

DIAGNOSTIC, CLINICAL AND THERAPEUTIC ASPECTS OF IMPORTED *FALCIPARUM* MALARIA IN THE REPUBLIC OF BULGARIA, IN PATIENTS TREATED AT THE CLINIC OF INFECTIOUS DISEASES - MILITARY MEDICAL ACADEMY, SOFIA

**Andrey Galev^{1,*}, Yonika Dimova¹,
Rainichka Mihaylova², Ralica Pravova¹**

¹ Department of parasitology, Applied Scientific Center for Military Epidemiology and Hygiene - Military Medical Academy, Sofia, Bulgaria

² Clinic of Infectious Diseases - Military Medical Academy, Sofia, Bulgaria

ABSTRACT:

The article presents six cases of imported *Falciparum* malaria, which occurred between 2015 and 2023. All patients had returned to the Republic of Bulgaria from malaria endemic countries (specifically Uganda and Nigeria). In all cases, no antimalarial drug prophylaxis was performed in advance. Malaria was diagnosed based on the presentation of clinical symptoms at different stages of the disease. The average period from the manifestation of the first symptoms to diagnosis of malaria was 3.6 days. Initial parasitemia and its dynamics during etiological treatment were monitored. Patients were hospitalized on average 10 ($\pm$ 1) days in an infectious disease clinic. In some of the patients, additional infections with COVID-19, Influenza A, *Chlamydia pneumoniae*, *Mycoplasma pneumoniae* were also found. Etiological therapy was carried out with good result. As a result of the etiological treatment with mono- and combined antima-

larial drugs, in addition to symptomatic and pathogenetic treatment, clinical and laboratory effects were established. Laboratory tests demonstrated the excellent efficacy of the treatment. After three negative malaria morphodiagnostic tests, the patients were discharged clinically healthy and parasitologically negative. They were referred for outpatient care and further monitoring by their general practitioner (GP) for a period of one year, with malaria testing at every instance of fever. There are currently no effective drugs for the treatment of *Falciparum* malaria registered with the Bulgarian Drugs Agency, meaning they are unavailable in the country's pharmacies.

Keywords: Falciparum Malaria, Imported Malaria, Diagnosis Treatment, Prevention

1. INTRODUCTION

Malaria is a life-threatening human disease spread by certain mosquito species. Malaria mostly spreads to people through the bites of some infected female *Anopheles* mosquitoes. Blood transfusion and contaminated needles may also transmit malaria. The first symptoms may be mild, similar to many febrile illnesses, and difficult to recognize as malaria. If left untreated, *P. falciparum* malaria can progress to severe illness and death within 24 hours [1].

There are 5 *Plasmodium* parasite species that cause malaria in humans and 2 of them – *P. falciparum* and *P. vivax* – pose the greatest threat. *P. falciparum* is the deadliest malaria parasite and the most prevalent on the African continent. *P. vivax* is the dominant malaria parasite in most countries outside of sub-Saharan Africa. The other malaria species which can infect humans are *P. malariae*, *P. ovale* and *P. knowlesi* [1]. Due to specific life cycle requirements they are found mainly in tropical countries. In 2022, 85 countries were listed as malaria endemic. Due to the lack of cases in three consecutive years East Timor and Saudi Arabia were removed from the list [2, 3]. In Bulgaria, cases of imported malaria are registered annually among Bulgarian citizens returning from tropical countries as well as among foreigners arriving in the country. Bulgaria has been free of malaria since 1965 and the registered cases are only imported, by both Bulgarian citizens and foreigners. Regarding the mortality rate, according to the annual analyses of the parasitic diseases in Bulgaria from 2021 to 2025, the

ADDRESS FOR CORRESPONDENCE:

Andrey Galev, DMSc
Department of parasitology, Applied Scientific Center for Military Epidemiology and Hygiene - Military Medical Academy, 3 G.Sofiski Blvd., 1606 Sofia, Bulgaria
phone: +359887200785
e-mail: andrey_galev@abv.bg

registered malaria cases were 49, of which 6 (12.2%) ended fatally [4]. This process will continue because of the constantly expanding international ties in all areas of life and increasing migration processes. Travelers to malaria-endemic regions should consult their GP several weeks before departure about the anti-malarial drugs appropriate for chemoprophylaxis for the country they are visiting [5].

