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Evaluation of malaria cases in individuals after traveling to endemic regions of the world

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Aim: This study evaluates types of malaria and treatment success in a series of identified cases among individuals who were presumed to have travelled to regions where malaria is endemic.

Materials and methods: In Sema Hospital, 25 cases of malaria (5 in women, 20 in men) were diagnosed during the 6-year period between 2006 and 2012. The mean age of the patients was 34.5 years. Diagnoses were established with thick and thin peripheral blood smears that were parasite-positive. These tests were then compared to the rapid diagnostic test based on *Plasmodium falciparum* histidine-rich protein 2.

Results: All cases demonstrated fever beginning with chills. Three patients had prophylaxis with doxycycline, but all stopped the prophylaxis early of their own volition. *P. falciparum* was the parasitic agent in all cases. A regimen of artemisinin and lumefantrine was administered in 18 of the 25 cases; quinine plus doxycycline was given in 3, and chloroquine was administered in the remaining 4. Usage of these regimens cured all cases of malaria without complications.

Conclusion: The importance of prophylaxis of malaria was demonstrated. Malaria should also be included in the differential diagnosis of patients with fever that have a history of travel to endemic regions.

Key words: *Plasmodium falciparum*, chemoprophylaxis, rapid tests

1. Introduction

Malaria, which is 1 of the 3 globally most important infectious diseases according to the World Health Organization (WHO), is endemic in many areas of the world and responsible for 2,000,000 deaths each year (1,2). According to the data collected by the Ministry of Health of Turkey, *Plasmodium vivax* is endemic in southeastern Turkey and other types of *Plasmodium* sporadically surface in other regions while *P. falciparum* is rare (1). Following the earnest battle against malaria that began in 1926, there has been a strong reduction in the number of cases over time. Specifically, there were 14,791 cases of malaria in 1926, 1263 in 1970, and 84 in 2009 (1).

The gold standard of diagnosis in malaria is thick and thin peripheral blood smears. Serology, molecular biologic methods, rapid antigen tests, and quantitative buffy coat blood parasite detection tests are defined as indirect diagnostic methods (3). Additional difficulties and differences in the diagnosis and treatment of *P. falciparum* malaria are present because of the parasite's relative rarity in Turkey. This is why we decided to evaluate the clinical and epidemiological features of our 25 serial cases, identifying the causative pathogen for each.

2. Materials and methods

In this study, 25 malaria patients that presented with fever, sweating, headache, diarrhea, fatigue, and nausea to our Infectious Disease Department between January 2006 and September 2012 were diagnosed through the use of appropriate tests.

All patients were hospitalized for the treatment. The epidemiological and clinical features such as use of prophylaxis, impact of specific causative pathogen on diagnosis, treatment, and response to treatment were evaluated retrospectively. Thick and thin peripheral blood smears were prepared from all obtained samples, and Giemsa stains were taken for evaluation using a light microscope for diagnosis; this diagnosis was then compared with that from the immunochromatographic card test for *P. falciparum* (P.F. Check 1, Veda Laboratory). A complete blood count, liver and kidney function tests, and prothrombin time test were run for all cases.

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3. Results

Of the 25 patients, 5 were female and 20 were male; the mean age was 34.5 with a range of 18 to 50 years. All patients had thick and thin peripheral blood smears done to reveal the presence of malaria; smears were evaluated as positive for *P. falciparum* due to erythrocyte morphology. Of these, 88% of the positive tests (22 patients) yielded a positive result with the rapid diagnostic test based on *P. falciparum* histidine-rich protein 2 (PfHRP2). All patients had a history of recent travel to sub-Saharan African countries that are endemic for malaria (Niger, Nigeria, Burkina Faso, Republic of the Congo, and Tanzania). Of all the cases, 80% were diagnosed between July and September 2012. Among the patients, 96% presented with fever that was typical for malaria, 88% had a daily fever, 48% had nausea and vomiting, 92% had headache, and 20% had diarrhea.

