Encephalitic Angiostrongyliasis

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1. Introduction

Angiostrongyliasis, caused by Angiostrongylus cantonensis, is an emerging infectious disease worldwide (Wang et al., 2008). A. cantonensis is a neurotropic nematode. The endemic areas are Southeast Asia, East Asia, and the Pacific Islands. Sporadic outbreaks and report cases are frequently reported globally.

There are three main clinical presentations of angiostrongyliasis including meningitic, encephalitic, and ocular form (Sawanyawisuth & Sawanyawisuth, 2008). Meningitic angiostrongyliasis is the most common form and has a good prognosis. In contrast, encephalitic angiostrongyliasis occurs in a minority of angiostrongyliasis cases but has high mortality rate. Clinicians worldwide should be knowledgeable and have low suspicious level of this condition due to its high mortality.

The chapter will cover the life cycle of A. cantonensis and its route of transmission. In addition, risk factors, pathology, clinical manifestations, treatment, prognosis, and prevention of encephalitic angiostrongyliasis will be reviewed.

2. Life cycle and transmission (Figure 1)

The adult worms of A. cantonensis or the rat lung worm reside in rat’s pulmonary arteries. The young adults migrate to pharynx, pass the esophagus and expose to the environment with the feces. The intermediate hosts are snails where the larvae become the later stages of larvae. Rats ingest the contaminated snails or slugs and the larvae migrate to the brain via gastrointestinal blood vessels. The worms then migrate back to the pulmonary artery and complete its life cycle.

Humans are an accidental host of this parasite and get infected by eating raw snails or other paratenic hosts such as shrimps, frogs, or monitor lizards. Contaminated slugs, vegetables, or juices (Tsai et al., 2004) are other possible sources of the parasites. Similarly to rats, A. cantonensis larva migrate to human meninges and brain causing eosinophilic meningitis and encephalitis, respectively. There is a report showed that some larva migrated to human pulmonary artery (Sonakul 1978) and died there.

3. Risk factors

Human angiostrongyliasis caused by A. cantonensis has three clinical presentations including eosinophilic meningitis, eosinophilic encephalitis, and ocular angiostrongyliasis. The vast of patients develop meningitic angiostrongyliasis. Gastrointestinal involvement is
also possible (Sawanyawisuth et al., 2010). One patient presented with clinical symptoms of gut obstruction and then developed encephalitic angiostrongyliasis afterward.

Fig. 1. *Angiostrongylus cantonensis* life cycle
Downloaded from http://www.cdc.gov/parasites/angiostrongylus/biology.html

There is a report comparing clinical presentations between meningitic and encephalitic angiostrongyliasis. The study aimed to find the clinical factors predictive for encephalitic angiostrongyliasis (Sawanyawisuth et al., 2009). The study was done in the Northeastern part of Thailand, the endemic area of angiostrongyliasis. There were 14 encephalitic angiostrongyliasis and 80 meningitic angiostrongyliasis patients in the study. Three significant risk factors for developing encephalitic angiostrongyliasis were older age, prolong headache and having fever with adjusted odds ratio (95% confidence interval) of 1.22 (1.05-1.42), 1.26 (1.03-1.55), and 37.05 (1.59–862.34), respectively. Unlike bacterial meningitis, fever is not common in meningitic angiostrongyliasis. Fever and neck stiffness are found only 10% and 50% in patients with meningitic angiostrongyliasis. In
contrasting to meningitic angiostrongyliasis, having fever and neck stiffness are more common in encephalitic angiostrongyliasis (71% and 86%, respectively).

Even though coma is a presenting symptom for encephalitic angiostrongyliasis, patients with encephalitic angiostrongyliasis always have preceding headache before an abrupt onset of coma. The median duration of headache in encephalitic angiostrongyliasis was significantly longer than those with meningitic angiostrongyliasis (18.5 vs 7 days). Finally, every a year of age increases a risk of being encephalitic angiostrongyliasis for 22% comparing to those who have meningitic angiostrongyliasis.

