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Management of Severe Malaria in Sub-Saharan Africa. What's new?

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Abstract

Purpose: Study epidemiological, clinical, paraclinical, therapeutic and evolutionary aspects of severe malaria

Patients and Method: Retrospective, 3-year descriptive study from January 1st, 2018 to December 31th, 2020. Were included in the study patients hospitalized for resuscitation at the Ziguinchor Peace Hospital for severe malaria with a positive rapid diagnostic test or thick blood smear at the time of hospitalization or previously, associated with one or more organs and/or metabolic dysfunctions.

Results: Twenty-seven patients were included, representing an incidence of 3.9% of hospitalizations. The average age of patients was 24.91 years with extremes of 3 and 70 years. The sex ratio was 1.7. The average time between onset of symptoms and admission to resuscitation was 5.1 days. The previous treatment was artesunate-based in 81.5%. All patients had neurological disorders. A quarter of the patients had respiratory failure. Liver failure was found in 14.8% and kidney failure in a quarter. Cardiovascular collapse was present in 7.4% and hemostasis disorders in three quarters. The treatment consisted of monitoring, basic intakes, vascular filling, oxygen therapy, hemodialysis, noradrenaline, blood products, antibiotic therapy and artesunate. The average length of hospitalization was 4.4 days. The cure rate was 81.5%. Death occurred in 7.4% from septic shock and multivisceral failure syndrome.

Conclusion: Severe pathology, malaria is responsible for a still high mortality. The basic treatment is still artesunate. Prevention involves proper treatment of simple malaria cases, public policy and vaccination.

Keywords: Malaria; Management; Artesunate; Intensive care Unit - Sub-Saharan Africa

Introduction

Malaria is a febrile erythrocytopathy caused by haematozoa of the genus Plasmodium and transmitted by the bite of a mosquito, the female anopheles. It represents the world's first parasitic endemic. It is a serious disease due to a fatal form mainly due to *Plasmodium falciparum* [1]. According to the WHO, about 40% of the world's population living in the poorest countries is exposed to malaria. According to the 2020 global malaria report, the number of malaria cases was estimated at 229 million, including 409,000 deaths. Africa supports 82% of malaria cases and 90% of deaths are recorded [2]. Malaria remains a major obstacle to the development and improvement of the health level of populations, especially in sub-Saharan Africa. However, WHO reports a 23% decrease in malaria cases worldwide [2]. In Senegal, 354 708 confirmed cases were reported in 2019, including 9 352 serious cases [3]. Despite this, a decrease in incidence and mortality was noted. Studies at the level of other regions of the country and in this context of decline of malaria is necessary to better understand the different aspects of this disease.

Patients and Method

This is a retrospective, descriptive study carried out in the general anesthesia and resuscitation department of the Ziguinchor Peace Hospital over 3 years from January 1st, 2018 to December 31th, 2020. The study population consisted of all patients hospitalized for resuscitation at the Ziguinchor Peace Hospital for severe malaria. The study included all patients hospitalized with severe malaria with a positive rapid diagnostic test or positive thick blood smear at the time of hospitalization or previously associated with one or more organ and/or metabolic dysfunctions. It is within this framework that this work is carried out at the Ziguinchor Peace Hospital in Senegal, with the objectives of studying the epidemiological, clinical, paraclinical, therapeutic and evolutionary aspects of severe malaria in resuscitation.

Results

During our study period, we collected 27 cases of severe malaria that met our inclusion criteria, the incidence was 3.9%. The majority of cases of severe malaria were recorded in October (29.6%) and September (25.9%). Patients ranged in age from 3 to 70 years with an average of 24.9 years. We also noted a predominance of teenagers and young adults. In our study, 62.9% of patients were male and 37% for female, a sex ratio of 1.7. The time between symptom onset and resuscitation management ranged from 2 to 14 days with an average of 5.1 days. The majority of patients, 81.5%, had received antimalarial treatment with artesunate before being admitted to resuscitation. Neurological failure was the primary reason for admission to resuscitation.

