AN ASSESSMENT OF RE-INFECTION RATES AND TREATMENT OUTCOMES OF PATIENTS WITH PULMONARY PARAGONIMIASIS

*Vicente Y. Belizario, Jr.**
Winifreda V. de Leon
Mark Philip G. Bugayong
Antonio D. de Guzman
Maria Theresa G. Valderama
Department of Parasitology
College of Public Health
University of the Philippines, Manila
P. Gil St., Ermita, M Manila

Abstract

Pulmonary paragonimiasis or lung fluke infection is a food-borne parasitosis that is acquired by ingestion of raw or insufficiently cooked fresh water crabs. If left undiagnosed and untreated, this can lead to a severe and disabling disease that reduces human productivity and quality of life. The presence of an Integrated Tuberculosis-Paragonimiasis Surveillance Program in the municipalities of Casiguran and Irosin in Sorsogon may not be enough in trying to control this public health problem. Data on finer points such as re-infection rates are still lacking. This information is especially relevant considering that people living in endemic areas may not necessarily alter their food preferences and eating habits easily even with a proven bout with lung fluke infection. In addition, there are no local studies about the extent of clinical and parasitological responses to praziquantel therapy, amidst reports of non-response to treatment. A follow-up survey was conducted in the municipalities of Irosin and Casiguran which gave special attention to these issues. Results showed that overall infection rate did not significantly differ from previous levels found in surveys done in 1997-1998. Also, in patients with past history of paragonimiasis, 11.5% were again found positive for lung fluke ova. Non-clearance for parasite eggs even after treatment was also seen in some patients. Our survey gathered valuable data that may help justify the need for follow-up and for better health education and promotion strategies that will prevent subsequent exposure and eventual disease, and probably, in the evaluation of existing treatment guidelines.

Keywords: Paragonimiasis, lung fluke infection, food-borne parasitosis, *Paragonimus westermani*, epidemiology, re-infection rates

Introduction

Pulmonary paragonimiasis or lung fluke infection is a food-borne parasitosis that is acquired by ingestion of raw or insufficiently cooked fresh water crabs and/or crayfishes. The types and severity of clinical manifestations may vary, oftentimes, presenting signs and symptoms similar to those of pulmonary tuberculosis (TB), which is one of the most important public health problems in the Philippines. If left undiagnosed and untreated, paragonimiasis can lead to a severe and disabling disease that reduces human productivity and quality of life. The public health and economic impacts of this disease are considerable in terms of morbidity, loss of productivity, and absenteeism, health care costs, and agricultural losses (WHO, 1995).

Data on re-infection with lung flukes remain lacking. This in the background of reports of recurrence of signs and symptoms and demonstration of lung fluke eggs on sputum examination in patients previously diagnosed to have and have been treated as pulmonary paragonimiasis and who were known to have clinically improved. This issue of possible re-infection is especially relevant considering that people living in endemic areas may not necessarily alter their food preferences and eating habits easily even with a proven bout with lung fluke infection. This valuable information may help justify the need for follow-up and for better health education and promotion strategies that will prevent subsequent exposure and eventual disease.

*corresponding author

In addition, as of 1999, there are no local reports about the extent of clinical and parasitological response to treatment with the drug regimen of choice, which is praziquantel 25 mg/kg for three doses for 3 days. In Irosin, only one patient with lung fluke infection has been described prior to 1995. Thereafter, 5 cases out of 9 patients not responding to anti-TB treatment were described (Belizario et al., 1997). This latter finding led to bigger cross-sectional surveys done from 1997 to 1998 in the municipalities of Irosin (Belizario et al., 1997) and Casiguran (Belizario *et al*, 1998) which were to describe the clinical epidemiology of paragonimiasis in relation to pulmonary TB. Results have shown that infection rates among patients clinically diagnosed or suspected to have pulmonary TB ranged from 16 to 25%. The said figures may represent an estimate of the extent of misdiagnosis of lung fluke disease as pulmonary TB or the extent of the clinical overlap of the two conditions. All patients found positive for paragonimiasis were treated with praziquantel and follow-up sputum specimens were requested after they finished their respective treatment courses. Of 47 patients who submitted follow-up sputum specimens, 5 were still sputum positive for lung fluke eggs and only 27 or 57.4% reported clinical improvement (Belizario et al., 1997;1998).