In summary, people who get infected with *A. cantonensis* may develop encephalitic angiostrongyliasis if one is elderly or has fever or long duration of preceding headache.

### 4. Pathology

A previous study showed that *A. cantonensis* larva might take about two or three days to reach human brain from gastrointestinal tract. The patient developed encephalitic angiostrongyliasis approximately two to three days after having localized peritonitis (Sawanyawisuth et al., 2010).

There are at least eleven proved cases of encephalitic angiostrongyliasis (Ko et al., 1987; Nye et al., 1970; Sonakul 1978). All cases had at least one *A. cantonensis* larva in the brain. The numbers of worm in autopsy cases vary and range from one to numerous larvae. Worms may be alive or dead and worm sizes are between 50-120 micron. Locations of worms were random. Of those, worms were also detected in cerebrospinal fluid examination in two cases. Seven cases were Thai and four cases were reported from Hong Kong.

Gross pathology showed diffused brain swelling, leptomeningitis, mild ventricular dilatation, and several small focal hemorrhage. On microscopic examination, there are four major findings including worm tracks, hemorrhagic spot, cell infiltration with granuloma, and parts of worms. The worm track size are between 0.1-1 mm in length and approximately 1 mm in diameter. Hemorrhagic spot may be found but not all cases, mostly are small in size. The cell infiltrations may be plasma cells, lymphocytes, and eosinophils. The granuloma is also presented. Charcot-Leyden crystals, an evidence of eosinophils, may be found. Parts of worm may also be shown in particular section. Vascular changes such as vessel wall edema, perivascular infiltration with lymphocytes and eosinophils. The granuloma and vascular changes are identical to a case of gastrointestinal involvement of *A. cantonensis* (Sawanyawisuth et al., 2010).

### 5. Clinical manifestations

The clinical manifestations of encephalitic angiostrongyliasis are similar to viral encephalitis (Sawanyawisuth et al., 2009). The main symptoms are acute fever with abrupt onset of alteration of consciousness to coma stage without significant motor weakness. Unlike viral encephalitis, seizures are rare.

Clinical clues for encephalitic angiostrongyliasis are history of exposure to *A. cantonensis* larva, cerebrospinal fluid eosinophils, and history of preceding headache prior to coma (Chotmongkol & Sawanyawisuth, 2002; Sawanyawisuth et al., 2009). The first two factors are very crucial. History of eating raw freshwater snails, slugs, frogs, shrimps, monitor lizards, contaminated vegetables, contaminated juice or even playing with snails (Wan & Weng, 2004) within the range of 90 days is the major risk factor for angiostrongyliasis.
Cerebrospinal fluid eosinophils more than 10% of the total white blood cells is also suggestive for encephalitic angiostrongyliasis. Even though there are several causes of cerebrospinal fluid eosinophils, history of exposure to *A. cantonensis* may support the diagnosis of encephalitic angiostrongyliasis.

In some patients, history of preceding headache before developing coma may be obtained from patients' relatives. This finding support the mechanism of developing encephalitic angiostrongyliasis that encephalitic angiostrongyliasis may be the progression of meningitic angiostrongyliasis. The median duration of headache is about 18 days (range 1-30 days).

The alteration of consciousness after the headache may take approximately two days to coma stage (range 1-4 days). Fever may develop before or together with the occurrence of alteration of consciousness. The duration of fever may range between 1-21 days.

The other histories or physical findings in encephalitic angiostrongyliasis are history of paresthesia (8%), vomiting (8%), sixth cranial nerve palsy (14%), seventh cranial nerve palsy (7%), papilledema (21%), and neck stiffness (86%) as shown in Table 1 (Sawanyawisuth et al., 2009). Most affected patients are male in either encephalitic or meningitic angiostrongyliasis (approximately 80%) due to habit of eating raw foods. Rare manifestations include radiculomyelitis (Graber et al., 1997; Kliks et al., 1982), localized peritonitis (Sawanyawisuth et al., 2009), or ocular blindness (Sawanyawisuth et al., 2007).

