
Chronic *Strongyloides stercoralis* infection in former British Far East prisoners of war

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Summary

Background: Chronic infections with the nematode worm *Strongyloides stercoralis* can occur in former WWII Far East prisoners of war (FEPOWs). The condition may be asymptomatic, but frequently causes a characteristic urticarial 'larva currens' rash. Under conditions of immunosuppression (particularly systemic corticosteroid treatment) potentially fatal dissemination of larvae ('hyperinfection') may occur.

Aim: To review our total experience of strongyloidiasis in former FEPOWs, and investigate its prevalence, characteristics and risk factors.

Design: Retrospective case series.

Methods: We reviewed 2072 records of all FEPOWs seen at the Liverpool School of Tropical Medicine, 1968–2002. Cases with strongyloidiasis were compared with non-infected controls.

Results: There were 248 (12%) with strongyloidiasis. Diagnostic features included larva currens rash (70%), eosinophilia (66%), positive faecal culture (30%), positive faecal microscopy (26%), and

positive serology (64%). Mean (\pm SD) age of cases was 65 ± 7 years, and as expected, their blood eosinophil counts were significantly higher than controls (775 vs. $238 \times 10^6/l$, $p < 0.001$). Captivity on the Thai-Burma Railway (vs. elsewhere) was significantly associated with strongyloidiasis (78% cases vs. 40% controls, OR 4.19, CI 2.70–6.81, $p < 0.001$). In terms of prevalence, strongyloidiasis occurred in 166/1032 men imprisoned on the Burma Railway (16.1%). Malaria (88% vs. 69%, $p < 0.001$) and tropical ulcer (53% vs. 42%, $p < 0.02$) were more common amongst cases than controls, probably because these diseases were very common on the Burma Railway.

Discussion: *S. stercoralis* infection is common amongst ex-FEPOWs, particularly those from the Thai-Burma Railway project. It is usually characterized by a 'larva currens' rash and marked eosinophilia. The condition is eminently treatable, and continued diagnostic surveillance is needed, if cases of potentially fatal hyperinfection are to be avoided.

Introduction

The fall of Singapore in February 1942 resulted in the capture of over 100 000 Allied troops—predominantly British, Dutch and Australian. They were held in Changi Jail on the outskirts of the city. Some stayed here for the duration of captivity, but in September 1942, large contingents (including 50 000 British prisoners) left Singapore in cattle

trucks for Thailand. There, they formed a slave labour force to build the notorious Thai-Burma Railway: 400 km of track over mountainous jungle from Ban Pong in Thailand to Thanbyuzayat in Burma. The project was completed in October 1943, at a cost of 13 000 British lives (and considerably more of the local Asiatic labour). The railway aimed

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to provide a troop and equipment transport system for a planned invasion of India, but this never materialized.

British troops were imprisoned in other parts of South-East Asia and the Far East (e.g. Hong Kong, Java, Formosa, Japan), but the largest numbers were imprisoned in Singapore or on the Burma Railway. In all areas of imprisonment, work was hard, food poor and scarce, and medical supplies scant. Malaria and dysentery (both amoebic and bacillary) were common, as well as cholera, tropical ulcers, and both 'wet' and 'dry' forms of beriberi. Prisoners on the Burma Railway fared particularly badly—devastating forms of nutritional deficiency syndromes were seen, and penetrating tropical ulcers were a frequent cause of amputation.^{1,2}

Following release, a variety of adverse health effects have been described in surviving ex-Far East Prisoners of War (FEPOWs). These include significant long-term psychiatric syndromes in up to one-third,^{3,4} as well as increased prevalence of osteoarthritis, duodenal ulceration and chronic obstructive pulmonary disease (COPD). There is also evidence of increased mortality from tuberculosis and cirrhosis in the early post-war years.⁵ With regard to cirrhosis, it is of interest that many years later, very high levels of hepatitis B serological markers were demonstrated in FEPOW survivors.⁶ There is also evidence of persistence of some tropical diseases after release.⁷ Occasional cases of quartan malaria, tropical ulcer, beriberi cardiomyopathy and intestinal amoebiasis have been found.^{7–9} Persisting nutritional neuropathies are well-described and occur in at least 5% of FEPOWs—usually in the form of painful lower-limb neuropathy, or reduced visual acuity due to nutritional amblyopia.^{10,11} The most frequent and documented of the long-term infective sequelae of the FEPOW experience, however, is continued infection with the nematode worm *Strongyloides stercoralis*.⁸

