

Clinical Studies on Human Strongyloidiasis in Okinawa, Japan

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Abstract

Clinical and parasitological aspects of 161 patients with strongyloidiasis in Okinawa, Japan were investigated. In parasitological examinations, the infective larvae of *S. stercoralis* were often detected in the sputa and on the perianal skin of patients with uncomplicated strongyloidiasis, suggesting that the internal autoinfection, as well as auto-reinfection through perianal skin, may occur frequently among the patients with chronic strongyloidiasis. Heterotopic parasitism in the respiratory system was also supposed from the results on rhabditiform larvae, eggs and adult females in the sputa.

In a prognostic study, it was found that about half of the patients who had been treated with various anthelmintics were found to be still harboring the parasite. Repeated treatment with thiabendazole was administered to the relapsed cases and a daily dose of 1,500 mg for 3 days, repeated 4 times every 2 weeks, showed satisfactory results. The authors recommended that the repeated courses should be administered for a complete cure even in chronic strongyloidiasis.

Key words: strongyloidiasis, *Strongyloides stercoralis*, prognosis, treatment, thiabendazole

Introduction

Strongyloidiasis caused by *Strongyloides stercoralis* is a human intestinal parasitic disease. The disease remains prevalent in Okinawa prefecture, Japan, a district where other parasitic diseases have been almost entirely eradicated in recent years. The infection rate of about 1.0 to 2.0% has been consistently reported in the surveys by the Okinawa Health Service Association, in which about twenty thousand inhabitants from various districts have been examined by the fecal culture method for the presence of the parasite every year for the past sixteen years. Recently, surveys conducted by us in 1983 showed that the prevalence levels obtained in the previous surveys considerably underestimated the true prevalence of the parasitic infection (Sato,

1986). When we examined stool specimens three consecutive days using a combination of various methods, the positive rate of the parasite was five to ten-times higher than those of the previous surveys in the same areas. Currently, the actual prevalence level in Okinawa appears to be 5 to 10% among the middle and upper-age brackets of the inhabitants.

The authors have treated more than 1,300 cases of strongyloidiasis during the past thirty-five years in Okinawa. In an attempt to determine the efficacy of previous treatments, a follow-up examination of the patients was done in the present study and further treatment was tried for the relapsed patients in order to evaluate the efficacy of various protocols for treatment with thiabendazole.

Materials and Methods

Patients

A total of 1,353 patients (799 males and 554 females) with strongyloidiasis had been diagnosed in the Izumizaki Hospital, Okinawa during the period from 1953 to 1988. On the basis of our

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criteria of clinical findings, the subjects were divided in three groups; they were an asymptomatic group (1,159 patients), a mildly symptomatic group (129 patients) and a group with severe infection (65 patients). The asymptomatic group included persons who were found infected in the general health examinations on inhabitants or in the hospital-based examinations for other diseases unrelated to strongyloidiasis. The majority of patients in the mildly symptomatic group showed vague abdominal discomfort without signs of severe diarrhoea and marasmus. Severe infection was defined as the presence of vomiting, long-term diarrhoea and abdominal distention in association with signs of dehydration and wasting. Of the 65 patients with severe infection, 31 (47.7%) died during the treatment of the disease. On the other hand, 6 (4.7%) in the mildly symptomatic group progressed to become fatal cases but no fatalities occurred in the asymptomatic group. The clinical and parasitological findings on these patients are summarized in the present study.

The prognostic studies were done on the 124 persons who had a previous history of the disease and consisted of 65 males and 59 females ranging in age from 20 to 83 years. Among the patients, 101 were in the asymptomatic group, 16 were in the mildly symptomatic group and 7 had a past history of a severe infection of the disease. The elapsing time after the first medical examination was more than 10 years in 77 patients (mean = 13 years).

Parasitological examinations

The stool specimens of the patients were examined in the laboratory by the following procedures: (1) direct smear, (2) formalin-ether concentration and (3) fecal culture with a filter paper strip. The examinations were performed two consecutive days. The intensity of the infection was determined by estimating the number of larvae in the direct smear procedure. In order to detect the larvae in sputum, the sputa were examined directly under a microscope. The cellulose tape collection procedure for detection of *Enterobius vermicularis* eggs was also used to detect the larvae on the perianal skin.

Anthelmintic treatments

The drugs of choice in previous treatments have been gentian violet (0.18 to 0.39 g daily for 6 to 14 days), dithiazanine iodide (0.2 g daily for 5 to 20 days), pyriminium pamoate suspension (5 mg/kg for 3 to 5 days) and thiabendazole (25 mg/kg for 4 days).

