Prevalence of Malaria among Acute Febrile Patients Clinically Suspected of Having Malaria in the Zeway Health Center, Ethiopia

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SUMMARY: Malaria diagnosis is a common challenge in developing countries with limited diagnostic services. Common febrile illnesses were assessed in 280 malaria-suspected patients, and each case was subjected to clinical and laboratory examinations for malaria, relapsing fever, typhoid fever, typhus, and brucellosis. Data were entered and analyzed using Epi Info version 3.1 software. Malaria accounted for 17% (CI, 12.6–21.4%) of febrile illnesses. The remaining cases were associated with typhoid fever (18.5%; CI, 13.95–23.05%), typhus (17.8%; CI, 13.32–22.28%), brucellosis (1%; CI, −0.17–2.17%), relapsing fever (2%; CI, 0.36–3.64%), and unknown causes (44%). Approximately 7% of patients had coinfections, and 2% of patients treated as monoinfections. Approximately 1.4% of the nonmalarial patients received antimarial treatment. The sensitivity and specificity of the CareStart Pf/pan rapid diagnostic tests in comparison with those of microscopy were 100% and 91%, respectively, with positive- and negative-predictive values of 94% and 100%, respectively. Compared with microscopy, the positive-predictive value of each malaria symptom was much lower than that of the symptoms combined: fever, 17%; sweating, 30%; headache, 18%; general body ache, 22%; loss of appetite, 21%. The study findings revealed a high proportion of nonmalarial illnesses were clinically categorized as malaria. Parasite-based diagnosis is recommended for the management of malarial and nonmalarial cases.

INTRODUCTION

Malaria has been widely prevalent throughout human history (1) and still causes 247 (152–387) million infections and 881 (610–1,212) thousand deaths worldwide annually (2). Approximately 91% of the deaths and 86% of the cases occur in Africa (2). The burden of the disease has generally declined with scaling up of prevention, diagnosis, and treatment coverage (3). According to a 2010 world health report, the number of cases of malaria increased from 233 million in 2000 to 244 million in 2005 but decreased to 225 million in 2009. The number of deaths due to malaria is estimated to have decreased from 985 thousand in 2000 to 781 thousand in 2009 (2). Ethiopia is the fourth malarious country in Africa after Nigeria, Democratic Republic of Congo, and Uganda (2). Malaria is a major public health problem in Ethiopia, covering 75% of the landmass; approximately 52 million (68%) of the population are at a risk of infection (4). Plasmodium falciparum and P. vivax are the 2 dominant parasite species, with relative frequencies of 60–70% and 30–40%, respectively (4). Malaria transmission is unstable and seasonal, mainly occurring from September to December, followed by April to May (5).

Many malarious countries are scaling up malaria intervention programs towards elimination of the disease, which demands accurate diagnosis (6). Hence, Ethiopia has set national goals in a strategic plan to eliminate malaria from specific geographical areas with historically low malaria transmission and near-zero malaria deaths in the remaining malarious areas by 2015 (4). Sensitive and effective detection of parasites is crucial to identify and treat patients and to control transmission of the disease (6). Malaria control strategies require accurate diagnosis and effective patient management (7,8), as its signs and symptoms are nonspecific and overlap with other febrile illnesses (9) such as typhoid fever, typhus, relapsing fever, and brucellosis. Overlap of clinical features and limited laboratory services in developing countries overwhelm the management of febrile patients (10). Therefore, presumptive treatment of fever with antimalarial drugs remains the standard of care in many developing countries (10–12). Identification of malarial illness is difficult for health professionals due to the absence of unique symptoms and different cultural interpretations of symptoms (11,13). No clinical predictors have been identified to reliably distinguish malaria from other febrile illnesses (12). Malaria symptoms are the least specific of all major diseases, ranging from fever alone to serious, life-threatening conditions. Therefore, it is impossible to know whether a febrile condition is due to malaria or another disease based solely on clinical presentation (14). Most febrile illnesses are commonly associated with poverty and underdevelopment, with significant morbidity and mortality (15). These illnesses share social circumstances that are essential to their transmission. Individuals in endemic areas are at a substantial risk of contracting acute disease or an acute infection superimposed on a chronic one (16).
In Ethiopia, microscopy and rapid diagnostic tests (RDTs) are used to diagnose malaria. However, diagnosis of malaria is most frequently based on clinical signs and symptoms (4). The aim of this study was to compare the accuracy of distinguishing malaria from other febrile illnesses using clinical criteria versus laboratory tests.

