Clinical Factors Predictive of Encephalitis Caused by *Angiostrongyulus cantonensis*

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**Abstract.** *Angiostrongyulus 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 angiostrongyliaisis 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 angiostrongyliaisis experiencing fever and prolonged headaches were at the highest risk of developing EA.

**INTRODUCTION**

*Angiostrongyulus cantonensis*, a disease caused by *Angiostrongyulus cantonensis*, has spread from the tropical endemic area to various regions throughout the world because of extensive international travel and eating habits. 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 angiostrongyliaisis.

Angiostrongyliaisis is diagnosed on the basis of clinical manifestations, 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 angiostrongyliaisis, the most common form, is acute severe headache. In contrast, encephalitic angiostrongyliaisis is rare, but fatal. Similar to viral encephalitis, encephalitic angiostrongyliaisis presents with acute deterioration of consciousness to a coma. Seizure attacks have never been reported in encephalitic angiostrongyliaisis. Limited information is currently available on the risk factors for encephalitic angiostrongyliaisis. 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 angiostrongyliaisis at Srinagarind Hospital, Khon Kaen University, Khon Kaen, Thailand. The clinical diagnostic criteria for angiostrongyliaisis were as follows: 1) CSF with a white blood cell count of > 10 cells/mm³, 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 cystercerosis, 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 encephalitic angiostrongyliaisis presented with acute coma. In addition, brain imaging must be normal in the encephalitis group. Clinical factors between both groups were studied, and the predictors were determined for encephalitic angiostrongyliaisis.

**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. 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. 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*, 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 included in subsequent multivariate analysis before administration of any treatment.

**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, as specified in Table 3.

Table 4 shows stepwise logistic multivariate analysis data on factors remaining in the final model predictive of encephalitis, which include older age (adjusted OR, 1.22; 95% CI, 1.05–1.42), prolonged duration of headache (adjusted OR, 1.26; 95% CI, 1.03–1.55), and fever (adjusted OR, 37.05, 95% CI, 1.59–862.35). Interaction terms for combinations of headache duration, age, and fever were forced into the model but were not statistically significant. For the final model, the Hosmer-Lemeshow value, Nagelkerke $R^2$, and the $c$ value were 6.30 ($P = 0.50$), 0.78, and 0.97, respectively.

**DISCUSSION**

Our results showed that older age, prolonged headache duration, and fever at presentation are predictive factors for
and produce pyrogenic cytokines. Generation of pyrogenic brain tissue by larvae may activate inflammatory processes in the encephalitic group. We propose that direct invasion of angiostrongyliasis experienced fever, compared with 71% in the absence of larvae, indicating a 37-fold higher risk of encephalitis.

Older age has not been identified as a risk factor for encephalitis caused by Angiostrongylus cantonensis. However, the neurologic manifestations of gnathostomiasis are rare, unique, and distinct from those of angiostrongyliasis.

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 encephalitis due to angiostrongyliasis.

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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>
<tr>
<td>Physical signs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fever</td>
<td>22.50</td>
<td>5.72–88.58</td>
</tr>
<tr>
<td>Papilledema</td>
<td>10.64</td>
<td>1.60–70.92</td>
</tr>
<tr>
<td>Stiff neck</td>
<td>6.63</td>
<td>1.39–31.56</td>
</tr>
<tr>
<td>Laboratory tests</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Percent eosinophils</td>
<td>0.93</td>
<td>0.88–0.99</td>
</tr>
<tr>
<td>CSF/plasma glucose ratio</td>
<td>0.94</td>
<td>0.89–0.98</td>
</tr>
</tbody>
</table>

* Oral temperature > 38°C.
† Equals [cerebrospinal fluid sugar / plasma glucose] × 100.
‡ Per additional day of duration of headache.

Table 4

<table>
<thead>
<tr>
<th>Results of multiple logistic regression analysis showing independent variables for encephalitis and their adjusted ORs</th>
<th>Adjusted OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)*</td>
<td>1.22</td>
<td>1.05–1.42</td>
</tr>
<tr>
<td>Duration of headache (days)†</td>
<td>1.26</td>
<td>1.03–1.55</td>
</tr>
<tr>
<td>Fever‡</td>
<td>37.05</td>
<td>1.59–862.34</td>
</tr>
</tbody>
</table>

* Per additional year of age.
† Per additional day of duration of headache.
‡ Oral temperature > 38°C.

REFERENCES