

Original Article

Clinical characteristics of imported malaria: An 11-year experience in a Serbian referral center

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Abstract

Introduction: Due to intercontinental traffic, population migration trends, natural disasters, and climate change, imported malaria remains important to consider in a febrile returning traveler. This study aims to raise awareness about malaria and help European clinicians maintain a working knowledge of this disease by reviewing the most important clinical characteristics in a non-endemic setting.

Methodology: Using medical records, a retrospective study was performed on clinical and laboratory data in order to analyze 103 malaria cases managed at the Clinic for Infectious and Tropical Diseases in Belgrade, from 2000 to 2010. Descriptive statistics, Chi-squared test, Spearman's rank correlation, and analysis of variance were used.

Results: Patients were predominantly male (89.3%) with a mean age of 46.66 ± 12.45 years, and most (98.06%) returned from Africa without having taken chemoprophylaxis (72.88%). Fever, arthralgia, myalgia, headache, vomiting, dark urine, and cough were common at presentation. Hepatosplenomegaly, jaundice, neurological and pulmonary findings, and thrombocytopenia were dominant findings on physical and laboratory examinations. Most (73.48%) were infected with *P. falciparum*. Few patients (17.55%) who were hyperparasitemic had significantly higher values of bilirubin and more frequent neurological complications. All patients were treated with artemisinin-based drug combinations regardless of *Plasmodium* species. Three (2.9%) patients succumbed to *P. falciparum* malaria.

Conclusion: We suggest a high index of suspicion of malaria be maintained when evaluating febrile patients returning from endemic regions, especially if thrombocytopenia and hemolysis are present. Hyperparasitemia, high bilirubin levels, and neurological symptoms are associated with severe malaria. The importance of adequate malaria chemoprophylaxis cannot be overstated.

Key words: malaria; clinical characteristics; parasitemia.

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Introduction

Malaria is a vector-borne infection caused by protozoan parasites of genus *Plasmodium*. The five species known to infect humans (*P. falciparum*, *P. vivax*, *P. ovale*, *P. malariae*, and *P. knowlesi*) are usually transmitted by anopheline mosquitoes. Most severe cases and deaths from malaria are associated with *P. falciparum* infection [1]. Although relatively uncommon in developed countries, where the disease occurs mainly in travelers who have returned from endemic regions, malaria remains one of the most prevalent human infectious diseases worldwide [2]. Malaria has been described as a “great imitator”, and as such must be considered in the differential diagnosis of a number of clinical conditions [3]. Fever is the most commonly reported symptom, recorded in 78% to 100% of cases. Patients may experience a wide

spectrum of other symptoms including chills, headache, malaise, nausea, vomiting, diarrhoea, abdominal pain, cough, myalgia, back pain, weakness, dizziness, confusion, and coma [4,5]. Fever and splenomegaly are the most frequent findings on physical examination. Elevated bilirubin and lactate dehydrogenase serum levels suggest hemolysis and are often a clue to diagnosis [2]. Thick and thin peripheral blood smears, stained with Giemsa, remain the gold standard for routine clinical diagnosis. Malaria smears permit both species identification and quantification of parasites. In non-immune individuals, hyperparasitemia (defined as the infection of $\geq 5\%$ of peripheral blood RBCs on smear examination) is generally associated with severe disease (defined as a disease complicated by multi-organ failure or abnormalities in the patient's blood or metabolism) [6,7]. Malaria in travelers is preventable.

Hence, epidemiologists at the Institute of Public Health of Serbia Dr. Milan Jovanović Batut, Belgrade, advise all potential travelers to endemic areas about the adequate chemoprophylactic regimen for malaria. Since no prophylactic regimen is 100% effective, all travelers must be told to seek medical attention immediately if they experience fever during or after travel [8]. Autochthonous malaria was eradicated from Serbia in 1964. However, numerous cases of imported malaria have been registered since. According to annual reports by the Institute of Public Health, 121 cases of imported malaria were reported in Serbia in the 2000–2010 period.

The aim of this study was to describe the most important clinical characteristics of malaria in a non-endemic setting and to raise awareness about the importance of considering malaria in febrile patients returning from malaria-endemic regions. A secondary goal was to correlate parasitemia levels to the clinical manifestations of the disease.

