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Association between parasitic infections and tuberculin skin test results in refugees

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ABSTRACT

Background: Parasitic infections are known to modulate the immune response necessary for controlling *Mycobacterium tuberculosis* infection. We sought to investigate species-specific effects of parasite infection on *M. tuberculosis* infection.

Methods: As part of the Refugee Health Assessment Program, stool examinations and tuberculin skin testing were performed on refugees seen at Boston Medical Center between 1995 and 2012. Tuberculin skin test (TST) and stool examination data were collected for 6669 refugees; 3349 (50.2%) were TST positive (≥10 mm).

Results: Among TST-positive subjects, 176 (5.3%) had helminth infections and 1149 (34.3%) protozoa. After adjusting for sex, age, and country of origin, helminth and protozoan infections were not associated with TST-positivity. When species-specific effects were examined, subjects infected with *Trichuris trichiura* and *Giardia lamblia* had reduced odds of TST-positivity (adjusted OR [aOR] 0.65 [95%CI 0.44–0.96; p = 0.03] and aOR 0.79 [95%CI 0.65–0.95, p = 0.01], respectively).

Conclusions: Our findings suggest that *T. trichiura* and *G. lamblia* may provide protection against *M. tuberculosis* infection. This study adds to a growing body of literature suggesting that immune response modulation and susceptibility to *M. tuberculosis* infection is parasite species-dependent.

1. Introduction

There were 10.4 million cases and 1.4 million deaths due to tuberculosis disease (TB) in 2015 [1]. There is a clear need to understand factors that alter susceptibility to infection with *Mycobacterium tuberculosis* (Mtb), and co-infection with parasites is a potential factor [2]. Helminth (e.g., hookworms) and protozoan infections geographically overlap with Mtb, making co-infection common. In fact, helminths are endemic in 21 of 22 high TB burden countries [1,3–5]. Understanding the implications of parasite infections on risk of Mtb infection and on interpretation of tuberculin skin test (TST) results is important in areas of co-endemicity and for migrants who come from these areas to more developed countries.

The potential for helminth interaction with Mtb infection rests on the divergent immune response. The systemic T-helper 2 (Th2) response (e.g., IL-4, IgE) to helminths [6] may interfere with the Th1-mediated (IFN γ) response required to control Mtb infection and respond to the TST [7]. Conversely, protozoan (*Giardia lamblia*) and intracellular organisms (*Helicobacter pylori*) boost production of IFNy [8].

Previous studies of the association between parasites and TB

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found that TB patients had an increased odds of helminth infection compared to controls [9,10]. Similarly, Brazilian patients with multi-bacillary lepromatous leprosy had increased odds of helminths compared to household contacts [11]. *Blastocystis hominis* by contrast was associated with a reduced risk of TB in Peru [12], and *H. pylori* with decreased risk of progression from latent tuberculosis infection (LTBI) to TB [13]. Murine models demonstrated selected helminth infections cause more severe TB [14,15].

Data on parasites and LTBI are limited. Kenyan children and refugees in Texas had increased odds of LTBI when infected with hookworms [16,17] and decreased odds with trichiuriasis and giardiasis [18]. Some studies question the interpretability of TST results in individuals infected with parasites, suggesting concomitant malnutrition and blunted immune response lead to anergy and false-negative TST results [19,20]; however, other studies have contradictory results [21–24]. The objective of this study was to establish an association between helminth and protozoan infections and TST response and define the species-specific effects.

2. Materials and methods

2.1. Study population

The Massachusetts Department of Public Health implemented the Refugee Health Assessment Program in 1995. The program offers health assessments for asylees, refugees, and parolees (henceforth collectively referred to as refugees), treats acute illnesses, provides vaccinations, and helps refugees initiate primary care [25]. Information is collected on demographics, route of migration, time in refugee camps, and medical conditions. Per screening protocol, among other tests, a complete blood count, stool examination for ova and parasites, and TST are performed (until 2013, when providers could use an IGRA for appropriate individuals). For refugees with eosinophilia or symptoms concerning for helminth infections, serologic testing is performed at provider discretion usually at the National Institutes of Health (NIH) for filaria and at the Centers for Disease Control (CDC) or a commercial laboratory for other helminths. Data from refugees seen at Boston Medical Center between 1995 and 2012, who had stool testing and a TST performed, were analyzed.

