Original Article

Febrile Illnesses of Different Etiology among Outpatients in Four Health Centers in Northwestern Ethiopia

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SUMMARY: Fever of different etiology is common in tropical and subtropical countries of the world. Etiological agents of febrile illnesses were assessed in 653 acute febrile patients aged 3 to 17 years who attended the outpatient departments of Dembecha Health Center, Jiga Health Center, Quarit Health Center, and Finoteselam Hospital in western Gojjam zone, northwestern Ethiopia. Malaria was the most prevalent illness, infecting 62% of all cases. Its prevalence varied significantly from 52% (Dembecha) to 72.7% (Quarit) (χ² = 15.02, P = 0.000). Plasmodium falciparum was the first cause of malaria (47.3%) followed by P. vivax (23%). Mixed infection of both P. falciparum and P. vivax was found in 7.2% of the cases. The other febrile infections were pneumonia (7%), typhoid (5.8%), typhus (5.1%), and brucellosis (2.6%). The availability of diagnostic facilities and the awareness of the community regarding the prevalence of non-malaria febrile illnesses are very low, and these illnesses are usually diagnosed clinically. As these illnesses are nonspecific, especially during the early stages of onset, misdiagnosis and mistreatment can occur. Therefore, it is recommended that the necessary diagnostic materials and awareness should be in place for prompt treatment of febrile cases in these districts.

INTRODUCTION

Febrile illnesses due to different etiologic agents are the most common causes of morbidity and mortality in developing tropical and subtropical countries. Such illnesses are a public health challenge in peripheral health care systems where clinical diagnosis is a common practice and diagnostic facilities are scarce (1). Clinical diagnosis lacks specificity, as febrile illnesses may be clinically indistinguishable, and results in classification errors. This leads to a potential misdiagnosis and mistreatment of patients (2) in addition to increasing the exposure to potentially toxic drugs (3) without solving the root cause of the problem. As a result, the prevalence and relative importance of the etiologic agents of these illnesses remain unknown. Public health personnel also have insufficient data to assess the disease burden, estimate priorities for health resources (4) and refine policy on the empiric management of febrile patients (5).

The lack of appropriate diagnosis and treatment facilities in most rural areas of Ethiopia led febrile patients to seek traditional medication (6-8) and self-treatment with antimarial drugs from local public shops. This might be due to the lack of awareness regarding the prevalence of febrile illnesses with different etiologies and the frequent episodes of malaria in the country, which resulted in frequent epidemics and the loss of many lives (6,9,10). Febrile illnesses are diagnosed clinically in most rural health centers, except for malaria, which is confirmed by microscopy. This study assessed the prevalence of the major causative agents of acute febrile illnesses in patients who presented to the outpatient departments of four health care systems.

PATIENTS AND METHODS

Study population: Acute febrile patients aged 3 to 17 years (living in three adjacent districts of Quarit, Dembecha, and Jabitelman) who attended Dembecha, Jiga, Quarit Health Centers and Finoteselam Hospital in western Gojjam zone, northwestern Ethiopia from September 2006 to November 2006, were included. Eligible subjects for the study were those with acute fever (body temperature >37.5°C), or a history of fever within the previous 3 days. Children with severe illness requiring inpatient treatment or those with chronic disease were excluded (2,4).

Clinical and laboratory diagnosis: Trained physicians of the respective health care systems took anthropometric measurements, recorded the common symptoms associated with febrile illnesses, and performed standard clinical examinations after obtaining verbal consent from the patients. They made diagnoses using all the available information including clinical characteristics, epidemiological information, laboratory data, and treatment and travel history. Patients were treated based on the clinical and laboratory findings.

Thin and thick blood films were made from finger pricks of patients described as acute febrile by physicians, fixed with methanol and stained with Giemsa for laboratory examination of human Plasmodium parasites within 10-25 min. Patients were given antipyretic drugs, and treatment started after the blood film result was known. Blood film was declared malaria negative only after the examination of 100 high power resolution fields. Borrelia sp. was observed on these slides during the diagnosis of malaria parasites. Pneumonia was diagnosed clinically and recorded as pneumonia with unknown etiology.

