CLINIQUE

The clinical spectrum of severe malaria in children in the east provincial hospital of Bertoua, Cameroon.

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Summary:

Severe malaria claims 1.5 to 2.7 million lives annually, most of which are young children in rural areas in sub-Saharan Africa.
We retrospectively reviewed the files of 387 patients, admitted and treated for severe malaria according to WHO guidelines, in the Bertoua provincial hospital, a peripheral health center in East Cameroon from 1st October 1998 to 30th October 2000. Our main objective was to study the epidemiological aspects, clinical presentation and outcome. The mean age was 2.7 years (range 2 months - 15 years) among them 214 males and 173 females giving a sex ratio of 1.2.
Transmission was observed all year round at variable frequencies with peaks in the rainy seasons.
Major symptoms were fever in 202 patients (52.2%), convulsions in 150 (38.8%), prostration in 79 (20.4%) and persistent vomiting in 78 patients (20.2%). Major clinical findings were severe pallor in 196 patients (50.6%) and splenomegaly in 75 patients (19.4%). The average time between onset of symptoms and consultation was 4.4 days (range 1 – 21 days).
Blood smears were positive for Plasmodium falciparum *in 288 patients (74.4%) and negative in 99 (25.6%). Concerning outcome, recovery was observed in 317 patients (81.9%), interruption of treatment (because of financial constraints) in 58 (15%) and 12 deaths (3.8%). Among the 317 patients who recovered, neurological sequelae were observed in six patients, blindness in four patients and deafness in three patients were the most frequent.*
We conclude that severe malaria constitutes a major challenge of early diagnosis together with implementation of appropriate treatment especially in rural areas. The use of WHO guidelines in the management of this disease and the recommended preventive measures of vector control have yielded good results in patients managed and followed up in our hospital.

severe malaria
Plasmodium falciparum
child
WHO guidelines
Bertoua
hospital
Cameroon
Sub-Saharan Africa

Résumé : **Présentations cliniques du paludisme grave de l'enfant à l'hôpital provincial de l'est à Bertoua, Cameroun.**

Le paludisme grave entraîne 1,5 à 2,7 millions de décès annuels dont l'immense majorité est enregistrée chez les jeunes enfants des zones rurales en Afrique tropicale.
Trois cent quatre-vingt sept cas de paludisme graves de l'enfant ont été colligés dans le service de pédiatrie de l'hôpital provincial de Bertoua, formation sanitaire périphérique situé dans l'Est du Cameroun, du 1e octobre 1998 au 30 octobre 2000. Ce travail a pour objectif l'étude des facteurs épidémiologiques, la présentation clinique et l'évolution sous traitement des enfants présentant un paludisme sévère selon la définition de l'OMS.
L'âge moyen des patients est de 2,7 ans avec des extrêmes de 2 mois et 15 ans. Deux cent quatorze patients sont des garçons et 173 des filles, soit un sex-ratio de 1,2. La transmission est observée sur toute l'année avec des pics pendant les saisons pluvieuses. Les symptômes majeurs observés : la fièvre chez 202 patients (52,2 %), les convulsions chez 150 patients (38,8 %), la prostration dans 79 cas (20,4 %) et les vomissements incoercibles chez 78 patients (20,2 %). Les principaux signes cliniques retrouvés sont : la pâleur importante dans 196 cas (50,6 %) et la splénomégalie chez 75 patients (19,4 %). La durée moyenne entre le début des symptômes et l'admission est de 4,4 jours avec des extrêmes de 1 et 21 jours. La goutte épaisse est positive pour le Plasmodium falciparum *chez 288 patients (74,4 %) et négative chez 99 autres, soit 25,6 %. L'évolution est marquée par la guérison chez 317 patients (81,9 %), le décès dans 12 cas (3,8 %) et l'abandon du traitement pour difficultés financières dans 58 cas (15 %). De 317 patients guéris, les séquelles neurologiques ont été observées chez six patients donc les plus fréquentes sont la cécité chez quatre patients et la surdité chez trois.*
Le paludisme grave de l'enfant est un défi majeur à relever en termes de diagnostic précoce et de prise en charge appropriée dans nos formations sanitaires périphériques. L'observance de recommandations de l'OMS dans notre prise en charge de cette affection et les mesures préventives préconisées dans la lutte anti-vectorielle dans notre milieu nous ont permis d'obtenir de bons résultats pour les cas régulièrement suivis dans notre formation sanitaire.