The other clinical findings were thrombocytopenia (44%), liver dysfunction (28%), splenomegaly (80%), hepatomegaly (60%), leukopenia (28%), prolonged prothrombin time (24%), and anemia (40%). Three patients who entered the study had undergone prophylaxis with doxycycline but then stopped of their own accord. The responsible parasitic agent was *P. falciparum* in all cases. Artemisinin and lumefantrine was administered in 18 cases; quinine and doxycycline were administered in 3 cases, and chloroquine was given in the remaining 4 cases. One patient who did not respond to treatment with chloroquine was switched to the quinine and doxycycline regimen. Fresh frozen plasma and thrombocyte suspensions were each used in 3 cases. The mean duration of hospitalization was 6.4 days, and all cases were resolved without any complications from the selected treatment regimens.

4. Discussion

Malaria has been endemic in many regions of the world for many years. In Turkey, many soldiers who served in the Ottoman Army died during the First World War due to malaria. After the foundation of the Republic of Turkey in 1923, the scourge of malaria was aggressively confronted, and cases have diminished in number and consequence over time, as noted earlier (1). In Turkey, *P. vivax* is common, while *P. falciparum* and *P. malariae* are rare. In a study from an Antalya group, 14% of cases were attributable to *P. falciparum* and 86% were due to *P. vivax* (4). *P. vivax* was also endemic in another study. It is remarkable that *P. falciparum* was responsible for all the cases of malaria in our study and, furthermore, that it had been acquired during overseas travel in all cases. Other cases of *P. falciparum* in Turkey were also determined to have originated overseas (5,6).

The diagnosis of malaria was established very easily and quickly with thick and thin peripheral blood smears (3,5) The purpose of establishing a diagnosis of malaria with Giemsa staining of peripheral thick and thin blood smears was to determine if schizogony or gametocytes of *P. vivax* were present in erythrocytes through the appearance of trophozoites or gametocytes of *P. falciparum*. WHO offers 2 types of rapid tests for malaria. One of them determines PfHRP2 and has 96% sensitivity with 99% specificity. The other test determines *P. falciparum*-specific lactate dehydrogenase (LDH) activity and pan-*Plasmodium* LDH; it is less sensitive (80%) than PfHRP2, but more specific (98%) (6,7). In our laboratory, there is 88% sensitivity with PfHRP2, as opposed to 100% with the Giemsa stain method. We offer rapid tests that keep treatment from being delayed in instances where it is impossible to undergo the thick and thin peripheral blood smear testing, or when one cannot connect with a malaria control center.

In our study, 80% of patients were men, and all patients studied were older than 18 years of age. These demographic statistics were similar to those present in other studies in Turkey (1,4,5,6). Traveling due to employment can help explain the male, middle-aged majority.

Malaria can appear in every season in Turkey, but it is common from May to November. Most of our cases were found from July to September, again similar to what was shown in other studies. Özbilgin et al. demonstrated an elevated incidence during the May–October period (1). Studies performed in Antalya, Diyarbakır, Bursa, and Manisa during different time periods also showed the highest incidence of malaria in summer and autumn (4–6). This incidence is likely because people travel abroad more often during summer. In a world marked by more global travel, many of those who return to Turkey after traveling in Africa manifest malaria due to the incubation period of 14–30 days. Sometimes, symptoms appear abroad and require treatment that starts in the country of travel and continues in Turkey.

The most important symptom of acute malaria is periodic episodes of high fever with chills (5,7). The febrile episodes could begin with or without nonspecific prodromal symptoms; these symptoms include headache, loss of appetite, fatigue, myalgia, arthralgia, diarrhea, nausea, abdominal pain, or sore throat, reminiscent of many viral infections. To provide a general sense of the frequency of these symptoms, patients with malaria have fever with chills in about 80% of cases; additionally, they frequently experience gastrointestinal symptoms (30%), fatigue (30%), loss of appetite (20%), and myalgia/arthralgia (20%) (5,7). In another study, Mert et al. presented a set of cases of malaria in which 95% of patients presented with fevers with chills, 50% with headaches, and 45%

with nausea and diarrhea (4). Finally, İnan et al. showed 100% incidence of fever with chills, 90% incidence of fatigue, 87.5% incidence of headache, 17.5% incidence of arthralgia, and 12.5% incidence of diarrhea (5). Our series of cases had similar incidence for these symptoms: 96% with episodes of fever and chills, 40% with headache, and 68% with gastrointestinal symptoms.

