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Original Article

Epidemiological, clinical and laboratory aspects of *Angiostrongylus cantonensis* infection: an integrative review

Aspectos epidemiológicos, clínicos e laboratoriais de infecção por *Angiostrongylus cantonensis*: uma revisão integrativa

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Abstract

This integrative literature review study analyzes the findings of the last 5 years of the parasite *Angiostrongylus cantonensis*. It is known that this nematode is found in the pulmonary arteries of rats, where it remains as a definitive host. From mice, the cycle spreads to animals, such as snails, which in contact with humans can trigger the disease. In humans, the parasite causes several neurological, abdominal manifestations and mainly meningitis. Based on the review of studies, its epidemiology shows worldwide distribution, although there are endemic cases for this parasite, such as asian countries. Laboratory findings generally showed altered CSF with turbidity, increased protein and eosinophilia, which generated meningeal signs in the patient, moreover MRI exams showed multiple alterations. Rare findings of the nematode in the eyeball, lung and signs of peritoneal inflammation were reported, which requires further studies to understand the whole pathophysiology. Finally, conservative treatment based on anthelmintics and anti-inflammatories brought good responses, although there are reports of deaths, which demonstrates the importance in the prevention and therapy of this disease.

Keywords: epidemiology, *Angiostrongylus cantonensis*, rat lungworm.

Resumo

Este estudo de revisão integrativa da literatura analisa os achados dos últimos 5 anos do parasita Angiostrongylus cantonensis. Sabe-se que esse nematoide é encontrado nas artérias pulmonares de ratos, onde permanece como hospedeiro definitivo. Dos camundongos, o ciclo se espalha para os animais, como os caracóis, que em contato com humanos podem desencadear a doença. Em humanos, o parasita causa diversas manifestações neurológicas, abdominais e principalmente meningite. Com base na revisão de estudos, sua epidemiologia mostra distribuição mundial, embora existam casos endêmicos para esse parasito, como países asiáticos. Os achados laboratoriais geralmente mostraram LCR alterado com turbidez, aumento de proteínas e eosinofilia, o que gerou sinais meníngeos nos pacientes, além disso, os exames de ressonância magnética mostraram múltiplas alterações. Foram relatados achados raros do nematoide no globo ocular, pulmão e sinais de inflamação peritoneal, o que requer mais estudos para o entendimento de toda a fisiopatologia. Por fim, o tratamento conservador à base de anti-helmínticos e anti-inflamatórios trouxe boas respostas, embora haja relatos de óbitos, o que demonstra a importância na prevenção e terapia dessa doença.

Palavras-chave: epidemiologia, *Angiostrongylus cantonensis*, verme pulmonar do rato.

1. Introduction

The parasite *Angiostrongylus cantonensis* is a nematode known as the mouse lungworm and responsible for the zoonosis called cerebral angiostrongylus. Morphologically, it has three protective layers of collagen, the male being smaller than the female, and possessing a copulatory pouch (Syed, 2021).

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Basically, the nematode's life cycle is to complete the maturation in mice, specifically in their pulmonary artery. In the artery, the L1 larvae, which hatch from the egg, will travel to the alveolus, and to the pharynx, where they will be swallowed and expelled in the rats excreta. Subsequently, some intermediate animals, such as slugs and snails, feed on these excreta, which have L1 larvae of the parasite. Inside the organism, they mature until L3, but do not reach the adult stage, the cycle is completed with the ingestion of such animals by rats. In the body, they travel to the brain and the rodent's subarachnoid, until they reach the vessels, that carry them to the pulmonary arteries, where they will evolve to L5 and complete their sexual maturation (Cowie, 2013).

The disease in humans occurs when these intermediates such as slugs or L3 larvae are ingested, as well as uncooked contaminated foods such as freshwater shrimp, crabs, mollusks and paratenic hosts or through water contaminated by parasite larvae. Thus, in the digestive system, it enters the blood circulation, and will have a tropism for the central nervous system (CNS), where the worm can deposit itself and cause inflammation, or go to the meninges, causing the known effects of meningitis, headache, nuchal stiffness and fever in an incubation time of 2 to 45 days (Xie et al., 2019).

However, this parasite does not survive for a long time in the human body, where it can die and settle down causing inflammation. Due to the proximity of the eyes to the brain, there may be cases of neurotropic translocation of this parasite to the eyeball, while translocation to the lungs is even rarer. The presence of infiltrated eosinophils and third-stage *A. cantonensis* larvae in the patient's cerebrospinal fluid (CSF) are two main pathological findings of this disease (Xie et al., 2019; Elghawy et al., 2020).

