Leading article – Tropical infection of the gastrointestinal tract and liver series

Strongyloidiasis: a conundrum for gastroenterologists

In 1876, Louis Normand, physician to the Naval Hospital of St Mandrier in Toulon, France, found a previously unrecognised worm in the stools of French troops who had been repatriated from Indochina with severe diarrhoea. These parasites were eventually shown to be larvae of a worm now called *Strongyloides stercoralis*.¹ Despite the fact that over 100 years have passed since its discovery, there is much about this parasite that remains enigmatic. This worm is unique among the commonly occurring helminth infections because it can replicate within the human host. Whereas, one hookworm larva or one roundworm egg becomes one adult worm, which dies after a year or so and the infection ends, one *Strongyloides* larva can multiply and has the potential to become many worms. This phenomenon fundamentally changes the nature and course of infection.

Life cycle

S. stercoralis has a complex life cycle (Figure). Infection is

Life cycle of *Strongyloides stercoralis*. Reproduced by permission from Grove DJ. Strongyloidiasis. In: Warren KS, Mahmoud AAF, eds. Tropical and geographical medicine. 2nd ed. New York: McGraw-Hill Information Services, 1990.

acquired when infective larvae in the soil, like those of hookworms, penetrate the intact skin. What happens then is a matter of debate. The traditional textbook view is that larvae pass by the circulation to the lungs where they break into the alveolar spaces, ascend the respiratory tree, are swallowed, and further their development in the small bowel.² An alternative hypothesis that has been advanced a number of times is the simpler idea that larvae may migrate directly from the skin to the duodenum through the connective tissues. Probably both routes are taken. There is rather more certainty as to what happens next. The larva moults twice to become an adult worm that lives in a tunnel between the enterocytes and which has openings into the lumen of the intestine. These parasitic worms are unusual, however, in that only female adults exist and they reproduce by parthenogenesis – that is, despite the absence of males, eggs are released into the duodenal contents.³ The eggs hatch in the bowel lumen. These parasites, known as first stage or rhabditiform larvae, were the forms first seen by Normand and are passed in the stools. In the external environment, and under the right conditions of temperature and humidity, one of two things happens. Some worms moult twice to become larvae variously known as third stage, filariform or infective larvae that are infective to humans. Other worms, however, moult four times and differentiate sexually into free living male and female worms. The adult worms mate and the fertilised female releases eggs that hatch, moult twice, and become infective larvae. These two routes are known as ‘homogonic’ and ‘heterogonic’ development, respectively, and take several days to several weeks to complete. The factors determining which route a given rhabditiform larva will take remain a mystery. From the point of view of survival of the worm, the second course has its advantages as multiplication of the worm enhances the chance of transmission to a new host.

But that is not the end of the story. Some larvae in the bowel lumen, probably after moulting, penetrate either the bowel mucosa or the perianal skin and retrace their predecessor’s steps to the small intestine. The first pathway is called ‘internal autoinfection’ whereas the second is known as ‘external autoinfection’; each cycle takes about two weeks and can go on indefinitely. What does all this mean to the practising gastroenterologist? Strongyloidiasis can turn up in the most unlikely patients with infection having been acquired while living in an endemic area many years before. The current record is 65 years!⁴

Epidemiology

S. stercoralis is endemic in the tropical world and infects perhaps 100 million people. Nevertheless, infection may be found unexpectedly. For example, the diagnosis was made in a 17 year old white schoolgirl from Nottingham, England who had never been abroad apart from a single day trip to Boulogne in France.⁵ Infection is usually acquired by walking barefoot or otherwise exposing bare skin to the ground in areas where human faeces have been deposited indiscriminately. It does not seem to be spread heterosexually.⁶ The worm is primarily a parasite of humans although sometimes dogs and cats may be infected. Nevertheless, it seems that

animal-human or animal-environment-human transmission is rare.⁷

Host-parasite relation

The interaction between *S. stercoralis* and its human host is a puzzle. There seem to be three levels of response. (1) Subjects mount an effective immune reaction and eradicate infection; (2) Subjects mount a partially effective immune response. They cannot eradicate the infection but do contain the intensity of infection. Such people have chronic strongyloidiasis; (3) Subjects who have previously contained the infection lose this ability. The parasites multiply unrestrainedly and larvae disseminate throughout the body. This condition has been labelled 'disseminated', 'hyperinfective' or 'massive, overwhelming' strongyloidiasis.