paludisme grave
Plasmodium falciparum
enfant
critères OMS
hôpital
Bertoua
Cameroun
Afrique intertropicale

Introduction

Between 300 and 500 million people in 100 developing countries suffer each year from malaria and most of the victims are children under 5. Malaria alone or associated with other diseases kills one child every 30 seconds and one million people every year (18). Because of its fatal complications, early diagnosis and appropriate treatment administered are mandatory. This challenge becomes much more difficult in rural areas where qualified health workers, laboratory equipment and basic drugs are often lacking to handle difficult cases and their complications.
Simple guidelines have been established by the World Health Organization and further complemented by the Cameroon's Ministry of Public Health to identify and to treat severe malaria especially for the use of health staff at the district level (9, 11, 14). We thus undertook this retrospective study in Bertoua in the East province of Cameroon to assess the amplitude of the problem and see how the WHO guidelines have been useful in managing cases of severe malaria in children of 2 months to 15 years.

Patients and methods

This is a descriptive transversal retrospective study, carried out in the General pediatric unit of the Bertoua provincial hospital, which is the reference hospital in this province. It is situated at 360 km from Yaounde, the political capital of Cameroon. The East province has a population of 710,000 inhabitants (Bertoua having 100,000 people) with 10 district hospitals and 126 health centers. As regards the epidemiologic transmission zone, it takes place in the equatorial belt where transmission is perennial with early premunition up to 5 years.
Patients' files were reviewed and an individual questionnaire filled for each patient featuring: age, sex, date of admission, presenting symptoms, physical findings, investigations, outcome and duration of stay in the hospital.
However, patients whose files had incomplete data or with concomitant illnesses were excluded.
The files of children aged 2 months to 15 years admitted from 1st October 1998 to 30th October 2000 (25 months) with the diagnosis of severe malaria were reviewed.
Included in this retrospective study were patients with one or more of the following criteria of severity:
WHO criteria:
- hyperpyrexia (13, 14)
- convulsions (11)
- behavioural disorders (11)
- respiratory distress (13)
- impaired consciousness (11, 13)
- hemoglobinuria (11, 13)
- severe anemia (11, 13)
- jaundice (11, 13)
- hyperparasitemia (> 5% parasitized red blood cells or 250,000 parasites/µl of blood) (14)

Additional criteria by the Cameroon's Ministry of Public Health (9):
- persistent vomiting
- dehydration

Long-term follow-up was not possible in most of our patients because they never turned up for reassessment appointments.
A lumbar tap was done in every patient with neurological symptoms to eliminate meningitis.
Asexual forms of *Plasmodium falciparum* were looked for, in the peripheral blood in all our 387 patients. Blood samples were collected by the laboratory technician before administering anti-malarial treatment on admission, and a thick blood smear done with Giemsa coloration. Some results of the parasitic density were reported qualitatively and others quantitatively when possible, so we had to use corresponding equivalents below as defined by WHO (12) in our analysis:
+ = 1-10 parasites/100 microscopic fields = 4 – 40 parasites/mm^3
++ = 11-100 parasites/100 microscopic fields = 40 – 400 parasites/mm^3
+++ = 1-10 parasites/microscopic field = 400 – 4000 parasites/mm^3
++++ = 11-100 parasite/microscopic field = 4000 – 40.000 parasites/mm^3
+++++ = > 100 parasites/microscopic field = > 40.000 parasites/mm^3
The patients selected in this study as having severe malaria had a strong clinical suspicion with a positive or negative smear, and all other possible causes of the presenting symptomatology eliminated. Quinine was administered according to the WHO treatment scheme: 20mg/kg body weight of quinine dichloride salt as loading dose in isotonic glucose solution in 4 hours, followed 12 hours after, with a maintenance dose of 10 mg/kg body weight in 2 hours and repeated every 12 hours till the patient can swallow oral medications, and oral treatment is maintained to make the complete treatment course of 7 days.
Artemeter was given intramuscularly when there was difficulty in maintaining a venous access, at a dose of 3.2 mg/kg loading dose on the first day, and followed with 1.6 mg/kg body weight maintenance dose per day for 5 days.
Transfusion was indicated when the hematocrit was less than 15% and / or hemoglobin less than 5g/dl, in the presence of imminent hemodynamic decompensation.
In patient with convulsions, diazepam was given at a dose of 0.5 mg/kg body weight, intra-rectally and repeated once after 20 minutes, if they persisted. Hydrosoluble phenobarbital was given by intravenous injection soon after administration of diazepam at a dose of 10 mg/kg body weight as loading dose and repeated every 24 hours with a maintenance dose of 5mg/kg body weight.
In case of clinically suspected hypoglycemia, 10% glucose drips were administered and when required, blood electrolytes were balanced, oxygen given and aspiration of secretions of the air ways done. When fever was present, tepid sponging was made and paracetamol given at 15 mg/kg body weight every 6 hours.
Pluvimetry values were obtained from the meteorological service of the Ministry of Transport in Bertoua .
Our results were analysed on epi-info version 6.0 software and graphs drawn on excel 5.