About 3 to 4 ml of venous blood was taken from each of the febrile cases and centrifuged for 5 min at 1,000 revolutions per minute. Sera was then tested for the presence of antibodies against febrile antigens using HumaTex febrile antigens (Human GmbH, Wiesbaden, Germany) intended to detect febrile infections such as salmonellosis (typhoid
fever), brucellosis, and typhus. The kit consisted of stained bacterial suspensions of *Salmonella* serotypes (S. *typhi* H, S. *typhi* O, S. *paratyphi* AH, S. *paratyphi* BH), *Brucella abortus* and *Proteus* OX19, which are used either for screening purposes by rapid slide agglutination, or for confirmation by tube agglutination (Widal test). Screening was performed using the qualitative slide agglutination test. Samples that showed agglutination in the screening were further confirmed by using the semiquantitative slide agglutination test. In brief, kit reagents and serum samples were first placed at room temperature, and antigen solutions were mixed thoroughly and gently before use. First, in the qualitative slide agglutination test, a drop of serum (50 μl) was placed in six separate cells on the slide provided with the kit for each serum sample. The same was done for positive and negative controls in parallel. Then a drop of the corresponding antigen was placed and mixed with disposable stick, and the fluid was spread over the entire area of the particular cell (a separate stick was used for each cell). The slide was tilted back for forth for 1 min so that the mixture rotated slowly inside the cells. At the end of the rotation, the results were read macroscopically under bright artificial light for the presence/absence of distinct agglutination within 1 min after rotation. Agglutination with *S. typhi* H, *S. typhi* O, *S. paratyphi* AH, *S. paratyphi* BH was considered typhoid infection, with *B. abortus* as brucellosis and with *Proteus* OX19 as typhus. A semiquantitative slide agglutination test was also made to confirm positive results in six separate cells as above. In this case, however, the six cells contained different dilutions. Dilution no. 1 (the first cell) contained a 100-μl specimen + 100-μl NaCl (9 g/l). This specimen was diluted at the following rates in order: 1/2, 1/4, 1/8, 1/16, 1/32, and 1/64 for each sample. Then the test was continued as described in the qualitative slide agglutination test employing each dilution as specimen. It was then examined macroscopically for the presence/absence of distinct agglutination within 1 min after rotation. The results were read at the highest dilution (titration) still showing agglutination. Samples that showed agglutination at a dilution of 1/32 or higher were considered positive.

**Statistical methods:** Data were entered into SPSS 12 software, and analysis was performed using the Pearson chi-square at a α = 0.05 confidence level to assess the presence of variation of the same infectious agent across the cases from the four health centers and among different age groups for a particular illness.

**Ethical consideration:** The Ethical Committee of the Aklilu Lemma Institute of Pathobiology, Addis Ababa University, approved the project. The physicians and researchers obtained informed consent from parents and caregivers of febrile children before taking samples.

**RESULTS**

A total of 653 acute febrile patients were diagnosed for different disease etiologies. The median age of the participants was 8.4 years old, and 48.5% of them were female. The most prevalent disease was malaria, which infected 62% of the cases (Table 1). The prevalence of the disease varied from 52% in Dembecha to 72.7% in Quarit significantly ($\chi^2 = 15.02, P = 0.000$). The most important cause of malaria was *Plasmodium falciparum* (47.3%) followed by *Plasmodium vivax* (23%). Mixed infection of both *P. falciparum* and *P. vivax* was found in 7.2% of the cases. *P. falciparum* and *P. vivax* infections were highest in Quarit and lowest in Dembecha. On the other hand, mixed infection of the two parasites was highest in Quarit (9.1%) and lowest in Jiga (3.5%). In general, Quarit district was highly affected by the disease compared to the other three study areas.

The prevalence of other febrile illnesses was also assessed from these patients. They were pneumonia (7%) (pneumonia with unknown etiology), typhoid (5.8%) (*S. typhi* H, *S. typhi* O, *S. paratyphi* AH, and *S. paratyphi* BH), typhus (5.1%) (*Proteus* OX19), brucellosis (2.6%) (*B. abortus*), and relapsing fever (1.7%) (*Borrelia* spp.). The prevalence of typhoid was higher in Dembecha and Quarit compared to Jiga and Finoteselam. *B. abortus* was highest in Finoteselam (6.3%) followed by Quarit (3%). Typhus fever (*Proteus* OX19) was the most important infection in Dembecha Health Center (12.8%) during the study. Although it existed at all four health centers, the infection was a relatively severe problem in the area during the study. *Borrelia* spp. were found in 6 cases from Dembecha, 3 cases from Finoteselam, and 1 each from Jiga and Quarit. About 28% of the cases were free of any of the above infections. However, infection with two or three of these causative agents was common, although in small proportions. For example, 4.3% of cases were infected with malaria and pneumonia, while 2.8% were infected with malaria and typhoid and 0.15% with pneumonia and *Brucella*.

