Helminths: an unrecognised disease burden prevalent among migrants in the gastroenterology clinic

P J Smith,^{1,2} B Theis,¹ S McCartney,¹ M Brown^{1,3,4}

¹Department of Gastroenterology, University College London Hospital, London, UK

²Department of Medicine, University College London, London, UK

³Hospital for Tropical Diseases, London, UK

⁴London School of Hygiene and Tropical Medicine, London, UK

Correspondence to

Dr P J Smith, Centre for Molecular Medicine, Rayne Institute, 5 University Street, London WC1E 6JJ, UK; pjsmith@doctors.org.uk

Accepted 23 November 2010
Published Online First
23 December 2010

Objective To estimate the prevalence of, and implement a diagnostic strategy for, imported helminth infection in the gastroenterology clinic.

Design A retrospective study of eosinophil count and probable tropical exposure (phase I) followed by a prospective study of parasitological investigation (phase II).

Setting Gastroenterology service of an inner London hospital.

Patients Adult patients newly attending general gastroenterology and inflammatory bowel disease clinics.

Interventions In phase I, evidence of undiagnosed helminth infection was sought by analysing patient records for associations between eosinophil count and ethnicity. In phase II, a UK guideline for investigation of eosinophilia in migrants was implemented and diagnostic yield determined.

Main outcome measures In phase I, prevalence of eosinophilia was determined; in phase II, helminth prevalence and degree of eosinophilia before and after treatment were reported. Information on symptomatic response to treatment was recorded. Ethnicity was used as a proxy measure for tropical exposure.

Results 426 new patients attended in a 12 month period. Eosinophilia was present in 27 (6.3%). 10/27 (37.0%) patients with eosinophilia were of African or Asian ethnicity whereas only 20% (85/426) of patients overall were from these ethnic groups ($\chi^2=5.27$, $p=0.02$). Following implementation of the protocol, 25/36 migrants with eosinophilia attended for parasitological investigations. Helminth infection was diagnosed in 10/25 (40%). Strongyloidiasis (six patients) and schistosomiasis (three patients) were the most common diagnoses. Median eosinophil count was $1.06 \times 10^9/l$ in those with helminths and $0.58 \times 10^9/l$ in those without ($p=0.004$). Eosinophil counts normalised in, and symptomatic improvement was reported by, most patients after treatment.

Conclusions Eosinophilia is associated with African or Asian ethnicity in an inner city gastroenterology service. This association is

probably explained by imported helminths, which are prevalent in this setting, may be a cause of gastrointestinal symptoms and is easily diagnosed and treated by standard protocols.

Introduction

Helminths are among the most prevalent gastrointestinal pathogens.¹ The global disease burden due to these infections is greatest among populations who are heavily exposed in low income countries in the tropics. However, some infections may persist for decades after migration from endemic countries.² Presentation to secondary and tertiary care settings with symptomatic disease belies a wider prevalence of asymptomatic infection among large migrant populations, particularly in inner city areas.^{3–8} Helminth infections are a common cause of eosinophilia. Studies suggest that >50% of migrants from endemic countries with peripheral eosinophilia harbour helminths.^{3–9} One prevalent intestinal nematode with a wide geographical distribution is *Strongyloides stercoralis*, which may disseminate following iatrogenic immunosuppression, with fatality rates as high as 80%.¹⁰ As immunosuppressive medications are commonly used within gastroenterology clinics, these patients are an ‘at risk’ population.^{11–12} This risk can be mitigated by screening and treating patients before immunosuppression. Disseminated infection is rare but diagnosis of chronic infection is warranted, even in immunocompetent hosts because it is associated with a range of non-specific gastrointestinal manifestations.^{13–17} Prompt diagnosis and treatment may therefore reduce expensive and invasive cycles of unnecessary investigations within outpatient clinics. We used a screening strategy for the parasitological investigation of eosinophilia, which was developed in our hospital, and forms the basis for a recently published national guideline.^{3–18}

Appropriate investigation of eosinophilia is based on the geographical region from which the person has migrated:

- ▶ All 'tropics' (Africa, Asia and Caribbean)—microscopy of concentrated stool for 'ova, cysts and parasites', charcoal culture for *Strongyloides* (if available) and *Strongyloides* serology
- ▶ All of Africa—above investigations, in addition to microscopy of terminal urine, *Schistosoma* and filaria serology
- ▶ West Africa—all of the above investigations in addition to referral for specialist filarial investigations.

