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Severe imported malaria in a Serbian referral center

Teška importovana malarija u tercijarnoj zravstvenoj ustanovi u Srbiji

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Abstract

Background/Aim. The World Health Organization estimates that 3.2 billion people are at a risk of being infected with malaria. Thus, the adequate diagnostic protocols for malaria, especially those aimed at determining disease severity, are paramount both in endemic and non-endemic setting. The aim of this study was to identify the demographic, parositological, clinical and laboratory characteristics associated with severe malaria in a non-endemic settings. **Methods.** We analyzed 22 patients with severe malaria and compared their clinical and laboratory findings with those of the patients with non-severe malaria in a search of predictors of disease severity. All patients were treated at the Infectious and Tropical Diseases University Hospital, Clinical Centre of Serbia in Belgrade, Serbia from 2000 to 2010. **Results.** The average age of patients with with severe malaria was 44.86 ± 12.33 years and men predominated (95.45%). The patients with severe malaria were infected *Plasmodium falciparum* (*P. falciparum*) significantly more frequently compared with those with non-severe disease (p =0.047). Jaundice was the most commonly observed feature of severe malaria, followed by anemia and renal failure. The multifactor analysis of variance showed that thrombocytopenia (p = 0.05) and high serum tumor necrosis factor-alpha levels (p = 0.02) were significantly associated with the disease severity. **Conclusion.** A high index of suspicion for malaria should be maintained when evaluating febrile patients returning from the malaria endemic regions. The elevated serum tumor necrosis factor-alpha levels and thrombocytopenia are associated with severe malaria in non-endemic settings.

Key words:
malaria; tumor necrosis factor-alpha; thrombocytopenia; severity of illness index; serbia.

Apstrakt

Uvod/Cilj. Svetska zdravstvena organizacija procenjuje da je oko 3,2 milijarde ljudi u riziku od inficiranja malarijom. Dakle, adekvatni dijagnostički protokoli za ovu bolest, naročito oni koji su namenjeni za utvrđivanje težine bolesti, od presudnog su značaja u enedemskim i neendemskim regijama. Cilj rada bio je identifikacija demografskih, parazitoloških kliničkih i laboratorijskih obeležja udruženih sa teškim oblikom malarije u neendemskim regijama. **Metode.** Analizirali smo 22 bolesnika sa teškom malarijom i uporedili njihove kliničke slike i laboratorijske analize sa nalazima kod bolesnika koji su imali manje teške forme malarije, a sve u cilju identifikovanja prediktora težine bolesti. Svi bolesnici bili su lečeni u Klinici za infektivne i tropske bolesti Kliničkog centra Srbije u Beogradu u periodu od 2000. do 2010. godine. **Rezultati.** Oboleli od teške malarije su bili prosečne starosti od 44,86 ± 12,33 godina i to pretežno muškarci (95,45%). *Plasmodium falciparum* (*P. falciparum*) je bio značajno češći izolat kod bolesnika sa teškom malarijom u odnosu na bolesnike sa lakšim formama malarije (p = 0,047). Oboleli sa teškom formom malarije najčešće su imali žuticu, a zatim anemiju i akutnu bubrežnu slabost. Multifaktorska analiza varijanse pokazala je da su trombocitopenija (p = 0,05) i visoke koncentracije faktora alfa nekroze tumora (p = 0,02) bile značajno povezane sa teškom malarijom. **Zaključak.** Pri evaluaciji febrilnih bolesnika koji se vraćaju iz područja koja su endemska za malariju potrebno je posumnjati na ovu bolest. Visoke koncentracije faktora nekroze tumora-alfa i trombocitopenija povezane su sa teškom malarijom u neendemskim područjima.

Ključne reči:
malarija; faktor nekroze tumora-alfa; trombocitopenija; bolesti, indeks težine; srbija.

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Introduction

The World Health Organization (WHO) estimates that some 3.2 billion people (about 44% of the world population) are at a risk of being infected with malaria and developing the disease [1]. Some 214 million cases of malaria were reported in 2015 and resulted in 438,000 deaths [2]. The WHO African region carries a disproportionately high share of the global malaria burden, considering it was home to 88% of malaria cases and 90% of malaria deaths in 2015 [2].

Severe malaria is defined by clinical or laboratory evidence of vital organ dysfunction [3]. In 1990, the WHO established the criteria for severe malaria in order to facilitate future clinical and epidemiological studies [4]. In the year 2000, these criteria were revised to include other clinical and laboratory abnormalities that portend a poor prognosis based on the clinical experience in the semi-immune patients [5]. *Plasmodium falciparum* (*P. falciparum*) is the most common cause of severe malaria, but *P. vivax and P. knowlesi* can also cause severe disease [6]. Although rare, *Plasmodium ovale* (*P. ovale*) were also reported in the patients with severe malaria [7].

