MALARIA PARASITEMIA AND CHILDHOOD DIARRHEA IN A PERI-URBAN AREA OF GUINEA-BISSAU

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**Abstract.** To examine the association between diarrhea in early childhood and malaria parasitemia, we conducted a nested case-control study in Guinea-Bissau of 297 children with diarrhea and a similar number of children without diarrhea matched for age, season, and residential area. There were no associations between diarrhea and parasite rate, parasite density, or clinical malaria. However, anti-malarials were easily available and frequently used, which was reflected by a 0.7% prevalence of children with a parasite density > 100/200 leukocytes. Thus, the findings do not preclude that diarrhea may be a sign of clinical malaria or high-parasite density in endemic areas with lower use of antimalarials.

Improvements in management of severely ill children in developing countries demand a set of simple indicators that can identify children at risk of severe illness and suggest an appropriate treatment for these children. This has previously been done mainly through vertical programs, with each focusing on one particular disease, e.g., malaria, diarrhea, or pneumonia. More integrated approaches have resulted in guidelines for treatment of fever with cough and fever with convulsions. However, no guidelines have been published on the relationship between two of the most common symptoms: fever with diarrhea. Both diarrheal diseases and malaria are highly prevalent in developing countries but whether malaria plays a significant part in the pathogenesis of acute gastroenteritis in these countries is a controversial issue.

The classic literature on tropical medicine states that malaria as a disease may present with almost any symptom, including watery or dysenteric diarrhea. An autopsy study from Nigeria (147 fatal cases of acute malaria, 80% less than 9 years of age) found that diarrhea with fever was reported in 34% of these cases during terminal illness, and at autopsy 14.9% had signs of enteric malaria with colitis. Malaria morbidity surveys based on hospital data suggest an association between diarrhea and malaria parasitemia with diarrhea reported in 6–40% of clinical malaria cases. In contrast, the limited number of epidemiologic community studies investigating this issue have not been able to demonstrate evidence for an association between malaria and diarrhea.

To reinforce an integrated approach towards management of severely ill children in developing countries, we conducted the present study to investigate whether children with diarrhea were likely to have malaria parasitemia since this could potentially have implications for treatment recommendations.

**Study population and definitions.** The study was designed as a nested case-control study. Cases and controls were selected from a longitudinal weekly household morbidity survey under the demographic health surveillance system in the area. Cases were defined as children who, according to the mother, had diarrhea and had passed 3 or more stools in the 24 hr preceding the weekly morbidity interview, and who had only had diarrhea for less than three days. For each case, a control was selected from the same morbidity survey, but without diarrhea, on the day of the interview and the two preceding days. Cases and controls were matched according to age and residential area. The matching for area was mandatory, but if no child was born in the same month as the case, we found a control born either in the preceding or the following month. A case or control was only eligible if he or she had not received antimalarial drugs or antibiotics in the two weeks prior to the interview.

Thirteen pairs were discarded from the study for this reason. A physician conducted a short interview in Criol, a local language, whereby the physician’s and the mother’s clinical judgement of the child was recorded, including whether the mother reported the child to have a fever. Stool samples and malaria smears were taken from all children, and the children (both cases and controls) were treated in case of a positive stool sample or blood smear. Malaria parasitemia was detected by direct microscopy. Parasite density was measured as number of parasites per 200 leukocytes. Clinical malaria was defined as maternal reporting of fever together with a parasite density > 10/200 leukocytes. Clinical malaria was defined as maternal reporting of fever together with a parasite density > 10/200 leukocytes. The rainy season was defined as June to December. The study was carried out between August 1, 1993 and November 30, 1994. The objectives of the study were explained orally to all mothers at their first visit to a health center and they were informed about the possibility of refusing to participate at any time during the study. The study was approved by the Danish National Ethical Committee (Copenhagen, Denmark).

