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Encephalitis Caused by Helminths

Raquel O Simões[1], Tainá C de C Monte[1], Márcio Bóia[1] and Arnaldo Maldonado Júnior[1]*

[1]Laboratório de Biologia e Parasitologia de Mamíferos Silvestres Reservatórios, Fundação Oswaldo Cruz, Brazil

***Corresponding author:** Arnaldo Maldonado Júnior, Laboratório de Biologia e Parasitologia de Mamíferos Silvestres Reservatórios, Fundação Oswaldo Cruz, Brazil, Email: arnaldomaldonadojunior@gmail.com

Published Date: August 20, 2016

ABSTRACT

The recognition of helminth as etiologic agent of encephalitis is essential for diagnosis in endemic and non-endemic areas. Thus, this chapter focus on *Angiostrongylus cantonensis*, *Gnathostoma spinegerum*, *Bayliascaris procyonis*, *Strongyloides stercoralis*, *Toxocara canis, Paragonimus westermani, Trichinella spiralis, Schistosoma* spp., *Taenia solium* and *Echinococcus granulosus* that can cause encephalitis summarizing the life cycle, epidemiology, symptoms, diagnosis, treatment and prevention.

INTRODUCTION

Many helminths can affect the human Central Nervous System **(CNS)** causing encephalitis via blood stream route or by migration in tissues [1]. Usually, it happens when human acts as the accidental host.

Neurological helminths infections are not common, although they are relevant due to the severity of clinical manifestations and the pathological consequence caused by parasite in the organ. Unfortunately, the involvement of the parasite in the CNS is misdiagnosed or undiagnosed in endemic areas due to lack of specific symptoms, often not be the main route of the parasite migration and some findings not typical [2].

Thus, the recognition of helminth as etiologic agent of encephalitis is essential for diagnosis, especially in non-endemic areas due to the increase of tourism and migration worldwide. In addition, the awareness of potential helminths in endemic areas is necessary for the correct diagnosis and treatment [2,3].

This chapter focuses on mainly helminths that can cause encephalitis summarizing the life cycle, epidemiology, symptoms, diagnosis, treatment and prevention.

NEUROANGIOSTRONGYLIASIS

Angiostrongyluscantonensis (Chen, 1935) is neurotropic nematodes that affect the Central Nervous System **(CNS)** of their hosts and is the etiological parasite of neuroangiostrongyliasis causing mainly three syndromes in humans: eosinophilic meningitis, encephalitis and ocular angiostrongyliasis. Among these, eosinophilic meningitis is the most common and is recognized as an emerging zoonotic disease [4,5].

Life Cycle

The life cycle of the nematode *A. cantonensis* is heteroxenic, requiring both hosts, definitive and intermediate. Sexually mature female and male worm's settles in the pulmonary arteries of rats (definitive host) where the female laid approximately 15,000 eggs per day. These eggs travel via the blood circulation to the lung parenchyma where they develop in about a week and contain the first-stage larvae (L1). The L1 larvae hatch and are eliminated into rat feces after trachea migration and attain the gastrointestinal tract. Mollusks are the intermediate hosts, in which the L1 larvae molt twice to produce the third stage larvae (L3), which are infective for vertebrate animals. Rats become infected by ingestion of an intermediate or a paratenic host, containing the L3 larvae. A few hours after ingestion, L3 larvae penetrate the rats' intestinal wall and enter its blood stream where they are dispersed via the circulation. Larvae that reach the brain undergo an additional moult to become fourth-stage larvae (L4). A fifth moult occurs in the subarachnoid space, where larvae become the young adult stage (L5). Young adult worms leave the **CNS** and migrate through the circulation, and at 25 dpi, are found in the pulmonary arteries. At 35 dpi, adults have reached sexual maturity and females begin producing eggs that hatch in the terminal branches of the pulmonary arteries [5-7]. Humans become infected accidentally by ingesting either intermediate or paratenic hosts containing the infective larvae (L3). In the case of human infection, the L3 larvae actively move or are transported by the vascular system to the **CNS** where causes neuroangiostrongyliasis [8].