Results

Epidemiological findings

Hospital morbidity
A total of 2108 patients were hospitalized within the time of study and 387 cases had severe malaria giving an admission rate of 18.4%. Malaria is the first cause of admissions in our hospital.

Age
296 patients (65.5%) are aged of 36months and only 11 (2.8%) more than 10 years. These results are shown in table I.
The mean age was 2.7 years (range 2 months – 15 years).

Sex
214 children were males and 173 were females giving a sex ratio of 1.2.

Clinical presentation

The main symptoms and clinical findings are represented in table II: 202 patients presented with fever and only 4 had rectal temperatures above 40°C. Distribution of presenting

Tableau I.

Age distribution and frequency of severe malaria.
Distribution selon l'âge et fréquence du paludisme grave.

age group (years)	frequency	%
<1	111	28.7
1 – 2	115	29.7
2 – 3	70	18.1
3 – 4	29	7.5
4 – 5	19	4.9
5 – 6	8	2.1
6 – 7	10	2.6
7 – 8	6	1.6
8 – 9	3	0.8
9 –10	5	1.3
10 – 15	11	2.8
total	**387**	**100**

Tableau II.

Distribution of presenting symptoms and signs*.
Distribution des symptômes et signes cliniques.

	frequency	%
symptoms		
fever	202	52.2
convulsions	150	38.8
prostration	79	20.4
persistent vomiting	78	20.2
behavioural disorders	32	8.3
respiratory distress	21	5.4
coma	12	3.1
dark coloured urine	11	2.8
signs		
pallor	196	50.6
splenomegaly	75	19.4
hepatomegaly	30	7.8
dehydration	26	6.7
jaundice	17	4.4

* Some patients had more than one symptoms and signs

symptoms and signs in the 288 patients whose blood smears were positive for *Plasmodium falciparum* are shown in table III. The average time between onset of symptoms and consultation was 4.4 days (range 1-21 days).

Tableau III.

Distribution of presenting symptoms and signs in the 288 patients with positive smears*.
Distribution des symptômes et signes cliniques chez les 288 patients présentant une goutte épaisse positive.

	frequency	%
symptoms		
fever	151	52.4
convulsions	111	38.5
prostration	61	21.2
persistent vomiting	53	18.4
behavioural disorders	27	9.4
respiratory distress	18	6.3
coma	9	3.1
dark coloured urine	7	2.4
signs		
pallor	163	56.6
splenomegaly	57	19.8
hepatomegaly	20	6.9
dehydration	18	6.3
jaundice	12	4.2

* Some patients had more than one symptoms and signs

Results of parasitemias

288 patients (74.4%) had positive parasitemia for *Plasmodium falciparum* against 99 (25.6%) whose result was negative. Our results are represented in 6 groups according to the parasitemias (table IV). Most of the patients with negative smears had received prior anti-malarial treatment at home or in other health centers before admission.