It is known that the parasite is widely distributed in Southeast Asia and the Pacific Basin, although globalization favors its appearance in other countries, such as Brazil, USA and Africa. Although there is no official treatment, it is usually based on controlling signs and symptoms, as well as anthelmintics and anti-inflammatory drugs (McAuliffe et al., 2019).

In view of this, this study aimed to evaluate the latest records on this parasite in the world, in order to analyze its worldwide distribution, its main manifestations, main findings in exams, treatments and, above all, to explain such findings based on the parasite life cycle.

2. Material and Method

This study was carried out in December 2021, through an integrative review, used within the scope of Evidence-Based Practice, in which previous studies are analyzed, in order to synthesize knowledge and assist in conduct and decisions. This review method is consisting of six steps: 1) identification of the theme and guiding question; 2) establishment of inclusion and exclusion criteria; 3) data collection from selected articles; 4) critical analysis of the articles in order to classify the evidence found; 5) interpretation of results; 6) synthesis of knowledge.

The database used in the search was PubMed, with the following descriptors: "Angiostrongylus", "cantonensis", "case human", in addition to the use of the Boolean operator (AND). Only full-text articles in English, Spanish and Portuguese that referred to the topic and whose theme were about case reports described in the last five years were included in the sample. Other research modalities and those whose theme did not correspond to the proposal of the present study were excluded.

Initially, using the descriptors in PubMed, 211 references were identified. By selecting only articles from the last 5 years, the sample was reduced to 46 publications. After reading the titles and abstracts, 18 articles were excluded because they did not deal with the topic. Finally, 28 articles were read in full and made up the sample of the integrative literature review (Figure 1).

3. Results and Discussion

The search returned 46 articles. After reading the titles, 14 were excluded because they were not the subject of the review. After reading the abstracts, 28 articles on the researched topic were selected. The most relevant information of the selected scientific articles is presented in the following Table 1.

In view of the results shown in Table 1, a series of variables are identified, some of them are worth to be mentioned. It is noticeable that there was no pattern or risk factor regarding the age or sex of the patients. There were both 78-year-olds being affected, as well as 8-month-old infants. Predominant infections were caused by the ingestion of snails and slugs, although there are many cases of ingestion of contaminated seafood, which can act as paratenic hosts. Rarer cases involving ingestion of the lizard of the genus *Varanus*, centipedes and African snail (*Achatina fulica*) have been reported. Some of the cases in which there was no explanation of the exact cause of the infection involved patients who were exposed to potentially contaminated environments, such as rats and snails that came into contact with vegetable gardens. This case shows the potential infection by ingestion of vegetables not properly washed (Dard et al., 2017 ;Wang et al., 2018).

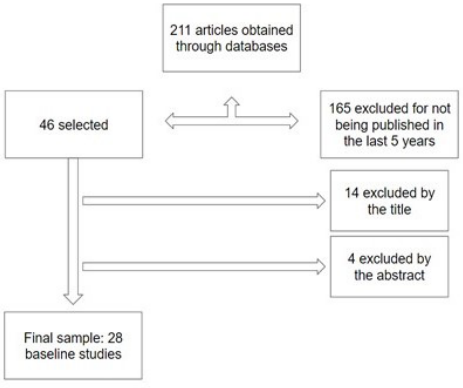

Figure 1. Flow diagram for selecting articles for integrative review.

Table 1. Studies published between 2017 and 2021 in the researched database that was selected for the integrative review.