2. PURPOSE

By presenting six clinical cases with imported *Falciparum* malaria (*F. malaria*), we are aiming to bring to the attention the important problems in diagnosis, prevention and treatment and their resolution in the Republic of Bulgaria.

3. MATERIALS AND METHODS

Initially, an immunochromatographic test (malaria rapid test, RDT) was performed to quickly confirm or rule out malaria, with the final diagnosis being confirmed by through microscopy (Giemsa-stained thick/thin smear); using Malaria P.f/P.v./Pan Rapid Test Cassette (Whole Blood). Persons returning from malaria-endemic regions should be tested for malaria. First, whole blood is tested with RDT that reports a positive or negative result. The aim is to quickly start etiological treatment. If the whole blood result is positive, thin and thick films are made on a glass slide. The thin film is fixed with methanol and then, together with the thick film, they are stained with Giemsa and examined microscopically. The parasitemia (parasite density) is recorded on the thick film and calculated using the formula (parasite count/200 X 10⁹ leukocytes/l (according to CBC). Species determination of parasite is made microscopically on the thin film.

4. RESULTS

4.1. Case 1: E.M.T., a 59-year-old man, with first symptoms on 03.01.16, was hospitalized at the Clinic of Infectious Diseases (Military Medical Academy-Sofia) on 08.01.16.

F. malaria was proven with Rapid Immunochromatographic Test and morphodiagnostically with hemopreparations stained according to Romanovsky-Giemsa. Clinical symptoms: fever, anemia, cytopenia, splenomegaly. Initial parasitemia 67,870/μl young ring trophozoites. Current parasitemia 1422/μl young trophozoites and gametocytes. Treatment with Dihydroartemisinin/Piperaquine phosphate.

4.2. Case 2: P.M.A., a 50-year-old man, with first symptoms on 20.12.15, hospitalized in the Military Hospital - Pleven, proven *F. malaria*, without data on the initial parasitemia. Upon admission, the patient had a malaria attack: fever of 40°C, ague and sweating. Clinical symptoms - fever, anemia, hepatosplenomegaly. Treatment was carried out with Dihydroartemisinin/Piperaquine phosphate. Due to a complication of malaria with acute renal failure, the patient was transferred to the CID -MMA-Sofia with high urea and creatinine values. Thick blood smears, stained according to Romanovsky-Giemsa were examined, and single young trophozoites and gametocytes were found, 1-2 per drop. Radical anti-relapse treatment was carried out with Mefloquine.

4.3. Case 3: V.I.B., a 47-year-old man, who has lived in Uganda where he was diagnosed twice with *F. malaria*. He returned on 03.04.17. First symptoms appeared on 06.04.17 with fever, cephalalgia, myalgia, arthralgia. Self-treatment with Artesunate/Mefloquine was initiated from 10.04.17. Hospitalized on 12.04.17 at the Clinical Hospital - Military Medical Academy – Sofia. Single destructured young trophozoites and gametocytes of *F. malaria* were found on thick blood smears, stained by Romanovsky-Giemsa. Treatment with Artesunate/Mefloquine continued until the completion of the course.

4.4. Case 4: R.A.A., a 32-year-old man, residing in Lagos, Nigeria. First symptoms started on 09.12.23 with fever, cephalalgia, chills and sweating. Proven positive result for malaria with Rapid Immunochromatographic Test. Self-treatment with Artemether 80mg + Lumefantrine 450mg, purchased in Nigeria, was started. Hospitalized in the CID – MMA, Sofia on 10.12.23. Laboratory results showed iron deficiency anemia, and elevated inflammatory markers, with high D-dimer values. Thick blood smears, stained by Romanovsky-Giemsa revealed young rings and single amoebic trophozoites of *P. falciparum*. Initial parasitemia reported 14,023 young trophozoites per μl. Treatment with Artemether 80mg + Lumefantrine 450 mg was started on 10.12.23. Against the background of the treatment, a decrease of parasitemia was reported (2,223 trophozoites in 1 μl and 58 destructured trophozoites per μl). Due to persistent fever, additional tests were scheduled. There were positive serological results for *influenza A* and *Chlamydia pneumoniae*. Treatment with Vibramycin was included.