To explore the prevalence of helminthiasis within a gastroenterology service of an inner London hospital, we investigated the associations between eosinophilia and migration status in the outpatient clinic. Following this, we implemented a modified screening strategy to identify and treat helminth infection in our service.

Method

Study site

This study was performed within University College London Hospital gastroenterology clinics. Patient computerised records were studied from all general gastroenterology and inflammatory bowel disease (IBD) clinics between January 2007 and August 2008.

Study design

We performed this study in two separate phases.

Phase I

We analysed a retrospective cohort comprising consecutive new attenders attending general gastroenterology clinics over a 12 month period between January 2007 and January 2008. Data were taken from the computerised hospital patient record relating to ethnicity and eosinophil count. Ethnicity was used as the best available proxy for migrant status as country of birth was rarely recorded. Travel history was also sought from referral or clinic letters. Patients without two full blood count results were excluded. Peripheral eosinophilia was defined as a raised absolute eosinophil count ($>0.4 \times 10^9/l$) on at least two occasions. Associations between presence of eosinophilia and ethnicity (as a binary variable) were analysed using a χ^2 test.

Phase II

Following this analysis, we introduced an evidence based protocol for efficient parasitological diagnosis in patients with eosinophilia. Outpatient clinic staff were trained appropriately. Patients not screened at clinic visits were invited to re-attend. Parasitological results were analysed for all migrants with eosinophilia attending general and inflammatory bowel disease clinics between April and July 2008. Those with eosinophilia and confirmed helminth infections were provided with appropriate treatment as per our Trust protocols. Post-treatment eosinophil counts were recorded from the computerised patient record. Assessment of clinical symptoms was obtained before

and after treatment through reading the outpatient clinic letters. Patients were ranked as 'no improvement', 'some improvement' and 'improvement'. Where this information was not recorded, patients were contacted and asked to rank their symptoms in comparison with their pretreatment visit. Associations between level of eosinophilia, ethnicity and helminth infections were explored. Information on symptoms was examined for evidence of improvement following antihelminth treatment.

Results

In the retrospective study, data were available for 426 patients' first attendance at a gastroenterology clinic. Eosinophilia on two or more occasions was identified in 27 (6.3%). Ten of 27 (37.0%) patients with eosinophilia were of African or Asian ethnicity whereas only 20% (85/426) of patients overall were from these ethnic groups ($\chi^2=5.27$, $p=0.02$).

Following the introduction of the diagnostic protocol, 36 patients of African, Caribbean or Asian ethnicity (21 male vs 15 female) with persistent eosinophilia ($>0.4 \times 10^9/l$ on two or more occasions) attended in the subsequent 4 months. Eleven had inflammatory bowel disease and 25 patients had a variety of gastrointestinal symptoms. African and Bangladeshi ethnicities were most prevalent, reflecting local population statistical data.¹⁹ Parasitological investigations were performed according to the protocol in 25 (69%) patients. The remaining 11 patients did not attend for further investigation, despite written invitation. Of the 25 screened, helminth infection was diagnosed in 10 (40%). Six (24%) had positive *Strongyloides* serology, three (12%) positive *Schistosoma* serology and one patient had trichuris eggs identified in stool microscopy (see table 1). Median eosinophil count was higher in those with a parasitological diagnosis ($p=0.004$, Mann-Whitney U test).

Among the 10 patients diagnosed with helminth infections, five were of African, two Bangladeshi, one Caribbean and two of non-specified Asian ethnicity. A summary of these patients is seen in table 2. The range

Table 1 Summary of parasitological investigations

	Results of parasitological investigations
Overall parasitological investigations performed	25/36 (69%)
Among patients investigated for helminths	
Total helminth infections diagnosed	10/25 (40%)
Positive <i>Strongyloides</i> serology*	6/25 (24%)
Positive <i>Schistosoma</i> serology	3/25 (12%)
Positive stool microscopy†	1/25 (4%)
Median eosinophil count in positive group	$1.06 \times 10^9/l$
Median eosinophil count in negative group	$0.58 \times 10^9/l$
p value (Mann-Whitney U test)	$p=0.004$

*Including one patient then found to have detectable larvae in stool.