Author	Country/Year	Age/Gender	Cause	Clinical Manifestations	Diagnosis	Exams	Treatments	Clinical outcome
Dard et al. (2017)	Basse-Terre/2017	8 months old/ Gender Not mentioned	Contact of snails and rodents in the vegetable garden	Meningeal signs, fever, vomiting	CSF sample PCR	Hypereosinophilia and altered CSF	Albendazole, ivermectin and corticosteroids	The patient recovered clinically (after 11 days). Normal laboratory values (after 25 days)
Flerlage et al. (2017)	USA/2017	12 months old/ Male	Possible contact with rodent excreta	Fever, irritability, vomiting and anorexia	Western blot	Altered CSF, MRI findings	Albendazole and corticosteroids	The patient's temperature returned to normal and his symptoms solved
Hammoud et al. (2017)	USA/2017	12 months old/ Female	Not mentioned	Fever, lethargy	CSF sample PCR	PCR altered, MRI with alterations	Albendazole and prednisone	Patient's symptoms have completely solved (after 64 days)
Meyer et al. (2017)	USA/2017	22 years old/ Male	Not mentioned	Headache, fever and diplopia	Not mentioned	MRI findings, chest CT findings	Corticosteroids and lumbar puncture	Headache solved
Nguyen et al. (2017)	French/2017	54 years old/ Female	Not mentioned	Fever, headache, nuchal rigidity, and photophobiaa	Western blot	Mild leukocytosis, altered CSF and altered abdominal CT	Prednisone, albendazole and CSF puncture	Complete regression of symptoms
Prasidthrathsint et al. (2017)	USA/2017	22 years old/ Male	Consumption of seafood	Headache, double vision, fever	CSF sample PCR	MRI with signs suggestive of CSF inflammation	Prednisone and lumbar puncture	Significant improvement in clinical symptoms (after 2 months)
Shen et al. (2017)	Not mentioned/2017	56 Years old/ Male	Not mentioned	Headache, cognitive impairment and urinary incontinence	Microscopic analysis of CSF	MRI findings	Not mentioned	Not mentioned
Andrade et al. (2018)	Brazil/2018	20 months old/ Male.	Contact with snails	Fever, lethargy and vomiting	CSF sample PCR	Findings on blood count and fundus examination.	Albendazole, prednisolone and vitrectomy	Symptomatic improvement
Defo et al. (2018)	French Guiana /2018	10 years old/ Male	Exposure to snails	Headache, vomiting and fever	Western blot and CSF sample PCR	Altered CSF, hypereosinophilia and MRI with alterations	Ivermectin, methylprednisolone and prednisolone	Progressive disappearance of symptoms and MRI normality (after 38 days)

Table 1. Continued...

Author	Country/Year	Age/Gender	Cause	Clinical Manifestations	Diagnosis	Exams	Treatments	Clinical outcome
Ma et al. (2018)	China/2018	15 months old/ Female	Exposure and accidental consumption of slug	Fever, irritability and constipation	CSF analysis and clinical findings	Eosinophilia and altered CSF	Levamisole, prednisone and mannose.	Recovery of all your symptoms (after 72 hours)
McAuliffe et al. (2019)	USA/2018	20 years old/ Male	Raw snail consumption	Headache, hyperesthesia and neck stiffness	CSF sample PCR	CSF and MRI findings	Albendazole, prednisolone and lumbar puncture	Improvement of symptoms but remained with erectile dysfunction, intermittent pain and central obstructive sleep apnea
Wang et al. (2018)	China/2018	78 years old/ Female	Centipede consumption	Headache and neck stiffnessl	ELISA with serum sample and CSF	Changed CSF	Albendazole and dexamethasone	CSF normality
Wang et al. (2018)	China/2018	46 years old/ Male	Centipede consumption	Headache and neck stiffness	ELISA with serum and CSF sample	Altered CSF and lung CT finding	Albendazole and dexamethasone	CSF normality and no lung findings
Berkhout et al. (2019)	Australia/2019	5 years old/ Female and 10 years old/Male	ingestion of the snail or contaminated vegetables	Headache and hemiparesis (boy)	CSF sample ELISA	MRI findings	Mebendazole and dexamethasone	Recovery of some function (after 5 months), but not to their previous state, with persistence of hemiparesis (boy)
Chotmongkol and Khamsai (2019)	Thailand/2019	38 years old/ Male	Raw snail and shrimp ingestion	Headache	Western blot	CSF and MRI changes	Prednisolone	Numbness in face and limb after 2 weeks on prednisolone. Improvement of symptoms after 6 months
Long et al. (2019)	USA/2019	44 years old/ Female	Seafood ingestion	Headache and paresthesia, urinary retention	CSF sample PCR	Eosinophilia, MRI with brain and spinal cord injury and altered CSF	Duloxetine and DMT (disease-modifying therapy)	Normal CSF and improvement of pleocytosis

Table 1. Continued...

