

Eosinophilia: A poor predictor of *Strongyloides* infection in refugees

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P Naidu, SK Yanow, KT Kowalewska-Grochowska. Eosinophilia: A poor predictor of *Strongyloides* infection in refugees. *Can J Infect Dis Med Microbiol* 2013;24(2):93-96.

BACKGROUND: Canada resettles 10,000 to 12,000 refugees annually. Despite this being a highly vulnerable population, there are little Canadian data on subclinical tropical diseases harboured in this population over the past 20 years.

OBJECTIVES: To determine the seroprevalence and predictors of *Strongyloides* infection in refugees arriving in Edmonton, Alberta.

METHODS: A retrospective chart review of all refugees seen at the New Canadians Clinic between March 2009 and April 2010 was performed. Demographic, symptom and physical examination data were collected from the charts. Laboratory results were obtained from the electronic laboratory records.

RESULTS: A total of 350 subjects were studied. The overall seroprevalence of strongyloidiasis was 4.6%. Equivocal results were found in 6.3%. In the positive group, the majority were male (62.5%); 75% were born in Africa ($P=0.004$) and 81.2% lived in refugee camps in Africa ($P=0.002$). Eosinophilia was present in 25% of the positive subjects ($P=0.05$), in none of the equivocal group and in 8.7% of the negative group.

DISCUSSION: Persistent asymptomatic *Strongyloides* infection is maintained for years through autoinfection. Traditionally, eosinophilia was used as one of the key tools to diagnose chronic but stable diseases, but it was shown to have a poor predictive value for strongyloidiasis in returning expatriates as well as in those presenting with a disseminated form of the disease. It is important to raise awareness of the severe limitations of eosinophilia as a marker for strongyloidiasis when managing patients who either are immunocompromised, or about to start immunosuppressive therapy.

CONCLUSIONS: The present study indicated that eosinophilia is a poor predictor of seropositivity and, thus, *Strongyloides* infection. Residence in Africa (birth/refugee camps) proved to be a significantly better predictor of *Strongyloides* seropositivity.

Key Words: Eosinophilia; Intestinal helminthes; Refugees; Strongyloides; Tropical parasites

Canada resettles between 10,000 and 12,000 refugees annually, which is the second highest number of refugees accepted after the United States (1,2). Despite the high epidemiological risks involved, there are little Canadian data on subclinical tropical diseases harboured in this population over the past 20 years. While *Strongyloides* infection is not life threatening in a normal host, any form of immune suppression, even pregnancy, can result in a hyperinfection syndrome, which can be fatal. We undertook the present study to determine the seroprevalence and predictors of *Strongyloides* infection in refugees arriving in Edmonton, Alberta.

L'éosinophilie : un mauvais prédicteur de l'infection à *Strongyloides* chez les réfugiés

HISTORIQUE : Le Canada accueille de 10 000 à 12 000 réfugiés par année. Même s'il s'agit d'une population hautement vulnérable, depuis 20 ans, peu de données canadiennes ont porté sur les maladies tropicales subcliniques, dont cette population est atteinte.

OBJETIF : Déterminer la séroprévalence et les prédicteurs de l'infection à *Strongyloides* chez les réfugiés qui arrivent à Edmonton, en Alberta.

MÉTHODOLOGIE : Les chercheurs ont procédé à l'examen rétrospectif des dossiers de tous les réfugiés vus à la *New Canadians Clinic* de mars 2009 à avril 2010. Ils ont colligé les renseignements démographiques et les données relatives aux symptômes et à l'examen physique à partir des dossiers et obtenu les résultats de laboratoire dans les dossiers électroniques de laboratoire.

RÉSULTATS : Au total, les chercheurs ont étudié 350 sujets. Ils ont constaté une séroprévalence globale de strongyloïdiase de 4,6 % et ont obtenu des résultats équivoques dans 6,3 % des cas. Dans le groupe positif, la majorité était de sexe masculin (62,5 %), 75 % étaient nés en Afrique ($P=0,004$) et 81,2 % avaient vécu dans des camps de réfugiés d'Afrique ($P=0,002$). Ils ont observé la présence d'éosinophiles chez 25 % des sujets positifs ($P=0,05$), chez aucun des sujets du groupe aux résultats équivoques et chez 8,7 % des sujets du groupe négatif.

