ORIGINAL CONTRIBUTION

Clinical Diagnosis of Malaria On The Thai-Myanmar Border

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Background: To evaluate the prevailing practice of presumptively diagnosing malaria in all cases of febrile illness in a clinic serving a refugee population on the Thai-Myanmar border.

Methods: A retrospective review of 3506 patient charts from December 1993 through June 1994 at the Mae Sot medical clinic to compare clinical signs of malaria to blood smear findings. Patients presenting without fever were assumed not to have malaria; the remaining 2111 patients presenting with fever had blood smears examined for malaria infection.

Results: Fever alone suffered from poor positive predictive value (54.7 percent) and specificity (59.3 percent). When fever was combined with hepatosplenomegaly and anemia, the positive predictive value and specificity improved (84.5 percent and 98.5 percent, respectively). However, this combination also resulted in an unacceptably poor sensitivity (16.5 percent) and false negative error rate (835/1000).

Conclusions. In this nonimmune refugee population, severe complications of falciparum malaria occur quickly and commonly; aggressive chemotherapy is necessary to reduce morbidity and mortality. Until laboratory facilities are made available, all cases of fever should continue to be treated presumptively as malaria.

INTRODUCTION

War, famine, and ethnic persecution displace great numbers of people. The United Nations High Commissioner for Refugees estimated over 18 million refugees scattered throughout the world in 1993 [1]. Refugee populations often lack immunity to the infectious diseases of the host country. This coupled to crowding and subsistence living, creates unique susceptibility to dangerous infections and high mortality rates [2].

Within the last decade, large numbers of Burmese refugees have entered Thailand. The political unrest, brought about by the Burmese military government, has sparked widespread violence throughout the country. Because the ethnic and

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Abbreviations: HSM, hepatosplenomegaly; MDR, multi-drug resistant; PPV, positive predictive value; NPV, negative predictive value.

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social persecution continues, there is a constant flux of new arrivals along the border near the city of MaeSot.

The MaeSot border region is an area of unstable malaria transmission. The constant flux of refugees makes this population nonimmune to the local strains of malaria. Therefore, all age groups suffer from severe disease and complications [3]. These conditions pose a serious health threat to this population.

One large clinic in MaeSot, dedicated to the refugee population, treats from 100 to 200 new malaria cases each month. The staff consists of Burmese doctors, medics, and laboratory technicians. Numerous non-government organizations supply the clinic with the necessary supplies and equipment.

The gold standard for the diagnosis of malaria is a positive parasite recognition on thick and thin blood smears [4, 5]. The clinic is fortunate to have an established lab, capable of diagnosing malaria with blood films. However, most of the Burmese people are not able to reach the MaeSot clinic due to economics, lack of infrastructure, politics, and distance. Most seek health care within the Karen State of Myanmar, a remote, dense jungle region with limited electricity and running water and few other resources. Medics from the MaeSot clinic are sent into the Karen State to operate remote health care posts and mobile clinics; such facilities lack diagnostic laboratories. Consequently, medics diagnose malaria based entirely upon their clinical findings.

The Burmese believe that fever is a good predictor of malaria infection. The lay population and the medics regularly treat all cases of fever with antimalarials. This generous use of antibiotics has greatly reduced malaria-related mortality. However, this same uncontrolled use of antimalarials results in drug toxicity and resistance. Indeed, many of the multi-drug resistant (MDR)* Plasmodium falciparum strains are found in this region [6-8]. This study compared clinical diagnosis to laboratory diagnosis in a representative sample of over 2000 febrile patients in an effort to identify practices that would lead to the greatest population benefit, with the least harm.

METHODS

The medical clinic in MaeSot provides health care for many of the Burmese refugees in the region. When patients arrived at the clinic, they were initially triaged by nurses. The nurses were young Burmese volunteers, trained by the clinic physicians, and both lived and worked at the clinic. Many of these were fluent in the three Burmese dialects and the five Karen dialects and thus could ascertain the patient’s chief complaint and any history of fever. The nurses also obtained the patient’s vital signs. Every patient who presented to the clinic with fever or who complained of febrile episodes was sent to the diagnostic laboratory to have a blood smear inspected for malaria parasites.

At the diagnostic laboratory, patients gave blood for microscopy examination. The laboratory technicians were trained by the medical doctors at the clinic. They utilized the gold standard for malaria diagnosis, parasite recognition on thick and thin blood smears with a Romanowsky stain; the results were recorded on the patient’s chart by species type and degree of parasitemia.

