Clinical Factors Predictive of Encephalitis Caused by Angiostrongylus cantonensis

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Abstract. Angiostrongylus cantonensis is mainly caused eosinophilic meningitis in humans, whereas a minority of patients develop encephalitic angiostrongyliasis (EA). EA is an extremely fatal condition, and the clinical factors predictive of EA have never been reported. A comparison study was conducted in a hospital situated in an endemic area of Thailand. We enrolled 14 and 80 angiostrongylisits patients who developed encephalitis and meningitis, respectively. Logistic regression analysis was used to assess the clinical variables predictive of encephalitis. Age (adjusted odds ratio [OR], 1.22; 95% confidence interval [CI], 1.05–1.42), duration of headache (adjusted OR, 1.26; 95% CI, 1.03–1.55), and fever > 38.0°C (adjusted OR, 37.05; 95% CI, 1.59–862.35) were identified as statistically significant factors for EA prediction. Elderly patients with angiostrongyliasis experiencing fever and prolonged headaches were at the highest risk of developing EA.

INTRODUCTION

Angiostrongyliasis, a disease caused by Angiostrongylus cantonensis, has spread from the tropical endemic area to various regions throughout the world because of extensive international travel and eating habits.1,2 The route of infection is through ingestion of raw freshwater snails, shrimp, or monitor lizards. A. cantonensis is a neurotropic parasite, which presents as three main clinical manifestations: eosinophilic meningitis, eosinophilic encephalitis, and ocular angiostrongyliasis.3

Angiostrongyliasis is diagnosed on the basis of clinical manifestations,4–8 including the presence of cerebrospinal fluid (CSF) eosinophils and history of larval exposure. The serologic tests vary in sensitivity, and availability is limited. Therefore, their clinical uses are restricted.

The presenting symptom of meningitic angiostrongyliasis, the most common form, is acute severe headache.5,6 In contrast, encephalitic angiostrongyliasis is rare, but fatal. Similar to viral encephalitis, encephalitic angiostrongyliasis presents with acute deterioration of consciousness to a coma.7 Seizure attacks have never been reported in encephalic angiostrongyliasis. Limited information is currently available on the risk factors for encephalic angiostrongyliasis. Here, we perform a hospital-based, comparison study to identify the clinical factors predictive of encephalitis caused by A. cantonensis.

MATERIALS AND METHODS

Study population. We recruited adult patients hospitalized for angiostrongyliasis at Srinagarind Hospital, Khon Kaen University, Khon Kaen, Thailand. The clinical diagnostic criteria4–8 for angiostrongyliasis were as follows: 1) CSF with a white blood cell count of > 10 cells/mm², 2) CSF eosinophils constituting > 10% of the total CSF white blood cell count, 3) negative tests for CSF Gram, acid-fast, and India ink staining, cryptococcal antigen testing, and cultures, and 4) history of ingesting raw freshwater snails or other paratenic hosts, such as shrimp and monitor lizards.

Exclusion criteria aim to eliminate other possible causes of CSF eosinophils included history of raw fish consumption, history of migratory swelling, clinical diagnosis of subarachnoid hemorrhage or myeloecephalitis, positive serologic test for gnathostomiasis or cisticercosis, abnormal brain computed tomography or magnetic resonance findings, symptomatic or serology-positive HIV infection, and active or previous history of tuberculosis or malignancy.

The mentioned clinical criteria were applied to both encephalitis and meningitis groups. As previously reported, both conditions were differentiated by a complaining symptom, in that encephalic angiostrongyliasis presented with acute coma.6,7 In addition, brain imaging must be normal in the encephalitis group.

Clinical factors between both groups were studied, and the predictors were determined for encephalic angiostrongyliasis.

Sample size. From previous studies, the proportions of potential parameters such as numbers of patients with fever or neck stiffness in the meningitis and encephalitis group were 10% and 40%, respectively.5,7–8 Using a two-sided significance level of 0.05, power of 80%, and the meningitis/encephalitis sample size ratio of 6:1, the approximate numbers of the encephalitis and meningitis groups were 14 and 86 subjects, respectively.9 The study protocol was reviewed and approved by the institutional review board and the ethics committee of Khon Kaen University.

