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# Family Practice Grand Rounds

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## Shaking Chills and Fever

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DR. JERRY E. JONES (*Assistant Professor, Department of Family Practice*): Malaria is a common parasitic disease worldwide, and patients with this infection may occasionally present to the family physician's office. Because of its relative rarity in the office setting, many physicians will not include it in the differential diagnosis of a patient presenting with fever and chills. In addition, many patients may fail to associate it with their symptoms or volunteer information about their travel history when coming to the office, especially if their travel occurred six to 12 months prior to the onset of symptoms. In our conference today we will discuss the case of an individual who presented to the office with complaints of chills, headache, and fever. A diagnosis of malaria was made in the office. The methods of diagnosis, treatment, and follow-up are discussed. Finally, a general review of the parasite responsible for malaria is presented.

### Case Report

A 24-year-old white man presented to the office complaining of chills, headache, and fever. The patient had felt essentially healthy until six days prior to the office visit, when he reported the sudden onset of shaking chills, sweating, and increased temperature. He reported the symptoms were like "coming down with the flu" and noted that the chills and fever lasted about six hours. The following day he felt well and continued his usual activities until one day prior to this office visit when again there was the sudden onset of severe, shaking chills, sweating, and high temperature. The patient volunteered that he had never experienced anything like that before where his "teeth chattered." This episode lasted approximately three hours, after which time the fever broke and left him exhausted. He lived alone, denied known exposure to infectious agents, and did not volunteer a travel history.

On detailed questioning, the patient reported

spending a month in Sierra Leone, West Africa, four months prior to the office visit. He reported that he took chloroquine prophylaxis while in Africa, but stopped taking the chloroquine upon returning to the United States. He denied any symptoms or problems during his stay in Africa.

Physical examination revealed a well-developed, flushed-appearing white man with multiple blisters about the mouth and nose. His blood pressure was 102/68 mmHg, pulse of 80/min, and temperature was 98.1°F. There were no rashes, splenomegaly, or lymphadenopathy. The lungs and heart were normal to examination. Urine examination was negative for hemolysed blood and red blood cells. A peripheral smear using a modified Wright's stain (Diff-Quik solution) showed moderate numbers of the ameboid trophozoites of a malaria parasite. The intracellular phase demonstrated enlargement and fimbriated edges of the infected erythrocyte, along with Schüffner's dots suggesting *Plasmodium ovale*.

The patient was started on oral chloroquine phosphate 600 mg, to be followed by 300 mg in six hours. He was then instructed to take 300 mg daily for two more days. After the completion of the chloroquine phosphate, he was to complete a course of primaquine diphosphate, 15 mg daily for 14 days.

Forty-eight hours into the course of treatment, the patient again experienced onset of temperature to 102°F without shaking chills. The patient was seen in the emergency room, and repeat blood smears were taken. No parasites were seen. The following day the patient felt much improved. He had completed his course of chloroquine and had started his course of primaquine. The remaining treatment course was unremarkable.

DR. ROBERT DAVENPORT (*Second-year resident*): Did the patient suspect he had malaria?

DR. JONES: The patient did not state any concerns about malaria. He did not even volunteer his travel history until asked. Apparently, he was in Africa for only three weeks and reported taking chloroquine prophylaxis. I suspect he felt that malaria was unlikely.

DR. LOUIS RILEY (*Third-year resident*): Why

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Fever has occurred within first 3 weeks of therapy, occasionally with eosinophilia or abnormalities in liver function tests, such as serum alkaline phosphatase, serum transaminases (SGOT, SGPT), bilirubin, cephalin cholesterol flocculation, prothrombin time, and bromsulphalein retention. Jaundice, with or without fever, may occur, with onset usually in the first 2 to 3 months of therapy. In some patients the findings are consistent with those of cholestasis. Rarely fatal hepatic necrosis has been reported. These hepatic changes may represent hypersensitivity reactions; periodic determination of hepatic function should be done particularly during the first 6 to 12 weeks of therapy or whenever an unexplained fever occurs. If fever, abnormalities in liver function tests or jaundice appear, stop therapy with methyl dopa. If caused by methyl dopa, the temperature and abnormalities in liver function characteristically have reverted to normal when the drug was discontinued. Methyl dopa should not be reinstated in such patients. Rarely, a reversible reduction of the white blood cell count with primary effect on granulocytes has been seen. Reversible thrombocytopenia has occurred rarely. When used with other antihypertensive drugs, potentiation of antihypertensive effect may occur. Patients should be followed carefully to detect side reactions or unusual manifestations of drug idiosyncrasy.

