Clinical Characteristics of Long-Term Complications of Severe Rat Lung Worm Disease in Hawai'i: A Survey of 4 Cases

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Abstract

Rat lung worm disease (RLWD) is endemic to Hawai'i, and cases of severe RLWD with long-term sequelae have been reported in Hawai'i. However, there are limited data on clinical features of the RLWD survivors with the long-term sequelae. The authors conducted a survey to report on clinical characteristics of RLWD survivors with the long-term sequelae. Four RLWD survivors had severe RLWD with persistent, neurological symptoms for years after RLWD. In conclusion, long-term sequelae of severe RLWD exist. The most common long-term consequence among participants was severe skin pain, which may relate to damage of the nerves or spinal cord.

Keywords

Angiostrongylus cantonensis, eosinophilic meningitis, numbness, pain, rat lung worm disease

Abbreviations and Acronyms

CBD = cannabidiol
CSF = cerebrospinal fluid
ELIS = enzyme-linked immunosorbent assay
OTC = over-the-counter
PCR = polymerase chain reaction
RLWD = rat lung worm disease
TENS = transcutaneous electrical nerve stimulation
THC = tetrahydrocannabinol
TNF-α = tumor necrosis factor alpha

Introduction

Rat lung worm disease (RLWD), caused by *Angiostrongylus cantonensis*, has several forms and clinical manifestations. Presence of cerebrospinal fluid (CSF) eosinophils of 10% or more is used as suggestive criterion for RLWD.[1–3] There are several forms of RLWD such as encephalitis or coma, ocular angiostrongyliasis, gastrointestinal angiostrongyliasis, or radiculomyelitis.[4–7] The most prevalent form is eosinophilic meningitis which is commonly reported from Thailand.[1,3] RLWD can be found worldwide particularly in Asia Pacific countries. In the US, RLWD is most commonly reported in Hawai'i.[8,9] There were 82 confirmed cases of angiostrongyliasis (severe and non-severe forms) reported in Hawai'i from 2007 to 2017.[9-11] Two deaths with eosinophilic meningoencephalitis have been reported in Hawai'i since 1962.[10]

Eosinophilic meningoencephalitis is a severe form of RLWD which can lead to coma and death. A report from Thailand found that this form occurred in less than 10% of RLWD cases but had a mortality rate of at least an 80%.[11,12] Several confirmed reported cases of RLWD from Hawai'i are published in literature.[13] At least 1 case of a long-term sequela of severe RLWD in Hawai'i was reported in the literature in 2013.[14] Severe RLWD or long-term sequelae of RLWD in Hawai'i may be underreported. Additionally, there are limited data on risk factors or clinical manifestations of the long-term sequelae of RLWD. This study aimed to report the clinical characteristics of long-term sequelae of RLWD in Hawai'i.

Methods

This study was conducted as a survey after the 6th International Workshop on Angiostrongylus and Angiostrongyliasis, which was organized by the University of Hawai'i at Hilo. The workshop was held on January 5-8, 2020 in Hilo, Hawai'i with survivors of RLWD attending. RLWD survivors who registered or attended for the meeting were invited to participate in the survey by personal approach during and after the conference. A self-reported questionnaire was used to evaluate the clinical course of RLWD and also the long-term sequelae from the RLWD. The questionnaire was developed for this study and was comprised of questions around demographic characteristics, diagnosis, treatment, outcomes, and long term sequelae as shown in **Table 1**. RLWD survivors were invited by purposive sampling and asked to fill out the questionnaire without personal identifiers by an online link or by printing it out and mailing to the authors. Data were tabulated and reported by using Microsoft Excel software version 11.1 (Mircrosoft Corp., Redmond, WA). The study protocol was waived for ethical consideration, Khon Kaen University, Thailand (HE631229).

Results

Five RLWD survivors were invited to participate the study. Four RLWD survivors agreed to participate (80%). All lived on Hawai'i Island. There were 3 men and 1 woman, and their average age was 63.5 years (range 50-78 years) as shown in **Table 1**. Three cases had exposure of RLWD by consuming salad or shrimp with an incubation period from 2 to 6 weeks. Persistent headache was a presenting symptom in one case, while the other two cases had flu-like symptoms and back/chest tightness as presenting symptoms. Overall, headache was reported in three cases (75%) at the presentation. All cases had several symptoms at the time of presentation such as skin pain (4 cases), urinary retention (Cases 1, 3, and 4), and constipation (Case 1). Two of 4 cases had positive confirmation test by PCR