Similarly, reports from the local surveillance team showed that of the 331 patients seen in a span of six months, 47 or 14.2% of them were found sputum positive for *Paragonimus* ova. Again, all patients found positive for paragonimiasis were treated with praziquantel. Of 28 patients initially positive and who were treated and followed-up 2 months post-treatment, 3 were still positive for the lung fluke ova (Belizario et al., 1998).

Objectives of the Study

This study was then committed to address the following objectives:

1. To determine *Paragonimus* infection rates in Casiguran and Irosin, Sorsogon;
2. To describe the clinical and parasitological responses of patients with pulmonary paragonimiasis following treatment with praziquantel;
3. To determine re-infection rates among patients previously diagnosed to have pulmonary paragonimiasis; and
4. To determine infection rates among patients diagnosed to have pulmonary tuberculosis.

Methodology

Study Site

The study was conducted in two municipalities in Sorsogon, namely Irosin and Casiguran where community-based surveys where conducted in 1997-1998. In 2000, Casiguran had a population of 25,804, and Irosin had a population of 45,086 (National Census and Statistics Office, 2001). Each municipality has a Rural Health Unit (RHU) headed by a Municipal Health Officer (MHO) and complemented by RHU staff, most of whom had been trained in 1998 for diagnosis and treatment of paragonimiasis.

Study Population

Patients were included in the survey if they satisfied any one or more of the following descriptions:

1. patients who were previously diagnosed to have paragonimiasis from 1995 to 1998;
2. patients who received anti-TB treatment without resulting clinical improvement or resolution;
3. patients with complaints of chronic cough with or without hemoptysis for the last four weeks.

Cross-sectional Survey

Patients who fulfilled any one of the above-mentioned criteria for inclusion were invited to consult at the RHU of each municipality on a designated date in October 2000. General data, particularly name, age, sex, barangay of residence and occupation were recorded on a Case Report Form (CRF). The clinical history was obtained from each patient and was focused on the following information: chief complaint/s, present illness, and past history of pulmonary TB and/or paragonimiasis, treatment and compliance with anti-TB treatment and/or praziquantel. Physical examination (PE) was done by the project physician who took note of auscultatory lung findings, particularly vocal fremitus and breath sounds. All history and PE findings were recorded on the CRF. Praziquantel 25 mg/kg for three doses for 3 days was given to patients who were found to have *Paragonimus* ova on sputum examination.

Sputum specimens were collected from targeted patients who were advised to cough out a deep catch specimen in the early morning of the day of the survey to be brought to the RHU when they consult. The sputum specimens were received by the assigned project staff for recording and forwarded to the RHU laboratory where processing and examination were done.

An Acid fast bacilli (AFB) smear was prepared from each sputum specimen received, after which the remaining specimen was processed for clearing and concentration purposes. An equal amount of 3% sodium hydroxide was added to the remaining specimen while it was in the sputum cup. It was allowed to stand for 3 minutes for digestion to take place, after which the specimen/sodium hydroxide mixture was shaken gently sideways. The digested sputum was then poured into a centrifuge tube and spun for 5 minutes at high-speed setting. The supernate was decanted and the sediment poured on to a glass slide and covered by a glass slip. The slide was then examined under low power magnification for scanning and high power magnification for verification. All of the sediments were examined before a slide was declared negative for *Paragonimus* ova. AFB smears were examined at the Department of Medical Microbiology of the College of Public Health, University of the Philippines Manila.