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Stop drug if involuntary choreoathetoid movements occur in patients with severe bilateral cerebrovascular disease. Patients may require reduced doses of anesthetics; hypotension occurring during anesthesia usually can be controlled with vasopressors. Hypertension has recurred after dialysis in patients on methyl dopa because the drug is removed by this procedure.

**Adverse Reactions:** *Nervous System/Psychiatric:* Sedation, headache, asthenia or weakness, usually early and transient; dizziness, lightheadedness, symptoms of cerebrovascular insufficiency, paresthesias, parkinsonism, Bell's palsy, decreased mental acuity, involuntary choreoathetoid movements; psychic disturbances, including nightmares and reversible mild psychoses or depression. *Cardiovascular:* Bradycardia, prolonged carotid sinus hypersensitivity, aggravation of angina pectoris. Paradoxical pressor response with intravenous use. Orthostatic hypotension (decrease daily dosage). Edema (and weight gain) usually relieved by use of a diuretic. (Discontinue methyl dopa if edema progresses or signs of heart failure appear.) *Digestive:* Nausea, vomiting, distention, constipation, flatulence, diarrhea, colitis, mild dryness of mouth, sore or "black" tongue, pancreatitis, sialadenitis. *Hepatic:* Abnormal liver function tests, jaundice, liver disorders. *Hematologic:* Positive Coombs test, hemolytic anemia. Bone marrow depression, leukopenia, granulocytopenia, thrombocytopenia. Positive tests for antinuclear antibody, LE cells, and rheumatoid factor. *Allergic:* Drug-related fever, lupus-like syndrome, myocarditis, pericarditis. *Skin:* Rash as in eczema or lichenoid eruption; toxic epidermal necrolysis. *Respiratory:* Nasal stuffiness. *Metabolic:* Rise in BUN. *Urogenital:* Breast enlargement, gynecomastia, lactation, amenorrhea, impotence, decreased libido. *Endocrine:* Hyperprolactinemia. *Musculoskeletal:* Mild arthralgia, with or without joint swelling, myalgia.

**Note:** Initial adult oral dosage should be limited to 500 mg daily in divided doses when given with antihypertensives other than thiazides. Tolerance may occur, usually between second and third months of therapy; increased dosage or adding a diuretic frequently restores effective control. Patients with impaired renal function may respond to smaller doses. Syncope in older patients may be related to increased sensitivity and advanced arteriosclerotic vascular disease; this may be avoided by lower doses.

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## SHAKING CHILLS AND FEVER

didn't the prophylaxis keep him from getting malaria?

DR. JONES: This is a very important point. Malaria prophylaxis is intended to prevent the symptoms of malaria. It does not prevent the individual from becoming infected with the parasite. In this case the patient became infected during his short stay in Africa. Upon returning to the United States, he stopped his chloroquine. The malaria parasite lives in the liver during one life cycle phase. It is this phase that is not treated by chloroquine. An individual must complete a course of a second drug in order to kill the parasite during this liver phase. To help clarify this further, allow me to review the malarial parasites.

There are four major species of the plasmodium parasite that infect man. The most important species is *Plasmodium falciparum* because it causes death and has increasingly shown patterns of drug resistance to chloroquine. The remaining species, *malariae*, *ovale*, and *vivax*, tend to cause a less severe type of infection.