Epidemiology

The nematode *A. cantonensis* was first described in Guangzhou, China, in 1935 [9] after examination of specimens recovered from *Rattus norvegicus* and *Rattus rattus*. Human infection was reported for the first time in Taiwan in 1945, but only in 1960 neuroangiostrongyliasis was recognized as a public health problem [6]. This nematode typically occurs in southeast Asia and

the Pacific Basin where the most cases of human infection have occurred. Human outbreaks started in Asia in 1984 (China), and include 160 cases in Beijing, outbreaks in Thai workers and in U.S. travelers which returned from Jamaica [10]. However, there are reports of presence of *A. cantonensis* in many parts of the world, including the Americas, in which the first report occurred in 1981 when infected rats and snails were found in Cuba [11]. Since them, several cases of disease in humans have been reported in the United States of America **(USA)**, Jamaica, Ecuador [12-14] and Brazil [15-18]. Currently, over 2,800 human cases have being reported from about 30 countries with most records been from tropical and subtropical areas in different parts of the world [5].

It is believed that the dispersion of *A. cantonensis* is related to the transport of infected definitive host (rats) on ships and airplanes, increased widespread travel of people in endemic areas and the spread of some species of snails to different parts of the world [5,6,19]. In most cases of human angiostrongyliasis, the exposure to infection probably is related to leisure time and the main mode of infection is the consumption of raw or undercooked molluscs and paratenic hosts, such as frogs, crabs, fish, planarias and prawns, as well as, contaminated vegetables and water [6,7]. Accidental infection may occur due hand manipulation of molluscs (mucus) [20].

Due *A. cantonensis* low specificity regarding its intermediate host the route of infection in human cases varies geographically. Many species of molluscs are susceptible to infection, including two species of exotic molluscs, the giant African snail, *Achatina fulica* and the freshwater snail of South America, *Pomacea canaliculata*, representing one of the main intermediate hosts of angiostrongyliasis in Brazil and China, respectively [18,19,21-23]. Other species of molluscs may act as intermediate hosts of *A. cantonensis*, such as *Bradybaena similaris, Subulina octona, Pomacea lineata*, other Pomacea species, *Doroce as laeve*, and species of Pila [18,22,24,25]. A. *fulica* has now been recorded in 25 of the 26 states and in the Federal District in Brazil, where the emergence of eosinophilic meningitis is a matter of concern [18,20,25,26].

Symptoms

The clinical manifestation of neuroangiostrongyliasis depends on larval localization and worm burden. This disease may be asymptomatic or can lead to severe sequelae, although very rarely [6]. Heavy infestations can produce encephalitis with severe neurological symptoms, such as meningitis with increased blood eosinophilia, radiculitis, cranial nerve abnormalities, ataxia, coma and even death (fatal in at least 3% of all cases). Headache, neck stiffness and fever is frequently observed in patients with eosinophilic meningitis being headache the most common symptom resulting from increased intracranial pressure produced by the widespread inflammatory reaction in the meninges due to the larval death. Other symptoms are diplopia or blurred vision, nausea, vomiting, abdominal pain and convulsions [4,6,20]. The incubation period for development of eosinophilic meningitis is about two weeks, but can range from one day to several months [18].

Diagnosis

The diagnosis of neuroangiostrongyliasis is based on history of larval exposure (intermediate or paratenic host consumption) within three months, history of headaches and eosinophilia in Cerebrospinal Fluid **(CSF)**, immunological and serological tests. Peripherical eosinophilia is common The definitive diagnosis is the presence of *A. cantonensis* larvae in the CSF or eye of suspected patients, although the detection rate is low [5,20,27].