All patients had coma-type neurological disorders, convulsions, delirium and agitation. Respiratory problems were present in a quarter of the patients. The clinical manifestations of these respiratory disorders were a polypnea with crackles and Kusmaul-like breathing, respiratory distress with bradypnea and apnea. Liver failure was diagnosed in 14.8%. Kidney failure was diagnosed in a quarter of patients. Cardiovascular failure was found in 7.4% of patients and was cardiovascular collapse. Hemostasis disorders were present in three-quarters of patients. All patients received monitoring that included: an electrocardioscope, a non-invasive blood pressure reading, a pulse oxygen saturation measurement, a bladder probe, a temperature measurement. Basic hydroelectrolytic resuscitation was done with 5% serum glucose enriched with NaCl and KCl depending on renal status and blood ionogram results. Mask oxygenation was indicated in 81.5% of patients with a SpO^2 target of 95%.

Some clinical situations required respiratory assistance in 18.5% of patients. These included neurological, respiratory and hemodynamic failures. The average duration of ventilation was 2.4 days with 24-hours and 7-days extremes. Six dialysis sessions were indicated in 7.4% of patients for threatening hyperkalemia. Amines were used in 7.4% of patients for hypovolemic shock and recovered cardiorespiratory arrest. Transfusion of labile blood products was required in 11.1% of patients. Antibiotics were used in 37% of patients with pneumonia. The antibiotics used were ceftriaxone and amoxicillin + clavulanic acid. All of our patients had first-line artesunate-specific treatment at a dose of 2.4 mg/kg at H0, H12, H24 and then every 24 hours. The duration of artesunate treatment ranged from 2 to 7 days with an average of 3.8 days. The relay of artesunate in case of favorable evolution could be done with an antimalarial per os.

Oral doxycycline was also associated with artesunate at 200 mg/day in two doses in 10 patients for up to 5 days.

Patient length of hospitalization averaged 4.4 days with one-day and 9-day extremes. The overall study of the progression of failures since admission shows the progressive decline of cases during the 3rd and 5th day of hospitalization. The evolution was favorable in 81.5% of patients. Complications were related to various organ failures and complications of resuscitation that are dominated by infectious complications particularly pulmonary. A patient was transferred to nephrology due to a persistent impairment of kidney function. We had a mortality rate of 7.4% secondary to shock and multiorgan failure syndrome. All dead patients had impaired consciousness at admission with a Glasgow 8 score.

Discussion

The incidence of severe malaria in our study over the three-year study period was 3.9%. This reduction in incidence is found in several studies [4,5]. This reduction is due to several collective and individual prevention measures, including the increasing use of insecticide-treated nets. Our study population was young, with an average age of 24.9 years. This corroborates the results of other studies in urban Africa in which subjects with severe malaria had an average age between 26 and 35 years [4,5]. These results suggest that teenagers and young adults are at high risk of contracting severe malaria, which could be explained by the low level of premunition in this population. This segment of the population therefore requires special attention [6,7]. The average time taken to manage resuscitation was 5.1 days. This period is three days for all cases of imported malaria in France [8].

The majority of patients, 81.5%, were able to receive initial treatment before being admitted to resuscitation with artesunate. This high rate of treatment failure may be explained by inappropriate treatment in terms of route of administration or dosage. Similar to previous publications, we found a high prevalence of neurological manifestations during severe malaria. Our results are consistent with work in Africa [9,10]. During severe malaria the main reason for transfer in resuscitation is neurological impairment whose depth is significantly related to mortality [11]. The evolution of disorders of consciousness is most often favorable and neurological recovery is often total. The factors likely to intervene in the occurrence of disorders of consciousness are numerous and often intimately related. It is interesting to note that many of them may, under certain conditions, be host-friendly, such as TNF and NO, which have pest control properties [12].

One of the main features of severe malaria coma is that it is generally totally reversible regardless of its initial depth [13,14]. Dominated by sequestration and immune activation, its pathophysiology probably involves a complex network of mediators (cytokines, NO, etc.), acting perhaps more locally than generally. In our patients there was no accurate description of a respiratory failure due to lack of blood gas. However, one third of patients had respiratory problems and 18.5% had ventilatory assistance. Severe malaria is a recognized cause of lesional edema, although its pathophysiology is poorly known [15].

There are also genuine acute respiratory distress syndromes developing in more than 80% of cases towards death despite treatment [16]. This rather rare respiratory failure is more

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common in adults than in children and is often associated with a multi visceral failure picture, thus poor prognosis. Apart from the direct role of the parasite, several factors can aggravate lung lesions: inhalation pneumonia in favour of coma, bacterial pneumonia associated, lesional edema secondary to bacteremia, hyperhydration especially in case of anuria [17]. Liver failure was reported in our series in 14.8% of patients. In the literature its incidence is very variable. The WHO estimates its incidence at about 2.5% in malaria endemic areas [18]. Other work has found higher impacts [19,20]. These results are influenced by the presence of other failures. Liver damage during severe *P. falciparum* malaria has been regularly described in the literature but no clinical-biological and histological correlation is clearly established. Findings are similar in all forms of malaria but appear to be more severe in *P. falciparum* malaria [1,21].