Methodology

This case series included 103 patients with malaria who were treated at the Clinic for Infectious and Tropical Diseases, Clinical Center of Serbia in Belgrade, from 2000 to 2010. This hospital is a tertiary-care facility where patients with infectious diseases from the entire country are referred. Data were obtained retrospectively from medical records (*e.g.*, clinical findings on physical examination and hematological, biochemical, parasitological, and other analysis). Two groups of patients were included in the study: patients with a parasitological confirmation of malaria, and patients suspected of having malaria based on clinical and epidemiological data, who also responded to antimalarial therapy (a parasitological confirmation was not required for this group). All patients returning from endemic areas and exhibiting signs and symptoms of malaria underwent a thick and thin peripheral blood smear examination (stained with Giemsa) within three hours of presentation. When available, a rapid test for histidine-rich protein II (HRP 2) detection (Visitect Malaria Pf, Omega Diagnostics Ltd., United Kingdom) was employed if *P. falciparum* infection was suspected. The level of parasitemia was expressed as a percentage of parasitized erythrocytes (1% of parasitized erythrocytes is equivalent to 50,000 parasites/ μ L). In order to assess the correlation of parasitemia levels to clinical and laboratory findings, patients were divided into two groups: patients with parasitemia levels \geq 5% (hyperparasitemia), and patients with parasitemia levels $<$ 5%. Most patients received artemisinin-based

combinations (ABCs), regardless the species of *Plasmodium*, because no antimalarials were registered in Serbia during the period studied. Since only a small contingent of antimalarials could be procured annually due to financial and legal constraints, experts settled on ABCs because they are effective against all *Plasmodium* species that cause malaria in humans. On rare occasions, chloroquine and primaquine were available.

All analyses were performed using an electronic database organized in the SPSS version 16.0 statistical package. The following methods were used in statistical analysis: descriptive statistics, Chi-squared (χ^2) test ($p = 0.05$), Spearman's rank correlation ($p = 0.05$), and analysis of variance (ANOVA) ($p = 0.05$). Spearman's rank correlation was utilized to test the correlation between clinical and laboratory parameters and parasitemia levels (a continuous variable). ANOVA was used to analyze the differences in clinical and laboratory parameters between two patient subpopulations (with and without hyperparasitemia).

Ethical approval for the study was obtained from the Ethical Committee of the School of Medicine, University of Belgrade.

Results

Patients were predominantly male (89.3%), with a mean age of 46.66 ± 12.45 years. The majority of studied patients (58.26%) belong to the working population (41–60 years of age). A minority of patients (27.18%) took chemoprophylaxis ($\chi^2 = 3.959, p = 0.05$). Most patients (98.06%) returned from sub-Saharan Africa, mainly Central and Western Africa, while only two traveled to Pakistan. One patient acquired malaria via kidney transplantation. Hospitalized patients had fever, arthralgia, myalgia, headache, vomiting, dark urine, and cough. Furthermore, some patients

Table 1. Symptom frequency.

Symptoms	Number of patients	Percentage of patients (%)
Fever	103	100
Arthralgia	68	66.01
Myalgia	61	59.22
Headache	53	51.45
Vomiting	34	33.00
Dark urine	23	22.33
Cough	15	14.56
Diarrhea	13	12.62
Abdominal pain	9	8.73
Neurological symptoms	4	3.88
Bleeding	1	0.97

experienced neurological symptoms, such as vertigo ($n = 2$), diplopia ($n = 1$), and sleep inversion ($n = 1$) (Table 1). The mean symptom duration prior to admission was 6.7 ± 3.91 days (range: 2.79–10.61 days).

Physical examination revealed that the most common finding was hepatosplenomegaly, followed by jaundice and neurological and pulmonary manifestations ($\chi^2 = 113.968$, $p = 0.01$). Most patients with neurological symptoms (72.73%) had mild consciousness impairment at presentation, while two patients were comatose (Table 2).