Data collection. We recorded the baseline characteristics, symptoms, physical signs, and laboratory results of all participants. Baseline characteristics included sex, age, season of admission defined by the Thailand meteorologic classification system (winter, summer, or rainy), incubation period (number of days after the last exposure to snails or paratenic hosts to the first day of developing symptoms), duration of headache (days), history of paresthesia, and history of vomiting.

Physical signs included fever (oral temperature of > 38°C), cranial nerve abnormalities, papilledema, and stiff neck. Laboratory examinations comprised complete blood count (CBC), serologic test for A. cantonensis,10 and CSF analyses. The serologic test was done by immunoblotting analysis using IgG antibodies to the 29-kd antigenic polypeptide of A. cantonensis. The specificity of the 29-kd antigen for human
angiostrongyliasis is 99.4%. All data were obtained at the initial presentation before administration of any treatment.

**Data analysis.** Baseline and clinical characteristics of both groups were compared using descriptive statistics. Wilcoxon rank-sum and Fisher exact tests were applied to compare the differences in medians and proportions between the two groups, respectively.

Univariate logistic regression analyses were applied to calculate the crude odds ratios (ORs) of individual variables for the development of encephalitis. All variables with \( P < 0.20 \) in univariate analysis were included in subsequent multivariate logistic regression analyses. All variables with \( P > 0.15 \) in the multivariate model were excluded with the stepwise approach, whereas those with \( P < 0.15 \) were retained in the final model. To account for possible interaction, interaction terms were calculated. The goodness-of-fit of the final model was evaluated using Hosmer-Lemeshow goodness-of-fit tests. The proportion of explained variance in the model, \( \hat{R}^2 \), was calculated using the Nagelkerke \( \hat{R}^2 \) statistic.

To evaluate the discriminatory power or accuracy of the model, the area under the receiver operating characteristic curve was examined. All data analyses were performed with SAS software version 8.2.

**RESULTS**

We enrolled 14 patients diagnosed with encephalitic angiostrongyliasis and 86 unmatched patients with meningitic angiostrongyliasis randomly selected from the hospital registration database (1996–2007). Six patients in meningitis group were excluded because of incomplete clinical information. The mortality rate in the encephalitic group was 79% (11 of 14 cases). On the other hand, no deaths were recorded in the meningitis group.

The baseline characteristics, physical signs, and laboratory findings of the both groups are presented in Tables 1 and 2. Approximately three fourths of the subjects in each group were men. The encephalitis and meningitis groups showed distinct clinical features in terms of age, season of presentation, duration of headache, history of vomiting, presence of fever, seventh cranial nerve palsy, papilledema and stiff neck, percentage of blood eosinophils, CSF white blood cell count, CSF eosinophil count, CSF protein level, and CSF/plasma glucose ratios. The sensitivity of the serologic test was 50% and 62% in the encephalitis and meningitis groups, respectively.

Univariate analyses showed that factors significantly associated with encephalitis were older age, summer season, longer duration of headache, fever, papilledema, neck stiffness, low percentage of eosinophils on CBC, and low CSF/plasma glucose ratio. The sensitivity of the serologic test was 50% and 62% in the encephalitis and meningitis groups, respectively.

**DISCUSSION**

Our results showed that older age, prolonged headache duration, and fever at presentation are predictive factors for...
encephalitis. After adjustment for other factors, the risk of encephalitis in infected patients increased by 22% for every additional year of age and by 26% for every additional day of headache, whereas fever at presentation was associated with a 37-fold higher risk of encephalitis.

Older age has not been identified as a risk factor for encephalitis angiostrongyliasis until now but is a known risk factor for encephalitis induced by other agents, such as West Nile virus.15 This may relate to compromised immunity in older individuals.