Kidney failure was found in a quarter of our patients. This rate is much higher than the average in the literature [10,17]. It would be much more common in the non-immune subject than in the subject living in malaria endemic zone [22]. The delay in management in a context of hypovolemia explains the high rate of renal failure and its severity in our series. Acute renal failure during severe malaria is almost the prerogative of adults [23, 24]. It is an acute tubular necrosis plurifactorial: dehydration, hemolysis, increase in renal blood viscosity related to parasitic sequestration. Diuresis can be kept but anuria is possible. It can be isolated and good prognosis with ad integrum recovery, with some extra-renal cleansing sessions. When it is associated with multi-visceral failure the prognosis is often fatal [25,26]. In our study the cardiovascular failure was present in 7.4% of patients. It is infrequent [27]. It is poor prognosis and often associated with multi-organ failure [26]. Hypovolemic involvement through multifactorial initial dehydration is common [22].

Myocardial involvement is rare, despite parasitic sequestration in heart vessels and the potential cardiotoxicity of several antimalarials [17]. A bacterial co-infection may contribute to the development of septic shock but *P. falciparum* may also be the only one responsible [22,26]. Bacterial co-infection is found in almost 30-50% of severe malaria cases associated with septic shock [17,28]. The frequency of bacterial co-infections during severe malaria may explain the use of antibiotics in our series. These can be both community-based and nosocomial bacterial infections [12]. However, in our study, no bacteriological evidence was established. The suspicion rested just on the clinical and paraclinical elements of presumption namely hyperleukocytosis and an increase in CRP. The risk was to overtreat and promote bacterial resistance. Bacteriological diagnostic capacities should be strengthened to improve the management of severe malaria cases. It should be noted that almost three quarters of our patients had thrombocytopenia, less than 150,000 platelets per mm^3. Thrombocytopenia is the most common biological manifestation during severe malaria.

It is rarely accompanied by abnormal bleeding because of the concomitant existence of activation and coagulation [29]. Still associated with the severity of malaria, thrombocytopenia is a hemostasis failure that is part of the current prognostic criteria for death in severe malaria [30,31]. In its new 2014 recommendations, the WHO recommends the use of injectable artesunate as a first-line treatment for severe malaria [25]. Two large-scale randomized controlled trials demonstrated that parenteral artesunate therapy reduced the number of deaths by 34.7% [32]. In addition, another multicentre study showed that the use of injectable artesunate resulted in a faster parasitic clearance, which is an important factor in reducing treatment duration and hospital stay [33]. In our series, all patients had received etiological treatment with artesunate intravenously. After improving their clinical condition (81.6%), they benefited from a relay through an ACT. Complications during hospitalization were dominated by infectious pulmonary disease in a quarter of patients. These pulmonary complications are related to inhalation pneumonia related to disorders of consciousness. A patient had been transferred to nephrology due to persistent impairment of kidney function.

This lack of recovery of renal function varies from 10% to 22% in different series [34-36]. It could be explained by several factors: the delay in management in nephrological environment, the histological nature of the lesion and the duration of the oliguria. The resuscitation mortality rate was 7.4%. This could be explained by the delay in management. Multiple organ system failure (MOSF) was the cause of death in half of our patients. This MOSF during severe malaria as observed in resuscitation has a pejorative value on evolution. Its pathogenesis remains unknown, but some teams have been able to evoke the role of endotoxins passing through the digestive wall favoured by parietal ischemia during the sequestration of parasitic hematies in mesenteric vessels [37].

Conclusion

Malaria remains a major obstacle to the development and improvement of the health level of populations especially in sub-Saharan Africa. However, WHO in 2020 reported a 23% decrease in malaria cases worldwide. This preliminary study should open other study perspectives for a better understanding and control of this scourge. Indeed, the study of these phenotypes and their impact on mortality will allow an improvement in the management of severe malaria access in intensive care. This work should be continued in parallel with investigations into parasites and host genetics.

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