MATERIALS AND METHODS

This cross-sectional study included 280 acute febrile patients clinically suspected of having malaria and presenting to the Zeway Health Center in November 2011. The center is located in the rift valley of central Ethiopia. Study participants were those with acute fever and body temperature > 37.5°C or a history of fever over the previous 48 h. After giving verbal consent, patients were examined clinically, and their clinical signs and symptoms were recorded. Eligible patients who were clinically suspected of having malaria were diagnosed using laboratory tests for malaria (microscopy and RDT) and febrile illnesses including relapsing fever (microscopy), typhoid fever, typhus, and brucellosis tests using HumaTex febrile kits (Human GmbH, Wiesbaden, Germany) containing 3 specific antigens.

Laboratory diagnosis: Thick and thin blood films stained with 10% giemsa solution for 10 min were prepared and examined microscopically by experienced technicians. Thick films were considered negative if no parasite (either the malarial parasite or Borrelia recurrentis) was seen in at least 100 consecutive oil immersion fields. CareStart HRP2/PLDH is a rapid, in vitro immunodiagnostic test for the detection of circulating P. falciparum histidine rich protein 2 (HRP2) and an antigen common to all 4 species of malaria, pan antigen (PLDH), in whole blood. The kit contains 2 specific monoclonal antibodies that have been immobilized across the test strip. The test was performed according to the manufacturer’s instructions. Briefly, 5 µl of whole blood was added to a sample pad impregnated with colloidal gold-labeled antibodies, which was then added to the malarial antigens. Buffer (60 µl) was added into the buffer well to facilitate the flow of the blood sample into the compartment, and the result was read after 20 min. The test is valid only if the control line is observed. The result was interpreted as P. falciparum infection if there was visible line on the hrp2 band. Samples were positive for P. falciparum infection or a mixed infection if positive on hrp2 and PLDH/pan antigen marks. Samples were positive for a mixed infection of all 3 P. vivax, P. ovale, or P. malaria if positive on the PLDH/pan antigen mark only. One limitation of this test is that it cannot distinguish P. falciparum infections from mixed infections.

HumaTex febrile antigens were used to detect antibodies against typhoid fever, brucellosis, and typhus. The antigen solution consists of stained bacterial suspensions used for screening suspected patients qualitatively (slide agglutination) and semiquantitatively (titration) for antibodies against febrile antigens in serum. The reagent contains bacteria that are vitally stained with 10\(^6\) S. paratyphi BH, Brucella abortus, and Proteus OX19. Production of the IgM somatic O antibody is the initial serologic response to acute typhoid fever, while the IgG flagella H antibody develops more slowly but persists longer. Two types of agglutination techniques are available: the slide test and the tube test (15). HumaTex febrile antigen reagent and serum samples were placed at room temperature, and the antigen solution was mixed before use. A drop of serum was placed in 6 separate cells on the slide, and a drop of positive and negative control was added in parallel. A drop of corresponding antigen was added on the serum, and the fluid was spread with a disposable stick over the entire area of the cell. The slide was mixed on an electric rotator for 1 min, and the result was observed for agglutination macroscopically under bright light. Agglutination on S. typhi O, S. paratyphi AH, and S. paratyphi BH cell indicated typhoid infection, while that on Proteus OX19 indicated typhus and B. abortus indicated brucellosis. Titration was performed for samples that were positive in the agglutination test. Serial dilutions (1:2) were performed on an initial solution of serum (100 µl) and saline (100 µl) through a 1/64 dilution. The test was performed for the slide agglutination using each dilution as the specimen. Samples that showed agglutination at a dilution of 1/32 or above were considered positive (17).

Statistical analysis: Data entry and analysis were performed using EPI Info version 6 software. The following quantities were determined: prevalence of malaria, relapsing fever, typhoid, typhus, and brucellosis among febrile patients; misprescription regardless of the laboratory results; and the sensitivity and specificity of the RDT and antibody tests.