4.5. Case 5: V.Z.I., a 60-year-old man, who resided in Uganda, where the first symptoms of the disease appeared on 05.05.23 and initial diagnosis of *F. malaria* was set. Treatment with Artesunate was carried out. On 20.05.23, malaria recurred and the patient was hospitalized in the CID-MMA-Sofia. In thick blood smears, stained according to Romanovsky-Giemsa, young trophozoites with a parasitemia of 25 187 parasites/ μ l were found. Radical treatment with Mefloquine was started. On subsequent blood smears on 23.05.23 - single trophozoites and the first gametocytes were found. Malarone, a drug with antigametocyte action, was included in the therapy. On 24.05.23, only 2 destructured gametocytes were found. Proven parapatology in the patient - COVID - 19, influenza A, *Mycoplasma pneumoniae* was found. Vibramycin was added to the therapy.

4.6. Case 6: A.G.G., a 58-year-old man, residing in Nigeria, who returned on 02.12.23. The first symptoms of malarial attack started on 07.12.23. Hospitalized on 15.12.23 in the Infectious Diseases Hospital - Sofia. The clinical diagnosis of *F. malaria* was confirmed by establishing ring forms and gametocytes during microscopy of thick blood cells. There was no evidence of initial parasitemia. Treatment with Mefloquine was initiated, against which parasitemia persisted and Rh. II degree to Mefloquine was proven. Treatment with Arthemether/Lumefantrine was initiated. Serology showed hemolytic anemia, high D-dimer values, liver cytolysis, hypoproteinemia with hypoalbuminemia, hyperbilirubinemia. Due to the need of resuscitation care, the patient was transferred to the Military Medical Academy-Sofia in a severely impaired general condition, delirious, somnolent, inadequate, with dysarthria. Clinical symptoms, laboratory tests and parasitological data proved severe tropical malaria. Additional treatment with Doxycycline and antigametocyte treatment with Atovaquone / Proguanil hydrochloride were started.

□ All patients presented were discharged after three consecutive negative results for malaria and referred for outpatient care by the GP at the place of residence, for a period of one year, with control tests for malaria in each febrile condition.

✓ All patients were diagnosed with imported *Falciparum malaria* after visiting a malaria-endemic region.

✓ The average period from the onset of the first symptoms to the diagnosis of malaria was 3.6 days,

which correlates with data on imported malaria in Brazil [6].

✓ In all cases, no antimalarial prophylaxis was administered.

✓ Currently, there are no registered medications for the etiological treatment of malaria in Bulgaria.

✓ In all cases, initial and therapy-induced parasitemia was reported. As a result of the etiological treatment with mono- and combined antimalarial drugs, as well as symptomatic and pathogenetic treatment, clinical improvement and negative laboratory results for malaria were established. Therapy was carried out in individuals with proven infections.

5. DISCUSSION

The epidemiology of all patients shows evidence of residence in malaria-endemic regions: Uganda and Nigeria. The individuals were not tested for malaria at the point of re-entry in Bulgaria, as there is no mandatory regulation for this. The patients were examined for malaria and treated after the onset of clinical symptoms (malarial attacks), as a timely diagnosis and the subsequent initiation of treatment were essential for preventing complications and improving the outcome of the disease.

Bacterial infections are major complications of malaria. In our patients both viral and bacterial infections were diagnosed requiring additional treatment. In some of the patients, fever persisted even after obtaining negative malaria results. Upon additional testing, co-infections with both viral and bacterial causative agents were identified, and treated specifically.

Bacterial infections and thrombocytopenia are risk factors for prolonged hospital stay. The high values of C-reactive protein and procalcitonin are risk factors for severe cases [7, 8]. Acute *Falciparum malaria* is often associated with hemolytic anemia and thrombocytopenia, associated with the clinical course of the disease. Complicated cerebral *Falciparum malaria* most often leads to a fatal outcome [9].