Thiabendazole was used in the present study by four different protocols designed as follows:

Group I: 3,000 mg (thrice a day) for 4 consecutive days.

Group II: 1,000 mg (single dose daily) every 2 days for a month.

Group III: 1,500 mg (single dose daily) for 3 consecutive days; the same treatment was repeated 5 times every week.

Group IV: 1,500 mg (single dose daily) for 3 consecutive days, repeated 4 times every 2 weeks.

The follow-up examinations were repeated every month for 6 months after the end of the treatments. That interval was considered satisfactory for evaluating the effects of treatment in strongyloidiasis.

Results

Clinical findings

The clinical symptoms of 161 patients with severe or mildly symptomatic strongyloidiasis are summarized in Table 1. Abdominal discomforts were the most common complaints. Pulmonary complications were also observed in many patients with severe infection. In few cases, dermatic signs, such as exanthem and itching, were found but no creeping eruption (larva currens) had been observed among the patients.

Table 2 shows the results of sputum examinations performed on the 139 patients. The filariform larvae were found in 42.4% of the patients. The detection rate of the larvae was as many as 81% of patients with severe infection. The positive results were also obtained in 44.7% of the mildly symptomatic group and even in 8% of the asymptomatic group by the repeated examinations. The rhabditiform larvae were detected in the sputa of 33% of patients with

Table 1 Prevalence of clinical symptoms in patients with strongyloidiasis in Okinawa, Japan

Symptoms	Frequency	
	mildly	severe
diarrhoea	30 (29.4)	39 (66.1)
mucous/bloody stool	2 (2.0)	3 (5.1)
loose stool	39 (38.2)	7 (11.9)
constipation	6 (5.9)	5 (8.5)
anorexia	16 (15.7)	15 (25.4)
nausea	4 (3.9)	12 (20.3)
vomiting	10 (9.8)	20 (33.9)
pyrosis	9 (8.8)	9 (15.3)
sense of abdominal fullness	21 (20.6)	7 (11.9)
rumbling sound	26 (25.5)	18 (30.5)
abdominal pain	26 (25.5)	19 (32.2)
epigastric pain	15 (14.7)	21 (35.6)
pruritus ani	13 (12.7)	14 (23.7)
cough	11 (10.8)	22 (37.3)
bloody sputum	1 (1.0)	6 (10.2)
discomfort in throat	1 (1.0)	10 (16.9)
chest pain		5 (8.5)
general fatigue	28 (27.5)	14 (23.7)
weight loss	22 (21.6)	38 (64.4)
dropsy	6 (5.9)	15 (25.4)
spontaneous pain of extremities	19 (18.6)	25 (42.2)
fever		20 (33.9)
dermatic symptoms		3 (5.1)

The results were summarized on 59 severe and 102 mildly symptomatic cases. Figures are numbers (percentages) of the subjects.

Table 2 Detection of *S. stercoralis* in sputa and on perianal skin of 139 patients

	severe (n = 42)	mildly (n = 47)	asymptomatic (n = 50)
sputum:			
rhabditiform larvae	14 (33.3)	8 (17.0)	0
filariform larvae	34 (81.0)	21 (44.7)	4 (8.0)
adult females	2 (4.8) ^{a)}	0	0
perianal skin:			
rhabditiform larvae	—	—	1 (33.3) ^{b)}
filariform larvae	—	—	3 (100) ^{b)}

Figures are numbers (percentages) of the subjects.

^{a)}Eggs were detected in a case.

^{b)}Perianal examination with a cellulose tape were done on three cases.

—: not examined.

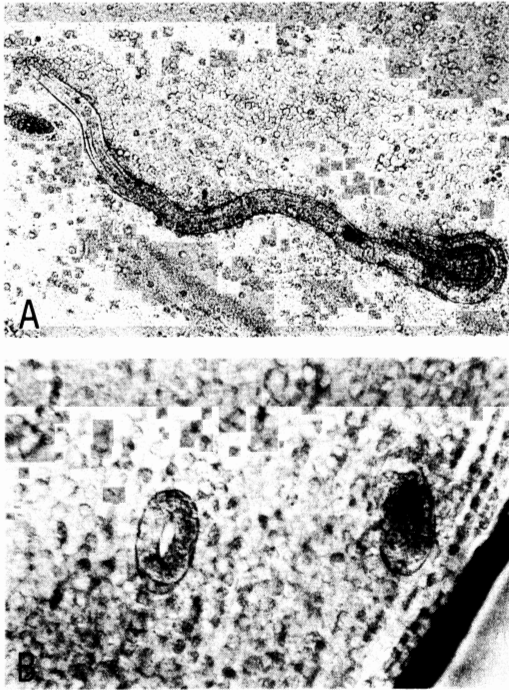


Fig. 1 Photomicrographs of a parasitic female (A) and eggs (B) of *S. stercoralis* in a wet mount of sputum from a patient.