†Trichuris isolated in the stool.

Table 2 Summary of patients with diagnosed helminthiasis

Patient	Ethnicity	Past medical history	Symptoms in clinic before diagnosis	Helminth identified	Pretreatment absolute eosinophil count ($\times 10^9/l$)	Post-treatment absolute eosinophil count ($\times 10^9/l$)	Symptoms after treatment
A	African	UC	Diarrhoea	<i>Schistosoma</i>	0.71	0.43	Improvement
B	African	Nil	Dyspepsia	<i>Strongyloides</i>	1.64	0.45	Improvement
C	African	Nil	RUQ pain	<i>Schistosoma</i>	0.62	0.25	No improvement
D	Asian not specified	Eosinophilic colitis	Diarrhoea	<i>Strongyloides</i>	1.2	N/A	Some improvement
E	Bangladeshi	UC	Diarrhoea	<i>Strongyloides</i>	1.12	0.34	Some improvement
F	Afro-Caribbean	UC	Dyspepsia and diarrhoea	<i>Strongyloides</i>	1.45	0.16	Some improvement
G	African	Pernicious anaemia	PR bleeding	<i>Schistosoma</i>	0.5	0.55	Improvement
H	Bangladeshi	Iron deficiency anaemia	Dyspepsia	<i>Trichuris</i>	2.96	0.08	Improvement
I	Asian not specified	Iron deficiency anaemia	Dyspepsia	<i>Strongyloides</i>	0.77	0.29	Some improvement
J	African	Prostate cancer, diverticular disease	Diarrhoea	<i>Strongyloides</i>	1.0	0.11	Some improvement

PR, per rectum; RUQ, right upper quadrant; UC, ulcerative colitis.

Figure 1 Absolute eosinophil counts ($\times 10^9/l$) of patients with helminth infections both before and after treatment. Post-treatment there was resolution of eosinophilia (absolute count $< 0.45 \times 10^9/l$) in eight of the nine patients with an available eosinophil count at follow-up ($p < 0.01$, Wilcoxon matched pairs signed ranks test).

of eosinophilia in this group was between 0.5 and $2.96 \times 10^9/l$. Helminth infection was suspected clinically in only one patient with eosinophilic colitis, who had confirmed *Strongyloides* infection (patient D). One patient (patient E) received a course of oral corticosteroids just prior to a diagnosis of *Strongyloides* for a flare of ulcerative colitis. Post-treatment there was resolution of eosinophilia (absolute count $< 0.45 \times 10^9/l$) in eight of the nine patients with an available eosinophil count at follow-up ($p = 0.008$, Wilcoxon matched pairs signed ranks test) (see figure 1). Nine patients reported improvement in symptoms post-treatment.

Discussion

In our clinic, 40% of patients presumed to have been born in the tropics and systematically investigated for peripheral eosinophilia harboured a significant helminth infection. A parasitological diagnosis was more common in patients with higher eosinophil counts but diagnoses were also made in those with

only moderately raised eosinophil counts, reflecting evidence from other settings.^{3,9,17,20} Implementation of an evidence based protocol for appropriate parasitological investigations can identify and exclude important infections (eg, *Strongyloides* and *Schistosomiasis*), which are prevalent in these patients and may explain their presenting symptoms. Hence in healthcare settings serving populations with a high migrant prevalence, active case finding and treatment of helminth infections may be appropriate. It is important to consider that eosinophilia may also be secondary to a number of non-tropical diagnoses such as Churg–Strauss and polyarteritis, so these should also be considered. However, studies have demonstrated a helminthic aetiology for eosinophilia in 50% patients with a travel history.³