Treatment

In all our patients, quinine drips were administered as first line treatment but artemeter had to be relayed intramuscularly in 8 patients (2.1%) because of difficulty in maintaining a venous access. 196 patients (51%) presented with signs of severe anemia on admission and 13 others (3.4%) during hospitalization. Thus 209 patients (54%) were transfused, and 26 had more than one transfusion.
In 4 out of the 150 patients who presented with convulsions, the latter persisted despite administration of diazepam and phenobarbital, and clonazepam had to be administered till complete cessation of the convulsions.

Outcome

Among our 387 patients, 317 (81.9%) completed treatment, while 58 patients (15%) did not complete treatment because of financial constraints and left hospital without medical consent. We noted 12 deaths (3.8%).

Neurological sequelae

Six patients (1.9%) out of the 317 patients assessed on discharge had neurological sequelae and 311 had no sequelae. The most frequent sequelae were blindness in 4 patients and deafness in 3. Our results are shown in table V.

Tableau V.

Neurological sequelae on discharge from the hospital*.
Séquelles neurologiques à la sortie de l'hôpital.

sequelae	frequency (n=6 patients)	% (with respect to the 317 patients recovered)
bilateral blindness	4	1.3
deafness	3	0.9
choreo-athetosis	2	0.6
decerebrate rigidity	1	0.3
decorticate rigidity	1	0.3
paraplegia	1	0.3
unilateral ptosis of the left eye	1	0.3
aphasia	1	0.3

* 6 patients had neurological sequelae on discharge and some had more than one sequelae.

Discussion

Epidemiological findings

Our results show that severe malaria is most frequent between the age of 2 months and 3 years with 296 cases (65.5%), and then the frequency drops. This agrees with the observations of SNOW and MARSH (16). It is established that in areas where falciparum malaria endemicity is stable, severe malaria is mainly a children disease for the first few months of life up to the age of 5 years and less common in older children and adults because of the acquisition of partial immunity (13). Children are relatively protected following birth due to acquired specific immunity from their mothers, and rarely manifest any severe features of malaria. In short, they behave rather like immune adults. Following the period of relative protection, children become increasingly susceptible to more severe clinical manifestations of disease (8). ASSIMADI *et al.* (2) found the peak

Tableau IV.

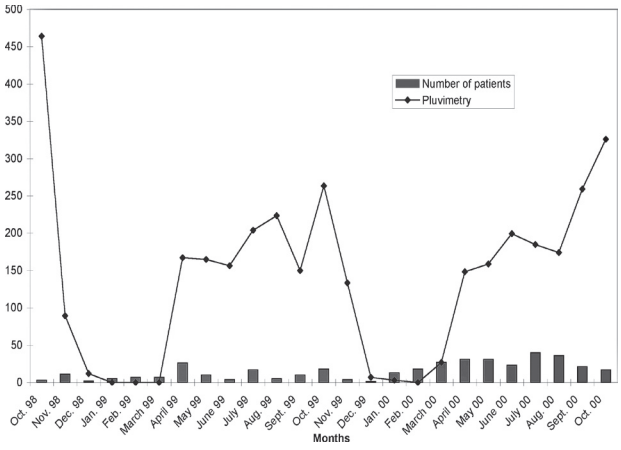
Results of peripheral thick blood smears.
Résultats de la goutte épaisse.

	group I 0	group II 4 - 40	group III 40 - 400	group IV 400 - 4000	group V 4000 - 40000	group VI > 40000	total
parasitemia/mm³	99	103	60	88	33	4	387
number of patients (%)	(25.6%)	(26.6%)	(15.5%)	(22.7%)	(8.5%)	(1.0%)	(100%)
total (%)	**99 (25.6%)**			**288 (74.4%)**			**387 (100%)**

frequency of cerebral malarial between 3 and 5 years indicating that active immunity is acquired late in Togolese children. Concerning sex distribution, the frequency was found to be higher in males than females, with a sex ratio of 1.2, similar to the one obtained by Assimadi *et al.* (3). Tchokoteu *et al.* (17) had 40 males and 38 females in Yaounde.
Concerning the monthly distribution of pluvimetry (figure 1) we observed that transmission occurs all year long (following the equatorial belt) but drops in the dry seasons (December, January and February), however it doesn't stop completely because *Anopheles gambiae* is frequently relayed by *Anopheles nili*, *Anopheles moucheti* and sometimes by *Anopheles funestus* which tends to survive much longer into the dry season in waters accumulated during the rainy seasons (10). Rainfall brings mosquitoes, larva pools and increases humidity thus giving them more chances to survive (15).