All species of plasmodia are transmitted to man by the female anopheline mosquito. The mosquito infects humans by injecting sporozoites during its bite. These sporozoites are phagocytized and transported to the liver. They enter the parenchymal liver cells and initiate the preerythrocytic cycle. In the liver the sporozoites multiply asexually to form the next life phase called merozoites. Nine to 15 days of incubation are needed before the newly formed merozoites are released into the blood. In all species except *Plasmodium falciparum* and merozoites, when they are released, may also invade other parenchymal liver cells, thus establishing or maintaining an exoerythrocytic cycle. It is during this exoerythrocytic cycle that additional merozoites are produced, which may give rise to relapses months or years later, such as in this case. With *P malariae* infections the merozoites may be released years or decades following primary infections, giving rise to latent malaria paroxysms.

DR. BRIAN MILLER (*Second-year resident*): So the sporozoite phase is not treated by prophylaxis.

DR. JONES: Yes, that's correct. Merozoites, which are formed within the individual liver cells, may also be unaffected by prophylaxis.

DR. MILLER: Does the patient have symptoms at this point?

DR. JONES: The patient may have prodromal



symptoms including headache, backache, myalgia, malaise, nausea, vomiting, chills, and fever. However, the initial symptoms are usually vague, and the characteristic fever pattern seldom appears until the infection is well established. The erythrocytic phase begins when the merozoites, which have been released by the liver, invade the red blood cells, beginning the trophozoite, or growing, phase within the red blood cell. Each species has a characteristic trophozoite development. At the time of maturity, the trophozoite's nucleus divides, initiating the schizogony phase. At this point the parasite is called a schizont. Each schizont divides into a new group of merozoites, causing the red blood cells to rupture. These red blood cell merozoites are the product of the erythrocytic cycle in contrast to the merozoites from the liver tissue. As the blood cells rupture, they release the parasite's metabolic wastes, pigment, and remains of the red blood cells into the host's blood stream. These materials precipitate a foreign protein and sensitization reaction. The classically described attack of malaria includes (1) shaking chills, (2) high fever and drenching sweats, (3) myalgia, (4) severe frontal headaches, and (5) exhaustion. These symptoms tend to take on a characteristic pattern depending on the infecting organism, with *P falciparum* malaria reactions occurring daily, *P vivax* and *P ovale* malaria reactions occurring every second day, and *P malariae* malaria reactions occurring every third day. There is broad variation in the clinical course, especially early in the disease or when more than one species is present.

DR. LES BECKER (*Third-year resident*): What do you look for on physical examination?

DR. JONES: In uncomplicated malaria, the physical examination may be normal. During the classic attack, the patient is febrile, drenched in sweat, and shivering. Mild anemia, hepatomegaly, and splenomegaly develop as the illness progresses, usually taking several months. I suspect that most of your practices will involve individuals much like the patient being discussed, who will be seen very early in the course of infection.

DR. MILLER: What complications should you watch for?

DR. JONES: The most severe effects are usually caused by *P falciparum*. The most dangerous complication of infection by this species is cerebral malaria, which has a high mortality. The clinical picture of this complication may appear sud-

dently or unfold over several days. The patient may complain of severe headache and drowsiness and rapidly slip into a coma. There may be associated hyperpyrexia, acute personality changes, and progressive deterioration of mental status. Deep coma, with focal or widespread neurologic signs, including generalized convulsions, may occur. The blood smear shows large numbers of parasites, and severe anemia and renal failure often occur. Renal failure may also occur independently of cerebral involvement as a result of hyperpyrexia, hemolysis, and secondary dehydration. Hemolysis that is due to repeated and intense destruction of red blood cells will cause hemoglobinuria with dark urine. Jaundice develops, and in severe cases the patient may lapse into hepatic coma. The severe anemia may also cause shock. With the potential for such complications, early and accurate diagnosis of malaria is of paramount importance.

DR. ROGER APPLGATE (*Third-year resident*): You expect us to make this diagnosis in the office?

DR. JONES: Any individual presenting with shaking chills and fever returning from an area with known malaria should be considered potentially to have malaria. Careful history of travel and drug prophylaxis regimen is important to obtain. If the patient reports having had contact with known malaria cases in the area of travel, he should be considered at risk.