Falciparum malaria was identified in 73.4% of patients ($\chi^2 = 184.551$, $p = 0.01$) while *P. vivax*, *P. malariae*, and *P. ovale* were diagnosed in 18.36%, 2.04%, and 1.02%, respectively (Table 3). Five (5.10%) patients were co-infected (*P. falciparum* and *P. vivax*; *P. falciparum* and *P. malariae*).

Co-morbidities were recorded in 22 patients (21.35%), half of whom were diagnosed with cardiovascular disease, including arterial hypertension. The mean values and standard deviations of common laboratory parameters are presented in Table 4. Thrombocytopenia (defined as a platelet count lower than $100,000/\mu\text{L}$) was present in 81.55% of patients ($\chi^2 = 41.019$; $p = 0.01$) [9,10].

In 15 patients (14.56%) with non-*falciparum* malaria, no data on the degree of parasitemia were available. Five patients (4.85%) had no parasites in erythrocytes on peripheral blood smear examination (those who were pretreated). In one case, a rapid test was positive, while microscopy was negative. Parasitemia was established in 71.84% patients. Only gametocytes were found in eight patients (7.76%). These patients self-medicated or received antimalarials at other hospitals and presented at the clinic because the signs and symptoms of malaria did not resolve. The majority of patients (82.45%) had parasitemia levels below 5% ($\chi^2 = 31.135$, $p = 0.01$).

The level of parasitemia in relation to clinical and laboratory parameters was analyzed using Spearman's rank correlation, and the statistically significant results obtained are shown in Table 5. Of note, a strong negative correlation was demonstrated between parasitemia levels and platelet counts.

Univariate ANOVA revealed that patients with hyperparasitemia had significantly higher values of bilirubin and more frequent neurological complications compared to those with lower parasitemia levels ($p < 0.1$) (Table 6).

Falciparum malaria patients were treated with artemisinins (mainly artemether) in fixed combinations with one of the following antimalarial drugs:

Table 2. Frequency of physical findings.

Physical findings	Number of patients	Percentage of patients (%)
Hepatosplenomegaly	76	73.86
Jaundice	12	11.65
Neurological signs	11	10.67
Abnormal findings on lung	9	8.73

Table 3. Patient distribution according to *Plasmodium* species.

<i>Plasmodium</i> species	Number of patients	Percentage of patients (%)
<i>P. falciparum</i>	72	73.48
<i>P. vivax</i>	18	18.36
<i>P. malariae</i>	2	2.04
<i>P. ovale</i>	1	1.02
Mixed infection	5	5.10
Total	98	100.00

Table 4. Mean laboratory result values.

Analysis	Mean value	SD
RBC ($10^{12}/\text{L}$)	4.18	0.88
Hemoglobin (g/L)	127.71	25.43
WBC ($10^9/\text{L}$)	5.76	2.52
Platelets ($10^9/\text{L}$)	100.11	60.85
Glycemia (mmol/L)	6.63	1.95
Urea (mmol/L)	7.23	6.48
Creatinine ($\mu\text{mol}/\text{L}$)	117.77	100.77
Potassium (mmol/L)	4.01	0.44
Sodium (mmol/L)	137.45	4.08
AST (U/L)	47.99	37.05
ALT (U/L)	50.75	38.77
Bilirubin ($\mu\text{mol}/\text{L}$)	30.72	60.85
AF (U/L)	73.56	32.33
GGT (U/L)	51.09	53.39
Prothrombin time (%)	78.57	15.11
Fibrinogen (g/L)	4.52	1.49
LDH (U/L)	640.05	458.82
CK (U/L)	230.86	552.63
Proteins (g/L)	65.43	8.07
Fe ($\mu\text{mol}/\text{L}$)	8.22	6.31

AST: aspartate aminotransferase; ALT: alanine aminotransferase; AF: alkaline phosphatase; GGT: gamma-glutamyltransferase; LDH: lactate dehydrogenase; CK: creatine kinase; Fe: iron.

mefloquine, chloroquine, or fansidar. Most patients with *vivax* malaria (approximately 67%) were also treated with these combinations. Others were treated with chloroquine alone when this drug was available. Eleven patients with *P. vivax* and *P. ovale* took primaquine to prevent a relapse. A total of 55 patients

Table 5. Correlation of parasitemia levels to clinical and laboratory parameters (Spearman's rank correlation).