Lumbar puncture in patients with suspected eosinophilic meningitis must be done to analyze the CSF and in some cases, to relieve the headache. The infected CSF usually is clear, with no color or turbity, which allows distinguishing from other infections, including infections by *Gnathostomaspp*. Nematodes that produce bloody CFS. The CSF protein concentration is elevated, whereas the glucose level is normal or slightly reduced. The diagnosis of neuroangiostrongyliasis is usually based on a CSF eosinophil count ≥ 10% of the cells or 10 eosinophils/ mL [5,20,27].

Imaging examination is required such as Magnetic Resonance Imaging **(MRI)** for diagnosis to identify abnormalities in many patients. Results revealed that the neuropathology of angiostrongyliasis includes cerebral congestion and thickened leptomeninges, microcavities in the brain and spinal cords due the migration of larvae. Some patients with clinical manifestations showed no abnormalities with MRI [5,20,27].

Treatment

Most human cases with eosinophilic meningitis caused by *A. cantonensis* are usually mild and symptoms can resolve spontaneously without any treatment. In severe cases, steroid therapy is effective in the treatment of headaches and lumbar puncture is required to reduce the intensity and duration of this symptom. The use of oral corticosteroids such as predinisolone for 14 consecutive days is adopted by the majority of hospitals. Albendazole alone or in combination with corticosteroids (decrease damage due to the increased inflammatory reaction that is triggered by massive parasitic death) is also used to treat the human angiostrongyliasis. Trials showed that the combination of anti-helminthic drug plus corticosteroids was not superior to predinisolone alone for the treatment [4,5,20].

Prophylaxis

The prevention of infection should not focus only in the *A. cantonensis* parasites once the numbers of definite, intermediate and paratenic hosts worldwide is very large. It is necessary education methods for prevention including educate populations about *A. cantonensis* and its hosts; not eating raw or undercooked intermediate or paratenic hosts of *A. cantonensis*; not eating unwashed vegetables and eradicating the intermediate hosts near houses and gardens. In countries where cultural habits include food based on raw and undercooked *A. cantonensis* hosts, these recommendations may be difficult to achieve. Physicians and other health professionals should be also educated about the symptoms and aware of the existence of *A. cantonensis* in both endemic and non-endemic areas [4,5].

GNATHOSTOMIASIS

Gnathostoma spinigerum (Owen, 1836) is a tissue nematode of dogs and cats capable of causing eosinophilic meningoencephalitis, cutaneous larva migrans syndrome and intraocular gnathostomiasis. Humans become infected indirectly through copepods and vertebrates (intermediate hosts) and are considered accidental hosts for larvae. Adults worms live in stomachs of carnivorous mammals [6,28,29].

Life Cycle

Domestic and wild felines and canines are the definite hosts of *G. spinegerum*. The adult worms produce a tumor in the gastric wall of their definitive hosts and lay eggs. These eggs are released into water and after development hatch into first-stage larvae (L1). These larvae are ingested by the first intermediate host, a crustacean copepod of the genus Cyclops, where they molt into second-stage larvae (L2). When the second intermediate host, such as freshwater fish, frogs, snakes and fowls, ingest the copepod infected by L2 larvae, they molt into third-stage larvae (L3) and later develop to the advanced infectious L3 stage. The definitive hosts become infected by ingesting any of intermediate or paratenic hosts (birds, reptiles and mammals) having the advanced third-stage larvae, and finally develops into an adult worm. Human become infected by eating raw or undercooked infected second intermediate and paratenic hosts or contaminated water. This larvae can invade eye, brain and other visceral organs causing illnesses [6,28,30].