EXPOSÉ : L'infection à *Strongyloides* asymptomatique persistante perdure des années à cause de l'auto-infection. On avait l'habitude d'utiliser les éosinophiles comme l'un des principaux outils diagnostiques des maladies chroniques, mais stables, mais les chercheurs ont établi qu'ils ont une mauvaise valeur prédictive de strongyloïdiase chez les expatriés et chez les personnes atteintes de la forme disséminée de la maladie. Il est important de sensibiliser les médecins aux limites importantes des éosinophiles comme marqueur de la strongyloïdiase dans la prise en charge des patients qui sont soit immunodéprimés, soit sur le point d'entreprendre un traitement immunosuppresseur.

CONCLUSIONS : Selon la présente étude, les éosinophiles sont un mauvais prédicteur de séropositivité et, par conséquent, de l'infection à *Strongyloides*. Le fait d'avoir résidé en Afrique (y être né ou avoir habité dans un camp de réfugiés) constituait un prédicteur beaucoup plus fiable de séropositivité à *Strongyloides*.

METHODS

A retrospective chart review of all refugees seen at the New Canadians Clinic (NCC) between March 2009 and April 2010 was performed. Demographic (age, sex, country of origin, refugee camp), symptom (fatigue, fever, respiratory) and physical examination (fever, anemia) data were collected from the charts. Laboratory results (*Strongyloides* serology, hemoglobin, eosinophil count) were obtained from the electronic laboratory records. On arrival in Edmonton, all refugees were housed in government-provided apartments located in the same building as the NCC. The medical history was collected by two nurses on a

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TABLE 1
Demographic, symptom and physical examination data`
(n=350)

| | Serology | | |
|--------------------|--------------------|-------------------------|----------------------|
| | Positive (n=16) | Indeterminate (n=22) | Negative (n=312)* |
| Age range, years | 10–67 | 1–61 | 0.5–77 |
| Sex | | | |
| Male (n=187) | 10 (62.5) | 11 (50) | 166 (53.2) |
| Female (n=163) | 6 (37.5) | 11 (50) | 146 (46.8) |
| Origin | | | |
| Africa (n=159) | 12 (75) | 15 (68.2) | 132 (42.3) |
| Asia (n=100) | 3 (18.8) | 5 (22.7) | 92 (29.5) |
| Other (n=91) | 1 (6.2) (Iraq) | 2 (9.1) (Iraq) | 88 (28.2) |
| Refugee camp† | | | |
| Africa (n=150) | 13 (81.2) | 15 (68.2) | 122 (39.1) |
| Asia (n=98) | 3 (18.8) | 7 (31.8) | 88 (28.2) |
| Other (n=77) | 0 (0) | 0 (0) | 77 (24.7) |
| Symptoms† | | | |
| Fatigue | 3 (18.8) | 2 (9.1) | 13 (4) |
| Fever | 0 (0) | 2 (9.1) | 17 (5.2) |
| Respiratory | 4 (25) | 1 (4.5) | 12 (3.7) |
| Examination† | | | |
| Fever | 0 (0) | 0 (0) | 19 (6.6) |
| Anemia | 2 (12.5) | 5 (22.7) | 38 (13.2) |
| Laboratory results | | | |
| Anemia | 4 (25) | 4 (18.2) | 30 (8.6) |
| Eosinophilia | 4 (25) | 0 (0) | 27 (8.7) |

Data presented as n (%) unless otherwise indicated. *Except for symptoms and examination in which n=287; †n=325