Parasitemia	R	P
Platelets (10 ⁹ /L)	-0.604**	0.000
LDH (U/L)	0.432**	0.000
Hemoglobin (g/L)	-0.296*	0.008
Bilirubin (μmol/L)	0.396*	0.000
Proteins (g/L)	-0.355*	0.003
Sodium (mmol/L)	-0.273*	0.016
Neurological complications	0.357*	0.001

LDH: lactate dehydrogenase; *Weak correlation; **Strong correlation.

Table 6. Univariate ANOVA analysis of the difference in clinical and laboratory parameters between patients with and without hyperparasitemia.

Parasitemia	F	Sig.
Prophylaxis	0.126	0.728
RBC (10 ¹² /L)	0.043	0.839
Hemoglobin (g/L)	0.066	0.800
Platelets (10 ⁹ /L)	0.234	0.636
Bilirubin (μmol/L)	9.304	0.008
Proteins (g/L)	0.737	0.404
Prothrombin time (%)	0.004	0.949
Sodium (mmol/L)	2.513	0.134
Fe (μmol/L)	0.018	0.896
LDH (U/L)	0.503	0.489
Neurological complications	3.824	0.069
Hepatosplenomegaly	0.126	0.728

Red Blood Count; Fe: iron; LDH: lactate dehydrogenase.

(53.4%) took doxycycline in addition to the aforementioned antimalarial drugs. Two patients received clindamycin with antimalarials. Due to concomitant infections, primarily pneumonia (confirmed by chest X-ray), 35 patients (33.98%) were also treated with broad-spectrum antibiotics (mostly third-generation cephalosporins). An exchange transfusion was performed in three (2.95%) patients. Fifteen (14.75%) patients received blood transfusions. Three (2.9%) patients succumbed to *P. falciparum* malaria.

Discussion

The present study examined imported malaria cases treated at the Clinic for Infectious and Tropical Diseases, Clinical Center of Serbia, during an 11-year period. There was no difference in the incidence of malaria compared to neighboring countries. However, other European countries (Germany, the United Kingdom) reported higher incidences of malaria, with a case fatality ratio of 2.91% (ranging from 0.6% to 3.8%) [11,14]. *Falciparum* malaria was the most

common isolate in Serbian patients, which is in concordance with Italian, Romanian, Belgian, and Spanish data [15,18]. The majority of studied patients belonged to the working population (41–60 years of age), which is similar to French data [19]. Patients from other European countries belonged to the working population as well, although they were younger (24–44 years of age) [11]. We assume that the patients' age distribution is a consequence of professional migration trends. Average symptom duration prior to hospital admission was approximately seven days (longer in severe cases), a fact observed by other authors [20,21]. Symptoms were often attributed to other, mundane diseases, and/or were intentionally disregarded by both patients and physicians. Only 27.18% of patients used chemoprophylaxis, despite the fact that most were made aware of its necessity by experts. Many people fallaciously believe that the side effects of the drugs used for malaria chemoprophylaxis outweigh their potential benefits and decide not to take them. In other studies, the percentage of patients who had used malaria chemoprophylaxis was highly variable, ranging from 2.5% to 56% [22-26]. Adequate antimalarial chemoprophylaxis, along with other preventive measures and prompt diagnosis, results in the cumulative protective effects on malaria morbidity and mortality among those traveling to endemic regions [27].

Most patients came from sub-Saharan Africa, endemic for *falciparum* malaria [28,29]. Parasitemia was below 5% in most treated patients (82.45%). Thrombocytopenia, anemia, hyperbilirubinemia, hypoproteinemia, hyponatremia, elevated LDH levels, and the occurrence of neurological complications were correlated with the level of parasitemia. In addition, patients with hyperparasitemia were more likely to develop higher bilirubin levels and neurological manifestations. Other authors also demonstrated such associations [30,31]. Parasitemia levels above 5% represent one of many risk factors for severe malaria. One study demonstrated that low parasitemia does not exclude the possibility of complications, as it was present in patients with severe malaria [32].