To avoid overinvestigation of patients for whom transient eosinophilia might be a stochastic phenomenon, we defined eosinophilia, and investigated for helminths, if the absolute eosinophil count was raised on at least two occasions ($>0.4 \times 10^9/l$). This may have underestimated the true burden of helminth infection in the clinic. Diagnosis was made principally on the basis of serological tests, with eight out of 10 diagnoses based on serological testing alone (five *Strongyloides* serology and three schistosomiasis serology) without microscopy confirmation. It is well recognised that *Strongyloides* serology may cross react with filarial infection and other nematodes,²¹ and may remain elevated in patients with cleared infection.¹⁷ However, for several reasons the infections diagnosed in our study are likely to reflect true infection. Firstly, those with positive *Strongyloides* serology had no clinical or epidemiological features to suggest filarial infection; secondly, among those treated for helminths, almost all patients demonstrated normalisation of a previously sustained eosinophilia. Furthermore, studies with longer follow-up do demonstrate normalisation of *Strongyloides* and decline in *Schistosoma* serology following treatment.^{20,22,23} The low prevalence of microscopy confirmed diagnosis is to be expected, given the limited diagnostic yield of single stool samples in proven helminth infection.^{24–26} In a cohort of patients with chronic *Strongyloides* infections, *S. stercoralis* larvae were demonstrated in most seropositive patients when a sufficient number of fresh stools were examined.²⁷

Ethnicity was used in this study as a proxy marker for endemic exposure to helminths. This was used because of lack of documentation regarding the patient's birth and travel history within the computerised notes, and this self-assessment of ethnicity appeared to provide a reasonable assumption on country of birth. A recent audit within our hospital revealed that >80% of patients reporting black African ethnicity were born in sub-Saharan Africa (M Brown, unpublished data). If anything, misclassification of migrant status by

ethnicity in this study is likely to have resulted in an underestimation of the true association between eosinophilia and migration.

In this study, the majority of patients with diagnosed helminth infection had non-specific gastrointestinal symptoms for which no cause had been found. Non-specific gastrointestinal symptoms often lead to long and expensive investigation cycles. The diagnosis could easily be missed in primary and secondary care,²⁸ leading to significant morbidity and costs associated with unnecessary investigations and ineffective treatment. Current protocols for investigation of gastrointestinal symptoms do not incorporate screening for clinically important helminth infections in migrants before referral for more expensive or invasive investigations. While the evidence for a causal role of chronic helminth infection in gastrointestinal symptoms is debated, some studies, and our clinical experience, recognise clear symptom associations with *Strongyloides*.^{2,13–17,29} Of note in this small and unblinded study the majority of patients reported an improvement in their symptoms at their follow-up visit. Clearly more rigorous studies should be designed to explore a causal relationship.

In studies of Asian migrants, up to 70% have been found to harbour *Strongyloides*.⁸ Prevalence studies in other settings suggest a similar rationale for screening all migrants for these infections although there are no adequate data to support this approach in UK healthcare settings. Cost effectiveness studies^{30–31} in the USA have demonstrated that empirical treatment of migrants is an appropriate intervention to prevent the rare circumstance in which subsequent immunosuppression may lead to disseminated strongyloidiasis, which has such a high case death rate. Three of our helminth infected patients with eosinophilia had inflammatory bowel disease and hence may have had exposure to corticosteroids at some point in their treatment. However, eosinophilia is frequently absent in proven helminth infection. In other studies from our hospital, 56% of patients with schistosomiasis and 19% of patients with strongyloidiasis had normal eosinophil counts.^{17,32} Indeed, eosinophil counts are often normal in patients with disseminated strongyloidiasis or in helminth infected subjects already receiving immunosuppressive medication, a phenomenon well established in animal models.^{11,33} Screening all patients who have lived in the tropics for *Strongyloides* infection, who are due to be immunosuppressed, is recommended by some guidelines³⁴ but the diagnostic yield among patients without eosinophilia is not known (and probably quite low) and further studies are warranted. A safe and pragmatic approach to avoid disseminated strongyloidiasis would be targeted screening, following the national guideline, of all migrants in secondary care clinics as part of local preimmunosuppression protocols. Attention paid to the eosinophil count during routine investigations will identify other patients

Box 1 What is already known?

- ▶ Chronic helminth infection is widespread in the tropics and may persist for decades after migration to low prevalence countries.
- ▶ Infection is often asymptomatic but has been associated with gastrointestinal symptoms and occasionally may cause severe disease in patients receiving iatrogenic immunosuppression.
- ▶ Infection is frequently associated with peripheral eosinophilia which is often unrecognised in primary and secondary care.

Box 2 What are the new findings?