Author	Country/Year	Age/Gender	Cause	Clinical Manifestations	Diagnosis	Exams	Treatments	Clinical outcome
Tiwari et al. (2019)	India/2019	70 years old/ Female	Feeding	Watering and redness in the eye	Direct analysis of the worm in the eye chamber	Eye sclerosis	Moxifloxacin eye drops, dexamethasone and atropine sulfate eye drops	Symptomatic improvement (after 1 week)
Xie et al. (2019)	China/2019	1 year old/Male	Not mentioned	Cough, mental fatigue and fever	CSF sample NGS	CSF and MRI findings	Albendazole and methylprednisolone	Improvement of symptoms (after 10 days) and CSF normality
Xie et al. (2019)	China/2019	1 year old/Male	Not mentioned	Cough, vomiting, mucosal herpes and fever	CSF sample NGS	CSF and MRI findings	Albendazole and methylprednisolone	Improvement of symptoms (after 10 days) and CSF normality
Cucueco et al. (2020)	USA/2020	29 years old/ Male	Not mentioned	Headache, fever, allodynia, erythematous flushing, and arthralgia	CSF sample PCR	Altered CSF and MRI	Ibuprofen, acetaminophen, gabapentin, fentanyl, prednisone, lidocaine…	Significant improvement
Dard et al. (2020)	Martinica/2020	8 cases: 3 kids (1 year old); 1 boy (11 years old), anos, 4 adults (age between 37 and 64 years old).	Consumption/ contact with mollusks	Headache, seizure, nuchal rigidity, radiculalgia, vomitingand diarrhea	Western blot or serum antigen search.	CSF and MRI with findings	Albendazole, corticosteroids, and lumbar puncture	2 people (no sequelae); 5 people (strabismus and intellectual disability); 1 person (fatal)
Elghawy et al. (2020)	USA/2020	50 years old/ Male	Not mentioned	Productive cough, bloody nasal secretions and dyspnea	Lung biopsy	Eosinophilia	Ivermectin	Symptom resolution
Feng et al. (2020)	China/2020	27 years old/ Male	Consumption of contaminated meat	Skin itching, emesis, myalgia, quadriparesis, headache and coma.	CSF sample NGS	Altered CSF and CT of the abdomen	Methylprednisolone, and immunoglobulin, ceftriaxone and linezolid	Died (after 38 days)
Meyer (2021)	USA/2020	10 cases (age between 47 and 78 years old): 4 female, 6 male	Not mentioned	Hyperparesthesia, sleep disorders, headache, Hypersensitivity and Urinary retention	CSF sample PCR, direct observation of eye	Altered CSF, eosinophilia	Prednisone, cannabis, lidocaine, tramadol, acupuncture…	Not mentioned

Table 1. Continued...

Author	Country/Year	Age/Gender	Cause	Clinical Manifestations	Diagnosis	Exams	Treatments	Clinical outcome
Monteiro et al. (2020)	Brazil/2020	43 years old/ Female	Ingestion of raw shellfish	Headache	ELISA and Western blot	Eosinophilia	Crystalline penicillin and albendazole	Improvement of symptoms
Monteiro et al. (2020)	Brazil/2020	35 years old/ Male	Ingestion of raw shellfish	Headache, fever and limb pain	ELISA and Western blot	MRI findings	Ivermectin, methylprednisolone and gabapentin	Improvement of symptoms
Monteiro et al. (2020)	Brazil/2020	31 years old/ Male	Ingestion of raw shellfish	Headache	ELISA and Western blot	Altered CSF, MRI findings	Ivermectin, methylprednisolone and gabapentin	Improvement of symptoms
Thu et al. (2020)	Vietnam/2020	9 months old/ Male	Not mentioned	Seizures and fever	Serum and CSF sample ELISA	CSF and MRI findings	Albendazole, dexamethasone, mannitol and prednisolone	Full recovery
Todaka et al. (2020)	Japan/2020	39 years old/ Male	Contaminated food	Headache, fever and nausea	Anti-A test in serum and CSF.	Leukocytosis, CSF findings	Ivermectin and olopatadine	Clinical improvement
Widder et al. (2020)	Japan/2020	20 years old/ Male	Raw snail consumption	Headache, neck stiffness, quadriplegia, polyneuropathy, diarrhea and dysuria	CSF sample PCR	MRI and funduscopic examination altered	Prednisolone Ceftriaxone, Acyclovir, Vancomycin, Steroids, Methylprednisolone and Lumbar Puncture	Improved but maintained severe neurological sequelae
Zhang et al. (2020)	China/2020	59 years old/ Male	Not mentioned	Headache, nausea, vomiting and fever	CSF sample NGS	Eosinophilia, altered CSF and MRI findings	Albendazole and methylprednisone	Improved consciousness and normal MRI
Yang et al. (2021)	Vietnam/2021	22 years old/ Male	Lizard meat ingestion	Headache, arthralgia, vomiting, diarrhea and nausea	CSF sample PCR	changed CSF	Dexamethasone, prednisolone, albendazole.	Improvement of symptoms
Yang et al. (2021)	Vietnam/2021	25 years old/ Male	Lizard meat ingestion	Headache, arthralgia and loss of appetite	CSF sample PCR	Not mentioned	Albendazole and steroids	Improvement of symptoms
Yang et al. (2021)	Vietnam/2021	24 years old/ Male	Lizard meat ingestion	Headache, arthralgia and neurological deficit	CSF sample PCR	Not mentioned	steroid and albendazole	Improvement of symptoms

Table 1. Continued...