<table>
<thead>
<tr>
<th>Variables</th>
<th>N (%) or median (range)</th>
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</thead>
<tbody>
<tr>
<td>Baseline characteristics</td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>11 (79)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>51 (26-78)</td>
</tr>
<tr>
<td>Summer season admitted</td>
<td>7 (50)</td>
</tr>
<tr>
<td>Incubation (days)</td>
<td>12 (1-30)</td>
</tr>
<tr>
<td>Duration of preceding headache (days)</td>
<td>18.5 (1-30)</td>
</tr>
<tr>
<td>Duration to coma stage (days)</td>
<td>2.3 (1-4)</td>
</tr>
<tr>
<td>Paresthesia</td>
<td>1/13 (8)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>1/13 (8)</td>
</tr>
<tr>
<td>Physical signs</td>
<td></td>
</tr>
<tr>
<td>Fever</td>
<td>10 (71)</td>
</tr>
<tr>
<td>Sixth cranial nerve palsy</td>
<td>2 (14)</td>
</tr>
<tr>
<td>Seventh cranial nerve palsy</td>
<td>1 (7)</td>
</tr>
<tr>
<td>Papilledema</td>
<td>3 (21)</td>
</tr>
<tr>
<td>Stiff neck</td>
<td>12 (86)</td>
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</table>

Table 1. Clinical manifestations of encephalitic angiostrongyliasis (Adapted from Sawanyawisuth et al., 2009).

The laboratory tests in encephalitic angiostrongyliasis are not diagnostic with the exception of the predominant of cerebrospinal fluid eosinophils. The median peripheral white blood cell counts is 10,850 cells/mm$^3$ (range 5,350-20,800) with percent of eosinophils of 8% (range 0-33) as shown in table 2. The cerebrospinal fluid findings are comparable with meningitic angiostrongyliasis. The median opening pressure of cerebrospinal fluid was 225 mmH$_2$O. The median of cerebrospinal fluid white blood cell was 623 cells/mm$^3$ but may be high as 1,500 cells/mm$^3$. The percentage of cerebrospinal fluid eosinophils may range from 16-70%. The cerebrospinal fluid protein and glucose range are 61-254 mg/dL and 17-240 mg/dL,
respectively. The cerebrospinal fluid glucose/plasma glucose ratio can be low as 19% (Sawanyawisuth et al., 2009).

<table>
<thead>
<tr>
<th>Variables</th>
<th>Median (range)</th>
</tr>
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<tbody>
<tr>
<td>Blood tests</td>
<td></td>
</tr>
<tr>
<td>White blood cell (cells/mm³)</td>
<td>10,850 (5,350-20,800)</td>
</tr>
<tr>
<td>Percent eosinophils</td>
<td>8 (0-33)</td>
</tr>
<tr>
<td>Cerebrospinal fluid findings</td>
<td></td>
</tr>
<tr>
<td>Opening pressure (mmH2O)</td>
<td>225 (140-580)</td>
</tr>
<tr>
<td>White blood cell (cells/mm³)</td>
<td>623 (57-1,500)</td>
</tr>
<tr>
<td>Percent eosinophils</td>
<td>44 (16-70)</td>
</tr>
<tr>
<td>Protein (mg/dL)</td>
<td>133 (61-254)</td>
</tr>
<tr>
<td>Glucose (mg/dL)</td>
<td>41 (17-240)</td>
</tr>
<tr>
<td>Cerebrospinal fluid glucose/plasma glucose ratio (%)</td>
<td>35 (19-53)</td>
</tr>
</tbody>
</table>

Table 2. Laboratory findings in encephalitic angiostrongyliasis (Adapted from Sawanyawisuth et al., 2009).

