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Original article

Severe *Plasmodium falciparum* malaria in the intensive care unit: A 6-year experience in Milano, Italy

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ABSTRACT

Background: Severe imported *Plasmodium falciparum* malaria is a potentially life-threatening disease with a reported mortality rate of 5–10% when patients are admitted to the Intensive Care Unit.
Methods: To retrospectively review the clinical aspects, the value of severity predictive scores and the management of patients with severe *P. falciparum* malaria admitted to an ICU in Milano, Italy between January 2010 and December 2015.
Results: Twelve patients were included: seven were male and five female with a median age of 43 years. All were initially treated with intravenous quinine. Median parasitaemia upon admission was 14,5% (range 1–20%). At the time of ICU admission, 3 patients (25%) had 5 or more World Health Organization criteria for severe malaria while another 6 of them developed one or more of the latter during their stay in ICU. Five required mechanical ventilation because of respiratory failure due to ARDS. Four patients required renal replacement therapy. Three patients underwent blood exchange transfusion. All patients survived.
Conclusions: Our retrospective evaluation of adults patients admitted to the ICU with severe imported *P. falciparum* malaria demonstrated a favourable outcome. Severity predictive scores currently in use probably overestimate the risk of malaria mortality in patients treated in health care systems of high income countries.

1. Introduction

Although declining worldwide, malaria was responsible in 2015 of 214 million clinically apparent cases and 438,000 associated deaths. A disproportionate majority (90%) of cases still occurrs in sub-Saharan Africa with deaths (67%) observed especially among children under-five years [1].

In 2012, 5,161 cases of imported malaria were recorded in the European Union (incidence rate: 0.88 cases per 100.000) with the United Kingdom (UK) and France contributing to the majority of cases [2]. Of the five species responsible of naturally transmitted infections in humans, *Plasmodium falciparum* is recognized as causing most of imported malaria cases in Europe and because infection with this microorganism may rapidly evolve to a life-

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threatening multi-system organ disease it is associated with almost all cases which require admission to the intensive care unit (ICU) [3–5]. Analysis of large database from France and UK showed that case-fatality rate associated with *P. falciparum* malaria was in the order of 0.4% and 0.73%, respectively [5–7]. However, ICU mortality in severe cases of *P. falciparum* infection is reported to be in the average of 5–10% [3,8,9]. Furthermore, a study of all malaria cases reported to the Centers for Diseases Control in the USA from 1985 to 2011 showed that *P. falciparum* was ten times as likely to cause death when compared with *P. vivax*, with a case-fatality rate of 0.9% [10].

In Western countries the risk of severe *P. falciparum* malaria and death was shown to be associated with several factors such as initial misdiagnosis [11,12], patient delay to seek medical attention, the time required to obtain a diagnosis of malaria and delays in treatment inception and appropriateness [13].

The present paper aims to review the clinical aspects of, and the management strategies used in, patients with severe *Plasmodium falciparum* malaria admitted to the ICU of a University hospital in Milano, Italy during a 6-year period.

2. Patients and methods

The Luigi Sacco Hospital (LSH) in Milano is a 550-bed Academic hospital that serves as a referral centre for patients with imported tropical diseases, including malaria. It has 2 infectious disease units with 76 inpatient beds and an 8-bed multidisciplinary ICU.

The records of all patients with severe *P. falciparum* malaria admitted to the ICU of LSH from January 2010 to December 2015 were retrospectively reviewed.

Severe and complicated malaria was defined according to the 2000 World Health Organization criteria [14]. In brief, in the presence of asexual forms of *P. falciparum* in the blood, the presence of one of more of the following features defines severe malaria: 1) impaired consciousness (Glasgow Coma scale < 11); 2) pulmonary oedema or adult respiratory distress syndrome; 3) circulatory collapse (systolic blood pressure< 80 mmHg despite adequate volume repletion); 4) severe anaemia with a haemoglobin level < 7 g/L (in adult patients); 5) hypoglicaemia with a blood glucose level < 40 mg/dL; 6) abnormal bleeding and/or disseminated intravascular coagulation (DIC); 7) renal failure with a serum creatinine concentration > 3 mg/dL and/or a 24-h urine output of <400 mL despite adequate re-hydration; 8) acidosis (blood pH < 7.35 or a serum bicarbonate level < 15 mmol/L or hyperlactataemia (plasma lactate level > 5 mmol/L); 9) jaundice or total bilirubin level > 3 mg/dL; 10) hyper-parasitaemia (parasite count > 5%); 11) repeated generalized seizures; 12) hemoglobinuria.