Strongyloidiasis is common in the tropics and subtropics. A larval cycle in the soil results in human infection by direct penetration of filariform larvae through intact skin, usually of the foot. Migration of larvae results in a classic skin 'creeping eruption' or 'larva currens'.^{8,11} From the lungs, larvae migrate up the trachea and to the gut. Rhabditiform larvae are excreted back to the soil, and an 'auto-infective' cycle can occur, with larval penetration of the lower large bowel or perianal skin, which then recycle in the human host potentially indefinitely, without new reinfection.^{11,12} As well as the larva currens rash, abdominal pain and diarrhoea can occur (although these symptoms are infrequent in the chronic auto-infective syndrome). If host immunosuppression

occurs (for example because of steroid treatment), patients with unsuspected strongyloidiasis can develop a 'hyperinfective syndrome', with massive larval invasion of the peritoneum, liver, lungs and central nervous system—often with bacterial peritonitis, meningitis and septicaemia.^{12,13} Mortality is high, and detection of *Strongyloides* infection is therefore highly important.

Chronic strongyloidiasis in ex-FEPOWs was first described by Caplan in 1949 in the UK.¹⁴ Further British descriptions were made in 1977;¹⁵ a larger series was reported by our group in 1979;¹¹ and a further group of cases from the UK was published in 1988.¹⁶ Other reports have concerned Australian,¹⁷ American,¹⁸ and Canadian¹⁹ ex-FEPOWs, as well as veterans of the WWII Burma Campaign^{20,21} and the Vietnam conflict.²² Former FEPOWs are now of advanced years and declining numbers. Many have been investigated at the Liverpool School of Tropical Medicine, but very few are nowadays seen. We have therefore collated our total experience, and report it here.

Methods

Patient details

Between 1968 and 2002, inclusive (35 years), a total of 2072 ex-FEPOWs were investigated. All were males formerly imprisoned by the Japanese in various parts of the Far East and South-East Asia, for 3½ years between 1942 and 1945. The majority were assessed via a British government initiative to arrange tropical investigation assessments for war pension purposes. They were either admitted to an in-patient tropical unit for 3–5 days, or investigated intensively as out-patients. All case records were examined, and duplicates were excluded (as some men were investigated on more than one occasion). Those in whom a diagnosis of strongyloidiasis was made were extracted, and a control series collected by taking the next FEPOW in alphabetical order for the particular year of assessment, in whom strongyloidiasis was not found. For cases, full diagnosis and clinical features of *Strongyloides* infection were noted; and for cases and controls blood eosinophilia was recorded, as well as location of imprisonment, diseases in captivity, and illness since repatriation in 1945. All information was entered onto an EPINFO-6 database.

Investigative methods

All men were fully assessed from both a general medical and tropical viewpoint. Parasitologically,

all had three fresh specimens of stool examined by direct microscopy, and after charcoal culture, by a technician experienced in the parasitological diagnosis of tropical infections. Up to 1985, a non-specific helminth complement fixation test (CFT) was performed, but after this date a specific and sensitive enzyme-linked immunosorbent assay (ELISA) was used.^{23–25} A few patients had duodenal secretions examined by the 'duodenal thread' technique.²⁶

Diagnostic criteria

Methods of diagnosis varied during the 35-year period of study, but criteria were generally as in our previous reports.^{11,15} Firm diagnosis was made if stool (either by microscopy of culture) or duodenal fluid was positive for strongyloid parasites. The early CFT was taken as only supportive evidence, but the later ELISA test used from 1985, was taken as diagnostic despite negative stool examinations, which are notoriously unreliable.¹⁷ The ELISA was developed by ourselves, using *S. stercoralis* antigen. When tested in a group of FEPOWs, we have shown the assay to be 99% specific and 97% sensitive.²⁴ Eosinophilia in ex-FEPOWs is highly suggestive of *Strongyloides* infection,²⁵ but was not considered diagnostic alone. Prior to availability of the ELISA assay, however, definite eosinophilia in the presence of a classical larva currens rash was accepted diagnostically.^{11,15}

Statistical methods

The EPIINFO-6 package was used for statistical analysis. Eosinophil counts were not normally distributed, and medians with inter-quartile ranges were calculated, and Mann-Whitney U tests used for comparison. Confidence intervals were estimated for proportionate data and cases and controls compared by Fisher's exact test. A *p* value of <0.05 was taken as showing statistical significance.