- ▶ Peripheral eosinophilia was associated with African or Asian ethnicity in an inner London gastroenterology clinic serving a population with a high migrant prevalence.
- ▶ Implementation of an evidence based screening protocol for investigating eosinophilia in migrants detected helminth infection in the majority of screened patients.
- ▶ Anthelmintic treatment resulted in symptomatic improvement in many of these patients under investigation for non-specific gastrointestinal symptoms.

Box 3 How might it impact on clinical practice in the foreseeable future?

- ▶ While the evidence for symptomatic benefit of treatment in patients with chronic helminth infection is unclear, opportunistic screening in secondary care to prevent future severe manifestations of disease is safe and inexpensive.
- ▶ New UK recommendations for investigation of eosinophilia should be incorporated into standard gastroenterological practice.

for whom simple parasitological investigations may reduce overinvestigation for non-specific gastrointestinal symptoms and prevent future morbidity.

Acknowledgements The authors would like to thank the gastroenterology clinic nurses and doctors who helped with this study, and the Parasitology Department at the Hospital for Tropical Diseases. This work was undertaken at UCLH/UCL which received a proportion of funding from the Department of Health's NIHR Biomedical Research Centres funding scheme.

Competing interests None.

Provenance and peer review Not commissioned; externally peer reviewed.

References

1. Hotez PJ, Brindley PJ, Bethony JM, *et al.* Helminth infections: the great neglected tropical diseases. *J Clin Invest* 2008;118:1311–21.
2. Gill GV, Welch E, Bailey JW, *et al.* Chronic Strongyloides stercoralis infection in former British Far East prisoners of war. *QJM* 2004;97:789–95.
3. Whetham J, Day JN, Armstrong M, *et al.* Investigation of tropical eosinophilia; assessing a strategy based on geographical area. *J Infect* 2003;46:180–5.
4. Al-Hasan MN, McCormick M, Ribes JA. Invasive enteric infections in hospitalized patients with underlying strongyloidiasis. *Am J Clin Pathol* 2007;128:622–7.
5. Bierman WF, Wetsteyn JC, van Gool T. Presentation and diagnosis of imported schistosomiasis: relevance of eosinophilia, microscopy for ova, and serology. *J Travel Med* 2005;12:9–13.
6. Caruana SR, Kelly HA, Ngeow JY, *et al.* Undiagnosed and potentially lethal parasite infections among immigrants and refugees in Australia. *J Travel Med* 2006;13:233–9.
7. Concha R, Harrington W Jr, Rogers AI. Intestinal strongyloidiasis: recognition, management, and determinants of outcome. *J Clin Gastroenterol* 2005;39:203–11.
8. Gyorkos TW, Genta RM, Viens P, *et al.* Seroepidemiology of Strongyloides infection in the Southeast Asian refugee population in Canada. *Am J Epidemiol* 1990;132:257–64.
9. Schulte C, Krebs B, Jelinek T, *et al.* Diagnostic significance of blood eosinophilia in returning travelers. *Clin Infect Dis* 2002;34:407–11.
10. Marcos LA, Terashima A, Dupont HL, *et al.* Strongyloides hyperinfection syndrome: an emerging global infectious disease. *Trans R Soc Trop Med Hyg* 2008;102:314–18.
11. Fardet L, Gnreau T, Poirot JL, *et al.* Severe strongyloidiasis in corticosteroid-treated patients: case series and literature review. *J Infect* 2007;54:18–27.
12. Ben-Horin S, Barshack I, Chowers Y, *et al.* Flare-up of ulcerative colitis after systemic corticosteroids: a strong case for Strongyloides. *World J Gastroenterol* 2008;14:4413–15.
13. Milder JE, Walzer PD, Kilgore G, *et al.* Clinical features of Strongyloides stercoralis infection in an endemic area of the United States. *Gastroenterology* 1981;80:1481–8.
14. Berk SL, Verghese A, Alvarez S, *et al.* Clinical and epidemiologic features of strongyloidiasis. A prospective study in rural Tennessee. *Arch Intern Med* 1987;147:1257–61.
15. Grove DI. *Strongyloidiasis. A major roundworm infection of man*. London: Taylor and Francis, 1989.
16. Pelletier LL Jr. Chronic strongyloidiasis in World War II Far East ex-prisoners of war. *Am J Trop Med Hyg* 1984;33:55–61.
17. Sudarshi S, Stmpfle R, Armstrong M, *et al.* Clinical presentation and diagnostic sensitivity of laboratory tests for Strongyloides stercoralis in travellers compared with immigrants in a non-endemic country. *Trop Med Int Health* 2003;8:728–32.
18. Checkley AM, Chiadini PL, Dockrell DH, *et al.* Eosinophilia in returning travellers and migrants from the tropics: UK recommendations for investigation and initial management. *J Infect* 2010;60:1–20.
19. Office for National Statistics, 2004. Neighbourhood statistics: Camden, London. <http://neighbourhood.statistics.gov.uk> (accessed 8 August 2010).
20. Loutfy MR, Wilson M, Keystone JS, *et al.* Serology and eosinophil count in the diagnosis and management of strongyloidiasis in a non-endemic area. *Am J Trop Med Hyg* 2002;66:749–52.
21. Conway DJ, Bailey JW, Lindo JF, *et al.* Serum IgG reactivity with 41-, 31-, and 28-kDa larval proteins of Strongyloides stercoralis in individuals with strongyloidiasis. *J Infect Dis* 1993;168:784–7.
22. Karunajeewa H, Kelly H, Leslie D, *et al.* Parasite-specific IgG response and peripheral blood eosinophil count following albendazole treatment for presumed chronic strongyloidiasis. *J Travel Med* 2006;13:84–91.
23. Doenhoff MJ, Wheeler JG, Tricker K, *et al.* The detection of antibodies against Schistosoma mansoni soluble egg antigens (SEA) and CEF6 in ELISA, before and after chemotherapy. *Ann Trop Med Parasitol* 2003;97:697–709.

