HELMINTH INFECTIONS ARE ASSOCIATED WITH PROTECTION FROM MALARIA-RELATED ACUTE RENAL FAILURE AND JAUNDICE IN THAILAND

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Abstract. Following studies showing an association between helminth infections and protection from cerebral malaria, we compared 22 patients with malaria-associated acute renal failure with 157 patients with moderately severe malaria. Helminths were associated with protection from renal failure (adjusted odds ratio [AOR], 0.16 [0.03–0.85], P = 0.03). Helminth-infected controls were less likely to have jaundice (AOR, 0.39 [0.16–0.96], P = 0.04) or to have peripheral mature schizonts (AOR, 0.2 [0.07–0.62], P = 0.005) than controls without helminths. This suggested that preexisting helminth infections may have been protective by influencing sequestration and obstructive jaundice, 2 possible determinants of acute tubular necrosis.

INTRODUCTION

Severe malaria kills > 1 million people every year. It is estimated that in 1% of Plasmodium falciparum malaria attacks a combination of host and parasite factors will lead to severe malaria. The potent immune mechanisms allowing hosts to tolerate repeated infections are incompletely understood. In low-transmission areas, immunity is weak, and people of all ages may be affected by severe malaria. In adults, jaundice and acute renal failure are common presentations of severe malaria. During severe malaria, acute tubular necrosis is thought to result from a multifactorial decrease of renal perfusion. Parasitized red blood cells are sequestrated in the kidney, but at a much lower scale than in the cerebral vasculature. Acute renal failure is strongly associated with jaundice, which can contribute to tubular necrosis. The pathophysiology of jaundice in malaria is related to an increase of bilirubin production in patients with high parasitemia in association with liver inflammation and cholestasis. We recently observed that helminth infections were associated with a dose-dependent protection from cerebral malaria. This protection remained when controlling for socioeconomic and nutritional confounders. Indirect elements suggested that cytoadherence was reduced among helminth-infected patients. Therefore, it was conceivable that helminths affected other severe manifestations related to cytoadherence phenomena. Our objective here was to determine whether preexisting helminth infections could also protect from malaria-related acute renal failure.

PATIENTS AND METHODS

Comparison groups. It has been suggested that at a population level, the relative rarity of complicated malaria reflects that of the most virulent strains. In the absence of known stable virulence markers, and because there is a positive correlation between parasite biomass and complications, we chose controls with no severe complications despite having a high parasite biomass and adjusted for the fever duration. Patients hence had parasites of comparable growth kinetics and only differed from the clinical status reflecting presence or absence of renal dysfunction. However, although this allows us to control for differences in the multiplication potential between cases and controls at the sampling phase, this cannot be considered as matching in the strict sense of the term. In subanalyses (e.g., studying schizont counts or jaundice), we looked at the distribution of exposure to helminths in each group separately, assuming that a homogenous population was a better choice than pooling case patients and controls, which were clearly different.

Definitions. The study took place at the Hospital for Tropical Diseases, Bangkok, Thailand. The study was approved by the Ethical Committee of the Faculty of Tropical Medicine, Mahidol University. Patients were selected prospectively and all gave informed consent. Between January and December 1998, we conducted a case record study on 22 consecutive patients with malaria-related acute renal failure without cerebral malaria, as defined by serum creatinine concentration > 3 mg/dL, and 157 moderately severe controls, defined by the absence of any of the 10 World Health Organization–defining criteria despite a high Plasmodium falciparum parasite biomass (defined as some combination of parasitemia > 5%, 200,000 parasites/μL, or the presence of schizonts in the peripheral blood smear).

Exposure. Intestinal helminths have common immunomodulatory effects: they increase Th2 lymphocyte activity. Therefore, we grouped them in one single exposure variable: presence of helminths. All patients underwent a stool examination; we used simple smear and concentration techniques to assess the samples. We did not include samples from deceased patients because they died shortly after admission and did not have a stool examination.

Statistical analysis. Matching was not used, and controlling for confounders was performed during analysis by logistic regression. We obtained crude odds ratios, then included adjustment variables in multiple logistic regression models. We calculated the chi-square value for linear trend for helminth quantification and number of different helminths. To compare medians, we used the Wilcoxon rank sum test. To adjust for potential confounders, we used quantile regression (nonparametric regression). Statistical significance was set at 5%.

RESULTS

Detail of helminth infections. Thirty-four patients (19%) were infected Ascaris lumbricoides, 45 with Trichuris tri-
chiura (25%), 63 with hookworm (34%), 26 with Strongyloides stercoralis (14%), and 4 with Opisthorchis viverrini.

**General data.** Table 1 shows that patients with renal failure were significantly older, had a higher body mass index, and were more jaundiced than controls. They also had increased schizont counts, and the symptoms’ duration before admission was longer than in controls.

**Differences between helminth-infected and uninfected patients.** Bilirubin. Among controls, the median conjugated bilirubin concentration was lower in helminth-infected patients, at 0.78 IU (interquartile range [IQR], 0.45–1.5) than in those without helminths, at 0.95 IU (IQR, 0.46–3.75) (*) = 0.12. When adjusting for parasitemia and schizont counts, this became significant (*P* = 0.005). Among patients with acute renal failure, there was no significant difference in median bilirubin concentration between helminth-infected patients (6 IU; IQR, 2.3–13.2) and patients without helminths (3.4 IU; IQR = 1.8–11.5) (*P* = 0.6). After adjustments for parasitemia and schizont counts, there was still no significant difference (*P* = 0.7).