severe strongyloidiasis and in 17% of the mildly symptomatic group, showing heterotopic parasitism in these patients. In two cases with severe infection, adult females were actually detected in their sputa (Fig. 1, A). A few eggs were simultaneously observed in the sputum of a patient (Fig. 1, B).

In perianal examinations on three patients with asymptomatic strongyloidiasis, filariform larvae were demonstrated in all of the patients. In a case, a rhabditiform larva was detected concurrently with the filariform larvae on the perianal skin.

Prognostic studies

Eight hundred and twenty-eight persons with a previous history of *Strongyloides* infection were urged by letter to comply with a follow-up examination, and 124 persons actually came to the hospital to have medical examinations. By stool examinations, 71 persons (57.3%) were

Table 3 Efficacy of previous treatments with various anthelmintics on patients with strongyloidiasis in Okinawa

Treatment	No. cases treated	No. cases cured	cure rate (%)
thiabendazole	47	24	51.1
pyrvinium pamoate	42	13	31.1
others*	15	10	66.7
untreated	20	6	30.0

The elapsing time after the first medical examination in the hospital was more than 10 years in 77 persons (mean = 13 years). The subjects consisted of 101 patients in the asymptomatic group, 16 in the mildly symptomatic group and 7 with a severe infection in the past history of the disease.

*They were treated with gentian violet or dithiazanine iodide.

found to be still harboring the parasite. The efficacies of the previous treatments on the 124 persons were compared in Table 3. A notable effect of therapy with thiabendazole upon *S. stercoralis* was observed in 51.1%, but pyrvinium pamoate only gave a cure rate of 31%, which did not differ from the spontaneous cure in non-treated persons. The cure rate with other anthelmintics, such as gentian violet and dithiazanine, was 66.7%, but these drugs are not currently used in Okinawa because of relatively severe side-effects.

The course of the disease on a patient who showed recurrent relapses of the infection following various medications is shown in Table 4. She was only 6 years old at the first medical examination in 1954. As indicated in the Table, various anthelmintic treatments have been tried over a thirty year period but a complete cure has not been achieved.

Treatments with different therapeutic regimens

The above 71 patients experiencing relapse were further treated with thiabendazole in different regimens and the effectiveness of the treatments could be evaluated over 6 months in 36 patients. The cure rates obtained were tabulated in Table 5. The rates were 60.0%, 53.8% and 57.1% in Group I, II and III,

Table 4 Course of the disease in a patient who relapsed repeatedly after various anthelmintic treatments

Year	Symptoms	Fecal larvae*	Treatment
1954	abdominal pain, vomiting, diarrhoea	+++	GV
1955	—	+++	GV
1956	—	+++	GV
1957	abdominal pain	+++	GV
1959	headache	+++	GV
1960	fever, abdominal pain	+++	DT
1961	epigastric pain	+++	GV, DT
1962	epigastric pain	+++	DT
1963	—	++	DT
1964	—	+++	PP
1965	epigastric pain	++	DT
1966	—	++	TB
1971	fever, bronchitis	+++	TB
1972	general fatigue	+	TB
1976	epigastric pain	+	PP
1977	dropsy of extremities	+++	PP
1978	general fatigue	+	TB
1979	headache, dullness	+	TB
1981	general fatigue	+	TB
1983	—	+	

GV: gentian violet, DT: dithiazanine, PP: pyrvinium pamoate, TB: thiabendazole

—: asymptomatic.

* Numbers of fecal larvae by the direct smear were scored as follows: +++; more than 30 larvae, ++; 11–29 larvae, +; less than 10 larvae.

