

Clinical picture of imported *Plasmodium vivax* malaria in patients of a Polish tertiary center

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Introduction *Plasmodium vivax* (*P. vivax*) is responsible for tertian malaria, a disease prevalent in many countries within tropical, subtropical, and moderate climate zones. It is also the second most common species responsible for imported *Plasmodium* infections in Europe.^{1,2} In Asia, *P. vivax* is diagnosed in more than half of all malaria patients, while in Central and South America it is responsible for 71% to 81% of cases.^{1,3,4}

Late onset of symptoms, related to the incubation period of several weeks or months, and clinical relapses contribute to challenges associated with imported vivax malaria. Relapses are caused by hypnozoites, the unique stage of *P. vivax* and *P. ovale* species, and can be prevented by using primaquine. Unlike falciparum malaria, tertian malaria has traditionally been considered a benign form of infection. However, severe manifestations, including fatalities, have been increasingly reported in *P. vivax* infections, especially during the last decade.⁵ The number of malaria cases in Poland is low and usually does not exceed 40 per year. All of them are imported because Poland was declared free from autochthonous transmission in 1963.

The aim of this study was to assess clinical features of imported *P. vivax* malaria in a group of patients diagnosed and treated at the University Centre for Maritime and Tropical Medicine in Gdynia, Poland, between the years 2003 and 2015, with a focus on the incidence and manifestations of severe cases.

Patients and methods A total of 85 cases of malaria were diagnosed at the University Centre for Maritime and Tropical Medicine during the study period, including 25 cases (29.4%) of primary vivax malaria, which were included in a detailed

analysis. A group of patients with falciparum malaria ($n = 51$) selected for comparisons did not differ with regard to demographic data. The diagnosis was based on the positive results of a microscopic examination of the Giemsa-stained thick and thin peripheral blood smears, rapid diagnostic test (RDT), and polymerase-chain reaction assay. The microscopic examination of stained peripheral blood smears was used as the primary diagnostic tool because it remains the gold standard for the diagnosis of malaria. However, its accuracy and effectiveness may be unsatisfactory for low parasite densities or in the case of low-quality blood smear. The RDT (OptiMAL-IT, Bio-Rad, Marnes-la-Coquette, France), which can distinguish between falciparum and nonfalciparum infection, was used as an alternative when microscopy was not available in urgent cases in order to obtain results in patients suspected of acute malaria. The test is highly specific and is capable of detecting as few as 50 to 100 parasites per μl of blood. To be a useful diagnostic tool, the RDT must achieve sensitivity greater than 95%. Patients with positive or negative RDT results were then subject to the microscopic examination to confirm the result. A nested polymerase-chain reaction assay targeting the *Plasmodium spp. 18S rRNA* gene was used to increase the sensitivity of malaria diagnosis, especially in the case of low parasite count and mixed infections when there was a difficulty in identifying the species.

Severe (complicated) malaria was defined according to the World Health Organization criteria.⁶ Latency was calculated as the number of days between arrival to Poland and malaria diagnosis. Long-term travel was defined as travel exceeding 24 weeks of stay in an endemic region. A retrospective analysis of medical records was performed.

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TABLE 1 Signs and symptoms reported in patients with imported *Plasmodium vivax* malaria

Signs and symptoms	Number (percentage) of patients with <i>P. vivax</i> malaria (n = 25)
splenomegaly / only splenomegaly without hepatomegaly	16 (64) / 2 (8)
hepatomegaly / only hepatomegaly without splenomegaly	15 (60) / 1 (4)
hepatosplenomegaly	14 (56)
shivers	11 (44)
fever	38–39°C 10 (40) >39°C 10 (40)
excessive sweating	9 (36)
headache	8 (32)
muscle pain	7 (28)
nausea	5 (20)
abdominal pain	2 (8)
impaired consciousness	2 (8)
respiratory failure	1 (4)
vomiting	1 (4)

Clinical and laboratory data were entered into a standardized data collection form and included into anonymous database, which was analyzed using Statistica 12 (StatSoft, Kraków, Poland). The comparison of categorical variables was performed using the Fisher exact test. Numerical variables were compared using the *t* test or the Mann–Whitney rank-sum test based on the distribution. A *P* value of less than 0.05 was considered statistically significant.

Results The mean age of patients was 33.7 years. Vivax malaria was more often diagnosed in patients returning from South and Central America or Asia compared to Africa, where *P. falciparum* infections predominated (*P* < 0.0001). Most cases of *P. vivax* infections (84%) were diagnosed in men. The majority of patients reported occupational travel to endemic areas (military duties and Christian missions). The mean duration of stay was 38.1 weeks. Chemoprophylaxis and personal protection measures against mosquito bites were used by a minority of patients. In 5 cases, a proper drug regimen without any missed doses was used to prevent malaria, 11 patients did not take any preventive medication, and 1 person used a proper prophylactic regimen but was not compliant. There were no data available for 8 patients.

In 5 vivax cases, the latency period was longer than 1 month. We found no significant associations between the late onset of symptoms and chemoprophylaxis use (*P* = 0.3), length of travel in the endemic region (*P* = 0.3), or history of malaria (*P* = 0.07).

The mean time between the onset of symptoms and diagnosis at the University Centre for Maritime and Tropical Medicine was 5 days. Fever occurred prior to hospital admission in each analyzed case. The details of reported signs and symptoms are presented in [TABLE 1](#).