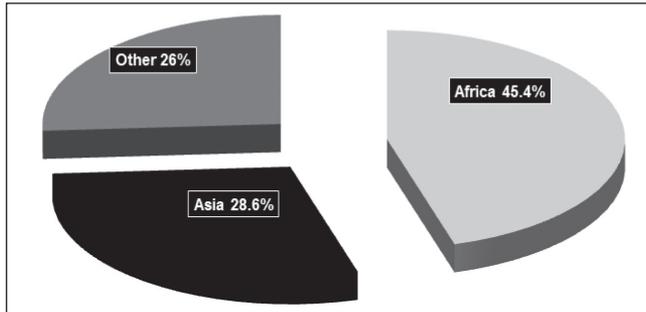


Figure 1) Origin of refugees (n=350)

standard data collection form that included questions on the presence of respiratory symptoms (cough, dyspnea) and abdominal symptoms (nausea, vomiting, diarrhea, loss of appetite and weight loss). All refugees seen at this clinic were given a complete medical examination and were routinely screened for HIV, syphilis, hepatitis A, B and C, and parasitic infections (including malaria, *Strongyloides*, and stool ova and parasites). Signs of these infections were also sought on physical examination.

Strongyloides serology was performed at the National Reference Centre for Parasitology with an enzyme immunoassay using recombinant protein antigen (NIE) developed by the National Institutes for Health. Sensitivity and specificity of the screening immunoglobulin G enzyme immunoassay is estimated to be 95%. Positive samples are confirmed with an immunoblot assay (specificity 98% and sensitivity approximately 95%) (3). HIV testing was performed at Alberta's Provincial Laboratory for Public Health. Fisher's exact test was used to calculate P values.

Ethics approval was obtained from the University of Alberta and Alberta Health Services Ethics Committees (Edmonton, Alberta).

TABLE 2
Countries represented in the present study

| Continent | Countries |
|-----------|------------------------------|
| Africa | Burundi |
| | Democratic Republic of Congo |
| | Egypt |
| | Eritrea |
| | Ethiopia |
| | Kenya |
| | Somalia |
| | Sudan |
| | Tanzania |
| | Uganda |
| Asia | Bhutan |
| | Burma/Myanmar |
| | Nepal |
| | Thailand |
| Other | Afghanistan |
| | Columbia |
| | Cuba |
| | Iran |
| | Iraq |
| | Russia |
| | Tajikistan |
| | Yemen |

RESULTS

A total of 1026 refugees were seen at the NCC since it was opened in July 2007, with an average of 340 annually. A total of 350 subjects were studied. There were 53.4% (n=187) males and 46.6% (n=163) females (Table 1). The majority originated in Africa (45.4%; n=159), with 28.6% (n=100) from Asia and the remaining 26% (n=91) from other countries (Figure 1, Table 2). Due to technical difficulties, symptom and physical examination data were not available for 25 subjects. The overall seroprevalence of strongyloidiasis was 4.6%. Equivocal results were found in 6.3%. Of these, 18% were family members of those with positive serology. In the positive group, the majority were male (62.5%) (Table 1); 75% were born in Africa (versus 42.3% of those with negative serology (P=0.004), 18.8% were born in Asia (as opposed to 29.5% of those with negative serology) and one (6.2%) was from Iraq (Figure 2). More than 81.2% of the patients with positive serology lived in refugee camps in Africa (versus 39.1% of those with negative results; P=0.002) with 18.8% having lived in refugee camps in Asia (as opposed to 28.2% of those with negative results). Seroprevalence among refugees from Asia was 3% (three of 100) and 7.5% (12 of 159) among those from Africa. A higher percentage of the seropositive subjects had complaints of fatigue and respiratory symptoms (18.8% versus 4% and 25% versus 3.7% of the seronegative subjects, respectively). However, these are nonspecific symptoms that cannot be attributed solely to strongyloidiasis because malnutrition, jet lag, exposure to a new climate and cultural environment are confounders, considering that these subjects were seen at the NCC less than one week after arrival. None of the seropositive subjects complained of or had a documented fever and none were HIV coinfecting. Eosinophilia ($>0.7 \times 10^9/L$) was present in 25% of the seropositive subjects (P=0.05), none in the equivocal group and in 8.7% in the seronegative group (Figure 3). Anemia was found in 25% of the seropositive subjects, 18.2% of the equivocal group and 8.6% of the seronegative subjects.