The details of some of these prodromal symptoms and other clinical findings can be summarized as follows.

Fever: Fever may not develop periodically in the first stage of *P. vivax* and *P. falciparum* infection. Fever as high as 40–41 °C is intermittent. Febrile episodes occurring once every other day signify *P. vivax* or *P. ovale*, while occurrence once every third day is typical of *P. malariae* and once every 1–2 days is *P. falciparum*. Daily fever was found in 88% of our cases.

Splenomegaly: The increased size of the spleen is the most important sign of malaria and a benchmark that allows determination of the duration of disease. Splenomegaly is present in between 11.5% and 97% of cases of malaria (5,7) and was shown in 91% of cases by Mert et al., 72.5% of cases by İnan et al., and 80% of cases in our study (4,5).

Hepatomegaly: Hepatomegaly was shown in 50% of patients with malaria by Mert et al. in a series of cases obtained in İstanbul, in 45% of patients by Inan et al., and in 60% in our study (4,5).

Blood-cell abnormalities (anemia, leucopenia, thrombocytopenia): Anemia and leukopenia, mostly with thrombocytopenia and (rarely) pancytopenia, can aid in the diagnosis of malaria (5). Studies of those with malaria revealed that half of the patients presented with anemia, 20% with leukopenia, and 70% with thrombocytopenia (5,7). This is roughly aligned with the findings of our study, in which 45% of the patients had thrombocytopenia, 28% had leukopenia, 12% had pancytopenia, and 40% had anemia.

Parasitemia: *P. falciparum* can cause a high degree of parasitemia (more than 5%) because it is capable of infecting erythrocytes of all ages. It can also cause severe complications such as deep anemia, cerebral malaria, acute kidney failure, acute pulmonary edema, hypoglycemia, lactic acidosis, and death in the absence of effective treatment (5,7). Mortality is 1% in *P. falciparum*-related malaria (5), but all of the patients were cured in our cases.

There is a wide variety of treatment options for malaria, some of which are more effective with specific pathogens. Chloroquine is offered in oral treatment of *P. vivax*, *P. ovale*, *P. malariae*, and chloroquine-sensitive *P. falciparum* (2). Atovaquone-proguanil, artemether-lumefantrine, quinine sulfate and doxycycline, and oral mefloquine are offered by WHO in East African and Central African countries due to the high resistance of *P. falciparum* to chloroquine (2). Quinidine gluconate, quinine dihydrochloride, or artemether are choices in parenteral treatment. Chloroquine is the first choice in prophylaxis of malaria (*P. vivax*, *P. ovale*, *P. malariae*, and chloroquine-sensitive *P. falciparum*) because it can also be used during pregnancy. Mefloquine, doxycycline, chloroquine and proguanil, or atovaquone and proguanil are other choices in prophylaxis of chloroquine-resistant *P. falciparum* (2,7).

In Turkey, malaria treatment is implemented and coordinated by the Ministry of Health of Turkey's Malaria Control Center. Treatment was applied through the guidance of this department in our study.

In conclusion, malaria should be considered in the differential diagnosis in every case of fever if the patient has a history of travel to an endemic area, a tropical country, Southeast Anatolia or the Çukurova area in Turkey. Prophylaxis of malaria is under the control of the Border and Coast Directorship of Turkey's Ministry of Health. Every country should fulfill its duty and collaborate in the global battle against malaria, and every citizen should inform himself or herself about malaria prophylaxis and about barrier methods against the mosquito before traveling to endemic areas and be willing to participate in malaria surveillance efforts after travel.

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