Epidemiology

The nematode *G. spinegerum* was first described in 1836 from a tumor of the gastric wall of a tiger at London Zoo [31]. Gnathostomiasis is endemic in southeast Asia, particularly in Thailand, where is considered to have a seasonal occurrence corresponding to rainy season. However, the prevalence of infection is increasing in Mexico and Central and South America [6,32]. There are also reports of infection in Korea, Loas, Myanmar, Vietnam, India, Bangladesh, Malaysia, Indonesia, the Philippines, Israel and a few cases from Australia, Ecuador, Spain, and Africa [30]. This nematode was identified as a cause of **CNS** infection in humans in several East Asian countries, including Japan and China. The fatal encephalomyelitis in 1967 was the first report of *Gnathostoma* as a cause of human CNS infection [6,33].

Humans become infected by ingesting raw fish, shrimp, snails, snakes, frogs, pigs and vegetables. Until 1988, at least 36 species of freshwater fish was found to be infected with the advanced third-stage larvae in Thailand, and there are several species of vertebrates serving as the second intermediate and/or paratenic hosts for *G. spinigerum*, including amphibians (2 species), reptiles (11 species), avians (11 species), and mammals (4 species). However, chicken and ducks constitute the most important source of human infection. Other modes of infection, less common, are ingestion of water containing infected copepods and penetration of infective third-stage larvae through the skin [6,28,30]. *Gnasthostoma spinegerum* infection in humans is

related to travel medicine as well as *A. cantonenis*. The reports about CNS and cutaneous diseases in patients that returned from the endemic areas, confirm great concern about the disease [6,34].

Symptoms

CNS gnathostomiasis is more severe than *A. cantonensis* infection. Initial symptoms resulting from penetration of larvae through the gastric wall include abdominal and epigastric pain, malaise, vomiting, diarrhea, anorexia and fever, although these symptoms last only 5 days. There are symptoms related to direct migration of the worm along cranial or peripheral nerves into the spinal cord, such as radicular pain, paresthesias of the trunk and extremities, paresis and paralysis. Other symptoms are severe headache, weakness, meningeal inflammation, myelitis or encephalitis, and damage to the cerebral vasculature can result in subarachnoid hemorrhages. The main factor of mortality in CNS gnathostomiasis are hemorrhagic lesions [6,32].

Diagnosis

The incubation period of CNS gnathostomiasis is four weeks but may last 3 or more months. Usually presents a bloody and xanthochromic **CSF** which is a helpful criterion to distinguish from eosinophilic meningitis caused by *A. cantonensis*. It has been usually observed increased eosinophilia in CSF (>10%). The protein levels also increased whereas the glucose level remained normal or slightly reduced. Peripherical blood eosinophilia is not always present. History of travel to endemic areas and the symptomology are suggestive of this disease.

Imaging examination may reveal lesions, areas of hemorrhage and even hydrocephalus. Serological and immunological techniques have been developed for detection of antibodies in CSF and antigen detection methods have been used for L3 larva confirmation. The definitive diagnosis of CNS gnathostomiasis is the presence of L3 larvae in CSF, although unusual. The morphological analysis of specimens (the presence of spines or hooks in regular rows, as well as the identification of the cephalic bulb) in cases of biopsy and necropsy of host tissue, also is considered as definitive diagnosis [6,32].

Treatment

The treatment of CSN gnathostomiasisis is basically supportive, using curative therapies, once no anthelminthic drugs and corticosteroids have been clearly defined for the treatment of disease due the concern about inflammatory reaction to dying helminths, as with *A. cantonensis*. The prognosis for CNS gnathostomiasis is uncertain, but full recovery can be expected in most of cases The mortality caused by the disease is low but permanent sequel may occur in until 50% of patients [6,32].

Prophylaxis

The main prevention for gnathostomiasisis related to food practice. Proper food handling is the necessary to eliminate and minimizes infection, such as boiling the food or freezing for at

least three days in order to kill existing L3 larvae. Not eating raw or undercooked intermediate or paratenic hosts of *G. spinegerum* as well as unwashed vegetables. Finally, it is necessary prevention and precaution about consumption of contaminated food and water when traveling to endemic areas [6,32].