The highest number of cases at all the health care services occurred in children less than 6 years old, and the number decreased as age increased (Table 2). However, the prevalence of the different illnesses was found to be similar in each age

<table>
<thead>
<tr>
<th>Health centers or hospital</th>
<th>Total (n = 653)</th>
<th>$\chi^2$</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total malaria positive</td>
<td>62</td>
<td>15.02</td>
<td>0.002</td>
</tr>
<tr>
<td>Falciparum malaria</td>
<td>47.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vivax malaria</td>
<td>13.17</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mixed malaria</td>
<td>3.89</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Typhoid</td>
<td>5.16</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brucellosis</td>
<td>18.10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Typhus</td>
<td>19.88</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pneumonia</td>
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<td></td>
</tr>
<tr>
<td>Relapsing fever</td>
<td>3.52</td>
<td></td>
<td></td>
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</tbody>
</table>

### Table 1. Percentage of patients with febrile illness in four health centers, West Gojjam zone, northwestern Ethiopia, 2006

- Total malaria positive ($n = 653$): 62 cases.
- Falciparum malaria: 47.3% ($n = 653$).
- Vivax malaria: 13.17% ($n = 653$).
- Mixed malaria: 3.89% ($n = 653$).
- Typhoid: 5.16% ($n = 653$).
- Brucellosis: 18.10% ($n = 653$).
- Typhus: 19.88% ($n = 653$).
- Pneumonia: 0.69% ($n = 653$).
- Relapsing fever: 3.52% ($n = 653$).
group except for *B. abortus*, which was higher in children aged 9 to 14 years old. No statistically significant difference was observed in the prevalence of each febrile illness among the different age groups.

**DISCUSSION**

This study revealed that fevers of different etiology are prevalent in Dembecha, Quarit, and Jabitehnan districts in northwestern Ethiopia. The most common illness was malaria followed by pneumonia, typhoid, typhus, and brucellosis. Febrile cases treat themselves with the locally available antimalarial drugs and other traditional medications believing that the disease is malaria. Only a few cases, especially those living near the health centers, consult medical personnel (personal communication with the health workers). This is also a common practice in other parts of the country (7,8). However, the proportion of cases that visited the health centers was not clear. Studies in Tanzania (11) and Togo (12) revealed that less than 21% of febrile children who were sick with malaria went to clinics on the first day of illness. As most of the residents of the study districts are farmers, their awareness regarding the prevalence of febrile illnesses with different etiology is minimal.

Clinical diagnosis of febrile cases is a common practice in most peripheral health care systems of Ethiopia, and *Plasmodium* is considered the main etiologic agent (7,8). However, symptoms of malaria and other febrile diseases are less specific in semi-immune individuals infected with malaria (13-15) and may overlap at the start of the clinical manifestation (16,17). There is considerable clinical overlap between malaria and pneumonia (18), between typhoid and malaria, and between malaria and many other viral and parasitic infections (19). This overlap in the clinical manifestation of febrile illnesses of different etiology has important implications for case management strategies and the evaluation of disease-specific interventions.

The possibility of multiple infections should also be considered (11). This is evident from the present observation of malaria and pneumonia, malaria and typhoid, and pneumonia and brucellosis infections. The treatment of febrile cases with antimalarial drugs remains important, as malaria due to *P. falciparum* is lethal. However, infection with other febrile illnesses may be overlooked and may cause unrecognized deaths. Laboratory diagnosis of malaria was being performed microscopically at the three health centers and at Finoteselam Hospital. It is a gold standard and a sensitive tool for diagnosing the disease. However, there was no laboratory diagnosis of other febrile illnesses aside from the Widal test for typhoid fever. This test is relatively cheap, easy to perform and requires minimal training. However, it is nonspecific (20), and patients may be treated for typhoid fever based on a single positive result. The rapid tests we used to assess the prevalence of typhoid, typhus, and brucellosis, HumaTex febrile antigens, are reported to be sensitive and specific with possible minimal diagnostic errors (21).