The circulating level of tumor necrosis factor-alpha (TNF-alpha) was shown to be a marker of organ failure and, as such, was correlated to malaria severity [8–10]. Low thrombocyte counts were also proven to be related to the severity both of vivax and falciparum malaria, although some authors questioned their usefulness for triage and prognostication [11–13]. Most studies correlating the platelet counts and TNF-alpha levels to disease severity were conducted in endemic settings [9–13].

In 1975, the WHO announced that malaria was eradicated from Europe, with what was then the Socialist Federal Republic of Yugoslavia designated as malaria free since 1964. This meant that malaria was also eradicated from Serbia which was one of the six republics constituting the federation [14]. However, imported malaria remained a concern in the years that follow [15].

The aim of this study was to identify the demographic, parasitological, clinical and laboratory characteristics associated with severe malaria in a non-endemic setting.

Methods

We conducted a case control study in order to analyze the clinical, laboratory and parasitological characteristics of severe malaria in the Republic of Serbia. The researchers browsed through the archived paper-based medical records and identified all patients who were treated for malaria at the Infectious and Tropical Diseases University Hospital, Clinical Centre of Serbia in Belgrade, Serbia in the 11-year period (2000–2010).

The Infectious and Tropical Diseases University Hospital is a tertiary health care facility that treats the patients with infectious and/or tropical diseases that cannot be diagnosed and/or treated in other hospitals in Serbia and the patients who reside in the capital city of Belgrade and present directly to the Clinic.

The researchers then analyzed the selected medical records and determined which subset of malaria patients met the criteria for severe disease. Severe malaria was defined according to the WHO criteria as the presence of one of the following: hyperparasitemia (more than 5% parasitized erythrocytes), shock, abnormal bleeding, pulmonary edema/acute respiratory distress syndrome (ARDS), jaundice (a bilirubin concentration higher than 50 μmol/L), renal failure (a urine output < 400 mL per 24 hours and a serum creatinine concentration higher than 265 μmol/L), severe anemia (a hemoglobin concentration less than 7 g/dL or a hematocrit less than 20%), hemoglobinuria, impaired consciousness (a Glasgow coma score less than 11), prostration, multiple convulsions (at least two convulsions in 24 hours), acidosis (a bicarbonate concentration less than 15 mmol/L or arterial/capillary pH lower than 7.25), hyperlactatemia (an arterial lactate concentration >5 mmol/L) hypoglycemia (a plasma glucose concentration lower than 2.2 mmol/L) [5]. The patients with non-severe malaria were used as controls.

The findings on physical examination, parasitological and immunological investigation and blood chemistry panel and complete blood count results were entered into a Microsoft Excel 2010 document. We determined the TNF-alpha concentration in the patients' serum using the ELISA-based standardized kit called the Quantikine ELISA Kit (R&D Systems, 614 McKinley Place NE, Minneapolis) and examined thick and thin peripheral blood stained with Giemsa. Parasitemia was expressed as a percentage of parasitized erythrocytes.

Statistical analysis was preformed using the IMB's SPSS Statistics v14 utilizing descriptive statistics, the χ^2 test, Fisher's exact test (where assumptions for the χ^2 test were not met) and multivariate analysis of variance (MANOVA). We analyzed an average age of the patients, malaria chemoprophylaxis compliance, immunity to malaria, the presence of comorbidities, symptoms duration before admission to hospital, severe thrombocytopenia (platelet count < 50,000 x 10^9/L) and the TNF-α level as possible predictors of severe malaria using MANOVA.

The authors obtained ethical approval from the Ethics Committee of the School of Medicine, University of Belgrade.

Results

We identified 103 patients treated for malaria at the Infectious and Tropical Diseases University Hospital, Clinical Centre of Serbia from 2000 to 2010. A subgroup of 22 (21.35%) patients met the criteria for severe malaria at presentation. Men (95.45%) predominated and the average age of the patients was 44.86 ± 12.33 years (ranging from 21 to 61 years). The age distribution of the patients with severe malaria is represented in Table 1. It was not statistically significantly different than the age distribution of patients with non-severe malaria (Fisher's exact test, $p = 0.759$).

All 3 patients who suffered a fatal outcome had severe malaria making the overall lethality of malaria 2.91% and the lethality of severe malaria 13.64%.