CNS BAYLIASCARIASIS

Bayliascaris procyonis is a nematode of the order Ascaridia, parasites of lower carnivores. This nematode is considered the cause of clinical larva migrans in animals and is usually associated with severe neurological disease. In the most severe form, *B. procyonis* can cause a fatal or neurologically devastating Neural Larva Migrans **(NLM)** in humans, particularly children [35].

Life Cycle

B. procyonis has a direct life cycle and inhabits the lumen of small intestine of raccoons (definitive host) where adult female worms produce 150,000-179,000 eggs/day. These thick-walled eggs are released in feces and are not immediately infective after shedding, requiring suitable environmental conditions to develop into infective second-stage larvae. Raccoons become infected when ingest the eggs, and then larvae hatch and enter the small intestine wall, where they develop into adult worms returning to the lumen of small intestine. Humans and other vertebrate species are considered the less adapted hosts (intermediate hosts) and when larvae are ingested, they migrate out of the intestine and are distributed to the tissues by the systemic circulation. These larvae can remain encapsulated in tissues but a small number of larvae can invade the CNS and produce disease, which can leads to death of the intermediate host [6,35].

Epidemiology

B. procyonis was first isolated from raccoons in 1931 in the New York Zoological Park [36]. These parasites are common in raccoons in North America and Europe and play the most important epidemiologic role in bayliscariasis in humans. These animals are native to the Americas from Canada to Panamá and were introduced into Europe (France, Germany, and The Netherlands), the Soviet Union, and Asia for the commercial trade and into Japan as pets. The prevalence of *B. procyonis* is much higher in juvenile raccoons than in adults [6,35,37].

Raccoons, in recent decades, are living in urban areas, which provide increased shared environments of raccoons and humans. The first reports of baylisiascaris in humans was in 1984 and 1985, in a 10- and 18-month-old infants who died from severe eosinophilic encephalitis in United States [38,39]. The risk of infection of animals and humans by *B. procyonisis* closely related to a huge number of eggs released in feces per day in areas where the prevalence of infected raccoons is high. The primary risk factors for human infection include contact with raccoon feces (latrines), geophagia, young age and male sex. Presence of raccoons in peridomestic areas is also important once people may be exposed to the eggs of this parasite [6,35,37].

The environmental conditions it should be taken into account. The egg development and survival vary based on temperature (22˚- 25˚C) and humidity (100%). With cooler and fluctuating temperatures, egg development will be lower and will take several weeks to months and under sufficiently warm but fluctuating temperatures, the eggs become embrionated in 3-4 weeks [37].

Symptoms

The period of incubation (2-4 weeks) and severity of baylisiascaris may vary according to number of eggs ingested. This disease may be asymptomatic or may produce visceral, cutaneous, neurologic or ocular larva migrans syndrome. Ocular disease is concomitant with neurological disease in many patients. The pathogenicity of the larvae is related to their aggressive migratory behavior in the tissues. The clinical manifestation of CNS disease is an acute meningoencephalitis with lethargy, ataxia, paralysis and usually is very severe leading to sequelae or death, especially in children and infants. Other symptoms are cranial nerve involvement, spasticity, paresis, seizures and fever (not prominent) [6,35,37].

Diagnosis

Elevated peripheral and cerebrospinal fluid eosinophilia can be detected in cases of meningoencephalitis. White matter disease on neuroimaging, with or without eye disease, may suggest the diagnosis of baylisiascaris. A history of exposure to raccoons feces should be requested. The diagnosis in live patients is difficult and a serology test is used with supportive evidence of other tests. Anti-Baylisascaris antibodies can be demonstrated in CSF and serum by indirect immunofluorescence, enzyme-linked immunosorbent assay, and Western blotting. The brain biopsy detecting presence of larva is the confirmatory diagnosis [35,37].