Table 1. Clinical Course and Characteristics of Rat Lung Worm Disease in Survivors with Long Term Complications in Hawai'i				
Factors	**Case 1**	**Case 2**	**Case 3**	**Case 4**
Age (years)	60	66	50	78
Sex	Female	Male	Male	Male
Ethnicity	White	White	White	White
Year of diagnosis	2015	2016	2019	2015
Route of infection	Shrimp	Prawn salad on Hawai'i Island	Slugs on lettuce from garden, North Kohala, Hawai'i	Contaminated water tank
Incubation	Unknown	6 weeks	9 days	2 weeks
Presenting symptom	Persistent headache	Flu like symptom with metallic taste	Strong pressure on upper middle back and chest	Weird feeling in the eye
Accompanying symptoms	Double vision Urinary retention Hip and leg weakness Nerve pain Constipation Severe itchiness Lethargy	Severe skin pain: itchiness and pain	Fitful sleep Restless legs Tingling in the tip of right thumb Progressive headache Cough Tingling/burning in neck, toes, and hands Fever, Strained urination Sore calves, shooting pain in legs, trouble walking Hiccups Night sweats Ice cold feet Stiff neck Blurred vision Nausea Severe nerve pain Bedridden	'Creepy' feeling in the back of the head, headache, pain in the leg, urinary retention
Basis of diagnosis	CSF PCR positive (Oct 13)	Clinically with CSF eosinophils	CSF PCR positive	ELISA test
Numbers of lumbar puncture, n; numbers of CSF white blood cells (cells/mm3), date (Parenthesis).	1. WBC 194 (Oct 9) 2. WBC 177 (Oct 15) 3. WBC 128 (Nov 20) 4. WBC 183 (Nov 30)	None	1. unknown WBC 2. unknown WBC	None
CSF eosinophils in each lumbar puncture	1. 42% 2. 59% 3. 15% 4. 2%	None	1. 0% 2. 7%	None
CSF glucose in each lumbar puncture	1. 37 2. 50 3. 50 4. 64	None	None	None
CSF protein in each lumbar puncture (normal range < 40 mg/dL)	1. 79 2. 73 3. 84 4. 52	None	None	None
Blood eosinophilia in each test	1. 6.8% of 6900 WBC 2. 11.0% of 6800 WBC 3. 14.9% of 9800 WBC	None	1. 5.7% 2. 7.4%	None
Other labs and imaging	Normal CT of brain	None	MRI brain: micro-hemorrhage in left brain	None
Treatment	IV antibiotics IV steroids Pain killers Oral steroid: 80 mg max for 6 months Gabapentin Albendazole	Unknown but treatment protocol for RLWD	IV morphine prn Fentanyl patch oxycodone oral IV steroid zolpidem	None

Table 1. Clinical Course and Characteristics of Rat Lung Worm Disease in Survivors with Long Term Complications in Hawai'i (Con't)				
Factors	**Case 1**	**Case 2**	**Case 3**	**Case 4**
Clinical course	Severe pain at buttocks, back of legs, feet (sharp pain) persistent pain 6 weeks high blood pressure with high pulse rate urinary tract infection sepsis insomnia Inflammatory arthritis	1 week of coma 5 weeks of bed ridden status	Phase 1 (month 1): walk with cane, slowly getting back to work Phase 2 (month 2-7): alternative therapy with slow improvement Phase 3 (month 8-10): able to work and walk without a walking aid	None
Current medications	Duloxetine Pregabalin Eszopiclone Magnesium d-mannose	None	Cerebrolysin (215 mg) injections Dihexa (20mg) every other day Perineural injection therapy to several peripheral nerves Mindfulness-based stress reduction	Traditional Chinese Medicine
Current status	Pain (numbness, stinging, burning, pin sensation, tingling) on 50% body, right side of head Uncontrollable sharp breaths, sometimes Constipation Poor short-term memory	Left leg neurologic pain Cranial nerve 6th palsy Sleep deprivation	Able to work and walk almost normal Pain/numbness in right leg Fatigue Mood swing Tingling and itchiness in arms, hands, and fingers	Fairly constant pain in left side of head, ear, neck, and arm.
Thoughts	Have to go through the stages of brief "Each day we are born again, What we do today is what matters most" Buddhism meditation Returning to physical activity may help: walking, yoga, Pilates Treatment with albendazole seemed to help even 3-4 years out Brain exercises: use an app called elevate Use mind, brain, body connection with mindfulness and meditation to improve pain: how we think is how we feel	Excruciating itchiness and skin pain was persistent for year and can be a symptom of RLWD	Albendazole is necessary but unavailable in the US* Increased education of providers in hospital ERs, urgent care and private practices Increased funding for research and education Improved response from agencies, esp. DOH. Alerting visitors about disease and protocols for avoiding it. We were one of the rare cases who actually knew exactly when I had contact with a semi-slug	None
Time elapsed since infection	5 years	3 years	1 year	5 years

Note. CSF: cerebrospinal fluid; ELISA: enzyme-linked immunosorbent assay; IV: intravenous; PCR: polymerase chain reaction; WBC: white blood cells; DOH: Department of Health; *patient thought but albendazole is available in the US.

method, while 1 case was diagnosed clinically, and another was diagnosed by enzyme-linked immunosorbent assay (ELISA) test. CSF eosinophils, ranging from 7%-59%, were found in 3 cases. One case presented with a small intracerebral hemorrhage.

