

TREATMENT OF EOSINOPHILIC MENINGITIS WITH A COMBINATION OF PREDNISOLONE AND MEBENDAZOLE

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Abstract. To study the efficacy of the combination of prednisolone and mebendazole for the treatment of eosinophilic meningitis, we conducted a pilot study among Thai patients with eosinophilic meningitis. Patients were given a two-week course of prednisolone, 60 mg/day, and mebendazole, 10 mg/kg/day. The primary observation parameter was the number of patients who still had headaches after the two-week course of treatment. Forty-one patients were enrolled in the study. Four (10%) patients still had headaches after the two-week course of treatment and the median length of time until complete disappearance of headaches was three days. Serious side effects were not detected. Treatment for two weeks with the combination regimen of prednisolone and mebendazole is safe and beneficial in relieving headaches in patients with eosinophilic meningitis.

INTRODUCTION

Worldwide, the commonest cause of eosinophilic meningitis is the rat lung worm *Angiostrongylus cantonensis*. Acute to subacute severe headaches with nonfocal neurologic findings, with the exception of occasional involvement of a cranial nerve, are the most common symptoms.¹ There is no specific treatment for this infection. Symptomatic treatment is indicated for symptoms such as headache, nausea, and vomiting. A two-week course of prednisolone, 60 mg/day, was shown to be beneficial in relieving headache.² Repeat lumbar puncture is performed in patients with increased intracranial pressure. A trial of specific treatment is still inconclusive. Thiabendazole, mebendazole, and albendazole have some effect in animal infections.^{3–5} Thiabendazole was ineffective in treatment of human angiostrongyliasis.⁶ Albendazole or the combination of prednisolone and albendazole have been used clinically with good results.^{7,8} Treatment with the combination of mebendazole and dexamethasone appeared to shorten the course of infection, but details of the trial were not demonstrated.⁹ To our knowledge, this is the first report of the outcome of the treatment of eosinophilic meningitis with the combination of prednisolone and mebendazole.

MATERIALS AND METHODS

Study population. Adult patients (≥ 15 years of age) who had eosinophilic meningitis and who came to Srinagarind Hospital, Muncha Khiri Hospital, and Nampong Hospital (Khon Kaen, Thailand) were studied. The diagnosis of eosinophilic meningitis was based on findings of $\geq 10\%$ eosinophils in the cerebrospinal fluid (CSF), with negative results for Gram, acid-fast bacilli, and India ink staining, cryptococcal antigen testing, and culture. Patients were excluded if they had undergone a previous lumbar puncture or if they were pregnant or nursing, or had concomitant conditions such as serious infections.

The severity of headache was classified by using a visual analog scale: 0 = no pain; 1–3, mild pain; 4–7, moderate pain; and 8–10, severe pain (with 10 indicating the worst pain imag-

inable). A CSF opening pressure ≥ 300 mm of H₂O after the patient was fully relaxed was defined as high CSF pressure.

The study protocol was reviewed and approved by the institutional review board and the ethics committee of Khon Kaen University.

Treatment. Subjects gave written informed consent before beginning the study and were given prednisolone, 60 mg/day orally in three divided doses, and mebendazole, 10 mg/kg/day orally in two divided doses, after meals for two weeks.

Studies to monitor efficacy and toxicity. Before treatment, the following studies were performed: complete blood count; measurements of blood glucose, electrolytes, serum blood urea nitrogen, and creatinine; and liver function tests. CSF samples were obtained for India ink, Gram, and Ziehl-Neelsen staining; culture for bacteria; determination of opening pressure; total and differential blood cell counts; glucose and protein levels; and cryptococcal and bacterial antigen tests. Chest radiographs was also obtained.

During treatment, two tablets of acetaminophen (500 mg each) were given to relieve headache every 4–6 hours if the headache persisted or recurred. Repeat lumbar puncture was done for patients with severe headaches that was not relieved by acetaminophen.

Evaluation. After a baseline evaluation, patients were evaluated at the end of treatment and every two weeks until they completely recovered. At each visit, a physical examination was done and any adverse events were assessed and recorded. During treatment and until the headache completely disappeared, the frequency of acetaminophen use and repeat lumbar puncture was also recorded. Compliance was checked by the pill-count method.

The day of complete recovery was defined as the first day that the patient thought the headache had disappeared and had taken no acetaminophen nor undergone lumbar puncture, if the headache did not recur within one month. For the patients who had post-lumbar headaches, the day of complete recovery was defined as the first day that the patient thought the headache had disappeared while the patient was supine and had taken no acetaminophen.