24. **Brown M**, Bukusuba J, Hughes P, *et al.* Screening for intestinal helminth infestation in a semi-urban cohort of HIV-infected people in Uganda: a combination of techniques may enhance diagnostic yield in the absence of multiple stool samples. *Trop Doct* 2003;33:72–6.
25. **Utzinger J**, Booth M, N'Goran EK, *et al.* Relative contribution of day-to-day and intra-specimen variation in faecal egg counts of *Schistosoma mansoni* before and after treatment with praziquantel. *Parasitology* 2001;122:537–44.
26. **Jongwutiwes S**, Charoenkorn M, Sitthichareonchai P, *et al.* Increased sensitivity of routine laboratory detection of *Strongyloides stercoralis* and hookworm by agar-plate culture. *Trans R Soc Trop Med Hyg* 1999;93:398–400.
27. **Genta RM**, Weesner R, Douce RW, *et al.* Strongyloidiasis in US veterans of the Vietnam and other wars. *JAMA* 1987;258:49–52.
28. **Boulware DR**, Stauffer WM, Hendel-Paterson BR, *et al.* Maltreatment of *Strongyloides* infection: case series and worldwide physicians-in-training survey. *Am J Med* 2007;120:545.e1–8.
29. **Gill GV**, Bell DR. Strongyloides stercoralis infection in former Far East prisoners of war. *BMJ* 1979;2:572–4.
30. **Muennig P**, Pallin D, Sell RL, *et al.* The cost effectiveness of strategies for the treatment of intestinal parasites in immigrants. *N Engl J Med* 1999;340:773–9.
31. **Muennig P**, Pallin D, Challah C, *et al.* The cost-effectiveness of ivermectin vs. albendazole in the presumptive treatment of strongyloidiasis in immigrants to the United States. *Epidemiol Infect* 2004;132:1055–63.
32. **Whitty CJ**, Mabey DC, Armstrong M, *et al.* Presentation and outcome of 1107 cases of schistosomiasis from Africa diagnosed in a non-endemic country. *Trans R Soc Trop Med Hyg* 2000;94:531–4.
33. **Boyer MH**, Basten A, Beeson PB. Mechanism of eosinophilia. 3. Suppression of eosinophilia by agents known to modify immune responses. *Blood* 1970;36:458–69.
34. **Rahier JF**, Ben-Horin S, Chowers Y, *et al.* European evidence-based consensus on the prevention, diagnosis and management of opportunistic infections in inflammatory bowel disease. *J Crohns Colitis* 2009;3:47–91.