Table 5 Efficacy of thiabendazole treatment with four different regimens on the patients who were unsuccessfully treated in the past

Treatment	No. cases treated	No. cases cured	Cure rate (%)
Group I	10	6	60.0
Group II	13	7	53.8
Group III	7	4	57.1
Group IV	6	5	83.3

respectively. On the other hand, repeated treatments, as in Group IV, revealed an enhanced efficacy and showed more than an 83% cure rate. The total dosage amount of the anthelmintics in each therapeutic regimens was 12 g for Group I, 15 g for Group II, 22.5 g for Group III and 18 g for Group IV. The treatment period was only 4 days in Group I, but was as long as a month

or more in others.

Side-effects of the drug were often encountered. They were seen in 64% in Group I, 18% in Group II and 63% in Groups III and IV, and were most commonly in the form of dizziness. Other less frequent side-effects, however, were generally mild and lasted no more than 12 to 24 hr. A transient elevation of SGOT and SGPT levels were observed in four patients.

Among the 14 patients who experienced relapse, the relapse occurred in 10 patients (71.5%) within 4 months after the end of treatments (mean = 3.5 months).

Discussion

In the present study, clinical and parasitological findings in the cases of uncomplicated and severe strongyloidiasis in Okinawa

were investigated. In the mildly symptomatic group, gastrointestinal symptoms were common complaints, and their frequency, as well as the intensity, increased significantly in the group with severe infection. Pulmonary discomfort was also significant among the severe cases. The clinical conditions of the present patients were similar to those reported by other investigators (Jones, 1950; Grove, 1980; Pelletier, 1984), but complete absence of "larva currens" (Arthur and Shelley, 1958) seemed to be one of the clinical features of our cases. The manifestation was frequently observed among the patients in the other areas (Doeglas and Berg, 1972; Stone *et al.*, 1972; Smith *et al.*, 1976). In the present examinations, we were able to find the filariform larvae in sputa collected from the mildly symptomatic group and even from the asymptomatic group, indicating that the internal autoinfection may occur frequently in chronic strongyloidiasis. The infective larvae are known to migrate via the respiratory tract to the small intestines, so it could be considered that the larvae are detectable in sputa from patients. However, this has been considered a rare occurrence in uncomplicated chronic strongyloidiasis. Likewise, the rhabditiform larvae were often observed in the sputa, suggesting the lodgment of adult worms in the respiratory system. Actually, adult females and eggs were demonstrated in the sputa from two severe cases in the present study. There have been few such reports of eggs and adult worms in the sputum (Kenney and Webber, 1974; Humpherys and Hieger, 1979; Wang *et al.*, 1980). Auto-reinfection through perianal skin, which has been suggested by the creeping eruption lesion on the perianal skin of strongyloidiasis patients, was also supposed from the results of perianal examination in which the infective larvae were actually demonstrated in all patients examined by a cellulose tape collection procedure.

In the present prognostic study, about half of the patients who had been treated with various anthelmintics were found not to have successfully overcome the infection. Under the highly sanitary conditions, it has been emphasized that the infection from the environment is extremely rare in present day Okinawa. The reason some

patients still harbored the parasite appeared to be due to unsuccessful treatment rather than an external reinfection.

Previous treatments with several anthelmintics especially with pyvrium pamoate, could not be considered to have had an adequate effect for permanent cure of strongyloidiasis. Patients who relapsed repeatedly after various treatments over a period of many years, as shown in Table 4, are often seen in Okinawa. However, the possible reason for such a resistance to anthelmintic treatments is unclear.

The results of a conventional 4-day therapy with thiabendazole were disappointing in the prognostic survey. Therefore, repeated therapies were conducted in the present study and a daily dose of 1,500 mg for 3 days, repeated 4 times at 2 week intervals, were recommended. A larger dosage or continuous, prolonged treatment may cause severe side-effects. The daily dose of 1,500 mg used in the therapeutic regimen is almost equivalent to the recommended 25 mg/kg. To relieve the symptoms of side-effects, such as dizziness, nausea and malaise which are most frequent in thiabendazole treatment, the single dose was recommended to be taken just before sleeping. Since thiabendazole is considered to have little effect on migrating larvae, several repeated courses of administration have been recommended for treatment of disseminated strongyloidiasis (Scowden *et al.*, 1978; Weller *et al.*, 1981). However, it was found in the present study that internal autoinfection may occur frequently in chronic strongyloidiasis and that a repeated therapeutic course is also necessary to achieve successful results even in chronic infection. The intermittent administration of medication at 2 week intervals to avoid serious side-effects to the liver function is based on the report of self-infecting study by Tanaka (1958) in which the intestinal adults appeared to become established in about 2 weeks after the infection.

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