The primary observation parameter in this study was the number of patients who still had headaches after the two-week course of treatment. The secondary parameter was the length of time until the complete disappearance of headache. Information obtained from the subjects and laboratories were

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TABLE 1
Initial clinical features of the study patients*

Feature	N = 41
Age, years, mean \pm SD (range)	37.3 \pm 11.90 (18–67)
Sex, male (%)	31 (75.6)
Incubation, day, median (range)	30 (1–365)
Signs or symptoms	
Headache	
Duration, day, median (range)	7 (1–30)
Degree	
Mild	1
Moderate	7
Severe	33
Vomiting	12
Stiff neck	12
Fever (temperature \geq 38°C)	0
CNP	0

* CNP = cranial nerve palsy.

recorded on case-record forms. Data was analyzed by descriptive statistics.

RESULTS

Study population. From October 2002 through November 2004, 45 patients were enrolled in the study. Four patients were excluded from the study because they were lost to follow-up and the clinical data were incomplete. Therefore, 41 patients were studied. The clinical and laboratory features of the patients are shown in Tables 1 and 2. Before illness developed, 36 had eaten raw pila snails, and 5 had eaten raw freshwater shrimp.

Outcome. Thirty-four patients reported complete disappearance of headaches 7 days after treatment, 37 at 8–14 days after treatment, and 41 at 15–21 days after treatment. The details of clinical outcomes are shown in Table 3. No gastrointestinal bleeding, hyperglycemia, or altered mental status was seen, and there were no cases of recurrent meningitis.

DISCUSSION

In humans, infection by *A. cantonensis* is caused by eating third-stage larvae in raw or inadequately cooked intermediate hosts, such as snails and slugs, or transport hosts such as freshwater prawns, frogs, and the yellow tree monitor. When third-stage larvae are ingested, they penetrate the blood vessels of the intestinal tract and are carried to the meninges, where they usually die. A presumptive diagnosis

TABLE 2
Initial laboratory features of the study patients*

Feature	N = 41
Blood eosinophilia (\geq 700 cells/mm ³)	31
Positive serologic result for antibody against the 29-kD specific antigen of <i>Angiostrongylus cantonensis</i> on immunoblotting†	2
CSF abnormalities	
High opening pressure (\geq 300 mm H ₂ O)‡	4
WBC/mm ³ , median (range)	850 (12–3,520)
Eosinophilia, %, median (range)	57 (12–84)
Protein content, mg/dL, median (range)	71 (17–320)
Glucose ratio, CSF: blood, %, median (range)	53 (27–100)

* CSF = cerebrospinal fluid; WBC = white blood cells.

† N = 10 patients.

‡ N = 17 patients.

TABLE 3
Clinical variables of study patients

Variable	N = 41
Headache after 14 days of treatment, no. (%) of patients	4 (9.75)
Time until complete disappearance of headache, day, median (range)	3 (1–20)
Repeat lumbar puncture, no. (%) of patients	4 (9.75)
Frequency of acetaminophen use in patients who had complete disappearance of headache within 14 days of treatment, median no. of times	5

may be made for patients who have symptoms of meningitis with CSF eosinophilia and a history of consumption of raw snails.

A number of serologic tests have been used to support the diagnosis of angiostrongyliasis. We found that a specific 29-kD antigen from young adult female worms may serve as a reliable marker for the diagnosis of human angiostrongyliasis.¹⁰ In our patients, immunoblot analysis for detecting the 29-kD antigen showed low positive results. However, *A. cantonensis* was most likely the causative agent of eosinophilic meningitis because most patients had a history of ingestion of raw snails or raw freshwater shrimp before this illness and had clinical manifestations that were similar to those in the patients described by Punyagupta and others.¹

Although headache is not fatal, it is a distressing symptom that interferes with the personal and professional lives of patients. Supportive treatment, such as analgesic drugs and repeat lumbar puncture are recommended. Punyagupta and others reported that after 14 days of treatment with analgesics alone, approximately 60% of 284 patients who had eosinophilic meningitis probably caused by *A. cantonensis* still had headaches.¹ A recent study demonstrated that a two-week course of prednisolone was beneficial in relieving headache, shortened the median time until resolution of headache, and reduced the need for repeat lumbar puncture. The number of patients who still had headaches after 14 days of treatment was 9.1% and the median length of time until complete disappearance of headache was 5 days.²

The role of antihelmintic agents is still inconclusive. Mebendazole was effective in the treatment of infection with *A. cantonensis* in mice and rats.⁴ Theoretically, the neurologic symptoms should be exacerbated as a result of the death larvae. However, the combination of mebendazole and dexamethasone was used clinically without serious side effects.⁹ In our study, we demonstrated good results with a combination of mebendazole and prednisolone. In addition, no harmful effects of treatment were demonstrated. The results of our previous study of the treatment of this disease with a combination of albendazole and prednisolone showed that 11.5% of the patients still had headaches after 14 days of treatment with a median time of four days until complete disappearance of headaches.⁸

In summary, treatment for two weeks with a combination of mebendazole and prednisolone is safe and effective for the treatment of eosinophilic meningitis. Further study is necessary to prove the efficacy of this regimen compared with prednisolone alone and a combination of albendazole and prednisolone.

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