The comparative importance of the adequacy of the host's immune system and of the parasite's ability to evade those responses is ill defined.⁸ Certainly, different 'biotypes' of *S. stercoralis* with varying capacities to infect animals have been described.⁹ Nevertheless, my suspicion is that the outcome is likely to depend more upon the effectiveness of the host response. There is no solid evidence to support this view but anecdotal experience points in this direction. For example, tens of thousands of British and Australian soldiers were imprisoned under appalling living conditions for several years as prisoners of war on the Burma-Thailand railway. Upon release, almost all of them had hookworm infection, yet 35 years later only 25–30% had chronic strongyloidiasis.^{10,11} Environmental conditions were such that all of them should have been exposed to *Strongyloides*; threequarters of them seem to have dealt with the infection. Similarly, strongyloidiasis is significantly less common than hookworm infection among the inhabitants of tropical countries, yet the manner and conditions of transmission of the two parasites are very similar. The mechanisms by which some subjects can eradicate infection are unknown but may well be determined genetically.

Equally mysterious are the means by which larvae that are cycling through the bloodstream and tissues can evade the cellular and humoral defence mechanisms in patients with chronic strongyloidiasis. A balance is reached with neither the parasite or the patient gaining the upper hand. When bowel specimens from such patients are examined histologically, worms may be seen in the mucous membrane but little inflammation is noted.

Under some circumstances, however, defences are disturbed and the balance is tilted in favour of the parasite. Replication of worms exceeds destruction of offspring and worm numbers increase enormously and are detectable in a variety of tissues. This has occurred in the context of immunosuppression, especially impairment of cell mediated immunity induced therapeutically, particularly with corticosteroids. It has also been noted after immunosuppression developing in association with diseases such as lymphoma, leukaemia, cancer, alcoholism, and malnutrition.¹² Although disseminated strongyloidiasis has been described in AIDS,^{13,14} it seems to be comparatively uncommon even though the human immunodeficiency virus and *S. stercoralis* coexist in many areas, particularly in Africa.¹⁵ If we knew why this were so, we would gain much more insight into the factors controlling the host-parasite relation in strongyloidiasis. One recent attempt to explain these diverse findings speculates that it is in fact not immunosuppression but a possible stimulatory effect of corticosteroids and their metabolites on moulting of larvae that enhances auto-infection.⁸ Of more immediate interest to gastroenterologists, it has been claimed that cimetidine may predispose to hyperinfection.^{16,17} It is difficult, however, to disentangle the role of this drug from other factors that may have influenced

the course of infection. Answers to these questions are only going to be found by continuing clinical observations and detailed analyses in animal models of infection. Unfortunately, *S. stercoralis* has a restricted host range and can only be studied satisfactorily in dogs^{18,19} and subhuman primates.²⁰

Clinical manifestations

Chronic strongyloidiasis is primarily a dermatological and gastroenterological disease.¹² Many people complain of urticarial eruptions in which crops of stationary weals, lasting one to two days, recur at irregular intervals, especially around the waist and on the buttocks. Less commonly, they have 'larva currens', an urticarial rash that migrates in a serpiginous fashion at a rate of several centimetres/hour. Gastrointestinal symptoms are more difficult to delineate, but in a controlled study, indigestion, cramping lower abdominal pains, intermittent or persistent diarrhoea, pruritus ani, and weight loss were found more commonly than in people without infection.¹¹ Thus, many of these patients could be mistakenly diagnosed as having an irritable bowel syndrome. The pathogenesis of these symptoms is unclear. Overgrowth of bacteria in the small bowel may play a part.²¹

At the other extreme, patients with massive, overwhelming strongyloidiasis may have intestinal obstruction, Gram negative septicaemia, respiratory failure, and meningitis. Large numbers of larvae enter the circulation and some take bowel organisms with them, resulting in sepsis. Such patients may present with severe, generalised abdominal pain abdominal distension, and shock. Ileus and oedema lead to small bowel obstruction, which may culminate in fatal necrotising jejunitis.²²

There is a spectrum of severity in strongyloidiasis, however, and patients may present with an illness of intermediate severity and with a variety of gastrointestinal features. These include haematemesis,²³ gastric ulcer,²⁴ jejunal perforation,²⁵ arteriomesenteric duodenal obstruction,²⁶ malabsorption,^{27,28} although this has been argued against,²⁹ massive lower gastrointestinal bleeding,³⁰ appendicitis,³¹ colitis,³² aphthous colonic ulcers,³³ colonic pseudopolyposis,³⁴ marked hypokalaemia,³⁵ peritonitis,³⁶ eosinophilic ascites in cryptogenic cirrhosis,³⁷ a pancreatic mass,³⁸ and in the fluid of a pancreatic cystadenocarcinoma.³⁹ In many instances, a cause and effect relation with *Strongyloides* is clear. In others, however, the infection may simply be coincidental and its role must be determined upon the basis of probabilities and upon the response to treatment.