History and physical exam were conducted by one of two physicians at the clinic, both trained in Western medicine in Rangoon, Myanmar. Fever was defined as an axillary temperature greater or equal to 37.5°C. History of fever included any episode of “feeling hot” during the current illness. Hepatomegaly and splenomegaly were determined by percussion and palpation. Liver edge greater than 3 cm below the costal margin or a vertical
Table 1. Total number of patients seen at the MaeSot clinic and malaria infection by month of presentation.

|       | Dec | Jan | Feb | Mar | Apr | May | Jun | Total |
|-------|-----|-----|-----|-----|-----|-----|-----|-------|
| Total patients | 595 | 304 | 392 | 341 | 465 | 702 | 707 | 3506  |
| Malaria infection | 184 | 120 | 110 | 99  | 213 | 257 | 172 | 1155  |

Table 2. Clinical signs and symptoms and malaria infection.

| Total patients | Malaria infection |
|----------------|-------------------|
| Any fever      | 2111              |
| Fever + anemia | 524               |
| Fever + HSM    | 642               |
| Fever + anemia + HSM | 226     |

Table 3. Performance characteristics of clinical signs and symptoms.

| Sens | Spec | PPV | NPV | FPER | FNER | LR (+) |
|------|------|-----|-----|------|------|--------|
| Any fever | 100% | 59.3% | 54.7% | 100% | 40.7% | 0% | 2.5  |
| Fever + anemia | 32.2% | 93.6% | 71.2% | 50.7% | 6.4% | 67.7% | 5.0  |
| Fever + HSM | 40.3% | 92.5% | 72.6% | 53.1% | 7.5% | 59.7% | 5.4  |
| Fever + anemia + HSM | 16.5% | 98.5% | 84.5% | 48.9% | 1.5% | 83.5% | 11.0 |

Patients presenting without fever or a reported history of fever were presumed to be malaria-free by clinic personnel, and were not referred for blood smears. Sens, sensitivity; Spec, specificity; PPV, positive predictive value; NPV, negative predictive value; FPER, false positive error rate; FNER, false negative error rate; LR (+), likelihood ratio positive.

Liver and splenic enlargement were considered together as hepatospleno-megaly (HSM). HSM and anemia were dichotomized for the analysis into present or absent. Fever was defined as the presence of fever or history of “feeling hot” (a span greater than 12 cm at the right mid-clavicular line and a palpable spleen beyond the rib cage were considered enlarged. Anemia was graded clinically according to a four-plus scale. All findings were recorded on patient charts. The patient received a diagnosis and a treatment plan. If medications were required, they were provided by the clinic. When the patient load was high, some of the patients may have been seen by medics. The medics, who had no health degrees, were trained at the clinic and supervised by the physicians.

A retrospective review of patient charts from December 1993 through June 1994 was conducted. All 3506 patient charts were reviewed to determine whether or not fever was present. Patients presenting with conditions other than febrile illness were assumed not to have malaria. The remaining 2111 patients presenting with fever had blood smears examined for malaria infection. This resulted in the diagnosis of 1155 patients with malaria. The relationship between clinical presentation and malaria infection was analyzed.
period of perceiving an elevated body temperature, without an attributable cause). Clinical categories analyzed were as follows: Any Fever; Fever + Anemia; Fever + HSM; and Fever + Anemia + HSM. Disease was defined by positive parasite recognition on blood smears. Clinical findings were compared to true disease state by smear using 2 x 2 contingency tables. From these, sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), false negative and false positive error rates were calculated using standard formulae [9].

RESULTS

A total of 3506 patient charts were reviewed. Of these, 2111 had fever and were evaluated for malaria. A total of 1155 were diagnosed with malaria based on direct visualization of parasites by microscopy (see Table 1). As shown in Table 2, 524 patients had fever and anemia, 642 had fever and HSM, and 226 had fever, anemia, and HSM. As shown in Table 3, the sensitivity was greatest for fever alone (de facto, as only febrile patients were evaluated with blood smears), while the specificity was greatest for fever, anemia, and HSM in combination. Similarly, the negative predictive value was highest for fever alone (again, de facto), while the positive predictive value was greatest for fever plus anemia and HSM. In general, the rate of false positive error fell, and the rate of false negative error rose, as clinical criteria were added to fever, as shown in Table 3. The best (highest) likelihood ratio positive was associated with fever plus anemia and HSM.

DISCUSSION

Throughout the world, regions endemic for malaria often suffer from very limited health care resources. Although the gold standard for malaria diagnosis is positive parasite recognition by microscopy, this is unavailable in many areas. Therefore, it is common practice to diagnose malaria based upon clinical manifestations. In many endemic areas, all cases of fever are treated empirically for malaria.

Numerous studies have shown presumptive diagnosis to overdiagnose malaria [10-12]. The obvious benefit to treating all cases of fever is a high sensitivity [13, 14], with prevention of disease sequelae by early antimicrobial treatment. This is especially true in regions such as the Thai-Myanmar border, where unstable transmission of P. falciparum and non-immune refugees create a dangerous mix. Severe disease and lethal complications of P. falciparum appear in all age groups. Presumptive diagnosis, however, results in unnecessary antimalarial use. This contributes to increased treatment costs, potential delays in the diagnosis and treatment of other causes of fever (false positives), avoidable exposure to the toxic effects of drugs, and drug resistance [14].