Table 1

Age distribution of patients with malaria

Age (years)	Number (%) of patients	
	non-severe malaria	severe malaria
0–10	1 (1.23)	0 (0)
11–20	1 (1.23)	0 (0)
21–30	6 (7.41)	3 (13.64)
31–40	14 (17.28)	4 (18.18)
41–50	22 (27.16)	6 (27.27)
51–60	24 (29.63)	8 (36.36)
61–70	13 (16.05)	1 (4.55)
Total	81 (100)	22 (100)

A majority of patients with severe malaria were infected with *P. falciparum* (90.9%) which was a statistically significant difference compared with the patients with non-severe forms of the disease (Fisher's exact test, $p = 0.047$). We identified *P. vivax* in the blood of 2 patients with severe malaria, whereas one patient had malaria caused by *P. ovale*. No patients with severe malaria were infected with *P. malariae*. A vast majority of patients with severe malaria (95.45%) had a single *Plasmodium* species as the causative agent. One patient had a mixed *P. falciparum* and *P. vivax* infection (Table 2).

Table 2

Patient distribution by *Plasmodium* species

Plasmodium species	Number (%) of patients	
	severe malaria	non-severe malaria
Plasmodium falciparum	19 (86.38)	56 (69.13)
Plasmodium falciparum + *vivax*	1 (4.54)	4 (4.94)
Plasmodium vivax	1 (4.54)	19 (23.46)
Plasmodium ovale	1 (4.54)	0 (0)
Plasmodium malariae	0 (0)	2 (2.47)
Total	22 (100)	81 (100)

Thirteen patients (59.10%) fulfilled only one criteria for severe malaria at presentation, while 9 (40.90%) had two or more criteria. A single patient fulfilled five criteria for severe malaria and suffered a lethal outcome (Table 3). No patient met more than five criteria. We did not analyze the correlation between the number of fulfilled criteria and disease outcome due to the sparsity of data.

Table 3

Distribution of patients with severe malaria according to the number of fulfilled the World Health Organisation (WHO) criteria

Number of fulfilled criteria	Number (%) of patients
1	13 (59.10)
2	4 (18.19)
3	3 (13.63)
4	1 (4.54)
5	1 (4.54)
Total	22 (100)

The distribution of patients according to the features of severe malaria is represented in Table 4. Jaundice was present in 28.21% of patients making it the most commonly fulfilled criterion for severe malaria in our cohort ($\chi^2 = 22.744$, $p = 0.05$). No criteria of disease severity aside from those represented in Table 4 were fulfilled by the patients in the study cohort.

Table 4

Distribution of patients according to the features of severe malaria

Features of severe malaria (WHO criteria)	Number (%) of patients
Cerebral malaria	3 (7.69)
Pulmonary edema/ARDS	2 (5.12)
Renal failure	4 (10.26)
Disseminated intravascular coagulation	1 (2.56)
Jaundice	11 (28.21)
Anemia	7 (17.95)
Haemoglobinuria	1 (2.56)
Hyperparasitemia	10 (25.65)

WHO – World Health Organization; ARDS – acute respiratory distress syndrome

Two patients with severe malaria had arterial hypertension, while one had diabetes mellitus. The rest had no comorbidities.

The average TNF-alpha serum level was 31.91 pg/mL. Fourteen patients (63.63%) had severe thrombocytopenia (less than $50{,}000 \times 10^9$ thrombocytes/L). MANOVA revealed that the patients with severe malaria had statistically significantly higher levels of TNF-α ($p = 0.02$) and a statistically significantly higher frequency of severe thrombocytopenia ($p = 0.05$) compared with the patients with non-severe malaria (Table 5).

Table 5

Multivariate analysis of variance (MANOVA)

Variables	Non-severe malaria	Severe malaria	F	*p*
Avarage age (years)	47.47	43.68	0.48	0.49
Lack of Chemoprophylaxis (% of patients)	75.31	77.28	1.69	0.20
Absence of Immunity (% of patients)	46.92	50.00	0.84	0.36
Comorbidities (% of patients)	23.45	13.63	0.15	0.70
Duration of symptoms (days)	6.47	7.23	0.03	0.85
Serum TNF-α level (pg/mL)	17.12	31.91	5.79	0.02*
Number of platelets < $50{,}000 \times 10^9$/L (% of patients)	18.52	63.63	4.10	0.05*

***statistically significant result**

Discussion

In the timespan analyzed in our study, 103 patients with malaria were treated in our Clinic. According to data provided by the Institute of Public Health of Serbia "Dr Milan Jovanović Batut", the total number of malaria cases reported in Serbia in that same period was 121 [16]. The patients not treated in our Clinic were treated in other hospitals, mostly in the Military Medical Academy in Belgrade which treated a number of patients with severe malaria, especially if an interdisciplinary approach was necessary [17].