For quality control, a reference microscopist crosschecked slides with an initial positive reading and re-examined slides with an initially negative reading.

Follow-up of Patients with Paragonimiasis

Patients who were found to have lung fluke ova during the cross-sectional survey and treated with praziquantel were followed up by their respective Rural Health Midwives (RHM) done 4 and 8 weeks after treatment to check on clinical response to treatment and to collect sputum specimens for presence or absence of lung fluke ova. All specimens collected in the field were processed and initially examined by the project microscopist. Thereafter, all specimens were preserved with 10% formalin and were forwarded to the Diagnostic Parasitology Laboratory of the College of Public Health, University of the Philippines Manila, where quality control procedures were done. The reference microscopist re-examined the specimens blinded to the initial readings. Findings were recorded in the Case Follow-up Form.

Data Processing and Analysis

Case Report Forms and Case Follow-up Forms were coded and encoded using Epi Info version 6 software. Descriptive statistics like frequency of distribution and rates were derived thereafter.

Results

Cross-Sectional Survey

A total of 81 patients were seen in October 2000 with 44 patients from Casiguran and 37 patients from Irosin consulting. The age range of respondents was from 22 to 81 years (mean=51.3 years; s.d.=13.4; median=51 years). Cough of at least 4 weeks duration was the most common presenting manifestation that was reported by 70 patients (86.4%). A majority of patients reported back pain, easy fatigability, dyspnea and chest pain. Hemoptysis was reported by almost half of those with cough.

Twenty-six (32.1%) respondents were patients who were diagnosed to have paragonimiasis anytime during the past 3 years with 14 patients from Casiguran and 12 patients from Irosin. Of those patients with a past history of paragonimiasis, 25 (96.2%) reported having complied with treatment with praziquantel. Most of them (23 out of 25 patients or 92.0%) reported clinical improvement after treatment. Only 2 (8.0%) patients did not experience clinical improvement.

Sixty-two (76.5%) patients reported a history of anti-TB treatment, and of these, 51 (82.3%) reported having complied with intake of anti-TB drugs for at least 6 months. Of these, only 35 (68.6%) reported clinical improvement, and 15 (29.4%) did not note any clinical improvement. No information on clinical response with intake of anti-TB drugs was noted in one patient.

Sputum examination showed that 16 (19.8%) out of 81 patients examined had *Paragonimus* infection. Of the 26 patients with a past history of paragonimiasis, 3 (11.5%) patients were again found to be infected in this survey. All three patients were diagnosed to have lung fluke infection between 1995 and 1998. Two patients had noted clinical improvement after intake of praziquantel and one patient had claimed not to have experienced clinical improvement after treatment.

Of 62 patients with history of intake of anti-TB medications, 13 (21.0%) patients were shown to have lung fluke infection. Six of these patients reported to have experienced clinical improvement with anti-TB treatment, while one did not experience any. No information was available about the other six patients. Of 70 patients who reported having cough for at least four weeks before the survey, 12 (17.1%) patients were shown to have paragonimiasis.

AFB smear of sputum specimens from patients surveyed showed that only 2 (2.5%) patients were positive for *Mycobacterium* infection with one patient each from Casiguran and Irosin. One patient, a 58 year old male from Casiguran, was found to have lung fluke infection in 1997 was treated with praziquantel with note of clinical improvement. He also noted having received anti-TB treatment and reported lack of compliance with anti-TB therapy.

Follow-up of Patients with Paragonimiasis

All 16 patients diagnosed to have lung fluke infection in October 2000 were followed up 4 weeks after treatment. Eight (50%) of the 16 patients reported improved clinical status 4 weeks after treatment. Five (31.3%) out of the 16 patients were shown to have *Paragonimus* ova on follow-up sputum examination, 3 (18.8% of 16) of whom did not report clinical improvement.

