Long-term Follow-up of Imported Gnathostomiasis Shows Frequent Treatment Failure

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Abstract. Gnathostomiasis is increasingly reported among travelers returning from endemic areas. Between 2000 and 2004, thirteen patients were diagnosed with imported gnathostomiasis and followed for at least 6 months after treatment. Nine patients presented with cutaneous signs, two with gastrointestinal signs, and two with neurological signs. The median age was 38 years and the female/male sex ratio was 1.6. The patients had visited South East Asia or Central America. The median interval between symptom onset and treatment (with albendazole in 12 cases and ivermectin in one case) was 3.5 months. Post-treatment follow-up lasted a median of 15 months. Eight patients relapsed, a median of 2 months (1–7 months) after initial treatment. These eight patients had a total of 13 relapses, the last occurring a median of 16 months (2–26 months) after initial treatment. Thus patients with imported gnathostomiasis should be monitored for at least 6 months to detect late treatment failure.

INTRODUCTION

Human gnathostomiasis is endemic in some south-east Asian and south and central American countries. This helminthic disease is acquired through consumption of raw or insufficiently cooked meat or fish. Humans are an accidental host: the ingested larvae do not mature, but cause cutaneous or, less frequently, visceral disorders.1 Imported gnathostomiasis is increasingly reported among travelers, especially since the beginning of this century.2,3

The effective treatments are albendazole (400 to 800 mg per day for 21 days), and ivermectin (0.2 mg/kg for one or two days). Cure rates in endemic countries (mainly Thailand), are 78.5–94% with albendazole, 76–95% with a single dose of ivermectin, and 100% with two doses of ivermectin.4–7 However, in a series of imported cases treated in Western countries, a single course of albendazole cured two of five French patients (40%), with cutaneous gnathostomiasis,8 and 81% of 16 British patients.9 Imported cases differ from autochthonous cases by the fact that relapses can be firmly attributed to treatment failure instead of reinfection. Late relapse has been reported in patients with imported cutaneous gnathostomiasis.1

The aim of this study was to evaluate long-term treatment efficacy in imported gnathostomiasis.

MATERIALS AND METHODS

We reviewed the files of all patients seen in our institution between January 1, 2000 and December 31, 2004 with gnathostomiasis that had at least 6 months of follow-up, and had not been re-exposed to a risk of infection. For the purposes of this study, gnathostomiasis was considered if two major criteria and at least two out of three minor criteria were present. The major criteria were compatible clinical signs based on two reviews of the literatures,1,8 and a positive serology. All the serologic tests were done by the Department of Helminthology, Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand, and a positive result was recorded if the 24-kD antigen had been detected by western blot (Dekumyoy P and others, a seven-year retrospective evaluation of gnathostomiasis and diagnostic specificity by immunoblot. March 2002, Proceedings of the first International Meeting on Gnathostomiasis, Culiacan, Mexico; unpublished data). At the routine diagnosis, gnathostomiasis has been detected by fixing serum dilution at 1:50, which diluted serum samples incubated with the antigen overnight. Minor criteria were travel to an endemic region, consumption of raw fish or meat, and blood eosinophilia > 500/mm3. All the patients had thorough parasitologic tests including Toxocara antibody (Department of infectious and tropical diseases, La Pitié Salpêtrière Hospital, Paris, France); and those with evidence of another helminthic disease were excluded.

A relapse was defined by the reappearance of compatible clinical signs with a serology that remained positive. Relapsing patients were re-treated with albendazole and/or ivermectin. Patients who relapsed after first-line treatment were compared with patients who were cured, in an attempt to identify criteria predictive of treatment failure, among the following variables: cutaneous versus non cutaneous forms; number of clinical episodes between symptoms onset and initial presentation; interval between symptoms onset and treatments; blood eosinophilia of pre-treatments; and post-treatments. Quantitative and qualitative variables were compared by using the Fisher and Mann-Whitney tests, respectively.

RESULTS

Thirteen patients had gnathostomiasis. Eight of the 13 patients with gnathostomiasis had all five diagnostic criteria, whereas the other five patients had two major and two minor criteria (blood eosinophilia was lacking in three cases and at-risk food consumption in two cases). Gnathostoma larvae were not recovered from any of the patients.

The median age was 38 years (27–60 years), and the female/male sex ratio was 1.6 (Table 1). All the patients had recently traveled to endemic regions, in South-East Asia in 11 cases (Cambodia, Laos, and China in 2 cases each, Myanmar, Japan, Sri Lanka, Thailand, and Vietnam in one case each), and Mexico in 2 cases. The purpose of travel was tourism in 11 cases, business in 1 case, and one patient was a French expatriate.

Eleven patients had consumed raw fish. Three of these patients had developed non-specific symptoms (malaise,
gastro intestinal symptoms, and itchy rash), compatible with the invasive stage of the disease, within 24–48 hours.

The median time between return to France and symptom onset (excluding the invasive stage) was 2 months (3 weeks–30 months). The presenting manifestations of gnathostomiasis were cutaneous in 9 cases, neurologic in 2 cases, and gastrointestinal in 2 cases (Table 1). Cutaneous manifestations consisted of local swelling in 6 cases, eyelid swelling in 1 case, and creeping dermatitis in 2 cases. The median interval between symptom onset and initial presentation was 2.5 months (0–83 months). The median number of clinical episodes before initial presentation was 2 per patient (range 1–10).

Hypereosinophilia was found in 10 cases, with a median value of 1332/mm³ (583–4000/mm³).

Treatment was started a median of 1 month (0–37 months), after symptom onset and consisted of albendazole in 12 cases (400 mg twice daily for 21 days), and single dose ivermectin in one case (200 µg/kg). Follow-up lasted a median of 15 months (6–49 months), after the beginning of first-line treatment.