The measurement of serum and cerebrospinal fluid immunoglobulin may be an additional diagnostic tool for encephalitic angiostrongyliasis. The intrathecal level of immunoglobulin particularly immunoglobulin E by using quotient diagram (Reibergram) comparing between cerebrospinal fluid and serum has been reported to be diagnostic (Dorta-Contreras & Reiber, 1998; Padilla-Docal et al., 2008).

The neuroimaging studies in encephalitic angiostrongyliasis are not specific (Jin et al., 2005; Jin et al., 2008; Kanpittaya et al., 2000; Tsai et al., 2003). The computed tomography of the brain always shows diffuse brain swelling, small area of attenuation with surrounding hypodense area, or meningeal enhancement. The magnetic resonance imagings may give some information but still not diagnostic. The lesions might be scattered or diffuse high-, or iso-, or low-signal on T1 weighted and high-signal on T2 weighted imagings. After the gadolinium injection, the lesions usually become nodular or stick-shaped enhancement. The involved area may be random in the brain such as basal ganglia, mudulla oblongata, globus pallidus, or cerebral peduncles. High signal on periventricular area, linear small hemorrhagic tract, or linear enhancement in the leptomeninges may be found. The MRI intensity in T1-weighted imaging may correlate with severity of headache, cerebrospinal fluid pleocytosis, and cerebrospinal fluid and blood eosinophilia (Tsai et al., 2003). Finally, communicating hydrocephalus may be the late complication of encephalitic angiostrongyliasis (Graber et al., 1997; Sawanyawisuth et al., 2006). Electroencephalogram in encephalitic angiostrongyliasis may reveal abnormal slow dysrhythmia or slow alpha rhythm (Ko et al., 1987; Wang et al., 2002).

Serological tests for *A. cantonensis* have been developed and are very useful in situations of equivocal diagnosis between angiostrongyliasis and other parasites; mostly gnathostomiasis and cysticercosis. There are various serological techniques for angiostrongyliasis such as Enzyme-Linked ImmunoSorbent Assay (ELISA), polymerase chain reaction (PCR), immunoblotting, or antigen detection (Chye et al., 2004; Eamsobhana et al., 2006; Eamsobhana & Yong, 2009; Eamsobhana et al., 2009, Intapan et al., 2003; Maleewong et al., 2001). The sensitivity, specificity, and cross-reaction are varied on each technique. Another concern about serologic test is its availability in health-care facilities. Most serological tests have very high specificity for human angiostrongyliasis. The two most common diagnostic
bands are 29- and 31-kDa antigenic polypeptide of *A. cantonensis* (Eamsobhana et al., 2006; Eamsobhana & Yong, 2009; Intapan et al., 2003).

6. Diagnosis

The definite diagnosis of encephalitic angiostrongyliasis is the detection of *A. cantonensis* larva in the cerebrospinal fluid or in any part of the brain by the pathological examination. However, the chance of the identification of *A. cantonensis* larva in the cerebrospinal fluid is extremely rare (Punyagupta et al., 1970). Therefore, the diagnosis of encephalitic angiostrongyliasis can be made by clinical criteria.

For patients who presenting with clinical of acute encephalitis or acute fever with alteration of consciousness, *A. cantonensis* may be the causative agent if meet the following clinical criteria: cerebrospinal fluid white blood cell count of more than 10 cells/mm³, cerebrospinal fluid eosinophils accounts for at least 10%, negative results of cerebrospinal fluid Gram, acid-fast, and India ink staining, cryptococcal antigen, and cultures, plus history of expose to *A. cantonensis* larva.

Some features may decrease the likelihood of encephalitic angiostrongyliasis including history of eating raw fish, history of migratory swelling, clinical diagnosis of subarachnoid hemorrhage or myeloencephalitis, positive serologic test for gnathostomiasis or cysticercosis, brain computed tomography or magnetic resonance imaging suggestive of gnathostomiasis, symptomatic or serology-positive HIV infection, and active or previous history of tuberculosis or malignancy (Sawanyawisuth et al., 2009).

Serodiagnosis may be helpful tool for equivocal case between angiostrongyliasis and other neuroparasitoses such as gnathostomiasis, cysticercosis, or paragonimiasis.

