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Research Article

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Current Aspect of Severe Malaria at the Infectious and Tropical Disease Service in Fann (Dakar)

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Abstract

Background: *Severe malaria occupies a significant place in Senegal. It is characterized by a multiple organ failure that is related to a very poor prognosis. The objective of this study was to determine the Current profile of severe malaria in the service of Tropical and Infectious Diseases of Fann Hospital in Dakar.*

Methods: *A retrospective study was conducted regarding patients hospitalized between 2014 and 2016 for whom the diagnosis of severe malaria was established using WHO criteria of severity.*

Results: *The number of cases of severe malaria was 176 cases, ie a hospital prevalence of 6%. The majority of patients were admitted between September and December. The median age averages 33 years [range: 11-86]. Nearly three-quarters of the patients were male (73.9%), a sex ratio of 2.8. Cerebral malaria was the most common (69.9%) and the most frequent signs of gravity were coma (68.2%), followed by jaundice (58.5%) and renal failure (29.6%). Hyperparasitaemia was noted in 13 cases. In all cases Plasmodium falciparum was the responsible parasite. Ninety-nine patients received quinine and 75 artesunate. Almost three quarters of patients (111 cases) had been hospitalized for up to 7 days. Case fatality rate reached 18.8%.*

Conclusion: *Severe malaria is still responsible of multiple organ failure and a life-threatening disease. The most frequent sign of severity is coma but jaundice and renal impairment are increasingly high. Parenteral artesunate's use is becoming consistent. Patients' surviving artesunate should be investigated.*

Keywords: Severe Malaria, Senegal, Dakar, Current Aspect, Lethality

Introduction

Malaria remains a major health problem on a global scale. According to the World Health Organization (WHO), in 2016, 91 countries reported a total of 216 million cases of malaria, an increase of 5 million cases over the previous year and the global tally of malaria deaths reached 445 000 deaths, about the same number reported in 2015 [1]. The WHO African Region continues to account for about 90% of malaria cases and deaths worldwide [1].

In Senegal, the epidemiology of malaria has changed significantly with the advent of rapid diagnostic tests (RDTs) and Artemisinin-based Combination Therapy (ACTs) in 2007, but also with the implementation of other strategies for malaria control. Thus, between 2011 and 2014, the morbidity recorded in the health structures decreased from 5.3 to 3.4% and during the same period, the hospital lethality of malaria was stable at less than 4% [2]. Despite these good results, Senegal is still classified among the countries of sub-Saharan Africa where malaria is endemic with seasonal transmission mainly during rainy season and malaria remains a major public health problem. Severe falciparum malaria is defined as one or more of the severity criteria, occurring in the absence of an identified alternative cause and in the presence of Plasmodium falciparum asexual parasitaemia [3].

Severe malaria occupies a significant place in Senegal. As of September 30, 2017, there were 2.7% of confirmed cases of malaria and the region of Dakar occupied 28.2% of cases of severe malaria [4]. Often described as a condition of the child, the pregnant woman and the non-immune subject, severe malaria also affects apparently immune subjects but also the young adult [5-8]. Severe malaria is mainly due to an infestation with Plasmodium falciparum. However, several series of cases of severe malaria with Plasmodium vivax and knowlesi has been recorded over the past years [9-12]. The risk is

increased in the case uncomplicated malaria treatment's delay. The rapid diagnosis and treatment of uncomplicated malaria is therefore of crucial importance.

At the service of Infectious and Tropical Diseases (SMIT) in the National University Hospital of Fann in Dakar, severe malaria occupies a place of choice and is among the medical emergencies [13].

In this context we have undertaken this study which objective was to describe the sociodemographic, clinical, paraclinical and outcome features of severe malaria at SMIT of Fann Hospital.

Methodology

Type and period of study, and inclusion criteria

A retrospective and descriptive study was performed from January 1, 2014 to December 31, 2016. All patients admitted in the service for severe malaria were included. The diagnosis of severe malaria was established in accordance with the WHO definition criteria of severe malaria of 2000 and revised in 2015 [3,14].