There was no consistent treatment regimen in these 4 cases. Intravenous steroids were given in 2 cases, and albendazole was given in Case 1. Cases 2 and 3 developed coma and bed-ridden status. Case 1 had urinary tract infection after long term use of steroid. Cases 1 and 3 reported use of mindfulness treatment for their remaining symptoms. The 4 respondents shared the following thoughts on RLWD care: using mindfulness and Buddha theory may reduce remaining symptom (Case 1), RLWD may have atypical symptoms (Case 2), RLWD care/diagnosis/knowledge for physicians should be improved (Case 3), and traditional Chinese medicine may be useful for long-term sequelae (Case 4) as shown in **Table 1**.

All 4 cases reported long term health consequences from RLWD for 1 to 5 years. Body pain was the most common symptom and reported in all 4 cases (**Table 1**). Other symptoms included breathing problems (Case 1), constipation (Case 1), poor short-term memory (Case 1), cranial nerve palsy (Case 2), sleep difficulty (Case 2), fatigue (Case 3), mood disturbance (Case 3), and tingling/itchiness (Case 3). Traditional or alternative medicine was used in all cases for the treatment of long-term sequelae.

Discussion

This study found that these 4 patients with severe cases of RLWD faced difficulties in arriving at the diagnosis of RLWD. Factors that may have been associated with diagnosis issues in these cases include unknown risk for or exposure to RLWD and low percentage of eosinophils in Case 1; and uncommon presentation of RLWD and diagnostic errors at the emergency

department despite obvious risk factor of consuming slugs prior to developing symptoms of RLWD in Case 3. These diagnostic issues indicate a need for education about RLWD among physicians not only in endemic areas but also in other countries due to heavy traveling to endemic countries.[15] Additionally, CSF eosinophils may not reach 10% in early cases. One study found 1 patient out of 9 patients diagnosed with RLWD had CSF eosinophils of 2%.[16]

Severe RLWD in Cases 2 and 3 may be associated with delayed diagnosis. A previous study found longer duration of headache or delayed diagnosis of RLWD for 1 day increased risk of coma or severe encephalitis form by 26%.[12] Older age is another risk factor associated with severe RLWD.[12] A study in Thailand found those with severe RLWD or RLWD with encephalitis had an average age of 51 years, compared with 33.5 years in those with meningitis or non-severe RWLD ($P = .002$).[12] The 4 cases in the current study were at high risk for developing severe RLWD as they were older than average age of patients with RLWD (33.5 years).[12] These 4 cases had symptoms of severe skin pain that is a pathognomonic sign for RLWD.[5] Other than an indicator for RLWD, this skin pain may also indicate a migration of *Angiostrongylus cantonensis* larvae to the spinal cord.[13] A previous autopsy of a person with severe RLWD suggested that a larva migrated to the spinal cord and caused severe skin pain such as that experienced by these 4 four cases. Long term sequelae of patients with RLWD was reported in Hawai'i but there is no previous report of long term sequelae of RLWD in Thailand, an endemic area.[11,14] One possible explanation may be due to a different vector. In Thailand, raw or uncooked freshwater snails are the main transmission mode. In Hawai'i, food or drink contaminated with slugs and shrimp are more common vectors and probably have a higher larva load.[9]

All 4 cases here continued to have long-term sequelae of RLWD with the longest duration of disease being 5 years (Cases 1 and 4). A previous report found that 57% of those who suffered from RLWD had full recovery.[17] Pain and numbness may indicate permanent nerve damage from the larva migration through the spinal cord or nerve root.[11] There is no previous study on treatment of these long-term consequences of RLWD in literature. From the patient perspective, mindfulness and meditation may be helpful. Previous studies showed that mindfulness normalized stress biomarkers such as TNF-α (from 57.1 to 45.4 pg/mL), and meditation increased brain oxygenation in the prefrontal cortex significantly (P-value < .0001) in patients with glaucoma.[18,19] Additionally, mindfulness may ameliorate stress, oxidative stress, inflammation, and parasympathetic nervous system activity resulting in reduction of pain from neurological system. Therefore, mindfulness and mediation may improve the damaged nerve or spinal cord that may cause severe skin pain.[20,21]

Regarding treatment with albendazole, Case 3 thought that it was not available in the US. But, albendazole is actually available in the US and most countries. There is no clinical data on the efficacy of albendazole for post-exposure prevention for RLWD. However, it may be effective to reduce the duration of headaches in patients with RLWD compared with placebo (8.9 vs 16.2 days; $P = .05$).[22] A systematic review found that corticosteroid treatment with or without albendazole is effective.[23] For post-exposure prevention of RLWD, a study found that pyrantel pamoate given at a dose of 11 mg/kg can reduce worm burden up to 72%.[24] However, further clinical studies are required.

There are several limitations in this study. First, RLWD survivors who were invited to the conference were mainly from Hawai'i and were invited to the study personally resulting in small sample size. Second, the questionnaire was developed for this study and not validated prior to use. Items in the questionnaire were general, and the data on long term sequelae were qualitative. Third, clinical data from each survivor were limited as hospital chart access was not available.[25,26] The data were self-reported, and were also subject to recall bias. Finally, no point of care test or predictive factors were studied.[27-29]

In conclusion, long-term sequelae of severe RLWD exist. The most common long-term consequence is severe skin pain that may relate to damage of nerves or spinal cord.

Conflict of Interest

None of the authors identify any conflicts of interest**.**

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