Only 4 out of the 5 patients who were found infected with *Paragonimus* were re-treated with praziquantel 4 weeks after treatment as the other was lost to follow-up. Eight weeks after initial treatment, 3 out of the 4 patients were followed up and all were found to be clinically improved and sputum negative for lung fluke ova.

Table 1 shows the age and sex distribution of patients with lung fluke infection in both municipalities. Patients' ages ranged from 25 to 68 years old with a mean age of 50.6 years (s.d.=12.9). Positivity rates of both sexes did not seem to differ significantly (18.6% vs. 21.1%), while lung flukes were demonstrated in all age groups from 15 years of age onwards.

Table 1. Age and sex distribution of patients with paragonimiasis in Casiguran and Irosin, Sorsogon (October 2000).

Age group (in years)	Male			Female			Total		
	No. of patients examined	No. of positive patients	Positivity Rate	No. of patients examined	No. of positive patients	Positivity Rate	No. of patients examined	No. of positive patients	Positivity Rate
15-45	13	3	23.1	14	3	21.4	27	6	22.2
46-60	17	2	11.8	16	3	18.8	33	5	15.2
>60	13	3	23.1	8	2	25.0	21	5	23.8
Total	43	8	18.6	38	8	21.1	81	16	19.8

Range: 25-68 yrs Median: 49.5
Mean: 50.6 Mode: 65.0
s.d.: 12.9

Tables 2 and 3 show the age and sex distribution of patients with lung fluke infection in the two municipalities. Lung fluke infection rate was 20.5% in Casiguran and 18.9% in Irosin.

Table 2. Age and sex distribution of patients with paragonimiasis in Casiguran, Sorsogon (October 2000).

Age group (in years)	Male			Female			Total		
	No. of patients examined	No. of positive patients	Positivity Rate	No. of patients examined	No. of positive patients	Positivity Rate	No. of patients examined	No. of positive patients	Positivity Rate
15-45	5	0	0.0	9	2	22.2	14	2	14.3
46-60	6	1	16.7	12	2	16.7	18	3	16.7
>60	6	2	33.3	6	2	33.3	12	4	33.3
Total	17	3	17.6	27	6	22.2	44	9	20.5

Range: 32-68 yrs Median: 55.0
Mean: 54.1 Mode: 65.0
s.d.: 12.2

Table 3. Age and sex distribution of patients with paragonimiasis in Irosin, Sorsogon (October 2000).

Age group (in years)	Male			Female			Total		
	No. of patients examined	No. of positive patients	Positivity Rate	No. of patients examined	No. of positive patients	Positivity Rate	No. of patients examined	No. of positive patients	Positivity Rate
15-45	8	3	37.5	5	1	20.0	13	4	30.8
46-60	11	1	9.1	4	1	25.0	15	2	13.3
>60	7	1	14.3	2	0	0.0	9	1	11.1
Total	26	5	19.2	11	2	18.2	37	7	18.9

Range: 25-65 yrs Median: 45.0
Mean: 46.0 Mode: 25.0
s.d.: 13.2

Cough and back pain were the most common clinical manifestations reported by patients who were found to have paragonimiasis - 12 (55.5%) out of the 16 infected patients. These were followed by dyspnea and chest pain. The list and frequencies of the reported clinical manifestations are shown in Table 4.

Table 4. Frequency of signs and symptoms reported by patients with paragonimiasis in Casiguran and Irosin, Sorsogon (October 2000). (n=16)

Signs and symptoms	No.	%
Cough	12	75.0
Back pain	12	75.0
Dyspnea/"Hika"	10	62.5
Chest pain	9	56.3
Headache	7	43.8
Easy fatigability	6	37.5
Night sweats	6	37.5
Weight loss	5	31.3
Hemoptysis	5	31.3
Anorexia	5	31.3
Fever	3	18.8

Tables 5 to 8 show the frequencies of lung findings among patients with paragonimiasis. In 7 out of the 16 infected patients, lung findings were unremarkable.