Were not included in the study patients with negative rapid diagnostic tests (RDTs) for malaria or negative microscopy of thick-blood smear slides for malarial parasites, or those with severe malaria but whose records were incomplete or lost.

Data collection

The data was collected using a standard questionnaire with four sections:

- A first part for sociodemographic data such as age, sex, geographical origin, marital status, occupation and level of education, but also case history;
- A second part with clinical and paraclinical aspects including data concerning severe malaria clinical and paraclinical signs as well as other associated signs;
- A third part concerned therapeutic data such as the antimalarial treatment and its duration as well as the other associated treatments;
- A fourth section concerning the evolutionary and prognostic aspects describing the outcome and complications.

Data entry and analysis

Data entry was done using Epi-Data software version 3.5.1 and their analysis was carried out using Stata/SE software version 12.1. Categorical variables were expressed in terms of frequency and percentage of data entered with 95% confidence intervals (CI). Quantitative variables were expressed in means with standard deviation or median with ranges when nonnormally distributed.

Results

Socio-demographic aspects and seasonality patterns

During our study period, among the 2937 patients hospitalized at SMIT Fann, 176 cases of severe malaria had been collected - a hospital prevalence of 6%. More than half of these cases were recorded in 2015 (89 cases) while in 2016, 64 cases were found. The majority of cases of severe malaria were recorded between September and December, regardless of the year. Case peaks were found in November with 6, 27 and 32 cases in 2014, 2015 and 2016 respectively. Figure 1 illustrates this monthly distribution of severe malaria cases from 2014 to 2016.

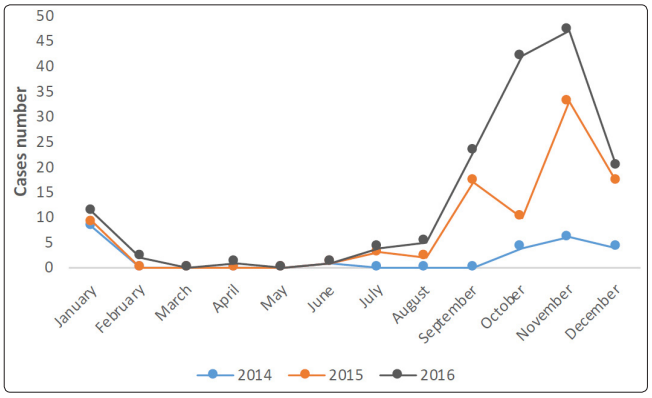

Figure 1: Monthly distribution of severe malaria cases at Fann SMIT from 2014 to 2016 (n=176).

The median age of the patients was 33 years [range: 11-86]. Patients younger than 25 years were the most affected with 60 cases (34.1%). Nearly three-quarters of the patients were male (73.9%), a sex ratio H / F of 2.8. The majority of patients came from the suburban area (85.7%), particularly from the suburbs of Dakar. Regarding marital status, it had been identified in 140 cases and most patients were single (67 cases or 47.9%). As for the profession, it had been specified in 57 patients. Of these, the majority were salaried employees or manual workers (26 cases or 45.6%). The level of education was identified in 24 patients. Half of the patients had a secondary level. These sociodemographic characteristics are represented in (Table 1). In our study population, half of the patients (88 cases) had comorbidity. The most frequent was smoking with 25 cases (14.2%) followed by asthma with 19 cases (10.8%) see (Table 2).

Table 1 : Sociodemographic characteristics of patients with severe malaria hospitalized in SMIT (Fann) from 2014 to 2016 (n=176)

Sociodemographic characteristics	Frequency (n)	Percentage (%)	95% CI
Year			
2014	23	13.1	8.3-19.6
2015	89	50.6	40.6-62.2
2016	64	36.4	28-46.4
Sex			
Male	130	73.9	61.7-87.7
Female	46	26.1	19.1-34.9
Age group (years)			
Less than 25	60	34.1	26-43.9
25-35	37	21	14.8-29
35-45	26	14.8	9.7-21.6
45-60	38	21.6	15.3-29.6
Over 60	15	8.5	4.8-14.1
Residence			
Urban	21	12	7.4-18.3
Suburban	150	85.7	72.5-100
Rural	4	2.3	0.6-5.9
Marital status			