Ethical clearance: This study was conducted after receiving approval from the Institutional Review Board of Akilul Lemma Institute of Pathobiology, Addis Ababa University.

RESULTS

A total of 280 acute febrile patients (63% women, 37% men) with suspected malaria were screened for different disease etiological agents. The mean age of patients was 24 years (median, 23). The common signs and symptoms of patients were fever (100%), sweating (56%), headache (93%), vomiting (33%), general body ache (74%), and loss of appetite (79%). Each clinical sign and symptom was compared with microscopy results and showed very low positive-predictive value (PPV) for malaria. Fever, sweating, headache, general body ache, and loss of appetite had PPVs of 17%, 30%, 18%, 22%, and 21%, respectively, for malaria with respect to microscopy (Table 1). In contrast, the combination of signs and symptoms had better PPV for malaria cases (fever and sweating, 31%; fever, sweating, and headache, 67.6%; and sweating, headache, vomiting, loss of appetite, and body ache, 80%).

Of total malaria-suspected patients, only 48 (17%; CI, 12.6–21.4%) were microscopically positive for malaria. Among positive patients, 45% were infected with P. falciparum and 55% with P. vivax. Six febrile patients (2%; CI, 0.36–3.64%) were infected with B. recurrentis determined by microscopic examination of blood films.
Table 1. Frequency of common clinical signs and symptoms of patients with acute febrile illness (n = 280)

<table>
<thead>
<tr>
<th>Demographic variable and clinical history</th>
<th>No. (%)</th>
<th>PPV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>280 (100)</td>
<td>17</td>
</tr>
<tr>
<td>Headache</td>
<td>261 (93)</td>
<td>18</td>
</tr>
<tr>
<td>Loss of appetite</td>
<td>220 (79)</td>
<td>21</td>
</tr>
<tr>
<td>General body ache</td>
<td>216 (74)</td>
<td>22</td>
</tr>
<tr>
<td>Sweating</td>
<td>156 (56)</td>
<td>30</td>
</tr>
<tr>
<td>Vomiting</td>
<td>92 (33)</td>
<td>—</td>
</tr>
<tr>
<td>Fever and sweating</td>
<td>86 (31)</td>
<td>31</td>
</tr>
<tr>
<td>Fever, sweating, and headache</td>
<td>189 (67.6)</td>
<td>67.6</td>
</tr>
<tr>
<td>Sweating, headache, vomiting, loss of appetite, and body ache</td>
<td>224 (80)</td>
<td>80</td>
</tr>
<tr>
<td>Others</td>
<td>18 (6.4)</td>
<td>—</td>
</tr>
</tbody>
</table>

PPV, positive-predictive value.

Fig. 1. Etiology and frequency of acute febrile illnesses.

Table 2. Distribution of febrile illnesses by age group

<table>
<thead>
<tr>
<th>Age (yr)</th>
<th>5–11</th>
<th>12–15</th>
<th>16–20</th>
<th>&gt;21</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malaria</td>
<td>8/32</td>
<td>9/33</td>
<td>15/63</td>
<td>14/152</td>
</tr>
<tr>
<td>Typhoid</td>
<td>1/30</td>
<td>5/33</td>
<td>10/63</td>
<td>32/152</td>
</tr>
<tr>
<td>Typhus</td>
<td>3/30</td>
<td>6/33</td>
<td>17/63</td>
<td>26/152</td>
</tr>
<tr>
<td>Rf</td>
<td>0</td>
<td>1/33</td>
<td>3/63</td>
<td>2/152</td>
</tr>
</tbody>
</table>

Rf, relapsing fever.

(Fig. 1). According to the CareStart HRP2/PLDH RDTs, 51 patients (18%) were positive for malaria. Of these, 8.5% were P. falciparum-positive, 51% pan-positive, and 40.4% P. falciparum-positive or pan-positive (Fig. 1). The sensitivity and specificity of CareStart Pf/pan in comparison with those of microscopy were 100% and 91%, with PPV and negative-predictive value (NPV) of 94% and 100%, respectively. The distribution of malaria cases in our cohort varied by age (Table 2). The incidence of malaria was much higher (25%) in malaria-suspected febrile children than that in those with nonmalarial febrile illnesses (typhoid, 3.3%; typhus, 10%; relapsing fever, 0%).