Treatment

Baylisiascaris is treated with anthelmintics and corticosteroids. Thiabendazole, fenbendazole, tetramisole, or ivermectin failed to prevent unfavorable outcomes and death. The anthelmintics are less effective against larvae in humans and intermediate host than in raccoons. Animal experiments suggest that albendazole and diethylcarbazine is more effective having the best larvicidal activity and CSF penetration. Only albendazole has been used in children although thiabendazole and albendazole has been used to treat the majority of human cases. The timing of treatment relative to larval invasion in the CNS is an important issue, should administered from day 1 to day 10 after the infection. Corticosteroids are used to reduce the inflammatory reactions [35,37].

Prophylaxis

Prevention and control of baylisiascarisis are made by simple measures. Education and awareness of public about the disease and contact with raccoons and their feces is required and most preventive step. Children and infants should be kept away from contaminated areas, especially those with geophagia. Raccoons latrines should be cleaned up at zoos and in or around homes, although the egg resistance makes successful environment clean up difficult [35,37].

STRONGYLOIDIASIS

Strongyloides stercoralis is an intestinal helminth that causes strongyloidiasis in man widespread in the tropical and subtropical regions. The infection can range from asymptomatic to a more severe form depending on the parasitic burden [40].

Life Cycle

The filarioids larvae penetrate in the human skin and migrate into blood reaching the lung. Then, the larvae are swallowed, becoming an adult in the small intestine. This form of infection is known as hetero-infection, besides; auto-infection and parthenogenesis features enhance the probability of infection persist for decades [41].

Epidemiology

It is an important disease in individuals immunocompromised due to a potential massive increase of larvae that can invade other organs as nervous system manifesting the severe symptoms. A massive infection with severe clinical manifestation is associated with corticosteroid administration even in non- immunosuppressive doses.

According to recent review [41], the cases of strongyloidiasis occur in developing countries mainly in poor communities, immunocompromised individuals, travelers, and people with soil contact and war veterans. About 80% of cases occur in tropical and subtropical regions [41]. The epidemiology of diseases is related to inadequate hygiene environment without sanitation where increase the risk of infection.

Symptoms

The neurological symptoms due to hyperinfection of *S. stercoralis* are rare [42]. The larvae that invades the CSN commonly is accompanied by a secondary bacterial infection aggravating the symptoms. Fever, headache, vomiting, nausea, meningismus, and confusion can occur depending on the brain involved area [40].

Diagnosis

Sorological tests as ELISA e wtern-blot, immunofluorescence are used for diagnosis. The ELISA method show a sensibility ranging from 85% to 95% and the specificity reach 90% [43] CT and MRI are used; however, the radiological features are non-specific. Most of diagnosis is made by findings of *S. stercoralis* larvae in CSN during the autopsy [40,43].

Treatment

Anthelminthic drugs as ivermectin, albendazole and nemiticides are used to treat the strongyloidiasis, however, this do not prevent reinfections. Any patient undergoing treatment with corticosteroids or other immunosuppressants should be investigated for the possibility of intestinal strongyloids infection.

Thus, the drug efficacy depends on the co-infection with HTLV-1 or HIV, history of drug use and immune system status [41].

Prophylaxis

The best strategy to prevent the severe form is identified and treat infected patients especially those of high risk as HIV seropositive. Furthermore, sanitation, good practices of hygiene and wearing shoes in potential infected areas can prevent the infection.

NEUROTOXOCARIASIS

The roundworm *Toxocara canis* belongs to Ascaridae family and is one of the most important zoonoses related to humans and dogs, foxes and cats [44].

Life Cycle

This helminth parasite lives in the small intestine of its hosts. It is transmitted mainly among canids by three routes: transplacental, trans-mammary and horizontal transmission. Man became infected by ingestion of embryonated eggs in the environment, in contaminated vegetables or by ingestion of larvae in paratenic hosts. In the intestine, larvae hatch eggs penetrate the intestinal wall and enter the bloodstream or lymphatic vessels reaching the lungs, liver, myocardium, musculature, eyes and CNS. The larvae do not develop into adults in man but become encapsulated by a granulomatous reaction producing a eosinophilic granuloma [3].