Figure 1.

Monthly distribution of patients and pluviometry.
Distribution mensuelle des patients et de la pluviométrie.



Clinical features

WHO has elaborated criteria for identifying severe falciparum malaria (14) and these criteria have further been complemented by the Cameroon's Ministry of Public Health (9).
Our results show that fever was the most frequent symptom in 202 patients (52.2%) and only 4 had rectal temperatures higher than 40°C. When the presenting symptoms and signs are considered in the 288 patients whose blood smears were positive, the general trend is similar as in the whole study population. Assimadi *et al.* (2) observed fever in 83.4% of their patients whereas Tchokoteu *et al.* (17) observed it in only 36% of their patients with 6 (28%) having temperatures above 40°C. Temperatures of 40-42°C increase risks of convulsions and neurological sequelae (14). Other common findings in our series were convulsions in 150 patients (38.8%), prostration in 79 patients (20.4%) and persistent vomiting in 78 patients (20.2%). Persistent vomiting makes oral treatment inefficient, and might lead to dehydration and impairment of consciousness if not adequately corrected early enough.
In African children, the presence of impaired consciousness or respiratory distress can identify those having a high risk of death (7, 19).
Severe pallor indicative of severe anemia was observed in 201 patients (51.9%) and splenomegaly in 75 patients (19.4%). The same trend was observed by Assimadi *et al.* (2), whereas Tchokoteu *et al.* (17), observed severe anemia in 18% of their patients.
Severe anemia is an important and life threatening complication of falciparum malaria in children. It is often multifactorial, and is attributable to malaria because of parasitemia and lack of an adequate alternative explanation (13). However the physiopathology of severe malaria is multi-faceted involving several pathogenic mechanisms (13, 20).
The least frequent symptom was dark-coloured urine in 11 patients (28%). Same observation was observed by Tchokoteu *et al.* (17) in 1 patient (1%) in Yaounde.

Investigations

After a thorough clinical examination and all other possible causes of the clinical presentation eliminated, and diagnosis of severe malaria suspected, a blood smear was performed for each patient. The results of our blood smears are similar to those of Assimadi *et al.* (2) who had 74% positive smears and 25.5% negative. The relationship between parasitemia and the severity of malaria depends on the immunity of the patient and malaria endemicity in the region. In non-immune children in areas of unstable endemicity, a peripheral parasitemia of 4% or more is a sign of severity, whereas in areas of stable endemicity, a parasitemia of 20% or more indicates severity (13). Parasitemias of more than 250,000/µl or more than 5% parasitized cells in peripheral blood is a biological indicator of poor prognosis in children and adults (14). Only 4 patients in our series had parasitemias higher than 250,000 parasites/µl of blood.
A major drawback with these smears is that precise parasite counts were not given for all the patients by the laboratory technicians so we had to use corresponding equivalents in the final assessment as directed by WHO (12). Discovery of parasitemia can quickly confirm clinical suspicion of malaria but in patients with symptoms compatible with severe disease, a therapeutic trial of parenteral antimalarial drugs is justified, even if the initial blood film is negative (13).
A negative blood smear does not exclude malaria after elimination of all other possible causes of the presenting symptoms. A negative smear is frequent in patients who had received prior anti-malaria treatment at insufficient doses or during sequestration in the microcirculation. Prior antimalaria treatment may explain the high frequency of negative smears in our series. According to Ambroise-Thomas *et al.* (1), negativity of a blood smear can only be confirmed after examination of 100 microscopic fields of a thick smear or 3000 microscopic fields of a thin smear. This is long and fastidious and hardly performed by unskilled impatient technicians who are quickly discouraged.
Financial constraints of our patients did not permit chest x-rays in those with respiratory distress (to eliminate acute pulmonary oedema), and our laboratory could not perform PHmetry and measure blood lactate levels.