Results

Prevalence

Of the 2072 ex-FEPOWs seen over the 35-year period, 248 met diagnostic criteria for strongyloidiasis, giving an overall prevalence of 12.0%. Past experience suggested that prevalence may be higher in those who worked on the Thai-Burma Railway project.²⁷ We therefore analysed this group separately, and found 166 cases amongst the 1032 ex-FEPOWs who had worked on the railway: a prevalence of 16.1%. At diagnosis, the mean age of

strongyloidiasis patients was 65 ± 7 (SD) years, and the time from repatriation (1945) to diagnosis was 37 ± 6 (SD) years.

Clinical and diagnostic features

These are outlined in Table 1. Nearly three-quarters of patients had the classic larva currens rash. This is an intensely itchy, serpiginous, rapidly-advancing urticarial wheal; occurring intermittently and in crops over the neck, trunk, shoulders, buttocks and thighs. The rash was often witnessed during admissions to the Liverpool Tropical Unit (Figure 1). Significant eosinophilia occurred in two-thirds of ex-FEPOWs, and positive serology in a similar number. Stool microscopy (with or without culture) was relatively insensitive, as is well known.^{11,16,17} Abdominal symptoms were relatively uncommon.

Location of captivity

Comparison of location of captivity between cases and controls is shown in Table 2. It can be seen that there was a positive association ($p < 0.0001$) with work on the Thai-Burma Railway, but not for other areas of captivity (including areas of Thailand apart from the railway project).

Disease in captivity

Table 2 also shows that a reported history of malaria ($p < 0.001$) and tropical ulcer ($p < 0.02$) was significantly more common amongst patients with strongyloidiasis.

Disease after repatriation

No statistical association was found between ex-FEPOWs with strongyloidiasis and other diseases

Table 1 Clinical and diagnostic features amongst ex-FEPOWs with strongyloidiasis

Feature	Present in
Typical larva currens rash	70%
Eosinophilia*	66%
Positive ELISA/CFT	64%
Positive stool culture	30%
Positive stool microscopy	26%
Gastro-intestinal symptoms**	16%

Data are presented for 172 patients for whom full information was available. Nine patients also had duodenal thread tests, of which three were positive. *Defined as $>500 \times 10^6/l$ ($n=143$). **Intermittent pain and/or diarrhoea of otherwise unexplained cause.



Figure 1. The typical strongyloid rash or 'larva currens' (creeping eruption).

Table 2 Comparison between ex-FEPOWs with (cases) and without (controls) strongyloidiasis, in relation to location of captivity, disease in captivity, and illness after release

Category	Cases	Controls	OR	95%CI	<i>p</i>
<i>Location of captivity (cases 213, controls 224)</i>					
Burma	78%	46%	4.19	2.70–6.50	<0.0001
Railway					
Thailand (other)	16%	14%	1.18	0.68–2.07	NS
Sumatra	11%	18%	0.54	0.30–0.97	NS
Hong Kong	0.5%	0.5%	0.08	0.00–0.02	NS
<i>Disease in captivity (cases 230, controls 220)</i>					
Malaria	88%	75%	2.49	1.45–4.28	<0.001
Dysentery	79%	75%	1.22	0.77–1.94	NS
Tropical ulcer	53%	42%	1.59	1.08–2.35	<0.02
Neuropathy	37%	44%	0.76	0.51–1.14	NS
Wet beriberi	70%	67%	1.10	0.73–1.68	NS
<i>Disease post-captivity (cases 230, controls 220)</i>					
Pulmonary TB	5%	2%	2.15	0.66–7.37	NS
Peptic ulcer	18%	13%	1.45	0.84–2.48	NS
Psychiatric disease	32%	35%	0.87	0.58–1.31	NS

There were 248 cases and controls, but numbers analysed are slightly less because of absence of relevant information in some records.

occurring after repatriation (reported at the time of investigation in Liverpool) (Table 2).