**Statistical methods.** The geometric mean parasite density, a combined measure of prevalence and parasite density, was calculated by assigning the parasite count value of 0.01 to a negative blood smear. Positive blood smears were assigned the real count/200 leukocytes. Groups were compared with Wilcoxon’s nonparametric paired t-test after the parasite counts had been transformed to the natural logarithm of the count. The geometric mean was calculated as the exponential
value of the mean. Univariate odds ratios (ORs) were estimated as maximum likelihood estimates by conditional logistic regression (EGRET software; Cytel Software Corp., Cambridge, MA).

RESULTS

Two-hundred ninety-seven pairs were included of which 142 pairs were sampled during the dry season and 155 pairs were sampled during the rainy season. The median age was 19 months (interquartile range = 12–24) for cases and 18 months (interquartile range = 12–24) for controls. Overall, 26% (95% confidence interval [CI] = 23.2–30.6%) of the study population had parasitemia, while 0.7% (95% CI = 0.2%–1.9%) of the study population had parasitemia > 100 parasites/200 leukocytes. Eighty-nine percent of the observed parasitemias were due to *Plasmodium falciparum*.

The characteristics of cases and controls, as well as the matched univariate analysis of selected determinants for diarrhea, are shown in Table 1. Malaria parasitemia (P = 0.44) and parasite density (P = 0.47) were not associated with an increased risk of diarrhea. No dose-response effect could be detected and the clinical malaria definition had no significant relationship with diarrhea. There was no difference in sex distribution between cases and controls (P = 0.54).

In a matched analysis of 22 pairs according to which both case and control had malaria parasitemias, the controls had the highest parasite density in 15 pairs, whereas cases had the highest parasite density in 7 pairs (OR = 2.1, 95% CI = 0.82–5.88). Overall, there was no difference in geometric mean parasite count between cases and controls, but in the dry season there was a tendency towards a higher geometric mean among cases (0.23 versus 0.08; P = 0.08).

Of the 84 children with parasitemias higher than 10/200 leukocytes, the mother identified 24 children (28.6%) with her reporting of fever. This is significantly more than the medical doctor, who with the clinically affected assessment identified seven (8.3%) of the 81 children (relative risk [RR] = 3.43, 95% CI = 1.56–7.51). The relationship was the same for children with diarrhea and without diarrhea (P = 0.82). Children who were reported by the mother to have a fever had an increased risk of malaria parasitemia (RR = 1.6, 95% CI = 1.2–2.0), and there was no modifying effect of diarrhea (P = 0.14) or season (P = 0.31).

DISCUSSION

There was no association between clinical malaria or parasitemia and symptomatic diarrhea, and no dose-response effect was found. Only children who had not been treated with chloroquine or antibiotics within two weeks of the interview were eligible for this study. In terms of a possible relationship between malaria parasite density and symptomatic diarrhea in the present study, this could have introduced a bias into the study. Chloroquine is a widely used first-line drug for any disorder in the community, and this drug is found in almost any household. By excluding children who had already received chloroquine, we may have excluded the severely ill children with the highest parasitemias. In the present study, only 0.7% had a parasite density > 100/200 leukocytes, while a malaria survey in the same area in 1990 found that 5.8% (95% CI = 3.6–8.8%) of the children in the area had parasitemias > 100/200 leukocytes in the months of May–July. Therefore, our study is an analysis of low–medium parasite densities, and does not allow for an assessment of a possible association with higher levels of parasitemias or severe clinical malaria. There was no difference in geometric mean parasite count and in the matched anal-

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**Table 1**

Characteristics of the study population and matched univariate analysis of selected determinants for diarrhea in 297 cases with diarrhea and 297 controls without diarrhea in Bandim, Guinea-Bissau

