (32)	3 (27.27)
WBC (mm ⁻³)	7383.87±1338.68	9038.13±3467.55	12053.49±6740.05	14295.24±4587.86	14230±4630.35
Hyperleucocytosis (%)	1 (2.86)	32 (37.65)	(53.49)	(80.95)	(80.00)
RBC (mm ⁻³)	4204000 ±605172.15	4050151.52 ±506124.01	2575116.28 ±843988.2	3711904.76±558995.7	2715000±516661.3
Haemoglobin (g dL ⁻¹)	12.47±0.82	11.16±1.32	5.716±1.35	10.37±1.04	6.15±1.27
Hct	36.76±2.23	32.45±4.40	16.99±4.69	30.1±4.17	17.96±3.88
Plaquettes (mm ⁻³)	207800±11820	223200±10190	201700±14220	156000±14580	162100±27820
Glycaemia (g L ⁻¹)	0.75±0.07	0.77±0.17	0.67±0.21	0.64±0.14	0.66±0.18

a: Means±SD, NR: Not relevant, MA: Malaria anaemia, UCM: Uncomplicated malaria, CM: Cerebral Malaria, WBC: White Blood Cells, RBC: Red Blood Cells, Hb: Haemoglobin, Hct: Haematocrit

Table 2: Clinical outcome of malarial patients according to disease severity

Parameters	UCM (n = 85)	MA (n = 51)	CM only (n = 25)	CM and MA (n = 11)
Fever resolution time (h)	33.9±22.88a	45.14±28.46	66±37.44	81.6±30.36
Coma resolution time (h)	NR	NR	16.33±10.04	16.2±8.02
Fits frequencies	1±0	1.25±0.5	1.57±0.66	1.4±0.97
Prostration resolution time (h)	28.70±19.19	45.45±23.91	56.25±26.55	59.4±36.93

A: Means±SD, NR: Not relevant, MA: Malaria anaemia, UCM: Uncomplicated malaria, CM: Cerebral Malaria

Table 3: Use of bed net and prevalence of some abnormalities on admission

Groups	Use of bed nets and abnormalities (%)							
	Use of bed nets	Hyper pyrexia	Coma	Impaired consciousness	Fits	Prostration	Hyper leucocytosis	Hypo glycaemia
Control	60.53	0.00	0.00	0.00	0.00	0.00	2.86	0.00
UCM	52.94	17.65	0.00	16.47	1.18	45.88	37.65	14.12
MA	41.18	17.65	0.00	49.02	7.84	74.51	53.49	37.25
CM	28.00	36.00	92.00	100.00	92.00	100.00	80.95	28.00
CM and MA	27.27	54.54	90.91	100.00	100.00	100.00	80.00	36.36

MA: Malaria anaemia, UCM: Uncomplicated malaria, CM: Cerebral malaria

with malaria anaemia, this is irrespective of whether this MA is combine with CM or not (5.72±1.35 and 6.15±1.27 g dL⁻¹ in children with MA and CM and MA respectively, p = 0.3379); Obviously Haematocrit follows this same trend. Complicated malaria (namely MA and CM) is associated with low glycaemia (0.67±0.21 and 0.64±0.14 g L⁻¹, respectively).

SMA compared to CM: Of the 62 children with MA, 51 had this anaemia without cerebral complications (28.7% of subjects recruitments), while 11 patients suffered combined severe anaemia and cerebral malaria (6.2% of recruitments). An additional 25 children had strictly defined CM alone (14% of recruitments). Compared to children with MA, children with CM were younger

(27.48±25.59 months and 47.84±39.33 months, respectively, $p = 0.0107$) and consequently weighed less (11.66±4.52 and 15.02±7.95 kg respectively). They also had higher admission temperatures and longer hospital stays. The case fatality rate was 11.1% in children with CM, but no death has been reported in MA patients.