There is a lack of data when it comes to the severe forms of malaria in countries where the disease is not endemic because most studies can include only a small number of patients [18]. The results of our study showed that 21.35% of patients had severe malaria according to the WHO criteria. Other authors found that the proportion of patients with severe disease varies from 1% to 38% of the total number of patients with malaria [19]. Variations in the percentage of patients with the severe form of malaria are best illustrated by the following: the disease was severe in 7.5% of patients with malaria in Canada, 15.9% in the US and 16% in the UK [20–22]. In Germany, 27.9% of patients with malaria caused by *P. falciparum* had severe disease [23].

The vast majority of patients in our study (approximately 91%) had malaria caused by *P. falciparum*, which is in concordance with data from other studies. Both this and other studies indicated that severe malaria can be caused by *P. vivax*, the so called "falciparum like" syndrome [24–27]. No cases of severe *P. knowlesi* malaria were reported in Serbia in the analyzed time span. In our study, *P. falciparum* was significantly over-represented in the subgroup of patients with severe malaria compared with those with non-severe malaria.

This study shows that the most common features of severe malaria are the following (listed by decreasing frequency): jaundice, hyprparasitemia, anemia, renal failure, cerebral malaria, pulmonary edema/ARDS. Haemoglobinuria (also called blackwater fever) and disseminated intravascular coagulation (DIC) occurred leach in one patient. According to the research by authors from Germany and Spain, hyperbilirubinemia and hyperparasitemia were most commonly associated with severe malaria [23, 28]. A multicentric study from Thailand showed that jaundice was present in 529 (50.4%) of 1,050 patients with severe malaria and hyperparasitemia was present in 33.3% [29].

Cerebral malaria, renal failure, ARDS, anemia and DIC were most commonly associated with a fatal outcome in the US [30]. In this study, the fatal outcomes occurred in 3 (2.91%) patients; the immediate causes of death being cerebral malaria, renal failure and pulmonary edema/ARDS.

Many studies have shown that increasing age is a risk factor for severe malaria although some authors questioned this view [31–35]. The average age of patients with severe malaria in this study was approximately 44 years and the statistical analysis led us to the conclusion that an old age was not a risk factor for severe malaria. The lack of chemoprophylaxis is the second most commonly cited risk factor for severe malaria [31, 36, 37]. Extensive research that had been conducted in France from 1996 to 2003 and included the results from 120 reference laboratories analyzed at the National Center for imported and autochthonous malaria, showed an association between the severe malaria and increasing age, lack of chemoprophylaxis and duration of symptoms before diagnosis [36]. No such associations were proven in this study. The absence of acquired immunity to malaria was not a risk factor for the development of severe disease; a finding was similar to those of French authors [38]. Moreover, previous research suggests that congenital immunity is of a greater importance, and that the acquired immunity depends on the long-term exposure to malaria parasites making it generally limited to areas of high endemicity [39].

According to the results of our study, the patients with severe malaria had significantly higher TNF-α levels and a significantly higher frequency of severe thrombocytopenia compared with the patients with non-severe disease. A retrospective study that had been conducted at the University Hospital of Heidelberg, Germany and included 122 patients with falciparum malaria, showed that thrombocytopenia was a significant predictor of severe malaria [23]. These findings were corroborated by other authors [22, 40]. In severe malaria, the concentrations of proinflammatory cytokines such as TNF-α, interleukin-1 (IL-1), interleukin-6 (IL-6), and interleukin-12 (IL-12) are elevated [41]. The high level of TNF-α in the patients with falciparum malaria correlates with disease severity, hypoglycemia, hyperparasitemia, jaundice, renal failure, cardiovascular complications and death [42]. Many studies showed a statistically significant correlation between the severe malaria and TNF-α levels, the presence of hyperparasitemia, jaundice and acute renal failure [43–44].

Conclusion

Even though it is a rare cause of morbidity in a non-endemic setting, a high index of suspicion for malaria should be maintained when evaluating febrile patients returning from malaria endemic regions. TNF-alpha is significantly higher and thrombocytes are significantly lower in the patients with severe malaria both in endemic and non-endemic settings and Serbia is no exception. Other proinflammatory cytokines may also represent a viable early diagnostic test for predicting malaria severity and presents us with an avenue of future research. Since *P. falciparum* causes a large proportion of imported malaria cases in Serbia and is most strongly associated with severe disease (lethal in one in eight patients), the identification of *Plasmodium spp.* in a patient's blood or even a febrile illness in a patient returning from a *P. falciparum* endemic region, should prompt the clinician to request a determination of the TNF-alpha levels and platelet counts in order to take measures to prevent and/or more effectively treat possible organ failure. Whether this approach is cost-effective remains to be elucidated.

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