Mild anemia was diagnosed in 8 patients (32%), and thrombocytopenia—in 16 cases (64%). The median platelet count in the vivax malaria group was significantly higher than in the falciparum malaria group ($86 \times 10^9/l$ [range, 30–137] and $54 \times 10^9/l$ [range, 28–129]; *P* = 0.04), while the mean parasite count was lower (0.17% [range, 0.01–0.1] and 1.7% [range, 0.01–7.4], respectively; *P* = 0.002). In 4 cases, mixed infection was detected.

An abdominal ultrasound examination showed spleen enlargement in 16 patients and hepatomegaly in 15 patients, while 14 patients were diagnosed with hepatosplenomegaly.

Abnormal radiographic findings included bronchiolitis obliterans organizing pneumonia (BOOP) and consolidations in 1 patient and hydrothorax in another patient. Those 2 patients (8%) fulfilled the criteria for severe malaria. The first patient was a 62-year-old man with hypertension and diabetes who returned from Venezuela and developed pulmonary distress (BOOP) after the introduction of antimalarial treatment. The second patient was an 18-year-old woman with a history of recent school trip to India, circulatory collapse, thrombocytopenia, and suspected *Klebsiella pneumoniae* ESBL (+) urosepsis. Both patients suffered from *Plasmodium* mono-infection.

Discussion All *Plasmodium* infections in Poland are treated in the hospital setting, and almost one-third of patients are admitted to the University Centre for Maritime and Tropical Medicine. In the years 2003–2015, 29.4% of patients at the Centre were diagnosed with *P. vivax*. This rate seems to be higher than that reported in other European studies (12.9%–25.4%) and may be explained by travel patterns of Polish citizens.^{2,11,12} In our patients, travel to South America or Asia was indicative of the highest relative risk of *P. vivax* diagnosis. On the other hand, the relative low popularity of VFR travel (“visiting friends and relatives”) to Africa could also contribute to this finding.

For years vivax malaria has been perceived as a benign disease; however, it has been recently associated with a range of severe and even life-threatening manifestations.⁷ In our study, 2 cases (8%) of *P. vivax* mono-infection fulfilled the criteria for severe malaria, and this rate was higher than 2.6% reported in an earlier multicenter European epidemiological study.² This result is consistent with the findings of other studies that showed a large increase in the number of severe *P. vivax* infections since 2000.⁸

Underreporting is considered an unlikely explanation for this phenomenon, and other factors have been discussed (ie, changes in *P. vivax* strains virulence and geographical heterogeneity). The limitation of our study is the low number of patients, and the unusually high rate of patients with severe vivax malaria should be interpreted with caution.

Although parasitemia is included in the World Health Organization criteria for the diagnosis of severe malaria, the parasite count over 2% is rarely detected in patients with severe vivax malaria.^{5,9} In both our patients, a parasite count of only 0.01% was noted. In addition, we found that *P. vivax* infections were associated with lower parasitemia than falciparum malaria, irrespective of the clinical severity.

The most common complications of vivax malaria include severe anemia, respiratory distress, and coma.^{5,10} Although there were no cases of severe anemia in the study group, radiological abnormalities (BOOP and hydrothorax) were seen in both patients with severe vivax infection. However, none of them required mechanical ventilation.

There were no fatal cases in the study group, and there were 3 cases (12%) of malaria relapse. Two patients used primaquine as recommended, while the third patient was noncompliant. Uptitration of a primaquine dose or extending treatment duration has been suggested to improve relapse prevention.¹¹

Mixed plasmodial infections have long been associated with diagnostic difficulties. In our study, infections with 2 *Plasmodium* species were diagnosed in 4 patients (16%) and were not associated with severe manifestations of malaria.

The efficacy of artemisinin-based combination therapy, which is currently the first-line treatment in uncomplicated falciparum malaria, has not been fully clarified in *P. vivax* infections. Resistance to chloroquine, together with a recent increase in the incidence of severe manifestations of vivax malaria, justifies the use of artemisinin-based combination therapy also in patients infected with *P. vivax*.

The period from the date of return to the diagnosis of malaria was 5.5 weeks in our patients, which was longer than the previously reported period for Polish citizens with imported *P. falciparum* infections.¹² It was longer than 1 month in 20% of the cases, and reached 20 weeks in 1 case.

Latency contributes to misdiagnosis and diagnosis delay because most patients do not spontaneously report travel to a tropical region in the case of the onset of symptoms several weeks or months after return. Chemoprophylaxis use was previously shown to significantly increase the latency period in imported vivax infections,² but we found no such association in our study. This issue has an important implication for clinical practice in nonendemic countries, highlighting the need to consider vivax malaria as a possible cause of fever in returned travelers, independently of the time elapsed after potential exposure and irrespective of chemoprophylaxis use.

In conclusion, the results of our study confirm that *P. vivax* is the second most common species responsible for imported malaria in a representative group of patients from Poland. To the best of our knowledge, this is the first study to focus on vivax malaria in travelers and provide details of clinical picture, including severe cases. Mixed

infections should be considered in patients diagnosed with imported malaria, and relapse prevention should be introduced when appropriate.

The latency period, which did not seem to be affected by chemoprophylaxis use in our study, may contribute to diagnostic challenges in patients with vivax malaria with late onset of symptoms. Our findings highlight the need for considering vivax malaria as a possible cause of fever in returned travelers, irrespective of the time from return from endemic countries and chemoprophylaxis use. This has also clear implication for pretravel medical advice with regard to destinations with *P. vivax* predominance, which should include the information about the possible long incubation period of tertian malaria.

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