Brucellosis was most prevalent, next to pneumonia, in patients from Finoteselam Hospital and Jiga Health Center. This illness is responsible for bovine brucellosis; humans acquire this infection through contact with infected livestock and consumption of unpasteurized dairy products. It causes heavy economic losses and human suffering, characterized by undulant fever that, if untreated, can develop into a chronic infection with symptoms persisting for several months and may result in infection of secondary tissues, including the heart and brain. Its pathological manifestations are diverse and include arthritis, endocarditis, and meningitis in humans, while animal brucellosis is characterized by spontaneous abortion (18). Most of the patients' caregivers were not aware of this infection and indicated that several farmers might have suffered with the problem due to their consistent contact with cattle and habit of drinking raw milk.

Relapsing fever caused by *Borrelia* spp., either louse-borne or tick-borne (22), has quite similar clinical manifestations (23). However, the tick-borne diseases are serious diseases that may kill if untreated (23) and pose the possibility of pregnancy loss (24). The mainstay of diagnosis of the disease is the demonstration of the spirochetes in Giemsa-stained thick blood smears. However, thick smears may be negative due to the low number of spirochetes in the blood stream (25). Therefore, this finding might have underestimated the actual number of patients that could have been infected with *Borrelia* spp.

In general, febrile illnesses such as typhoid, typhus, pneumonia, brucellosis, and relapsing fever are prevalent in addition to malaria in Dembecha, Quarit, and Jabitehnan districts in northwestern Ethiopia. The highest number of cases in all the health care systems, in terms of age group, involved children aged 6 years old or younger. This could be due to their immature immune system, low level of hygiene and frequent exposure to the pathogens. Community-wide assessment and treatment of children and mothers for febrile illnesses remains important in order to reduce the associated morbidity and mortality. However, significant reduction of these diseases is attained when community awareness is gained both throughout the health care systems and at the household level, and accurate diagnosis and prompt treatment are in place.

The HumaTex febrile antigens test used in this study has some limitations (21). False negative results may be obtained in the early phase of disease, prozone (brucellosis), cases undergoing antibiotic treatment, and low or non-immune responders. Serological cross-reactions with *Brucella* have

<table>
<thead>
<tr>
<th>Age group</th>
<th>Cases</th>
<th>fm</th>
<th>vm</th>
<th>fm+vm</th>
<th>Typhoid</th>
<th>Relapsing fever</th>
<th>Typhus</th>
<th>Pneumonia</th>
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<td>3-5</td>
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<td>23.0</td>
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<td>6-8</td>
<td>113</td>
<td>46.9</td>
<td>16.8</td>
<td>8.0</td>
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<td>2.7</td>
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<td>9-11</td>
<td>109</td>
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<td>22.9</td>
<td>6.4</td>
<td>4.6</td>
<td>4.6</td>
<td>5.5</td>
<td>7.3</td>
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<tr>
<td>12-14</td>
<td>90</td>
<td>46.7</td>
<td>26.7</td>
<td>6.7</td>
<td>6.6</td>
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<td>8.9</td>
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<tr>
<td>15-17</td>
<td>89</td>
<td>50.6</td>
<td>27.0</td>
<td>6.7</td>
<td>1.1</td>
<td>1.1</td>
<td>3.4</td>
<td>7.9</td>
</tr>
<tr>
<td>Total</td>
<td>653</td>
<td>47.3</td>
<td>23.0</td>
<td>7.2</td>
<td>5.8</td>
<td>2.6</td>
<td>5.1</td>
<td>7.0</td>
</tr>
</tbody>
</table>

fm, falciparum malaria; vm, vivax malaria; fm+vm, mixed falciparum and vivax malaria.
been reported in cases of infection or vaccination with some strains of *Vibrio cholerae*, *Pasteurella*, and *Proteus OX19*. Therefore, test results need to be interpreted with care, and other relevant information such as past histories, epidemiology, and clinical manifestations must be considered.

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**REFERENCES**