Author	Country/Year	Age/Gender	Cause	Clinical Manifestations	Diagnosis	Exams	Treatments	Clinical outcome
Yang et al. (2021)	Vietnam/2021	24 years old/ Male	Lizard meat ingestion	Headache, weakness and numbness in limbs	CSF sample PCR	Not mentioned	Albendazole and steroid	Improvement of symptoms
Yang et al. (2021)	Vietnam/2021	31 years old/ Male	Lizard meat ingestion	Nausea, vomiting and arthralgia	CSF sample PCR	Not mentioned	Albendazole and steroids	Improvement of symptoms
Yang et al. (2021)	Vietnam/2021	36 years old/ Male	Lizard meat ingestion	Not mentioned	CSF sample PCR	Not mentioned	Herbal remedies	Not mentioned
Yang et al. (2021)	Vietnam/2021	32 years old/ Male	Lizard meat ingestion	Not mentioned	CSF sample PCR	Not mentioned	Herbal remedies	Not mentioned

Its worldwide distribution has shown increasing diversity, compared to the fact that it is endemic in Southeast Asia and the Pacific Basin. Although many cases occurred in Hawaii, Vietnam and Thailand, there were also reports from Asian countries that are not endemic to this parasite, such as Japan, China and India, and cases from Oceania, specially a case reported in Australia (Wang et al., 2018; Berkhout et al., 2019; Tiwari et al., 2019; Todaka et al., 2020).

Cases were also identified in regions with low frequency of this parasite, such as an autochthonous case in Paris (2017), in which a woman presented eosinophilic meningitis. Such cases have also been reported in Central America, with a presence in the Caribbean, specifically in the city of Basse Terre (Guadeloupe) (Dard et al., 2017; Nguyen et al., 2017; Cucueco et al., 2020).

In North America, specially in Texas and Tennessee (United States of America), infected patients had no previous travel abroad, which does not allow the possibility that they were infected in another country. In South America, there were cases reported in Brazil, in the cities of Porto Alegre and São Paulo, and no history of previous travel by the infected patients (Flerlage et al., 2017; Hammoud et al., 2017; Andrade et al., 2018; Monteiro et al., 2020).

However, some cases occurred due to previous trips, such as the history of a patient who returned from a trip to Guatemala, where she already had the first symptoms, and later came to the USA and was admitted to the hospital. The explanation for these reports, in a worldwide spreading, can be explained by international travel, especially on ships, which are large reservoirs of rats, great transmitters of *A. cantonensis* (Elghawy et al., 2020).

Regarding laboratory findings, there was great variation in blood counts and CSF analysis. In general, patients used to present standardized alterations such as blood hypereosinophilia, with cases of 68% concentration of eosinophils in the serum. In CSF, there were more findings as high C-reactive protein (value of 73 mg/dL, with the normal range: 0.08 - 3.1 mg/dL), as well as eosinophilic pleocytosis, hyper proteinorrachia (values such as 130 mg/dL, with the normal range: 15 - 45mg/dL) and low glucose. Many of the CSF were cloudy, as a consequence of the meningeal process triggered by the parasite and have shown high pressures, which required a lumbar puncture for relief (McAuliffe et al., 2019; Dard et al., 2017; Nguyen et al., 2017; Long et al., 2019).

The diagnoses were often based on the analysis of the parasite's DNA found in the CSF, by methods such as PCR or Western blot. But, there are reports of direct identification under the microscope of a suspected dead *A. cantonensis* worm in the cerebrospinal fluid (CSF), that dispensed conventional diagnostic methods. Other cases were identified in a 9-month-old patient, who presented findings of the live and mobile parasite of white color in his CSF. Besides that, there were findings of the translucent worm of about 15 mm in length moving freely in the anterior chamber of the eyeball (Shen et al., 2017; Tiwari et al., 2019; Thu et al., 2020).