Single	67	47.9	37.1-60.8
Married	51	36.4	27.1-47.9
Divorced	13	9.3	4.9-15.9
Widow(er)	9	6.4	2.9-12.2
Occupation			
Salared	13	22.8	12.1-39
Labourer	13	22.8	12.1-39
University student	8	14	6.1-27.7
School student	8	14	6.1-27.7
Trader	6	10.5	3.9-22.9
Retired	4	7	1.9-18
No occupation	3	5.3	1.1-15.4
Housewives	2	3.5	0.4-12.7
Educational level			
Primary	1	4.2	1.1-23.2
Secondary	12	50	25.8-87.3
University	5	20.8	6.8-48.6
Koranic	4	16.7	4.5-42.7
No education	2	8.3	1-30.1

Table 2 : Distribution of patients with severe malaria hospitalized in SMIT (Fann) in 2014-2016 regarding existence of comorbidities (n=176)

Comorbidities	Frequency (n)	Percentage (%)	95% CI
Smoking	25	14.2	9.2-21
Asthma	19	10.8	6.5-16.7
Alcool	12	6.8	3.5-11.9
High blood pressure	11	6.3	3.1-11.2
Psychiatric disorders	7	4.0	1.6-8.2
Diabete	5	2.8	0.9-6.6
Ulcera	4	2.3	0.6-5.8
HIV	3	1.7	0.4-5
Epilepsy	2	1.1	0.1-4.1
No	88	50	40.1-61.6
Total	176	100	

Malaria severity signs

The clinical signs of severity were dominated by coma (120 cases) and jaundice (103 cases). As for the biological signs defining severe malaria, the most represented were renal impairment (52 cases) and severe malarial anemia (20 cases). All cases of severe malaria were due to Plasmodium falciparum. The median of P. falciparum asexual parasitemia was 4,800 p/µl [46- 603,636]. Hyperparasitaemia was found in 13 cases (7.4%). (Table 3) represented patients' distribution according to presence of signs defining severe malaria. The median number of severity criteria found in patients was 2 [range: 1-5]. The most frequent locations of severe malaria were neurological (69.9%), hepatic (58.5%) and renal (41.5%). The different forms of severe malaria are represented in (Table 4).

Table 3 : distribution of patients hospitalized in SMIT (Fann) in 2014-2016 according to presence of signs defining severe malaria (n=176)

Signs of severe malaria	Frequency (n)	Percentage (%)	95% CI
Clinical signs			
Coma Glasgow <11	120	68.2	56.5-81.5
Jaundice	103	58.5	47.8-71
Macroscopic haemoglobinuria	32	18.2	12.4-25.7
Seizures	31	17.6	12-25
Pulmonary oedema	15	8.5	4.8-14
Circulatory collapse or shock	9	5.1	2.3-9.7
Abnormal bleeding	4	2.3	0.6-5.8
Prostration	1	0.6	0.01-3.2
Biologicical signs			
Renal impairment	52	29.6	22.1-38.7
Severe anaemia	20	11.4	6.9-17.6
Hypoglycaemia	1	0.6	0.01-3.2
Parasitological sign			
Hyperparasitaemia	13	7.4	3.9-12.6

Table 4 : distribution of severe malaria diagnosed at SMIT in Fann Hospital from 2014 to 2016 according to the location

Location	Frequency (n=176)	Percentage (%)	95% CI
Cerebral malaria	123	69.9	58.1-83.3
Hepatic	103	58.5	47.8-71
Renal failure	73	41.5	32.5-52.1
Cardiovasculary	35	19.9	13.9-27.7
Pulmonary	12	6.8	3.5-11.9
Hematological	4	2.3	0.6-5.8
Metabolic	2	1.1	1.3-4.1

Other symptoms

In addition to severe malaria criteria, others symptoms were also found and are represented in (Table 5). These were mainly fever (96.5%), vomiting (71.3%) and headache (71.3%).