DISCUSSION

This study set out to describe the clinical spectrum and haematological characteristics, as well as to understand the trend in pattern of morbidity of the disease in our setting, particularly to look for variation in different disease severity groups. We found that there seems to be a strong link between bed net usage and the reduction of the disease severity (60.53, 52.94, 41.18 and 28% prevalence of bed net utilization in Control, UCM, MA and CM, respectively). This prove that impregnated mosquitoes bed net to prevent malaria transmission is still working and remain a very interesting tool to implement in order to prevent severity when its occur (Noor *et al.*, 2007).

CM seems to be predominant in younger children and MA in older children. A different trend was noticed in others studies in Burkina-Faso, Ghana and Zambia as well as in some part of Uganda (Modiano *et al.*, 1998; Biemba *et al.*, 2000; Idro *et al.*, 2006). This difference is essentially due to transmission intensity that differs with the settings. In these others African settings, the fact that severe malaria tends to affect children of relatively older ages could be related to slower acquisition of clinical immunity in the urban environment as a consequence of lower levels of exposure to infected mosquitoes (Imbert *et al.*, 1997). However, since we are under high transmission, it is likely that CM (who seems to be more associated with poor prognosis) will affect much younger children (Snow *et al.*, 1999; Gupta *et al.*, 1999). In present setting, due to the high transmission intensity, children get continuous exposure to infection and quickly develop protective immunity against the deadly CM, so that during subsequent episodes, they suffer less severe forms or uncomplicated malaria (Barragan *et al.*, 1998; Rogier *et al.*, 1999). However, MA is generally more prevalent than CM in our setting; a similar trend has been observed in Zambia (Biemba *et al.*, 2000). Any way, CM seems to be more associated with poor prognosis than SMA; this is particularly noteworthy from present study, as far as the clinical outcome is concerned. As stated earlier, fatal cases have been reported in the CM group, whilst none has been reported in the SMA group; Biemba *et al.* (2000), in a study performed in Zambia, reported a case fatality rate of 18.9% in all CM cases, but only a case fatality rate of 7.3% in children with SMA.

In this study, anaemia occurred more frequently at low parasite densities than CM. This is consistent with

findings from Ghana where more than 80% of severely anaemic children exhibited no parasitaemia but presented with detectable plasma levels of soluble malaria antigens (Mockenhaupt *et al.*, 2004). This result may reflect chronic and/or repeated infections that eventually lead to gradual decrease in Hgb concentrations. Moreover, the low prevalence of hyperpyrexia in our patients with severe anaemia provides evidence for a chronic course of the disease. This corresponds to findings in a study of Tanzanian children with severe anaemia who were frequently asymptomatic or showed non-specific symptoms (Schellenberg *et al.*, 2003).

A non to be neglected prevalence of prostration and impaired consciousness were observed in children who were finally classify as UCM patients; Although prostration has been described in similar frequencies in other areas of Africa with high or low transmission, most large studies of severe malaria have not included assessment of the frequency of prostration, a defining criterion in the WHO, 2000 definition of severe malaria (Imbert, 2003). Prostration appears to have a lower case fatality rate than some other manifestations of severe malaria; however, because it is the main reason for hospital admission for patients with malaria, it will be important to educate health care workers about the characteristics and frequency of this presentation of severe malaria (Idro *et al.*, 2005).

CM and MA both seem to be strongly associated with hypoglycaemia (28 and 37%, respectively). This confirms the WHO 2000 definition of severe malaria where glycaemia is among the main criteria.

CONCLUSIONS

This study highlights differences in clinical presentation and outcome as well as in some laboratory parameters according to disease severity. Such study would also contribute to the management of the disease. The pattern in clinical presentation varies in different geographic location and in years and seasons, due to transmission intensity and climate changes. Therefore, it is necessary to monitor it time to time, taking into account some parameters which have been undermined up to now, like prostration, impaired consciousness and hypoglycemia. Future studies will focus on investigating and identifying parameters associated with disease severity, so as to be able to understand pathways leading to severe malaria.

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