Table 5. Vocal fremitus findings among patients with paragonimiasis in Casiguran and Irosin, Sorsogon (October 2000).

Vocal fremitus	Casiguran		Irosin		Total	
	No.	%	No.	%	No.	%
Normal	4	44.4	6	85.7	10	62.5
Decreased	2	22.2	1	14.3	3	18.8
Increased	2	22.2	0	0.0	2	12.5
Unknown	1	11.1	0	0.0	1	6.3
Total	9	100.0	7	100.0	16	100.0

Table 6. Breath sound findings among patients with paragonimiasis in Casiguran and Irosin, Sorsogon (October 2000).

Breath sounds	Casiguran		Irosin		Total	
	No.	%	No.	%	No.	%
Clear	3	33.3	6	85.7	9	56.3
Harsh	5	55.6	1	14.3	6	37.5
Unknown	1	11.1	0	0.0	1	6.3
Total	9	100.0	7	100.0	16	100.0

Table 7. Rales among patients with paragonimiasis in Casiguran and Irosin, Sorsogon (October 2000).

Rales	Casiguran		Irosin		Total	
	No.	%	No.	%	No.	%
Absent	5	55.6	5	71.4	10	62.5
Present	3	33.3	2	28.6	5	31.3
Unknown	1	11.1	0	0.0	1	6.3
Total	9	100.0	7	100.0	16	100.0

Table 8. Wheezing among patients with paragonimiasis in Casiguran and Irosin, Sorsogon (October 2000).

Rales	Casiguran		Irosin		Total	
	No.	%	No.	%	No.	%
Absent	6	66.7	6	85.7	12	75.0
Present	2	22.2	1	14.3	3	18.8
Unknown	1	11.1	0	0.0	1	6.3
Total	9	100.0	7	100.0	16	100.0

Discussion

An overall *Paragonimus* infection rate of 19.0% in this study may mean that this problem remains as a not uncommon clinical condition in the areas studied. This was not markedly different from levels of 25.0% described in Casiguran in 1997 and 16.3% described in Irosin in 1995 by the same study team (Belizario et al., 1997; Belizario et al., 1998). This may imply the need for improved efforts targeting better control that should include more active case finding and treatment as well as effective health education and promotion that should focus on transmission of the disease, submission to sputum examination, treatment, and prevention. Better integration of such efforts at the local health unit would be ideal since it is at such level where patients with signs and symptoms of TB, and thus probable paragonimiasis, usually seek consult, diagnosis, and treatment.

An infection rate of 11.5% among patients with a past history of paragonimiasis may mean continuing lung fluke infection even after treatment, which may be due to an initially heavy lung fluke burden or heavy intensity infection. If so, this may be addressed by follow-up re-treatment if sputum examination done 90 days after treatment shows non-clearance of parasite ova (Calvopiña et al., 1998). A lack of clinical improvement may actually mean a missed diagnosis of tuberculosis or a poor response to praziquantel therapy due to poor compliance, drug resistance, and other possible reasons. Another explanation for this occurrence may be the possibility of re-infection and/or double infection. The former, particularly in those patients who reported clinical improvement after receiving treatment and who submitted sputum negative for paragonimus ova on follow-up, could be addressed by improved health education and promotion interventions that will seek to prevent repeated exposure. The latter could be a scenario wherein a patient with pulmonary tuberculosis was misdiagnosed to have paragonimiasis, hence the continued manifestation of lung disease even after praziquantel therapy, before the true lung fluke infection sets in. In this situation, the solution may be the screening for both pulmonary TB and paragonimiasis at initial consult among patients coming from endemic areas or having possible exposure because of travel to endemic areas in the past few months, again reiterating the need for an Integrated Tuberculosis-Paragonimiasis Surveillance System (Belizario et al., 1998).