The definitive diagnosis is made by peripheral blood smear. Taking a sample by finger stick or venous puncture is simple. You can make your own slides; in our case, the slide was stained with a simple Diff-Quik technique. If you see the parasites, you have the diagnosis. Several thick and thin Wright's stained smears then can be prepared. Most often this preparation is done by the medical technician in the hospital setting. The differentiation of species requires considerable experience and should be a consideration when accepting a report of malaria by species.

If a diagnosis is made or strongly suspected, therapy should be started immediately. If an individual has a high fever, shaking chills, and a history of being in a high-risk area, treatment can be started once peripheral smears have been taken. In uncomplicated attacks, chloroquine phosphate can be used regardless of the species. The recommended dosage is 600 mg of chloroquine base initially and 300 mg of base six hours later on the first



day. This is followed by 300 mg of base on the second and third days.

Strains of chloroquine-resistant *P falciparum* are found mainly in southeast Asia. However, certain areas of Africa and South America have also reported resistant strains. References are available that list countries reporting resistant strains.<sup>1,2</sup> Malaria patients who have been in these regions should be assumed to be resistant to chloroquine therapy. In this setting, a combination of drugs is recommended. One regimen is 650 mg of quinine sulfate three times daily for 10 to 14 days, plus 25 mg of pyrimethamine twice daily for 1 to 3 days, plus 500 mg of sulfadiazine four times daily for 5 to 10 days. An alternative regimen is quinine sulfate three times daily for 10 to 14 days, plus 250 mg of tetracycline four times daily for 10 days. Cure (eliminating both the liver and blood phase) of malaria is important to consider in infections caused by *P vivax*, *P ovale*, and *P malariae* species, as relapses may occur after clinical cure with chloroquine. Eliminating the liver phase is accomplished by adding 15 mg of primaquine phosphate daily for 14 days. However, the addition of primaquine adds the potential complication of intravascular hemolysis in patients with glucose-6-phosphate dehydrogenase deficiency. This deficiency appears more commonly among black and middle-eastern populations and can be tested before treatment with primaquine. Some reports suggest that up to 10 percent of the male, black population may have this deficiency.<sup>3</sup>

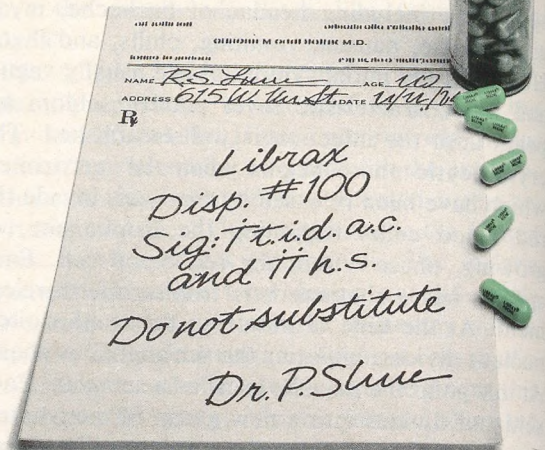
In closing, our case today brings up several important issues. First, malaria continues to be a serious medical problem in many areas of the world. Second, with the increase in worldwide travel and the arrival of refugees, a patient may present to your office with a malarial illness. Third, getting the appropriate history is the first step in getting the correct diagnosis. Fourth, a diagnosis can be made in the office using a simple peripheral smear, as with our case today. Finally, it is important to recognize the potentially fatal complications of *P falciparum* and begin treatment after appropriate smears are obtained if these complications are suspected.

## References

1. Wyler DJ: Malaria—Resurgence, resistance, and research. *N Engl J Med* 1983; 308:875-878
2. Neuman HH: Foreign Travel and Immunization Guide. Oradell, NJ, Medical Economics, 1982
3. Trenholme GM, Carson PE: Therapy and prophylaxis of malaria. *JAMA* 1978; 240:2293-2295

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