Table 5 : distribution of patients hospitalized in SMIT (Fann) in 2014-2016 according to presence of other signs not defining severe malaria (n=176)

Other symptoms	Frequency (n/N)	Percentage (%)	95% CI
Fever	168/174	96.5	82.5-100
Vomiting	124/174	71.3	59.3-85
Headaches	124/174	71.3	59.3-85
Joints pains	85/176	48.3	38.6-59.7
Myalgias	85/176	48.3	38.6-59.7
Diarrhea	30/153	19.6	13.2-28
Abdominal pains	21/158	13.3	8.2-20.3

Hepatomegaly	15/176	8.5	4.8-14.1
Meningeal signs	13/176	7.4	3.9-12.6
Cough	8/153	5.2	2.2-10.3
Dizziness	6/153	3.9	1.4-8.5
Splenomegaly	2/176	1.1	0.1-4.1

Other biological aspects

Regarding the other biological tests, the mean haemoglobin level was 10.4±3 g/dl (n=163) and median white blood cells were 8,900/mm3 [range: 2800 - 33300]. Hyperleukocytosis was noted in 44 cases (26.8%) and leukopenia in 7 cases (4.3%). The median platelet count was 75,000/mm3 [range: 11,000-586,000] (n=164). Median CRP was 96 mg/l [range: 5.1 - 373.8] (n = 128). For transaminases, the median AST level was 73 IU/L [range: 13.7-576.6] and 46.5 IU/L [range: 6.2-222.5] for ALTs. Eleven cases of associated bacterial infections were diagnosed (6.3%). They were divided into 5 cases of bacteraemia with 4 due to Staphylococcus aureus and 1 to Staphylococcus saprophyticus; 4 cases of urinary tract infection with two caused by Staphylococcus aureus, one by Escherichia coli and another one by Streptococcus D; one case of vaginal infection due to Escherichia coli was found as well as one case of skin infection in which Staphylococcus saprophyticus was responsible.

Therapeutic aspects

Severe malaria treatment was dominated by intravenous quinine use in 99 cases (56.3%) versus75 cases for parenteral artesunate (42.6%) and two cases of artemether injection (1.1%). Other treatments had also been associated with the antimalarial treatment. Thus, 80 patients (46.2%) had received antibiotic therapy, 15 (8.7%) received blood transfusion and 5 patients (2.9%) required renal replacement therapy such as intermittent hemodialysis.

Evolutionary et prognostic aspects

The mean time to hospitalization for patients with severe malaria was 6.7 ± 7.1 days. The duration of stay had been obtained in 174 patients. It reached of 6.2 ± 3.7 days. Nearly three quarters of patients (111 cases) had been admitted for up to 7 days. During our study period, 33 patients died (18.8%) and 139 survived (78.9%). Complications were noted in 65 patients (37%) distributed as follows: 56 cases of organ dysfunction, 5 cases of infectious complication and 4 cases of decompensation of the underlying defect.

Discussion

Senegal is classified among the countries of sub-Saharan Africa where malaria is endemic with a seasonal transmission mainly during the rainy season. Our study reveals peaks of severe malaria frequency between September and December. This period corresponds to the post-rainy season, commonly known as the "tail of malaria" characterized by the epidemic peak of severe malaria in Senegal [8,13,15,16]. More than half of the patients in our study (50.6%) had been admitted in 2015. This is due to heavy rainfall during that year, which led to flooding in some suburban neighbourhoods of Dakar this evolving on a background of recurrent poor sanitation. This prevalence is increasingly high in this service since 2003 [15]. This is linked to the galloping urbanization of Dakar leading to a reduce premunition towards malaria. Other studies especially in Abidjan had also reported this increase of cases in urban and suburban area. In our series, the majority of our patients (85.7%) came from the suburban area [5]. During rainy season, this area is the most affected by the floods creating the appropriate conditions for the multiplication of the vector. The rapid urbanization in periurban areas increases population density in and around anopheles aquatic habitats ,increase the risk of malaria transmission [17]. With urbanization, cities become populated with more individuals who reach adulthood without significant malaria immunity [17]. It had already been shown that the urban Malaria is a new transmission zone with the potential to induce clinical forms of severe malaria in non-immune populations [18].