The WHO has supported presumptive diagnosis of malaria in endemic regions without diagnostic laboratories. Nevertheless, numerous studies have sought to find improvements in clinical criteria for malaria infection. Most studies have found signs and symptoms to have low specificity and low PPV [11, 13, 15, 16]. Other studies have suggested a limited role for clinical diagnosis [10, 14].

The results of this study are largely consistent with the prior literature. Fever has a high sensitivity, but also a low PPV and specificity. Over treatment of malaria (false positives) occurs when fever is the sole diagnostic criterion. The PPV and specificity improve as clinical signs and symptoms accumulate. The combination of fever, anemia and HSM resulted in a PPV of 84.5 percent and a specificity of 98.5 percent. However, had this been the diagnostic criterion, the false negative
error rate would have been 83.5 percent. During the study period, 964 patients of the 1155 with malaria would not have been treated during their initial visit. Such a delay in treatment, or nontreatment, would certainly have resulted in a dramatic increase in morbidity and mortality [15].

This study was limited by the fact that the clinical setting operated on the assumption that all cases of malaria would present with fever or provide a history suggestive of fever. This results in a de facto sensitivity of 100 percent for fever as a diagnostic sign for malaria infection. While a patient with malaria might present without a history of fever, this is considered rare, and prior studies have relied on a similar assumption [10, 14]. Olivar used body temperature greater than 38°C. as an inclusion criterion for his study [17]. Svenson found 100 percent of cases to have a reported history of fever [13]. A history of fever should ideally be defined as a history of a measured elevated body temperature. In this study it is defined as “feeling hot” (a period of perceiving an elevated body temperature, without an attributable cause). The refugee population lacks thermometers. This doubtless introduces some random error, as different patients have different ideas for defining the feeling of “hot.” Further random error may have been introduced by variability in clinical assessments, variability in interpretation of blood smears, and patient self-treatment for malaria before presentation to the clinic. Use of antimalarials may reduce the parasitemia below detectable levels in the blood smears. Despite this limitation, the prior literature supports the assumption that a negative blood smear indicates a non-disease state [16].

While some refugees arrived recently in the Mae Sot area, others may have been there for more than five to ten years. The latter group may have developed some clinical immunity, and their parasitemia may not be the actual cause of fever [10]. Further, after numerous malaria infections, many individuals will have a permanently enlarged spleen. Therefore, an enlarged spleen on clinical exam may have little to do with the current cause of fever.

The limitations to this study represent constraints typical of remote regions. In such regions of unstable malaria transmission, it is of critical importance to diagnose and treat the infection early. In regions such as the Thai-Myanmar border, the refugee population is predominantly non-immune. When immunity is low, the population will experience high rates of complications and severe disease in all age groups [3]. Therefore diagnostic tests with a high false negative error rate cannot be accepted.

It has been suggested that a switch to microscopy from clinical diagnosis, would actually decrease overall malaria-related costs [18]. Savings would result from eliminating unnecessary dispensing of antimalarials. Under some circumstances the new antigen capture assay tests, such as the ParaSight F dipstick, may prove effective [19]. This diagnostic approach eliminates the need for expensive laboratory equipment and well-trained technicians. Antigen capture assay tests represent a significant advance in the diagnosis of malaria, but provide limited information and are quite expensive.

Chloroquine has been widely distributed throughout the world and has become readily available to the lay population. Chloroquine is inexpensive and relatively safe. However, indiscriminate use of antimalarials leads to drug resistance by subtherapeutic dosing and short courses. Chloroquine is largely useless against P. falciparum species, and quinine is beginning to lose its effectiveness. It is of great importance to control the distribution and availability of new antimalarials such as artesunate. Trained health care providers must help ensure proper dosages and courses, to avoid toxicity and the develop-
ment of drug resistance. Remote regions would likely benefit from efforts aimed at improving the clinical acumen of health care providers. It is important that clinicians in such settings be able to recognize other common causes of fever, both to avoid overdiagnosis of malaria, and to promote use of potentially life-saving antibiotics for other conditions [11, 17].

SUMMARY

The clinical diagnosis and presumptive treatment of malaria suffers from poor specificity and PPV. This approach to diagnosis should be utilized only when microscopy is not available. Under such conditions, as no constellation of clinical signs or symptoms is pathognomonic for malaria, fever should continue to be used as an indication for antimalarial therapy. The overuse of antimalarials that results must be accepted in remote, endemic regions as the price for avoiding a high rate of severe complications from delays in treatment.

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