**Odds ratios.** Table 2 shows that helminth infections were associated with protection from acute renal failure. When quantifying helminth infections in low, medium, and high worm burden, the chi-square value for linear trend was 3.94 (1 degree of freedom; *P* = 0.047). Among patients with moderately severe malaria, helminth-infected patients had less mature parasite populations with a lower frequency of circulating schizonts than patients without helminths (Table 2). Among patients with moderately severe malaria, helminth-infected patients were also less likely to be jaundiced than patients without helminth infections (Table 2).

**DISCUSSION**

Here we observed that there was an association between helminth-infections and protection from acute renal failure. Socioeconomic and nutritional factors associated with helminths could have been potential confounders. However, controlling for body mass index did not alter the association. In a previous study, the protection of helminths against cerebral malaria remained after adjusting for numerous socioeconomic confounders. Therefore, we believe the observed association between helminths and protection from jaundice and renal failure was not an artifact.

Mature schizonts express knobs allowing them to be sequestrated in the deep vessels, whereas younger parasites do not express knobs. Observing them in peripheral smears usually reflects a highly sequestered proportion of parasites. Therefore, the proportion of sequestered parasites in helminth-infected controls seemed to be lower than in controls without helminths. In other words, these patients were more tolerant to high burdens of malaria parasites. Hence, cytokadherence and jaundice, 2 possible contributors of tubular necrosis, were reduced in helminth-infected patients with moderately severe malaria.

Nitric oxide has a protective effect against ischemic tubular necrosis. We recently observed that helminth-infected patients had significantly higher reactive nitrogen intermediates concentrations than patients without helminths, suggesting that during malaria infection, preexisting immunoglobulin (Ig) E–anti-IgE immune complexes in helminth-infected patients could generate nitric oxide release via the CD23–nitric oxide pathway (unpublished data).

**Table 1**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Acute renal failure</th>
<th>Controls</th>
<th><em>P</em> value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years (IQR)</td>
<td>31 (23–37)</td>
<td>23 (19–33)</td>
<td>0.007</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>22.4 (20–24.7)</td>
<td>20.1 (18.3–22.1)</td>
<td>0.003</td>
</tr>
<tr>
<td>Median of fever duration, days (IQR)</td>
<td>6 (4–7)</td>
<td>4 (3–6)</td>
<td>0.06</td>
</tr>
<tr>
<td>Median parasitemia, parasites/µL (IQR)</td>
<td>122,550 (13,695–423,520)</td>
<td>110,400 (31,680–266,560)</td>
<td>0.68</td>
</tr>
<tr>
<td>Median schizont counts, schizonts/µL (IQR)</td>
<td>49 (0–142)</td>
<td>25 (0–44)</td>
<td>0.045</td>
</tr>
<tr>
<td>Median total bilirubin, mg/dL (IQR)</td>
<td>7.5 (14.5–19.7)</td>
<td>2.5 (1.6–4.25)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

† Wilcoxon’s rank sum test.
† Adjusted for parasitemia and schizont counts by logistic regression.
* Adjusted for age, ethnicity, symptoms duration, parasitemia, and body mass index by logistic regression.

**Table 2**

<table>
<thead>
<tr>
<th>Group</th>
<th>Helminths (%)</th>
<th>No helminths (%)</th>
<th>Crude odds ratio (95% CI)</th>
<th>Adjusted odds ratio (95% CI)</th>
<th><em>P</em> value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients with acute renal failure (n = 179)</td>
<td>6 (6)</td>
<td>16 (19)</td>
<td>0.28 (0.11–0.75)</td>
<td>0.16 (0.03–0.85)</td>
<td>0.03</td>
</tr>
<tr>
<td>Controls</td>
<td>89 (94)</td>
<td>68 (81)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderately severe malaria (n = 157)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Schizonts</td>
<td>59 (66)</td>
<td>54 (79)</td>
<td>0.5 (0.24–1.05)</td>
<td>0.2 (0.07–0.62)†</td>
<td>0.002</td>
</tr>
<tr>
<td>No schizonts</td>
<td>30 (34)</td>
<td>14 (21)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderately severe malaria (n = 157)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jaundice</td>
<td>32 (36)</td>
<td>32 (46)</td>
<td>0.65 (0.34–1.22)</td>
<td>0.48 (0.24–0.97)‡</td>
<td>0.04</td>
</tr>
<tr>
<td>No jaundice</td>
<td>57 (64)</td>
<td>37 (54)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Adjusted for age, ethnicity, symptoms duration, parasitemia, schizont counts, and body mass index by logistic regression.
† Adjusted for age, ethnicity, symptoms duration, parasitemia, and body mass index by logistic regression.
‡ Adjusted for parasitemia and schizont counts by logistic regression.
for background data did not alter this association. The mechanism explaining the lower bilirubin concentrations in helminth-infected patients with moderately severe malaria may have been related to decreased cytoadherence in the liver or to decreased liver macrophage proliferation due to Th2 lymphocyte stimulation, both reducing bilirubin retention. There were no significant differences in bilirubin concentrations among patients with renal failure, possibly because in this subgroup of patients, cytoadherence phenomenon had already occurred and differences were no longer there.

Thus, in humans and in animal models, helminth infections appear to be protective against both cerebral malaria and acute renal failure, possibly reflecting a mutual equilibrium between some of the most widespread human parasites.

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