Before diagnosing *A. cantonensis*, many previous tests are usually performed, in view of the confusion of suspicions with other diseases. Most of them used initial tests, such as the parasitological examination of feces (which presented negative results for *A. cantonensis*, considering that humans do not act as a source of infection), serological examination for *Toxocara spp., Trichinella spp., Schistosoma spp., Taenia solium, Gnathostoma spp., Fasciola hepatica, Toxoplasma gondii*, HIV, fungal staining and tests for bacteria such as CSF microscopy by gram stain and detection of bacterial antigens by latex agglutination. All these tests were negative, and only specific analyzes by Western blot, CSF PCR or even the direct identification of the larva, when it was removed alive, were conclusive tests (Nguyen et al., 2017; Feng et al., 2020).

Furthermore, there was a case in which intestinal manifestations, such as diarrhea, were confused as a consequence of infection by *A. cantonensis*, but in the reality the patient, in addition to being infected with this parasite, was also infected with rotavirus, the real responsible for the diarrhea, which was diagnosed through examination of feces. As well, there were cases in which the serum was positive for *Strongyloides stercoralis* IgG, this may explain the intestinal manifestations of emesis found in the reported patient. Although the species *Angiostrongylus (Parastrongylus) costaricensis* is responsible for abdominal manifestations, *A. cantonensis* also presented similar manifestations in some cases, with vomiting, anorexia, loss of appetite and abdominal pain. (Hammoud et al., 2017; Dard et al., 2020).

In general, regarding the clinical manifestations, most of them had brain involvement, with a strong presence of headache and fever. However, some specific findings reported the presence of seizures in patients, four of them were children under 11 years old, and four adults between 37 and 64 years old. One of the cases with a 9-month-old infant had peripheral eosinophilia, with observation of the live parasite in the CSF, with magnetic resonance imaging (MRI) showing exaggerated meningeal enhancement on T1 in both cerebral hemispheres, suggesting meningoencephalitis, which was responsible for increased intracranial pressure. and probably seizures. After using albendazole, intravenous dexamethasone and mannitol for the first three days, followed by five days of oral prednisolone, the patient fully recovered (Thu et al., 2020).

Another study carried out by eight patients, also with manifestations of seizures, found abnormalities, with abnormal enlargement of the cerebral ventricles or cortical atrophy, and also presented cranial nerve dysfunction, headaches, axial hypotonia, radiculalgia and neck stiffness, with neural angiostrongyliasis. During hospitalization, five patients had fever and three digestive symptoms (vomiting, abdominal pain, loss of appetite and/or diarrhea). These seizure findings indicate a strong local inflammatory reaction in the brain, in a mechanism similar to neurocysticercosis, as represented by the MRI findings of lesions, or may indicate a consequence of strong meningeal inflammation (Dard et al., 2020).

In addition, seven cases of angiostrongyliasis were reported in the articles by raw ingestion of monitor lizards, known as a paratenic host, and four of them had abdominal symptoms, including abdominal pain, nausea, vomiting and diarrhea. Another common manifestation

in this case were body aches, headache and arthralgias (Yang et al., 2021).

There was also evidence of the parasite in the eyeball. A case report with 10 cases of infected people, one of them was diagnosed with *A. cantonensis* from the direct observation of the parasite in the eyeball. In another study, the patient experienced tearing, redness, mild conjunctival congestion, corneal fog and a foreign body sensation in the right eye. On slit lamp evaluation, a translucent worm of about 15 mm in length was found moving freely in the anterior chamber without any attachment to the iris. Both eyes had grade II nuclear sclerosis. He underwent surgical removal of the live worm in order to avoid blindness or systemic damage, thus having a good prognosis (Tiwari et al., 2019; Meyer et al., 2017).

There was a case of a patient whose fundus examination revealed a pale optic disc, subretinal tracks, vitreous opacities, peripheral traction retinal detachment and a dead worm in the vitreous cavity. Ultrasonography was performed and showed partial posterior vitreous detachment, tractional retinal detachment in the nasal wall, and posterior cortical vitreous division (vitreoschisis). Elevation of his optic disc was present, suggesting an inflammatory process, which led him to undergo a pars plana vitrectomy, from which he had a good recovery (Andrade et al., 2018). Ocular involvement, as demonstrated by Widder et al. (2020) may also be subtle, with the presence of moderate bilateral papilledema without hemorrhage on dilated funduscopic examination.

Due to the proximity of the eyes to the brain, cases of neurotropic translocation of this parasite to the ocular route are explained, although this is rare. Two mechanisms currently hypothesize the role of the parasite in the optic pathway, one of them would be the larval migration along the surface and base of the brain, where it would travel between the nerve and the sheath until reaching the optic nerve and the other way would be through direct invasion by the bloodstream (Elghawy et al., 2020; Andrade et al., 2018).