In the study areas described, paragonimiasis was shown in the adult age groups that were likewise shown to be of higher risk in the two previous surveys. No patient was seen in the age groups less than 15 years old unlike in Cateel, Davao Oriental where age-specific lung fluke infection rate was 15.0% (Belizario *et al*, 1999). In the latter case, exposure of the younger age group was probably a result of consumption of infected intermediate hosts as viand at home with a general background of a food shortage. In Sorsogon, exposure to lung fluke metacercariae probably occurs with consumption of *kinagang*, a local dish consisting of juice from small fresh water crabs added to grated coconut, wrapped in banana leaves and steamed (Yogore et al., 1958).

Light lung fluke infections are asymptomatic, although eosinophilia may be detected in peripheral blood and incidental lung lesions may be observed on routine x-ray films. Lung findings may seem normal or unremarkable. When infections are heavier, cough is the most common clinical presentation. In addition, dyspnea and chest pain may be frequent manifestations of paragonimiasis. Similarly, these symptoms were also described in a majority of patients who were proven to be infected in this study. If chronic cough is the only presenting manifestation, patients may be misdiagnosed to have bronchitis, bronchial asthma, or bronchiectasis. In most cases, clinical history is also suggestive of TB, and the frequent confusion with pulmonary paragonimiasis. Thus, if treatment for these mentioned conditions seems lacking in efficacy and with a background of possible exposure, it may be worth considering and attempting to demonstrate lung fluke infection by sputum examination and/or serologic examination (WHO, 1995). The need for laboratory diagnosis will entail collection of early morning deep catch sputum specimen, proper processing, and careful examination of sputum sediment. Laboratory staff adequately trained in parasitology will be essential for the provision of laboratory support for diagnosis.

Conclusion

For clinicians to successfully diagnose and treat patients with pulmonary paragonimiasis there is need for adequate laboratory support that will help detect and follow-up patients with lung fluke infection. In addition, there is a need to know the currently accepted treatment regimen consisting of praziquantel 25 mg/kg for three doses in one day. Drug availability needs to be ensured as the drug is not commercially available in the Philippines. At the moment, it is only available with the Department of Health and in Regional and Provincial centers where schistosomiasis is a public health problem.

Praziquantel is highly effective in the treatment of lung fluke infections. The drug given 25 mg/kg three times a day for two to three consecutive days procures cure rates approaching 100%. The drug has been noted to have a range of side effects, primarily affecting the gastrointestinal tract and the central nervous system, and the 3-day dose regimen may not be ideal for use in remote areas where most cases occur. There may be a need to try out in the local setting triclabendazole, a highly effective and well-tolerated drug that will require only a single dose, thus encouraging compliance. Trials conducted overseas have shown that a single dose of 10 mg/kg is effective and well tolerated in paragonimiasis (Calvopiña et al., 1998).

For public health workers and practitioners, paragonimiasis should be known as an emerging food-borne disease that is treatable, preventable and controllable. Its continued existence in hard to neglect levels may suggest the need for more effective strategies in case finding, treatment, prevention and control. The lack of substantial changes compared with the levels of disease a few years ago may imply the need to do more. Different sectors, including health, agriculture and education, can and should integrate their activities to reduce the prevalence of infection, morbidity and transmission. A strong recommendation that the results of this study advocate is the integration of tuberculosis and paragonimiasis surveillance.

Acknowledgement

Sincerest thanks

National Research Council of the Philippines

Source of Research Funds

Special thanks to

Dr. Michael Angelo Wambango
Dr. Ana Belinda de los Reyes
Field Clinicians

Dr. Ronald Lim
Dr. Fernando Roque
Rural Health Unit Staff
Casiguran and Irosin, Sorsogon

Dr. Allan Lucanas
Ms Lea Agsolid
Provincial Schistosomiasis Team

Dr. Arturo Perdigon
Provincial Health Office of Sorsogon

Dr. Gerardo Bayugo
Regional Director
Center for Health Development Bicol

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