2.2. Definitions

TST-positivity was defined as ≥10 mm, per CDC guidelines for immigrants from high-prevalence countries in the US for <5 years [26]. TST was also categorized by size (0–4, 5–9, 10–14, and ≥15 mm). Country of birth was categorized into WHO regions, except Somalia, Sudan, Egypt, Morocco, and Libya, which were categorized as part of Africa.

2.3. Statistical methods

Data were analyzed using SAS 9.3 (SAS Institute Inc., Cary, NC, USA). We used chi-square tests and t-tests for bivariate analyses. To estimate the association between TST positivity and parasite infections, we used multivariate logistic regression to adjust for potential confounding variables.

2.4. Ethics statement

The Institutional Review Board at Boston University Medical Center considered the protocol exempt.

3. Results

3.1. Study population

We analyzed data from 6669 refugees of whom 3532 (53%) were male. The mean age was 25.4 years (range <1–88; Table A.1). Overall, 2696 (40.4%) participants were from Africa (of which 42.9% were from Somalia), 2102 (31.5%) from Europe (77.7% from Bosnia), 728 (10.9%) the Americas (66.2% from Haiti), 574 (8.6%) from the Eastern Mediterranean region (58.5% from Iraq), 404 (6%) from the Western Pacific (73.3% from Vietnam), and 164 (2.5%) from South-East Asia (88.4% from Burma). The most common countries of origin were Bosnia (24.5%), Somalia (17.3%), Haiti (7.2%), Iraq (5.0%), and Liberia (4.9%). Among all participants, 653 (12.8%) reported having been in refugee camps, and 167 (2.5%) had written documentation indicating that they received BCG.

3.2. LTBI and TB

A positive TST was found in 3349/6669 (50.2%) refugees; of these, 1410/3349 (42.1%) had a TST of 10–14 mm and 1939/3349 (57.9%) ≥15 mm. TST-positive individuals were older than those who were TST-negative (mean 29.9 vs. 20.7 years; $p < 0.001$) and more often male (OR = 1.41; 95%CI 1.28–1.55; $p < 0.001$). Compared to refugees from Africa, those from Europe were more likely to be TST-positive (OR = 1.19; 95%CI 1.07–1.34; $p = 0.002$) and those from the Eastern Mediterranean were less likely (OR = 0.55; 95%CI 0.45–0.66; $p < 0.001$). TB disease history was reported by 43 (1.28%) of TST-positives and 14 (0.42%) of TST-negatives.

3.3. Helminth infection

Among 6669 refugees, 459 helminth infections were identified in 365 (5.5%) participants; 286 (78.4%) had a single helminth and 79 (21.6%) had ≥2 species (Table A.2). *T. trichiura* was the most commonly identified (n = 121; 26.4%) followed by *S. stercoralis* (n = 82; 17.9%). Compared to helminth-uninfected participants, those with ≥1 helminth were more likely to be male (OR = 1.34; 95%CI 1.07–1.67; $p = 0.02$), younger (OR = 0.85 for 10 year increase in age; 95%CI 0.79–0.92; $p < 0.001$), and from Africa (OR = 10.84, 95%CI 6.85–17.15; $p < 0.001$), Western Pacific (OR = 9.51; 95%CI 5.39–16.78; $p < 0.001$), South-East Asia (OR = 4.61; 95%CI 1.92–11.08; $p < 0.001$) or the Americas (OR = 4.05; 95%CI 2.26–7.28; $p < 0.001$) compared to Europe.

3.4. Protozoan infection

Protozoa were found in 2317 (34.7%) refugees including 1856 (80.1%) with *B. hominis* and 573 (24.7%) with *G. lamblia;* 2021 (87.2%) had a single species (Table A.3). Protozoa-infected refugees were younger than those without (OR = 0.94 for 10 year increase in age; 95%CI 0.91–0.97; $p = 0.005$). Compared to European refugees, protozoa were more common in those from the Americas (OR = 1.25; 95%CI 1.05–1.49; $p = 0.013$), the Eastern Mediterranean (OR = 1.24; 95%CI 1.02–1.5; $p = 0.014$), and Africa (OR = 1.22; 95%CI 1.08–1.38; $p < 0.001$), and less likely in those from the Western Pacific (OR = 0.72, 95%CI 0.56–0.92; $p = 0.006$). Helminth and protozoa co-infection was identified in 170 (2.55%) participants.

3.5. Association between helminth and protozoa infections and TST

Infection with a single helminth was not associated with TST results in bivariate analysis or in models adjusted for age, sex, and region of birth. Adjusting for these confounders and the presence of