Our study highlights again that cases of severe malaria are more frequent in males. This had already been reported by most previous studies [5–8, 15]. Similarly, the young adult age of patients with severe malaria seems to be a consistent feature. In our study, more than a third of patients were under 25 years old. This corroborates the results of other studies in urban Africa in which subjects with severe malaria had a mean age between 21 and 38 years [5,7,8,15,19]. This segment of the population therefore requires particular attention to malaria prevention and control measures.

Patients were hospitalized on average 7 days after onset of symptoms. This delay on admission was highlighted in the same department [15]. One of the causes is multiple consultations at different levels of the health pyramid prior to their hospitalization. Thus, for the most part, these patients had received treatment prior to admission (72%), in particular the use of intravenous quinine in almost one third of patients. This has already been attested in other studies in the same department [15, 20]. The other main causes of delayed care are to be found in use of self-medication and visiting a traditional doctor [20]. In case of self-medication, dosage regimen or duration of treatment times are often inappropriate [5]. In these patients, hospital settings are the last resort well after visiting traditional therapists.

The patients also had various comorbidities. It was most often smoking and asthma in our series. Elsewhere prevailed high blood pressure [16]. The presence of these comorbidities may further complicate malaria. Clinically, cerebral malaria is the most frequently encountered form of severity [5,7,13,15]. Our study does not deviate from this rule with 69.9% of cases cerebral malaria. Thus, criteria of severe malaria were dominated by coma with 68.2% of cases while seizures were ranked fifth with 17.6%. The second most common clinical form was hepatic with jaundice found in 58.5% of cases. Jaundice is increasing compared to previous data [7,13,15,16] and has supplanted anemia in the service and represented 11.4%. These results could be influenced by the traditional phytotherapy often used by patients before admission. Jaundice is regularly accompanied by a failure of liver function. In our study, the median levels of AST and ALTs were moderately high.

Although its importance is lower, anaemia is still relevant; patients had an average haemoglobin level of 10.4±3 g/dl. Anaemia is mandatory during severe malaria, due to haemolysis and poor medullar regeneration; however, it tends to worsen during evolution due to persistent haemolysis and red blood cells weakening [21,22]. We identified 20 cases of severe anaemia as defined by the WHO severe malaria criteria showing that anaemia is still a problem [5,7,13].

Renal impairment ranked third and accounted for 29.6% of cases. Its frequency is increasing [5,7,15]. Acute renal failure has been attributed to ischaemic tubular necrosis from hypovolaemia

resulting from vasodilatation due to endothelial injury [23]. In some cases, organic renal failure develops and probably its origin is multifactorial, involving: cytoadherence, shock, haemolysis, disseminated intravascular coagulation (DIC), rhabdomyolysis [24]. In our study, 16 cases of oligo-anuria had been identified, and five patients had undergone intermittent haemodialysis. Haemolyses will result in the accumulation of haemoglobin and red cell debris in the renal tubules leading to macroscopic hemoglobinuria [23].

Our results show that macroscopic hemoglobinuria accounted for 18.2% of cases and thus placed in fourth place of signs of severe malaria. Other signs of severity were present, but to a lesser extent. These included notably pulmonary oedema, circulatory collapse and hypoglycaemia. Thrombocytopenia is not exceptional during severe malaria [22, 25]. In our study, the proportion of thrombocytopenia average 74%. Various mechanisms have been proposed to explain thrombocytopenia during malaria episodes, including disseminated intravascular coagulation (DIC), platelet destruction by immune mechanisms, low medullar platelet production, platelet sequestration in organs, such as the spleen or brain and systemic sequestration [22,26-28]. The role of platelets is somewhat controversial. The thrombocytopenia is a predictor of both outcome and severity [27, 29]. However, some studies have suggested that it only predicts the level of parasitemia and is associated with favourable outcome [25, 30].