Diagnosis

The key to diagnosing strongyloidiasis is to think of the possibility. It may be suggested by the classic triad of diarrhoea, abdominal pain, and urticaria, particularly the pathognomonic larva currens. Clues to the diagnosis may be provided by non-specific laboratory tests, such as the incidental discovery of an eosinophilia, but this is by no means invariable.¹¹ The definitive diagnosis is made by finding the parasite, usually in faeces but sometimes in other body fluids or tissue samples. Unfortunately, larvae are often difficult to find in faeces; they are usually present in small number and excreted intermittently. The chances of making the diagnosis are proportional to the number of occasions in which the faeces is examined. An alternative is to seek worms in duodenal fluid obtained either by use of the Enterotest capsule⁴⁰ or by duodenoscopy or in duodenal biopsy specimens. Care must be taken to ensure that worms really are *S. stercoralis* and not free living nematodes.⁴¹ Overall, these techniques seem to be less sensitive than faecal examination but may be useful in individual cases.⁴² In patients with

Drugs used in the treatment of strongyloidiasis

Drug	Standard regimen	Extended regimen
Thiabendazole	25 mg/kg twice daily for 3 days	25 mg/kg twice daily for 1 day each month
Mebendazole	200 mg daily for 3 days	200 mg daily for 28 days
Albendazole	400 mg daily for 3 days	400 mg for 1 day each month
Ivermectin	0.2 mg/kg daily for 3 days	0.2 mg/kg for 1 day each month

disseminated infection, larvae may be found in sputum, bronchial washings, cerebrospinal fluid, vomitus, ascitic fluid, and urine. In difficult cases, the finding of specific antibodies in blood may be very helpful; unfortunately, this test does not differentiate reliably between past and present infection.⁴²

Appearances on upper gastrointestinal endoscopy are often normal. Sometimes there is evidence of gastritis or duodenitis^{16,43,44} but this is not necessarily because of *Strongyloides* infection. Sigmoidoscopy and colonoscopy are generally normal but colitis, which may be ulcerating is sometimes seen.^{32,33} Barium meal examination is usually normal but may show duodenal dilatation or disclose duodenal stenosis with ulceration.^{45,46} Barium enema examination is usually normal although occasionally localised or generalised colitis is seen.^{45,47} Computed tomography may show bowel wall thickening.⁴⁸

Treatment

Treatment of strongyloidiasis may be a major problem. Unless the treatment eradicates all parasites, those remaining will replicate and little is achieved. The Table summarises the drugs that have been used.

Thiabendazole, a benzimidazole, is the traditional treatment but is often ineffective.⁴⁹ Experimental studies show that it has little effect on adult worms but temporarily impairs their fecundity – that is, their ability to produce offspring. Other benzimidazoles are poorly absorbed and are thus often ineffective against larvae in the tissues. Short courses of mebendazole are useless although there are reports that daily administration for several weeks (thus exceeding the recycling time) may be effective.^{50,51} Albendazole is available in many countries and is perhaps superior to both thiabendazole and mebendazole but is still not reliable.⁴⁹ Ivermectin, one of a new class of anthelmintics, probably has similar efficacy to albendazole.^{52,53} Effectiveness of treatment can never be assumed.

When all agents fail to eradicate infection in immunosuppressed patients, a practical approach is to minimise the worm burden by giving short courses of thiabendazole or another drug each month (Table).

Patients with disseminated strongyloidiasis and intestinal obstruction are a difficult problem. Such patients will probably need intravenous fluids as well as suction and drainage. Bacterial superinfections need to be treated with intravenous antibiotics. Unfortunately, no preparations of benzimidazoles suitable for parenteral use are available. Options include thiabendazole suspension given through a nasogastric tube or rectal administration; successful use of retention enemas given in a dose of 1.5 g (1 g/10 ml) twice daily has been reported recently.⁵⁴ Alternative strategies include attempting to locate a parenteral formulation of ivermectin and giving 0.2 mg/kg per day, considering the use of cyclosporin (3 mg/kg daily) as this has been effective in experimental animals,⁵⁵ and stopping immunosuppressive treatment. Despite intensive measures, many patients with overwhelming strongyloidiasis still die.

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