7. Differential diagnosis

There are several causes of cerebrospinal fluid eosinophils such as neurognathostomiasis, cysticercosis, paragonimiasis, toxocariasis, tuberculosis, or malignancy. However, clinical manifestations of each condition are quite obviously different.

Neurognathostomiasis is almost always presenting with radicular pain, bloody CSF, and pertinent neurological deficit such as hemiparesis or paraparesis (Ramirez-Avila et al., 2009; Schmutzhard et al., 1988). Seizures may be the predominant symptom of neurocysticercosis. Eosinophilic cerebrospinal fluid due to Paragonimus infection is rare, usually accompanied with pleuro-pulmonary lesions, and less likely to cause alteration of consciousness (Solomon et al., 2006). Eating raw freshwater crab is a risk factor for paragonimiasis. Exposure to dog and raccoon feces may be risk factor for neurotoxocariasis and *Baylisascaris procyonis* infection, respectively. The last two diseases are predominant in children (Solomon et al., 2006). Active tuberculosis and malignancy may also cause eosinophilic cerebrospinal fluid but fluid, but they are rarely reported to have cerebrospinal fluid eosinophils.

8. Treatments

Even though meningitic angiostrongyliasis will be successfully treated with corticosteroid (Chotmongkol et al., 2000), there is no effective treatment for encephalitic angiostrongyliasis. The combination between corticosteroid and anthelminthic agents may be beneficial.
Albendazole may be the preferred combination regimen due to its high absorbable through gastrointestinal tract and high concentration in cerebrospinal fluid. A report from China showed that the regimen of dexamethasone (20 mg, qid), gamma-globulin (0.5 g/kg), 20% mannitol, and Chinese herbs (Xing Nao Wan) was an effective treatment regimen for a patient with encephalitic angiostrongyliasis. The patient recovered from coma stage quickly and had only mild memory loss at discharge (Li et al., 2008).

9. Prognosis

Generally, the prognosis of encephalitic angiostrongyliasis is poor (Ko et al., 1987; Martínez-Delgado et al., 2000; Pascual et al., 1981; Chotmongkol & Sawanyawisuth, 2002). The mortality rate is approximately 80% and the rest are likely to be bed-ridden stage. The causes of death are hospital acquired infections or severe brain edema and herniation.

10. Prevention

The effective prevention is to avoid contaminated foods particularly raw freshwater snails, slugs, frogs, shrimps, contaminated vegetables and juice including playing or contact with snails.

11. Conclusion

Encephalitic angiostrongyliasis, a rare manifestation of human angiostrongyliasis, can be diagnosed by clinical criteria. Clinical clue for this condition are history of exposure to A. cantonensis larva, evidence of eosinophils in cerebrospinal fluid more than 10% without other possible causes of eosinophils in cerebrospinal fluid. Serological tests may be used as a confirmatory test. Currently, there is no effective treatment. Corticosteroid, anthelminthics, or gamma-globulin may be optional treatments. Due to the high mortality rate, prevention is the most important strategy.

12. References


Many infectious agents, such as viruses, bacteria, and parasites, can cause inflammation of the central nervous system (CNS). Encephalitis is an inflammation of the brain parenchyma, which may result in a more advanced and serious disease meningoencephalitis. To establish accurate diagnosis and develop effective vaccines and drugs to overcome this disease, it is important to understand and elucidate the mechanism of its pathogenesis. This book, which is divided into four sections, provides comprehensive commentaries on encephalitis. The first section (6 chapters) covers diagnosis and clinical symptoms of encephalitis with some neurological disorders. The second section (5 chapters) reviews some virus infections with the outlines of inflammatory and chemokine responses. The third section (7 chapters) deals with the non-viral causative agents of encephalitis. The last section (4 chapters) discusses the experimental model of encephalitis. The different chapters of this book provide valuable and important information not only to the researchers, but also to the physician and health care workers.

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