Acute lung injury was defined as the acute onset of bilateral pulmonary infiltrates on chest X-ray or CT scan with a PaO_2/FIO_2 < 300 mmHg, regardless of positive end-expiratory pressure (PEEP) levels. Patients with acute lung injury and a PaO_2/FIO_2 below 200 mmHg were classified as having ARDS [15].

Parasite counts were calculated as the percentage of parasitized red blood cells (RBC) observed by direct microscopy in a thin blood film. The treating physician ordered serial peripheral blood film examinations during the clinical management of patients with a frequency that was at his discretion and until malaria parasites could not be observed any longer.

The decision to employ red blood cell exchange was taken by the treating physician, in conjunction with specialists in transfusion medicine.

Three prognostic malaria scores were calculated for each patient admitted in the ICU, namely the Malaria Score for Adults (MSA), the Coma Acidosis Malaria (CAM) score and the Malaria Severity Score. Malaria Score for Adults (MSA) is obtained by the sum of the following conditions each assigned a pre-definite point and ranges from 0 to 10: 1 x (severe anemia [haemoglobin level < 5 g/dL]) + 2 (acute renal failure [creatinine level>3 mg/dL])+ 3 (respiratory distress, requiring mechanical ventilation)+ 4 x (cerebral malaria, [GCS < 11 V), in which each variable was scored as 0 or 1 [16]. Coma Acidosis Malaria (CAM) score is calculated as the base deficit score (0–2) as follows: base deficit < 2 = 0; 2 to <10= 1; >1 = 2 plus the Glasgow Coma Score (GCS; 0–2): 15 = 0; >10 to 14 = 1; <10 = 2. Respiratory rate-based CAM score (0–4) is calculated as the respiratory score (0–2) as follows: respiratory rate < 20 = 0; 20 to <40=1; >40 = 2 plus the GCS score (0–2) as previously described [17].

The Malaria Severity Score that defines dysfunction in 7 organ systems with 3 levels of severity and assigning 1, 3 and 5 points to level I, II and III severity of organ dysfunction respectively. The score ranges from 0 to 21 with risk of mortality calculated for each score [18].

Clinical severity at ICU admission was also assessed using the APACHE II score [19], SAPS II score [20] and SOFA score [21].

3. Results

Between January 2010, and December 2015, 177 adult patients with 180 diagnosis of malaria were cared for at the LSH in Milano (data not shown). Except for 30 *P. vivax*, seven *P. ovale*, four *P. malariae* and three mixed *P. falciparum* –*P. vivax* infections, all other patients (136, 75.5%) suffered from *P. falciparum* malaria.

Twelve patients (6.6%), with a median age of 43 years (range 28–59 years) were admitted to our ICU due to the presence of clinical and laboratory features of severe *P. falciparum* malaria according to WHO criteria (Table 1). Seven patients were male and five female; except for 4 African patients all were Italians. Upon admission to the ICU, 3 patients (25%) had 5 or more WHO criteria for severe malaria while during the ICU stay 6 additional patients developed one or more WHO criteria for severe malaria.

Five patients were admitted directly to the ICU from our Emergency Department (ED), four were transferred from the ED of neighbouring hospitals, two were transferred from the infectious diseases and internal medicine departments of our Hospital and one was airlifted from Africa and directly hospitalized to our ICU upon arrival in Italy.

All individuals had acquired the infection in sub-Saharan countries of West or Central Africa: 3 from Senegal, 2 from Nigeria, 2 from Cameroon, 2 from Ivory Coast and 1 each from Congo, Sierra Leone and Uganda. Eleven patients were returning to Italy while one was visiting our country for the first time. The main clinical and epidemiological characteristics of each patient are summarized in Table 1. Of note, none of them had taken antimalarial chemoprophylaxis. In all patients who were diagnosed with malaria while in Italy (n = 11) symptoms appeared within a median of 10 days (range 8–14 days) from arrival. The median time between symptoms onset and the time when patients first sought medical attention was 3.5 days (range 1–13 days) and corresponded in all cases but three (patient # 10 #11 and #12), with the time when the diagnosis of malaria was made. The 3 patients in whom the diagnosis of malaria was initially overlooked were either discharged by the ED without ruling-out a diagnosis of this infection or, in one case, the patient was hospitalized with an erroneous diagnosis (acute pyelonephritis).

The median delay with which the diagnosis of malaria was made in these patients was 8 days (range 3–9 days). For all other individuals who were correctly diagnosed at the first observation, the median time from presentation to the ED and the parasitological diagnosis of malaria was 2.7 h (range 1,16-9,30 h) while the