The prevalence of other febrile illnesses was also assessed in malaria-suspected patients. Of total febrile patients, 39% tested positive for typhoid antibody in the screening test (slide agglutination); of these patients, only 18.5% (CI, 13.95–23.05%) tested positive in the confirmatory test (titration >4-fold). Of total febrile patients, 32.8% were typhus antibody-positive in the slide agglutination test, of which only 17.8% (CI, 13.32–22.28%) were positive in the confirmatory test (titration >4-fold); 3.2% of patients were positive for brucellosis in the agglutination test, and only 1% (CI, −0.17–2.17%) were positive in the titration test (Fig. 1). The sensitivity, specificity, PPV, and NPV of direct agglutination, and titration above 4-fold were calculated as indicated in Table 3. Concurrent infections with more than 1 etiologic agent of febrile illness were present in approximately 7% of the cohort, with 1.4% concurrently infected with malaria and typhoid fever, 1.4% infected with malaria and typhus, and 4.3% infected with typhoid fever and typhus. Among 7% coinfected cases, 2% were treated as though infected with a single agent. Approximately 1% of the malaria and typhus coinfected patients were treated as malaria only; 0.7% of the malaria and typhoid fever coinfected patients were treated as malaria only; and 0.36% of the typhus and typhoid fever coinfected cases were treated as typhus only. Approximately 1.4% of the nonmalaria patients (negative microscopy and RDT results) received antimalarial treatment; 1 case treated as falciparum with Quarters; and 3 treated as vivax with chloroquine.

**DISCUSSION**

Among 280 malaria-suspected acute febrile patients, the prevalence of malaria was only 17% microscopically (18% with CareStart Pf/pan malaria RDTs). The remaining 83% had other fever-causing illnesses or nonmalarial, undifferentiated fever. According to test results, typhoid fever, typhus, relapsing fever, and brucellosis accounted for 18.5%, 17.8%, 2%, and 1% of illnesses, respectively. Of 280 patients, 7% were con-
laboratory-based diagnostic tests. In Ethiopia, fewer method will be a useful malaria case prediction in detection of symptoms had a high predictive value. This predictive value for malaria, whereas using a combination of single signs and symptoms had a low sensitivity or specificity to be useful. Axillary temperature failed to achieve sufficient sensitivity in relation to the detection of life-threatening illness.证券投资 resulted in sensitivities unacceptable in high rates of overtreatment. Any narrower combination of symptoms resulted in sensitivities unacceptable in relation to the detection of life-threatening illnesses. Axillary temperature failed to achieve sufficient sensitivity or specificity to be useful. In this study, observation of single signs and symptoms had a low predictive value for malaria, whereas using a combination of symptoms had a high predictive value. This method will be a useful malaria case prediction in developing countries, where there is less access to laboratory-based diagnostic tests. In Ethiopia, fewer than 20% of malaria infections are confirmed by laboratory methods; the remainder is diagnosed through clinical histories and examinations. Clinicians almost invariably respond to positive malaria tests by prescribing antimalarials but often ignore negative test results and prescribe antimalarials anyway. When diagnostic facilities are available, more than half of patients with negative test results are still treated for malaria. In the absence of diagnostic facilities, the proportion is even higher. Overdiagnosis of malaria is substantial in the formal healthcare sector throughout Africa, as it is based on clinical symptoms alone.

In developing countries, malaria diagnosis is primarily based on clinical symptoms alone and antimalarials are prescribed without obtaining a blood test, despite the lack of accuracy of using fever, symptoms, and signs to diagnose malaria. Clinicians seem to make malaria treatment decisions based on a complex mixture of conventional clinical logic and diagnostic algorithms on the one hand and social factors with no obvious basis in clinical logic on the other hand. Targeting the use of antimalarials to those who have malaria and identifying and treating other causes of serious febrile diseases is an undisputed goal but is far from the current state of affairs. Clinicians need to believe in the diagnostic accuracy of rapid tests for confirming or ruling out malaria, and such change could come by developing fever treatment algorithms for malaria-negative patients. Although most acute febrile patients in endemic areas do not have malaria, they continue to receive antimalarial therapy.