<table>
<thead>
<tr>
<th>Characteristics of the study population and matched univariate analysis of selected determinants for diarrhea in 297 cases with diarrhea and 297 controls without diarrhea in Bandim, Guinea-Bissau</th>
<th>Cases n = 297 (%)</th>
<th>Controls n = 297 (%)</th>
<th>Maximum likelihood estimate of odds ratio (95% CI)*</th>
<th>P†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parasitemia</td>
<td>Yes</td>
<td>80 (26.9)</td>
<td>72 (24.2)</td>
<td>1.16 (0.79–1.69)</td>
</tr>
<tr>
<td>No</td>
<td>217 (73.1)</td>
<td>225 (75.8)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Parasite density</td>
<td>&gt;10 parasites/200 leukocytes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>39 (13.1)</td>
<td>45 (15.1)</td>
<td>0.84 (0.52–1.35)</td>
<td>0.47</td>
</tr>
<tr>
<td>No</td>
<td>258 (86.9)</td>
<td>252 (84.4)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Mother’s perception: child has fever</td>
<td>Yes</td>
<td>102 (34.3)</td>
<td>47 (15.8)</td>
<td>3.82 (2.39–6.12)</td>
</tr>
<tr>
<td>No</td>
<td>195 (65.7)</td>
<td>250 (84.2)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Clinical malaria definition‡</td>
<td>Yes</td>
<td>13 (4.4)</td>
<td>11 (3.7)</td>
<td>1.18 (0.53–2.64)</td>
</tr>
<tr>
<td>No</td>
<td>284 (95.6)</td>
<td>286 (96.3)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Geometric mean parasite count§</td>
<td>Rainy season</td>
<td>0.04 (0.03–0.06)</td>
<td>0.05 (0.03–0.08)</td>
<td>–</td>
</tr>
<tr>
<td>Dry season</td>
<td>0.23 (0.11–0.47)</td>
<td>0.08 (0.02–0.17)</td>
<td>–</td>
<td>0.08</td>
</tr>
<tr>
<td>Overall</td>
<td>0.07 (0.05–0.11)</td>
<td>0.06 (0.04–0.09)</td>
<td>–</td>
<td>0.83</td>
</tr>
</tbody>
</table>

* Estimated by conditional logistic regression. CI = confidence interval; † = not applicable.
† The P values for the geometric means were obtained from a Wilcoxon paired t-test.
‡ Defined as more than 10 parasites/200 leukocytes with a maternal history of fever.
§ Values in parentheses are 95% confidence limits around the geometric mean.
ysis of cases and controls with a positive blood smear, controls tended to have higher parasite levels than cases.

Although the classic literature reports that malaria may present as acute diarrhea, malaria is unlikely to be an important cause of diarrheal diseases in public health terms. The possible exception would be children with severe disease in which case malaria is likely to be suspected.

Maternal reporting of fever was correlated with parasitemia and parasite density regardless of whether the child had symptomatic diarrhea. The mothers were better at identifying children with parasitemia by maternal history of fever compared with the clinical judgement of a medical doctor. This emphasizes the importance of obtaining a clinical history from the mother.

Most studies linking malaria and diarrhea are hospital studies in which cases are children hospitalized with clinical malaria. The cases in our study were children sampled through a health survey in the community, and our findings support those of other community studies and larger epidemiologic studies that were unable to demonstrate an association between malaria and diarrhea. In a Gambian study that monitored the effect of maloprim malaria prophylaxis, no reduction was recorded in morbidity or mortality from malaria. The cases in our study were children sampled in a health survey in the community, and our findings compared with the clinical judgement of a medical doctor. This emphasizes the importance of obtaining a clinical history from the mother.

On a routine basis, there is no reason to treat cases of diarrhea with anti-malarials. However, if the mother reports a history of fever, the child should have a blood smear taken. In health facilities without functioning laboratory services, the child with diarrhea and a maternal history of fever should be treated with an anti-malarial. It was not possible to evaluate the relationship between severe or complicated malaria and symptomatic diarrhea because of the study design. This possible relationship needs to be investigated further in prospective community studies.

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