DISCUSSION

Strongyloides stercoralis is endemic in developing countries, with an estimated one-third of the world's population infected (4). In Canada, the majority of the infections are apparent in immigrants and refugees from areas with the highest prevalences, such as Africa and South and Southeast Asia (5).

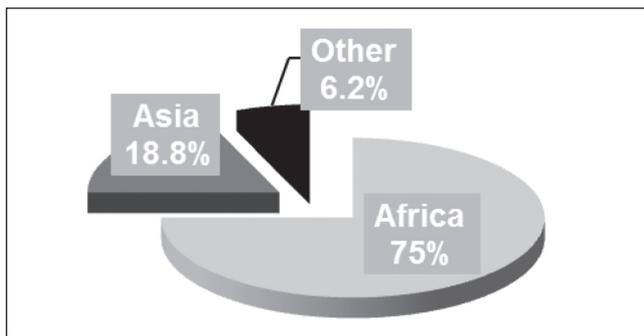


Figure 2) Origin of seropositive subjects

Persistent asymptomatic infection is maintained for years through autoinfection – the organism's ability to multiply within the host. Sudden and dangerous increase in worm burden can be triggered by drugs or disease-induced defect in cellular immunity. This leads to dissemination of the organism to organs and tissues (hyperinfection syndrome). In the absence of postarrival screening, the average time to diagnosis of *S stercoralis* in the United States is 61 months after migration (6), with case reports of *Strongyloides* infection manifesting disease >50 years after leaving an endemic area (7,8). No data were available on the situation in Canada.

Although traditionally eosinophilia was used as one of the key tools to diagnose chronic but stable diseases, it was shown to have a poor predictive value for strongyloidiasis in returning expatriates as well as those presenting with disseminated form of disease (6,9). This may not be true for populations with more intense exposure such as refugees originating from highly endemic countries. In a study from Boston (USA) (10), eosinophilia was present in 12% of newly arrived refugees and in 39% of the seropositive patients. Our study showed lower rates, with an 8.9% overall rate of eosinophilia and 25% in the seropositive subjects.

Although standard stool microscopy remains the gold standard for diagnosis, it has a very low sensitivity, particularly when simple stool specimens are examined (11). Additionally, direct examination of stool for *Strongyloides* larvae greatly depends on the skill and experience of the microscopist, thus further impacting its sensitivity as a detection tool. Serology is thus far the most sensitive method for diagnosis of strongyloidiasis (sensitivity 89% to 98%, specificity 93.3% to 97.7%) (12,13) which is why it is now the method of choice for diagnosis, particularly when confirmed with western blot.

The seroprevalence of strongyloidiasis in the present study was also lower (4.6%) than that reported in 1990 in a Canadian study of Southeast Asian refugees (11.8% among Vietnamese, 76.6% among Cambodians and 55.6% among Laotians) (6). An Australian study reported seroprevalence rates from 11% in East Africans to 42% in Cambodian newly arrived refugees (14). The Centers for Disease Control and Prevention's (Georgia, USA) serosurvey published in 2007 showed a 46% prevalence rate of *Strongyloides* in Sudanese refugees and 23% in Somali Bantu (15), despite having arrived in the United States after implementation of presumptive albendazole treatment. Subsequent to this, the Centers for Disease Control and Prevention recommended treatment of all refugees originating from the Middle East, South/Southeast Asia and Africa with ivermectin before departure to the United States (16). Australia now recommends predeparture treatment for intestinal helminths with albendazole (17). There are no presumptive/predeparture treatment guidelines or recommendations at present for immigrants to Canada.

There were a few limitations in our study. Because of its retrospective nature, long-term outcomes could not be assessed because subjects were followed by family and community physicians. Serology used to diagnose infection could represent an overestimate because we do not know whether some refugees experienced previous infections that