All patients had fever as a presenting symptom, which is in concordance with other authors' data [26-28]. Arthralgia and/or myalgia and headache were also commonly reported in this and other studies [23,26,28]. More than half the patients (54.35%) had gastrointestinal symptoms (diarrhea and vomiting), while 8.7% had abdominal pain. Abdominal pain was reported by 8.2% and 6.6% of German and American patients, respectively [26,33]. Cough was more

common among Serbian than European and American patients [11,33]. Hepatosplenomegaly was the most prominent physical finding (73.86%) in this study, a Singaporean (62.5%) one, and especially an Indian study (93.3%) [22,30]. The number of patients with jaundice was in accordance with other authors' data [26,33].

Neurological symptoms were present in as many as 10% of patients. The prevalence of neurological complications varied, from 1.9% to 46.6% in other studies [30]. Mishra *et al.* describe impaired consciousness, irritability, restlessness, sleep inversion, and behavioral changes in patients with *falciparum* malaria as the most severe neurological complications [34].

Thrombocytopenia, the most common laboratory abnormality, occurred in over 80% of analyzed patients. Thrombocytopenia is considered to be an important indicator of the presence of malaria in febrile patients returning from endemic areas [8,35]. Anemia was found in 35.92% of patients, which is similar to other authors' data [8,36]. Kain *et al.* recorded WBC counts lower than 5.0×10^9 in 47.5% of patients, which is similar to our results (50%) [12]. The proportion of Serbian patients with elevated serum aminotransferase activity was higher than was demonstrated in other studies in patients of different nationalities [8,12]. We speculate that alcohol abuse contributed to this, bearing in mind the sociologic profile of the patients (male gender, age, long periods of time away from home, etc).

Study patients with *falciparum* malaria were mostly treated with ABCs, which are recommended by the World Health Organization (WHO). ABCs are the most important drugs for the treatment of *falciparum* and chloroquine-resistant *vivax* malaria. American authors also consider artemisinin drugs to be the most effective antimalarial drugs [37]. Their short half-lives can lead to post-treatment recrudescence, precluding artemisinin monotherapy. Chloroquine was used in the treatment of malaria caused by *P. vivax*, but more than two-thirds of patients got artemisinins, because no other antimalarials were available at the time. Eleven patients with *P. vivax* received primaquine to prevent a malaria relapse. Chloroquine is still the drug of choice in the treatment of malaria caused by *Plasmodium vivax*, with the exception of regions where resistance has been recorded [38]. More than half of these patients received doxycycline and/or clindamycin. Despite the slow antimalarial action of these antibiotics, some of them had been clearly demonstrated as effective antimalarial agents [37]. ABCs were also given to patients with no proven parasitemia and to those who self-medicated

with antimalarials prior to presentation, given that self-medication is a major cause of resistance. In the latter group, parasite replication was suppressed, its morphology changed, yet it was not eliminated altogether [39].

Conclusions

Bearing in mind that 99% of cases of malaria in Europe are imported and that it was eliminated from Serbia, malaria remains an important tropical disease to consider in febrile patients who have returned from endemic regions [40]. Serbian migrant workers with malaria were, on average, older than their European counterparts. Given that malaria always presents with fever, and that a significant delay in diagnosis was recorded, we recommend that a high index of suspicion at all levels of care should be constantly maintained when evaluating febrile returning travelers, especially if there is evidence of thrombocytopenia and hemolysis. Only 1.94% of patients diagnosed with malaria at our hospital in an eleven-year span did not reside in Africa prior to infection. Therefore, a history of travel to the African continent is important to consider from an epidemiologic standpoint. Thrombocytopenia was commonly observed, and an analysis of its positive predictive value for malaria is a potential research avenue in the future. Hyperparasitemia, high bilirubin, and neurological signs and symptoms are associated with severe malaria. Most patients with malaria did not use chemoprophylaxis, illustrating the key failure of malaria prevention in Serbia and other developing countries. Despite the fact that no antimalarials are registered in Serbia, limiting treatment options, results are satisfying, mostly due to the efficiency of ABCs against all *Plasmodium* species.

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