Treatment

This study was not designed to investigate treatment outcomes, which we have reported elsewhere.²⁸ In the present series, details of drug treatment were available for 220 infected POWs. Of these, 134 were treated with thiabendazole (61%), 67 with albendazole (31%), 18 with mebendazole (8%), and one with ivermectin.

Discussion

Our major finding was an overall prevalence rate for strongyloidiasis amongst UK ex-FEPOWs of 12.0%, increasing to 16.1% for those who worked on the Thai-Burma Railway. The reason for an increased prevalence on the railway project almost certainly relates to a high local presence of the disease,²⁹ probably due to the hot and humid conditions favouring the soil-based larval stages of the cycle. Additionally, FEPOWs working on the railway frequently had poor or no footwear, again favouring larval skin penetration by strongyloid filariform larvae. In our original survey of 602 Liverpool-based FEPOWs, published in 1979, we found a 15.0% overall prevalence of strongyloidiasis,¹¹ and in an extended series of 898 men (published in 1982), the rate was 13.0%.³⁰ The only other British report of strongyloidiasis in FEPOWs was by Hill in 1988.¹⁶ This was of a group of 500 men collected from various military and other British hospitals, and 78 (15.4%) had *Strongyloides* infection. These figures are broadly in agreement with the present survey results. However, a re-analysis of our 1979 series of 602 FEPOWs showed a wider (and again statistically significant) differential between strongyloidiasis prevalence amongst FEPOWs from the Burma Railway (21.4%) and those who had worked elsewhere (8.8%).²⁷

There have been studies from outside the UK reporting strongyloidiasis prevalence amongst FEPOWs. In Australia, Grove¹⁶ found *Strongyloides* infections in 44/160 FEPOWs (27.5%), all of whom had been imprisoned on the Burma Railway. In the USA, Pelletier¹⁷ found the condition in 52/142 FEPOWs (37.0%), again all from the Burma Railway. A Canadian study showed strongyloidiasis in only 4/694 FEPOWs (0.6%), but these FEPOWs were almost exclusively interned in Hong Kong, an area of low strongyloidiasis prevalence. A study of Dutch FEPOWs showed *Strongyloides* infection in 26/145 who had worked on the Burma Railway (17.9%), but none in a cohort of 56 FEPOWs from the Dutch East Indies.³¹

The geographical area of imprisonment is clearly the major factor accounting for these variable prevalence rates, with our results and those of others confirming the high risk from internment in Thailand and/or Burma. A further confounding factor may be the occurrence of *S. stercoralis* outside SE Asia. For example, the infection is well described in the southern and eastern USA,³² and this may partly account for the especially high rates reported in American FEPOWs.¹⁷ Indigenous cases have also been described from parts of Europe, though these

are mostly rare and sporadic.³³ Our large series reported here was over a much longer period of time than previous studies (35 years in total, up to the present day). There was considerable awareness of strongyloidiasis amongst the FEPOW community in the UK in the 1980s, and far fewer diagnoses have been made by us in the last decade. This may explain why our overall figures of prevalence are a little lower than our previous shorter-term studies, and surveys from other countries. Nevertheless, our figures are robust and substantial, and confirm a significant problem in Far East veterans.

A final reason for variations in reported prevalence figures is diagnostic technique. Strongyloidiasis is notoriously difficult to diagnose parasitologically. We used three separate stool samples, as do most other centres, but it is known that many more may be needed to make a diagnosis.³⁴ In the American FEPOW study, up to 12 stool samples were examined,¹⁷ and this diagnostic diligence may partially account for their high detection rate. Stool culture on a charcoal medium improves diagnostic yield.^{11,34,35} Examination of duodenal fluid also appears to be diagnostically better than faeces. Goka and colleagues³⁶ showed only a 33% sensitivity for faecal microscopy, but a sensitivity of 76% for duodenal fluid. The easiest way of sampling this fluid is via the 'duodenal thread' technique.²⁶ We used this in a small number of our patients (Table 1), but found it time-consuming and inconvenient; there were also supply problems with the thread and capsule. Peripheral blood eosinophilia, present in two-thirds of our patients, has been shown to be very suggestive of strongyloidiasis in FEPOWs²⁵ and other travellers returning from the tropics.³⁷ The indirect ELISA test has greatly helped diagnosis.^{24,38,39} In good hands, and with a reliable antigen, this assay is almost 100% sensitive and specific, and has superseded previous unreliable serological tests. A positive ELISA test, regardless of parasitological investigations, can be taken as evidence of strongyloidiasis quite sufficient to require treatment.