About the brain findings, several types of lesions were identified through MRI. Overall, patients had nodular lesions in the cortex and optic nerve, diffuse stippled areas of cortical infarctions, hyperintense signal on T2-weighted images, signs of leukoencephalopathy, abnormal T2 and FLAIR signals in the cerebellar hemisphere and occipital lobe, which were clinically manifested by diplopia, papilledema, VI cranial nerve palsy, paroxysmal dizziness and mainly headache (Hammoud et al., 2017; Meyer et al., 2017; Prasidthrathsint et al., 2017; Zhang et al., 2020).

Chotmongkol and Khamsai (2019), for example, revealed in a patient with eosinophilic meningitis, a focal image with a lesion in the corpus callosum, which exhibited low signal intensity on T1-weighted images, high signal intensity on T2-weighted images, and nodular enhancement after gadolinium administration. Other similar lesions were found in the right parieto-occipital region and left lentiform nucleus, which culminated in headache with a continuous pressure sensation and bilateral involvement for 3 days.

Widder et al. (2020) in their study demonstrated MRI of the brain, cervical spine, thoracic and lumbar spine with leptomeningitis, myositis, and demyelination and involvement of the anterior horn and hemorrhagic tracts due to possible larval migration. This patient had polyneuropathy, papilledema, motor weakness and diarrhea for two days. Bilateral thigh myalgia, dysuria and constipation, headache, paresthesia, stiff neck, and quadriplegia, which led to treatment with prednisolone, ceftriaxone, acyclovir, vancomycin, as well as lumbar puncture-based treatment for intracranial hypertension. Although the patient improved, he developed severe neurological sequelae.

Berkhout et al. (2019), when reporting the case of two children (a boy and a girl) also brought MRI analysis, which demonstrated a possible inflammation of their left optic nerve. A second MRI of the brain demonstrated unusual tubular structures in the post superior left cerebellar hemisphere with contrast enhancement and T1 Hyperintensity, reported as probable nematode larvae, that caused severe headaches. In the boy, MRI showed mild ventriculomegaly with moderate hydrocephalus, responsible for persistent hemiparesis.

Shen et al. (2017) demonstrated in their case a MRI of the brain without contrast, multiple microbleeds over the bilateral cerebral and cerebellar hemispheres, as well as the presence of dead worm in the CSF. This patient had urinary incontinence, difficulty eating and bathing, forgetfulness, disorientation, generalized pain, intermittent dizziness, headache, tachypnea and tachycardia. Physical examination revealed drowsiness, stiff neck, general weakness, and stiffness of four limbs.

Other not so common findings were itchy skin, emesis, myalgia and quadriparesis with progressive weakness of the four limbs. The study by Feng et al. (2020) presented an atypical picture of an infected patient with manifestations of hyperpyrexia, headache, persistent coma and Guillain-Barré syndrome. In addition, when performing CT of the abdomen, it demonstrated that the peritoneum was focally thickened, indicating the possibility of peritonitis. His treatment was based on intravenous methylprednisolone and immunoglobulin, but he worsened, with subsequent death from severe angiostrongyliasis 37 days after the onset of the first manifestations.

Some studies with infected patients by *A. cantonensis* showed alterations in other complementary exams, such as one by Meyer et al. (2017), whose non-contrast chest CT demonstrated multiple peripheral nodules in the lungs, and the case by Nguyen et al. (2017), in which chest and abdominal CT showed hepatic hypodensity. Other changes found in other case reports were a high-intensity nodule located in the posterior lateral segment of the lower lobe of the right lung, which after treatment with albendazole (40 mg/day) for 21 days and dexamethasone (10 mg/day) for 16 days improved and the nodule disappeared (Wang et al., 2018).

It is also worth mentioning the case reported by Elghawy et al. (2020), who performed a biopsy of the patient's lung tissue, which revealed Wegener's pulmonary polyangiitis, which manifested through pulmonary angiitis, night sweats and chills, shortness of breath, productive cough and nasal secretions of blood. The exact pathophysiological mechanism for parasitic pulmonary

angiitis is not fully understood, but appears to be due to the direct invasion of the parasite into endothelial cells.

Other hypothesized mechanism for the angiitis includes autoimmune T and/or B cell reactions triggered by parasitic antigens, which attack self-cells due to epitope mimicry and subsequent immune complex vascular deposition, and/or antigen-induced T cell activation, respectively by type 3 and 4 hypersensitivity reaction. The histological features, in addition to the parasite, include eosinophilic vasculitis or vascular necrosis (Elghawy et al., 2020).