Investigations conducted in Tanzania indicated that clinicians frequently prescribed antimalarials due to patient’s expectation of a prescription. They also used tests to confirm their suspicions rather than as a way to make a diagnosis or allocate treatment. In this study, we found that 7% of patients were concurrently infected with more than 1 fever-causing agent; 2% of patients were coinfected but received treatment as for only 1 agent. Similar studies conducted in 653 acute febrile patients in northwestern Ethiopia reported malaria as a major cause of febrile illness (62%), followed by pneumonia (7%), typhoid fever (5.8%), typhus (5.1%), and brucellosis (2.6%). The incidence of malaria was lower in our patient cohort, possibly due to the overall reduction of malaria cases in the country between 2009 and 2011 and epidemiological differences between seasons and between northern and central Ethiopia.

A study of febrile illnesses in travelers returning to Australia reported only 27% of diagnoses were malaria, followed by respiratory tract infection (24%), gastroenteritis (14%), dengue fever (8%), and bacterial pneumonia (6%) (18). In India, 88% of patients with acute fever tested for malaria did not have evidence of malaria by light microscopy or malaria RDTs (9). Similarly, we found that 83% of the acute fever cases were nonmalarial. In another study, among nonmalarial febrile patients, approximately 40% received antimalarial treatment despite the negative results on RDTs (9). We also observed a small fraction of patients (1.4%) who were treated with antimalarials despite negative test results.

A large proportion of patients with febrile illness in places where malaria is common is treated with antimalarial drugs without a specific diagnosis (19,20). Prescription of antibiotics to febrile patients is also high (21). The Federal Ministry of Health report (22) has indicated that in a nonepidemic year, there are 5–6 million clinical malaria cases, only approximately 600 thousand of which are confirmed. The observation of fever alone or fever in combination with chills and/or headache was sensitive in diagnosing malaria, but both criteria resulted in high rates of overtreatment. Any narrower combination of symptoms resulted in sensitivities unacceptable in relation to the detection of life-threatening illnesses. Axillary temperature failed to achieve sufficient sensitivity or specificity to be useful. In this study, observation of single signs and symptoms had a low predictive value for malaria, whereas using a combination of symptoms had a high predictive value. This method will be a useful malaria case prediction in developing countries, where there is less access to laboratory-based diagnostic tests. In Ethiopia, fewer than 20% of malaria infections are confirmed by laboratory methods; the remainder is diagnosed through clinical histories and examinations. Clinicians almost invariably respond to positive malaria tests by prescribing antimalarials but often ignore negative test results and prescribe antimalarials anyway. When diagnostic facilities are available, more than half of patients with negative test results are still treated for malaria. In the absence of diagnostic facilities, the proportion is even higher. Overdiagnosis of malaria is substantial in the formal healthcare sector throughout Africa, as it is based on clinical symptoms alone.

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The finding that 83% of patients with clinical malaria did not have evidence of malaria by microscopy or RDT indicated that inaccurate diagnosis continues to obstruct effective management of febrile patients. This shortcoming is mainly due to the absence of differential diagnosis, presumptive treatment of febrile cases, nonspecific clinical presentation of different febrile illnesses, a high prevalence of asymptomatic infections, and the incidence of coinfection. Nearly equivalent burdens of typhoid (18.5%), typhus (17.8%), and malaria (16.5%) were observed in malaria-suspected patients in the health center. The use of a combination of signs and symptoms resulted in higher PPV for malaria than did individual signs and symptoms. Given the lack of reliable clinical predictors, availing accurate diagnostic tests is likely to be of great clinical value. This finding showed that parasite-based diagnosis is recommended to distinguish malarial from other febrile illnesses. The antibody-based tests presently used in health facilities, particularly the agglutination test, are too inaccurate to reliably distinguish the real cause of illness. Alternative diagnostic tools are thus needed.

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Conflict of interest None to declare.

REFERENCES