Treatment

Quinine and artemeter and its derivatives are the two drugs recommended by WHO (14) in the treatment of severe malaria. 379 patients received quinine drips whereas 8 received artemeter at the recommended dosages. 54% of our patients were transfused because of severe anemia. Assimadi *et al.* (3) and Tchokoteu *et al.* (17) observed severe anemia in 49.18% and 18% respectively in their patients. Before transfusion each blood sample was screened for the HIV (Human Immunodeficency Virus) to avoid contamination.
In African children, transfusion should be reserved for high-risk patients with the following clinical features: (i) respiratory distress (ii) impaired consciousness (iii) massive parasite loads with low hemoglobin levels. Children with respiratory distress are contrary to usual belief, very rarely in congestive heart failure and the sicker the child is, the more rapidly the transfusion has to be given (13).

Outcome

Our lethality rate of 3.8% falls below the range of 59 to 350‰ observed by SNOW *et al.* (15) in Ethiopia. An average case -fatality of 16% has been reported in recent studies (13). ASSIMADI *et al.* (2) found a lethality rate of 18.7% in his series of patients with cerebral malaria. In a recent study by ASSIMADI *et al.* (3) on severe malaria in Togo, a lethality rate of 18.94% was observed. TCHOKOTEU *et al.* (17) had no deaths nor sequelae in their series in the Yaounde General Hospital. But their study was made in a reference urban hospital, which is a tertiary hospital in Cameroon and most of the patients admitted there, belong to higher socio-economic class. Our low mortality rate might not be quite significant , given that 58 patients interrupted treatment and left hospital so we could not determine their outcome. This large number of patients who interrupted treatment is indicative of the poor socio-economic conditions of the rural masses who often can't afford treatment when sick and most of the time will resort to traditional ineffective treatment, and will only come to hospital when the case is severe.
However we had a good success rate with 81.9% patients cured. This could be explained by the high index of clinical suspicion we developed with the use of WHO guidelines for the diagnosis and management of severe malaria.

Neurological sequelae

We observed neurological sequelae in 6 (1.9%) out of the 317 patients assessed on discharge. This figure is probably low considering the 58 patients (15%) who interrupted treatment and left hospital without assessment, and were lost to follow-up. Blindness was the most frequent sequelae occuring in 4 patients followed by deafness in 3 patients. One patient with severe choreo-athetosis, deafness and blindness was referred to a neuropediatrician in Yaounde for management.
In some studies sequelae were observed in 5.3% (2) and 2.73% (3) of their patients whereas in others no sequelae were observed (17).
Residual neurological sequelae is reported in 5-10% patients with cerebral malaria (6, 14, 15); in 12% of patients (5); and in 23.3% of survivors of cerebral malaria (4). Hypoglycemia, repeated convulsions and diminution of cerebral irrigation associated with increased intra-cranial pressure, hypoxia and tissular lesions are risk factors for neurological sequelae (15). The depth of coma on admission, multiple convulsions and duration of unconsciousness were the only three independent risk factors in several studies (4,5). In general, children with only one neurological abnormality are more likely to make full recovery than those with multiple abnormalities (4).
We observed that the delay between onset of symptoms and consultation in our unit was 4.4 days, which is quite long and is surely a contributing factor to increasing mortality, and installation of neurological sequelae. Most patients first resort to automedication at home, local traditional doctors or go to peripheral health centers which often lack human and material resources to handle severe cases.

Conclusion

This study, one of the first in Cameroon to assess the clinical spectrum and management of severe malaria using WHO guidelines in a rural area, deserves some attention. It shows that severe malaria levies a heavy burden especially in children under 5 in terms of morbidity.
In rural areas where human and material resources to handle patients with severe malaria and its complications are often limited and poverty rampant, WHO guidelines are very helpful in early diagnosis and management.
By doing so, morbidity and mortality induced by severe malaria especially in vulnerable groups could be reduced, and the purpose of reducing by 50% the mortality rate of malaria by the year 2010 could be expected to be reached.

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