It is known that the worm initially invades the intestinal vessels after human ingestion, where they go to the CNS. In this system, they remain for about five weeks, where they mature into L5 larvae. Subsequently, they go to the subarachnoid space, venous system and pulmonary capillaries, where they perform their sexual maturation. In the majority of cases in humans, the larvae die in CNS, whereas in babies, whose immune system is still maturing, may occur the migration of the parasite to the pulmonary artery, which can lead to embolism, respiratory failure or even death (Xie et al., 2019; Berkhout et al., 2019; Thu et al., 2020).

Most parasites of the *A. cantonensis* species tend to die in the nervous system, generating eosinophilic meningitis or by activating the immune response mediated by TH2, which can help in the formation of eosinophils, which release factors such as the main basic protein by their granules, in which in a chronic condition it can form local inflammatory infiltrate, abscess and eosinophilic meningitis (Xie et al., 2019).

About the treatments, most were based on more conservative methods, such as the use of anthelmintics and corticosteroids, in order to fight the parasite and contain inflammation at the meningeal level. Among these drugs, there were prednisone, albendazole, dexamethasone, ibuprofen and ceftriaxone, which in general presented significant clinical improvements to patients. Other cases also used the surgical removal of the worm at the ocular level, as well as lumbar puncture to treat cranial hypertension resulting from meningitis. Some unconventional treatments were also used, such as acupuncture and cannabis use, but no results about clinical improvements by these treatments were presented (Meyer et al., 2017; Nguyen et al., 2017; Andrade et al., 2018).

Many patients after such treatment had a good prognosis, in a way that after hospital admission and treatment, they improved after 72 hours, there were also cases of improvement after 64 days. However, certain cases, although they guaranteed the patient's life, they had some sequelae, such as the case of a 10-year-old boy, who five months after the infection, he had recovered his function, but with hemiparesis persisted (Hammoud et al., 2017; Ma et al., 2018; Berkhout et al., 2019).

In a study conducted by McAuliffe et al. (2019), the patient even after treatment had erectile dysfunction, extensive narcotic regimen for pain control, urinary hesitancy and later developed central obstructive sleep apnea. On the other hand, in a case study of neural angiostrongyliasis, with eight patients who had different clinical manifestations, and underwent treatment based on albendazole and corticosteroids, two of them showed improvement, five of them got strabismus and intellectual disability and one case was fatal for a 58 years old man (Dard et al., 2020)

In more atypical cases, a 27-year-old man infected after consumption of contaminated meat died of severe angiostrongyliasis about 38 days after the diagnosis and 37 days after the onset of symptoms, having used intravenous immunoglobulin methylprednisolone as his treatment. Meanwhile, another interesting case of an infected man after ingestion of snail and raw shrimp was treated with prednisolone and after 2 weeks he presented numbness on the left side of the face and in the left upper limb, but after six months of follow-up he showed clinical recovery (Chotmongkol and Khamsai, 2019; Feng et al., 2020).

As a form of prevention in general, it is observed how variable it may be, so good hygiene habits are essential, such as washing vegetables potentially contaminated with rat and mollusk excreta before consumption and keeping such animals away from vegetable gardens. Furthermore, it is important to avoid consumption of certain animals that are usually hosts of this parasite, such as snails and slugs, and animals that act as paratenic hosts, such as lizards and centipedes. Above all, the education of the population, especially in endemic countries, is essential for such measures to be consolidated (CDC, 2021).

4. Conclusion

To conclude, it is noticeable the complexity of manifestations, diagnosis and treatment of the species *A. cantonensis.* This nematode showed no predilection for age or sex, but it is widely distributed throughout the world, either autochthonous or by tourists returning from endemic places. Its form of infection was mainly through the ingestion of infected snails and slugs, although rare cases of ingestion of lizards and centipedes have also been recorded. CSF exams always revealed alterations, with findings of high proteinorrachia, low CSF glucose or even the direct presence of the worm in the CSF. In the clinical manifestations, there was variety, so that headaches and seizures were recorded and in more severe cases, meningeal signs were detected. And complementary exams revealed changes on MRI, as well as atypical findings on CT of the chest and abdomen, which opens theories to explain the pathophysiology of these worms in such unusual regions.

The treatments were based especially on anti-inflammatory and anthelmintic drugs, which brought satisfactory results to the patients. Therefore, although the treatment for this parasite shows a good prognosis, further studies are required, in order to understand its cycles and pathophysiology, especially in rare locations such as those present in the eyeballs and abdomen, and thus propose therapies more efficient, as well as prophylactic measures to protect the population, mainly those from endemic countries.

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