Each of the cases was confirmed at the Reference parasitology laboratory in the National Center of Infectious and Parasitic Diseases and reported to The European Surveillance System (TESSy). WHO recommends that suspected cases of malaria are confirmed with rapid diagnostic tests and by microscopic examinations [5]. Based on the amendments to the current Regulation No. 17/25.10.2024 for conducting diag-

nostics, prophylaxis and control of imported parasitic diseases and for the treatment of imported tropical parasitic diseases for which there are no medicinal products authorized in the country, the medical institutions providing hospitalization for persons with such pathology are obliged to maintain a stock of medicinal products for etiological therapy in accordance with the Regulation of the Law on Medicinal Products in Human Medicine, Art. 9, para. 1. At this stage, the absence in the pharmacy network of life-saving preparations for the treatment of tropical malaria and resistant strains of *P. falciparum* may lead to an unfavorable outcome of the disease.

Another problem is the reported rise of imported malaria in some areas, including the southern states of USA [11], and Australia,. In epidemiological terms, imported malaria is determined by geographical location, data on travelers to malaria-endemic destinations and the origin of migrants [12].

During the follow-up period no mortality was reported among the patients treated for malaria. According to studies, mortality can range from 3,6% in mild and medium forms of Falciparum malaria and up to 10% among those with severe malaria [13].

Late diagnosis of malaria is associated with a higher risk of developing a severe clinical picture. It is necessary to revise the training programs for health professionals, as well as their actions aimed at travelers. It is necessary to improve the cooperation between GPs, parasitologists, clinicians, and epidemiologists actively involved in the diagnosis, prevention, treatment and epidemiological investigation of malaria cases [14].

6. RECOMMENDATIONS

6.1. It is necessary to carry out antimalarial prophylaxis before, during the stay and after returning from malaria-endemic regions. In case of medical contraindications, a parasitologist should be consulted to select an appropriate medication for prophylaxis. Due to the side effects of the drugs used for malaria pharmacoprophylaxis, individuals working in malaria-endemic regions often avoid it. In Uganda, as in many other places, partial or complete resistance to artemisinin derivatives and Lumefantrine has been established [15]. Better awareness and implementation of preventive measures for travelers to malaria-endemic regions is needed [16].

6.2. If clinical symptoms appear (febrile, cephalalgia, myalgia, enterocolitis symptoms), a malaria test with

Rapid Immunochromatographic Test should be performed immediately. In case of positive result, treatment should be initiated as soon as possible. If *P. falciparum* is found to be resistant to the monodrug used for treatment, it is necessary to replace it with a combined antimalarial drug. Despite the proven clinical effectiveness of artemisinin preparations in *Falciparum* malaria in Africa, when *Plasmodium falciparum* strains become resistant to them, alternative treatment is required [14]. For a radical effect of the treatment of malaria with a mono-drug from the group of artemisinin derivatives, it is necessary to complete the course of treatment with Mefloquine to avoid malarial relapse up to 5-6 days after therapy [17].

6.3. When gametocytes are detected in the tested blood smears, gameticidal treatment is necessary to prevent patients from becoming a source of malaria, especially during the malaria season.

7. CONCLUSION

The means for reducing the risk of malaria infection is the implementation of chemoprophylaxis before, during the stay and after returning from a malaria-endemic region, as well as the strict adherence to personal preventive measures. It is recommended that all citizens returning from malaria-endemic regions, based on epidemiological indications, are tested for malaria before the appearance of clinical symptoms. Early treatment prevents complications and an unfavorable outcome of the disease. Timely diagnosis and treatment of patients with malaria guarantee their recovery.

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Ethical approval

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Availability of Data and Material

The database used and analyzed during the current study is available from the corresponding author and will be available on request.

Conflicts of Interest

The authors declare no conflicts of interest.

Declaration of generative AI and AI-assisted technologies in the manuscript preparation process

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18. Abbreviations: F. malaria, Falciparum malaria; ICT, immunochromatography-based antigen detection rapid tests; TESSy, The European Surveillance System; MMA, Military Medical Academy; CID, Clinic of Infectious Diseases.
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