Severe adult malaria often realizes a multi-organ failure syndrome and several manifestations are described. In our study, the median number of severity criteria found in patients was of 2 [range: 1-5]. Apart from the signs of severe malaria, other symptoms of uncomplicated malaria are also present especially fever, vomiting and headache as previously described [5, 15]. Universal access to parasitological diagnosis of malaria is now possible with the use of quality assured rapid diagnostic tests (RDTs) which is one of the core principles of WHO's guidelines in this subject [3]. To confirm the diagnosis, all cases had a parasitological test either microscopy examination of thick and thin blood films or RDT for detecting Plasmodium falciparum histidine-rich-protein-2 (PfHRP2) in accordance with the recommendations of WHO. Thus, Plasmodium falciparum was the only plasmodia species found in our patients.

According to most West African series [5,7,15,31]. The mean density of parasites matches perfectly those previously described in our clinic [15, 16]. Hyperparasitaemia was noted in 13 cases whereas it was non-existent in the last studies in this matter carried out in the service [15, 16]. This could be related to the increase of populations with lesser premunition in urban and suburban areas [17].

Regarding co-infections, eleven cases of bacterial infections had been diagnosed, proving again that this association is not uncommon [13, 16,32]. They were mostly dominated by bacteraemia and urinary tract infections; they can be community-acquired as well as nosocomial [32]. The most frequently isolated organism during these infections in our study was Staphylococcus aureus. This aspect deserves to be investigated further. Other co-infections are possible such as meningitis, typhoid fever and lung infections [13, 16,32].

In 2014 recommendations, WHO advocate for the use of parenteral artesunate as a first-line treatment for severe malaria. In a systematic review of artesunate for severe malaria, randomized controlled trials conducted both in Africa and Asia show that in comparison with quinine, parenteral artesunate reduced mortality of severe malaria by 40% in adults and hypoglycaemia during treatment by 45% [33]. In our facility, parenteral artesunate use started in late 2015 explaining that the proportion of patients who received artesunate was 42.6%. In addition, artesunate appears superior to quinine at reducing the mean 50% and 90% Parasite Clearance Time (PCT) [33]. To improve the use of artesunate as first line in severe malaria, it was made available and free in 2018 in various settings of the country by ministerial decree despite all its effectiveness is poor. Also, its adverse effects such as delayed haemolysis and late-onset anemia in hyperparasitemia patients hould be monitored by hospital practitioners [3, 34-36]. As for the use of arthemeter in our service it was 1.1%. At the moment, data show that artemether is probably less effective than artesunate at preventing deaths from severe malaria but where artesunate is not available; artemether is an alternative to quinine [37]. After the improvement of their clinical status, 132 patients had benefited from a relay by artemisinin based combination therapy (ACT). These new therapeutic strategies reduce the duration of Treatment and hospital stay. In our patients, almost three-quarters had no more than 7 days of hospitalization and the mean duration of stay was 6.2±3.7 days in accordance with previous studies [15, 32].

The prognosis of severe malaria remains serious. Case fatality rate reached 18.8%. Lethality seems stable for several years in our sub region and it ranged between 8% and 26.7% [5,7,15,16,31,38]. Thus, despite the availability of artesunate, the inflection of mortality pattern is yet to be felt. In addition, the actual proportion of artesunate in lethality is not established because more than half of the patients had received quinine. In the literature several risk factors for death in severe malaria have been identified, such as older age, Glasgow score, hyperparasitaemia, jaundice, prolonged hospitalization and delayed start of treatment. [15,32,39]. In our context, it will be necessary to determine the predictors of death in order to improve the management of patients with severe malaria.

The limitations of the study reside in its retrospective nature causing the missing data and the lack of patient records management software. This study is also remarkable for the transition from quinine to parenteral artesunate. A study on the outcome of patients' receiving parenteral artesunate should be conducted as well as the monitoring of adverse effects related to this drug.

Conclusion

Severe malaria is still a reality and realizes a multiple organ failure. The main signs of severity are dominated by coma, but jaundice and renal impairment are increasing. The prognosis remains serious with still high lethality despite the increasing use of parenteral artesunate. For better management of patients with severe malaria, the use of parenteral artesunate should be systematic. Also, prospective study identifying the factors of poor prognosis should be conducted in the service as well as the patients' receiving artesunate outcome.

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