Epidemiology

The prevalence of human toxocariasis is higher in developing countries, particularly, in rural areas. Moreover, children present more risk of infection than adults due to their poor hygienic habits and their close contact with dogs [44-46]. The first report of neurotoxocariasis was described by Beautyman and Wollf [47] in 1951. A larva was found in the left thalamus of a child during the autopsy. Since then, more than 50 cases have been reported around the word. The occurrence of CNS granulomas because of larva *migrans* in 308 children autopsies was 0.68%. The frequency of this form of disease is rare and some time is misdiagnosed with other diseases that affect the CNS [3].

Symptoms

The manifestations in affected patients depend on burden and previous infections besides genetic factors [48]. The severity of clinical manifestations is related to the inflammation, damage and number of larvae in the brain. The symptoms are weakness, fever, headache, sensitivity to light, confusion, epilepsy, lethargy, tiredness, irritability, nuchal rigidity, ataxia, rigor, and neuropsychological disturbances [3,44,46].

Moreover, in 2013 was reported a case of 54-year-old man that exhibited neurological toxocariasis symptoms with autonomic neuropathy associated to paralytic ileum and neurologic

bladder, without parasitic cysts and presence of larval forms inside the medullary canal and examination of CSF with eosinophilia atypical [49]. Thus, there are large spectrums of clinical manifestations hindering the recognition of the disease caused by the parasite.

Diagnosis

The Diagnosis is based on the clinical neurologic investigation, history, cerebral **MRI** and **CT** scan, cerebral angiography, blood cells count, determination of antibodies against *T. canis* antigen in the CSF and eosinophilia in the serum or CSF. Recently, Polymerase Chain Reaction **(PCR)** of CSF has also been used for diagnosis [44,49].

Treatment

There is no specific protocol concerning the treatment of encephalitis caused by *T. canis* due to the rarity. Albendazole is the drug of choice due to less toxicity, better penetration into the CSF and permeate higher serum concentrations. A combination with corticosteroids is also used [3,44].

Prophylaxis

Avoid eat undercooked meat from potential paratenic host; possess good hygienic practices; wash adequately vegetables and give anti helminth to pets regular mainly for puppies.

CEREBRAL PARAGONIMIASIS

Paragonimus westermani is the most etiological agent of the disease knows as Cerebral paragonimiasis. This trematode parasitizes the lung of their hosts, causing disease in humans, but extrapulmonary infections are also encountered [6].

Life Cycle

Mammals including human and some carnivores are the definitive host of this trematode in which sexual reproduction occurs. The adult worms are usually harbored by encapsulation in the lungs. The eggs through expectoration or swallowing reach the fresh water environment which takes 2 weeks to become embryonated. After this period, the egg hatching occurs and miracidia escape to become free swimming. These ciliated larvae must infect molluscs (intermediate host) for development of cercariae. The crustacean host may be infected by ingestion of molluscs or direct penetration of cercariae, in which the cercariae encyst and become metacercariae. When the definitive hosts ingest raw or undercooked crustacean host, the metacercariae excyst in small intestine migrate through the intestine wall and reach the abdominal cavity. The larvae will migrate through the diaphragm to the lung where they develop into adult worms. The worms can also be found in other organs (ectopic locations) such as the brain and the heart, in which the life cycle is not completed [6,50].