Our patients suffered from chronic *S. stercoralis* infections related to the auto-infective life cycle. This process can maintain infection indefinitely, despite the host being removed from an area of indigenous infection.⁴⁰ There is evidence that these chronic infections differ clinically from more acute infections. Though both forms can of course be asymptomatic, acute infection may be associated with diarrhoea and abdominal pain, with the larva currens rash being rare. Dysenteric and malabsorptive syndromes are also described. In chronic strongyloidiasis however, the creeping eruption is common, and bowel symptoms unusual and relatively mild⁴⁰ (16% of our patients, and only 5%

of our previous series¹¹). This marked difference in clinical presentations may relate to immunological differences in the acute and chronic forms of the infection. Acute infections are associated with a prompt serum IgE response, but our research has shown that FEPOWs with chronic strongyloidiasis have a markedly impaired response.⁴¹ This finding has been supported by Atkins and colleagues,⁴² who found that the immunological response to infection declined with age and probably infection duration. The implication is that chronic infection may be associated with hypersensitivity response down-regulation, and perhaps an acquired 'immunological tolerance', which may modify the clinical features of the disease.⁴¹ An additional, and more simplistic explanation for the frequency of larva currens, and the rarity of diarrhoea in chronic strongyloidiasis, may be that autoinfection results in more tissue larvae migrating from the lower bowel to the lungs (causing the larva currens rash).

Until the introduction of albendazole and ivermectin, traditional treatment for strongyloidiasis was with thiabendazole, and this was our practice until 1993 (from when albendazole has been our drug of choice). Thiabendazole is frequently ineffective, probably in at least one-third of patients, and is prone to troublesome side-effects (including nausea, vomiting, dizziness, and neuropsychiatric symptoms).^{35,43} Mebendazole is too poorly absorbed to be active against the tissue stages of strongyloidiasis.⁴⁴ Our experience with albendazole is that it has a 75% cure rate in FEPOWs after an initial course (400 mg twice daily for 3 days), and many non-responders are cured with a repeat course.²⁸ Side-effects are minimal. An albendazole dosage regimen of 400 mg daily is much less effective.⁴⁵ It is also known that ivermectin is highly effective.^{46,47}

The critical importance of the detection and adequate treatment of strongyloidiasis in FEPOWs, is that it prevents the risk of hyperinfection. It is likely that this may have occurred many times, and gone undiagnosed and unreported. An Australian FEPOW however was described in 1989 with a bronchogenic carcinoma, and who developed jejunal perforation and pneumonitis, both shown to be due to previously undiagnosed *S. stercoralis* infection.⁴⁸ The patient recovered with surgery, antibiotics and thiabendazole. Absence of septicaemia, multi-organ involvement and the patient's survival itself, make this case not typical of true hyperinfection. However, an earlier UK report in 1985 clearly was.⁴⁹ This concerned a British FEPOW with steroid-treated polymyositis, who died of definite hyperinfection (with Gram-negative septicaemia, *E. coli* meningitis, and pneumonia).

Larvae were found in widespread tissues. We have also recently described a case of disseminated strongyloidiasis in a former Far East soldier (not imprisoned) who was immunologically suppressed (steroid treatment and bronchogenic carcinoma). The infection was probably acquired in 1945, and was diagnosed just before death in 2002, 57 years later.⁵⁰

Strongyloidiasis continues to be a major problem in some endemic tropical and sub-tropical areas, and its association with HTLV-1 infection is a recent and problematic aspect of the disease.⁵¹ The infection is also seen in returning travellers from the tropics,³⁷ and still occasionally presents in the UK amongst former veterans of the Far East WWII conflict.⁵⁰ Indeed, the UK Chief Medical Officer has recently drawn attention to the condition in a publication circulated to all British doctors.⁵² Our results show that surveillance is particularly indicated amongst those who were imprisoned on the Thai-Burma Railway, and also that blood eosinophilia is strongly suggestive of *Strongyloides* infection in at risk individuals. As sero-diagnosis and treatment are now relatively straightforward, there is a case for screening surviving war veterans from South-East Asia, and certainly those from the Thai-Burma Railway project who have not already been assessed, using modern sero-diagnostic techniques.

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