All the patients initially responded to first-line treatment. Five patients (all treated with albendazole) did not relapse during follow-up and were considered cured. The cure rate with albendazole was 41.7% (5/12 patients). Eight patients (including one treated with ivermectin), had 13 relapses (1 to 4 relapses per patient) during follow-up (Table 1). All together, 3 patients received 4 courses of single dose ivermectine and relapsed in 2 instances (Table 1). The median interval between initial treatment and the first relapse was 2 months (1–7 months). The intervals between successive relapses were 5 and 30 months in the two patients who had two relapses (all relapses were cutaneous), both of whom were initially diagnosed with cutaneous gnathostomiasis. The third patient with multiple relapses was initially diagnosed with a neurologic form and the first relapse was 2 months (1–7 months). Blood eosinophilia returned to normal in 6 cases, decreased in 3 cases, slightly elevated in a case, and was not available in the 4 other cases.

Cutaneous versus non cutaneous forms, number of clinical episodes between symptoms onset and initial presentation, interval between symptoms onset and treatments, blood eosinophilia of pre-treatments and post-treatments were not significant variables for predicting treatment failure (P > 0.18).

**DISCUSSION**

This study of 13 cases is the second largest reported series of imported gnathostomiasis. The most significant result is the low cure rate obtained with standard albendazole therapy (41.7%), in sharp contrast to reported efficacy in endemic areas (> 78%). We also confirm the possibility of late relapse after apparently effective initial treatment: the maximum number of relapses was four (patient no. 13), and the longest interval between initial treatment and the last relapse was 26 months (patient no. 13).

None of the cases were confirmed by larva extraction, and the diagnoses were therefore only “probable.” However, all the patients had traveled to countries at risk or having ever reported gnathostomiasis and had compatible clinical manifestations and positive serologic findings. Similar diagnostic criteria were used to include patients in a clinical trial of treatment of cutaneous gnathostomiasis, in which a large number of potential cases were also excluded. Moore and others reported a series of 16 cases of imported gnathostomiasis managed in the United Kingdom. Unfortunately, only four cases were detailed, making it difficult to compare with our study. One of our patients has been included in a series of five cases of imported cutaneous gnathostomiasis. The patients in the two largest series were similar in terms of age and gender, but most of the British patients had returned from the Indian subcontinent (India and Bangladesh were the destinations at risk in 7 of the 11 patients whose destinations were known). The median interval between symptom onset and diagnosis was 12 months (3 weeks to 5 years) in the British study, whereas the median interval between symptom onset and initial presentation was 2.5 months (0–83 months) in our series pointing out the urgent need to inform physician about this disease.

At-risk food consumption was found in only three of the 16 British cases, compared with 11 of our 13 cases, but it was one of the minor criteria contributing to the diagnosis.

Of the 11 patients who had consumed raw fish, 3 had developed symptoms compatible with the invasive stage of the disease, within 24–48 hours. A similar invasive phase has been described in a fishing community in Mexico, where 5 adults presenting an acute episode of vomiting and abdominal pain a few minutes after eating ceviche prepared with spotted sleeper perch (*Eleotris picta*). All five patients developed 3 to 12 edematous, migrating skin lesions between 5 and 6 days later.

Hypereosinophilia was present in 7 of the 16 British cases (44%), and in 10 of our 13 cases (77%). In a study of 300 cases of creeping cutaneous gnathostomiasis in Mexico, hypereosinophilia was present in 69% of cases. A normal eosinophil count does not therefore rule out gnathostomiasis.
The main originality of our study is the long-term follow-up (minimum 6 months), which allowed us to identify late relapses, as in a previous small series of imported cutaneous gnathostomiasis.3 None of our patients returned to an endemic region during follow-up, allowing us to rule out reinfection. The median follow-up in our study was 15 months, compared with 4 months,6 6 months,4 and 12 months,7 in clinical trials of albendazole therapy in autochthonous gnathostomiasis.

The low cure rate obtained with albendazole in our study (41.7%), contrasts with the rates generally reported in the literatures (78.5–94%). One partial explanation may be that our series included both cutaneous and visceral forms. Furthermore, the clinical trials were done in Thailand, where the responsible species might be different from the species infecting our patients, only one of whom had visited Thailand. However, the most likely explanation is the exceptionally long follow-up in our study, which enabled us to identify very late relapses. Indeed, initial relapses occurred up to 7 months after first-line treatment, and the maximal period between two relapses was 15 months (patient no. 13). Therefore, a long-term follow-up should be mandatory in any study of anthelmintic drug efficiency. Unfortunately, we were unable to identify criteria predictive of treatment failure, probably owing to a lack of statistical power. More numbers of follow-up cases and a sero-diagnostic test should be determined in a study of anthelmintic drug efficiency. When comparing between pre- and post- treatments, serum antibodies of the same patient at 1:50 fixed dilution were reacted against 24 kDa. The pre-treatment mostly showed stronger reaction than post-treatment of the same case. Antibodies of post-treated cases gradually decreased at 24 kDa and also other antigen-antibody banding pattern. Antibodies of the recurrent cases perhaps showed a little bit stronger than the previous serum samples, subsequently, intensity of antibody to 24 kDa gradually decreased until disappearance when further comparing as mentioned. Resolution of eosinophilia should be the earlier indicator for responsiveness to treatment of cutaneous gnathostomiasis.11

CONCLUSION

At a time when the incidence of imported gnathostomiasis is increasing, this study strongly suggests that standard treatment with albendazole is not sufficiently effective. Our results suggest that patients should be followed for at least one year to ensure they are cured. These findings also have implications for therapeutic trials.