The A. cantonensis larvae usually localized in the subarachnoid spaces and meninges in humans, leading to nonfatal headaches or meningeal forms. However, if a headache is disregarded by patients or diagnosis is missed or delayed, the larvae may attempt to migrate to the pulmonary arteries, as observed in rats, their definitive hosts.16 During migration, larvae may damage brain tissues, resulting in severe inflammatory processes, production of pyrogenic cytokines, and development of the encephalitic form. The presence of CSF eosinophils in the encephalitic group supports this theory.

Unlike in bacterial meningitis, only 10% of meningitic angiostrongyliasis experienced fever, compared with 71% in the encephalitic group. We propose that direct invasion of brain tissue by larvae may activate inflammatory processes and produce pyrogenic cytokines.17 Generation of pyrogenic cytokines may additionally contribute to fever, although the underlying mechanism of action in encephalitic angiostrongyliasis remains unknown.

Overall, the clinical manifestations of encephalitis and meningitis angiostrongyliasis are relatively dissimilar. Clear differences are evident in the duration of headache between the groups, with a median of 7 days for the meningitis group and 18.5 days for the encephalitis group (P = 0.002). Thus, in clinical practice, if meningitic angiostrongyliasis patients have the triad of elderly, febrile, and headache > 7 days, they should be considered at high risk of encephalitis. Such patients may benefit from combination therapy, such as corticosteroids and albendazole.18

The primary limitation of this study was the small number of patients in the encephalitis group. This led to wide confidence limits of ORs for the fever variable. Because of the retrospective design of the study, some information may be missing or unavailable. Finally, despite strict clinical criteria, a minor proportion of cases may be attributed to other causes such as gnathostomiasis. Clinically, the serologic test for angiostrongyliasis is not routinely used, and its sensitivity is only ~50–60%.12 However, the neurologic manifestations of gnathostomiasis are rare, unique, and distinct from those of angiostrongyliasis.1 History of ingestion of uncooked fish, migratory swelling, subarachnoid hemorrhage, myeloencephalitis, and unusual intracerebral hemorrhage are suggestive of gnathostomiasis.

Goodness-of-fit statistics indicated a good fit to the model. The Nagelkerke $R^2$ value suggested that 78% of data were accounted for in the final model. The $c$ statistic value or area under the ROC curve value of 0.97 signified effective discrimination of a random pair of patients with and without encephalitis. However, prospective interventional studies are needed because of the small sample size.

In summary, elderly patients with angiostrongyliasis experiencing fever and prolonged headaches are at the highest risk of developing encephalitis. Awareness, prompt diagnosis, and aggressive treatment are important factors in preventing the development of encephalitic angiostrongyliasis.

### Table 3

<table>
<thead>
<tr>
<th>Baseline characteristics</th>
<th>Crude OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>1.08</td>
<td>1.03–1.31</td>
</tr>
<tr>
<td>Season</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Winter</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Summer</td>
<td>5.60</td>
<td>1.58–19.90</td>
</tr>
<tr>
<td>Rainy</td>
<td>0.96</td>
<td>0.20–4.74</td>
</tr>
<tr>
<td>Duration of headache</td>
<td>1.16</td>
<td>1.06–1.26</td>
</tr>
</tbody>
</table>

### Table 4

<table>
<thead>
<tr>
<th>Physical signs</th>
<th>95% CI</th>
</tr>
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<tbody>
<tr>
<td>Fever*</td>
<td></td>
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<tr>
<td>Papilledema</td>
<td></td>
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<tr>
<td>Stiff neck</td>
<td></td>
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<tr>
<td>Laboratory tests</td>
<td></td>
</tr>
<tr>
<td>Percent eosinophils</td>
<td>0.93</td>
</tr>
<tr>
<td>CSF/plasma glucose ratio†</td>
<td>0.94</td>
</tr>
</tbody>
</table>

*$^{a}$ Oral temperature > 38°C.

† Equals [cerebrospinal fluid sugar/plasma glucose] × 100.

‡ Oral temperature > 38°C.

### REFERENCES