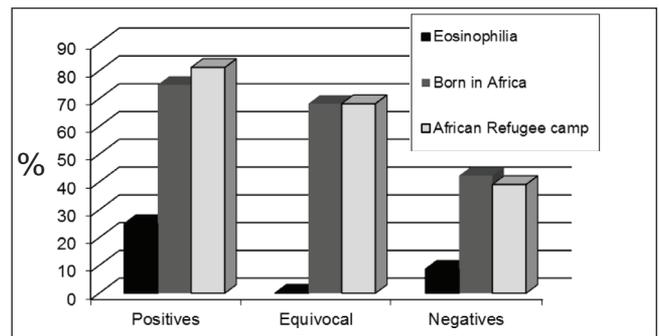


Figure 3) Comparison of eosinophilia and residence in Africa (birth or refugee camps) (percentage) according to serology result

were recently treated in their home country or refugee camp, but still had detectable *Strongyloides* immunoglobulin G. Information on predeparture antihelmintics represents another unknown that could have had an impact on the results of the present study. Eosinophilia, a common marker of acute strongyloidiasis, may be intermittent in chronic infection and absent in severe or disseminated disease, particularly hyperinfection syndrome (18,19). Although the latter is unlikely to be a factor in our patient population, the single measurement in our study most likely has contributed to lack of utility of eosinophil counts for screening refugees. Finally, only recently arrived refugees were studied; therefore, the results cannot be extrapolated to all immigrants from endemic countries.

Although strongyloidiasis is generally controlled by the normal host cellular immunity, any form of drug- or disease-induced immunosuppression can lead to the potentially fatal hyperinfection syndrome, with the prevalence reaching 26% (20). This may pose a major problem when patients with hyperinfection syndrome are admitted to hospitals, particularly intensive care. Filariform larvae generated during this stage of the parasite life cycle can be present in fecal matter and respiratory secretions, creating significant risks for hospital personnel such as respiratory therapists, nurses and housekeeping staff (21), as well as additional costs for the hospital itself (8,22). The British Infection Society recommends that all patients from endemic countries be screened for *Strongyloides* before commencement of immunosuppressives, including corticosteroids (23). It seems reasonable such guidelines should exist for Canada as well.

The recent guidelines published by the Canadian Collaboration for Immigrant and Refugee Health recommend screening newly arriving refugees from low-income countries in Southeast Asia and Africa with serology for strongyloidiasis and treating all who tested positive with ivermectin (first line) or albendazole (if ivermectin is contraindicated) (24). This may be further confounded by a widespread perception among the majority of physicians that eosinophilia constitutes evidence of parasitic infection. An argument can be made that with a falling prevalence of strongyloidiasis and the potential morbidity of unrecognized chronic infection, as well as lack of utility of eosinophilia as a predictor of the disease, it may be more cost effective to treat all newly arriving refugees from Africa only. Treatment with ivermectin, the drug of choice, is of short duration, highly effective (number needed to treat = 2, 95% CI approximately 1 to 3) with few unfavourable side effects (24).

Another important issue is to raise awareness of severe limitations of eosinophilia as a marker for strongyloidiasis when managing patients who are either immunocompromised, or about to start immunosuppressive therapy. This is particularly important in view of the fact that quite often travel history is collected for the periods not extending beyond the preceding two to three years.

The present study confirms that eosinophilia is a poor predictor of *Strongyloides* infection ($P=0.05$) (5,14). History of residence in Africa or Southeast Asia (from birth or in refugee camps) proved to be a significantly better predictor of *Strongyloides* seropositivity ($P=0.004$ and

P=0.002, respectively) and, thus, infection. Considering the risk of dissemination and nosocomial infections, the cost effectiveness of routine screening for strongyloidiasis versus empirical treatment of refugees arriving from South/Southeast Asia and Africa needs to be re-evaluated.

ACKNOWLEDGEMENTS: Prenilla Naidu has not received any financial assistance for this project and has no conflicts of interest. Dr Stephanie K Yanow has not received any financial assistance for this project and has no conflicts of interest. Dr Kinga T Kowalewska-Grochowska has not received any financial assistance for this project and has no conflict of interest. Dr Kowalewska-Grochowska and Dr Stephanie K Yanow received a University Hospital Foundation Medical Research grant for another project from which some data were used for this project. The authors thank Diane Grice and Dr Valerie Krinke from the New Canadians Clinic, Dr Stan Houston, Department of Infectious Diseases, Faculty of Medicine, University of Alberta and Alberta Health Services for access to medical files.

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