Epidemiology

P. westermani was first described in Bengal tiger of Amsterdam Zoo in 1878 and in humans in 1879 [47]. This trematode is endemic in Asia, Africa and South America such as China, Japan, Nigeria, Liberia and Venezuela. Cases were also reported in Europe and Australia. At least 293.8 million people are at risk of infection with *Paragonimus* spp. in China, where this parasite is responsible for 3.5% of CNS infections. In Japan, since 1980s, the paragonimiasis has been re-emerging due to the increased number of infected immigrants. The human infection is related to food habits and food exchange expands, since *P. westermani* is transmitted by ingestion of infected crustacean hosts, plus the increased human travel, similar to other helminths that cause CNS disease. Cerebral paragonimiasis is the most common and severe complication of *Paragonimus* infection, which accounts for 50% of all extrapulmonary cases of paragonimiasis [6,48,52-54].

Symptoms

In cerebral paragonimiasis, the main clinical manifestation is epilepsy such as occurs in cerebral cysticercose. Other symptoms are headache, motor and sensory disturbance, aphasia, hemiplegia, visual disturbance, blindness, nausea, seizures, meningitis and in severe cases even death. Paravertebral pain, urinary dysfunction, abnormal tendon reflexes, paresis, and muscular spasms can reflect spinal involvement. The clinical signs are associated with the intensity and duration of infection, the number of reinfections and the susceptibility of the host. Hosts with a small number of worms have general clinical signs whereas those with moderate/high number of worms can present more pronounced clinical signs [6,50].

Diagnosis

Cerebral paragonimiasis may be difficult to detect. CSF eosinophilia is not present in all paragonimiasis cases but high peripheral blood eosinophilia may be observed. Imaging examination **(MRI)** is required to detect chronic silent lesions and conglomerations of multiple ring-enhancing lesions with surrounding edema and a “tunnel sign” that demonstrated the migratory track of the adult worm. Immunofluorescence, ELISA, and Western Blotting are the main methods for diagnosis. The definitive diagnosis in pulmonary and skin paragonimiasis is a presence of eggs in feces or the worms in sputum and biopsy specimens, but detection of eggs in CSF is not usual, since most CNS lesions occurs in the parenchima [6,50,54].

Treatment

Praziquantel and triclabendazole are the most antihelminthic drugs recommended by World Health Organization **(WHO)** to fluke worms. Praziquantel is the most common used in China and the efficacy is 80% to 90%. Mebendazole and Bithionol are less effective with cure rate of 70% and 50-60%, respectively. In selected cases, surgical removal of cerebral and nodules may be necessary to relieve mass compression effects [6,50,54].

Prophylaxis

The reduction of transmission is essential to control the paragonimiasis. Control of snail population, reduction of the sources of infection through effective treatment, protection of ponds and aquaculture systems from contamination with feces from people and other definitive hosts, treatment or sterilization of feces; and implementation of educational campaigns. Eliminate the consumption of raw and undercooked crustacean (crabs, shrimp or crayfish) although this may be a difficult strategy in some endemic areas where people are habituated to eating raw and undercooked food [50].

NEUROTRICHINELLIASIS

Trichinelliasisis is a food-borne parasitic disease caused by *Trichinella spiralis* or *Trichinella* spp.. This nematode can infect several animals, including humans, causing CNS involvement in 10-20% of the cases.

Life Cycle

The life cycle of *T. spiralis* consists in three phases with three developmental stages: adult worm (intestinal), muscle larvae (muscular) and newborn larvae (migrant). All three phases occurs within a single host which can be several animals, including humans. When muscle larvae are ingested by the host, through raw and undercooked meat of pork and wild animals, penetrate the intestinal mucosa and develops into adult worm. After mating, the newborn larvae migrate through the lymph and blood vessels to the skeletal muscle, where they mature into muscle larvae, encysting in the tissues remaining thus quiescent for years. Transmission between hosts can only occur through the ingestion of meat with infective stages of the parasite. Human can be infected and neurological manifestations can occur caused by the disseminated migration of larvae [6,55].

Epidemiology

Trichinella spp. is common in Southeast Asia and has been found in 66 countries in domestic and wild animals. Human trichinelliasis has been documented in 55 countries and this disease is particularly related with those countries with well-established food behavior that includes consuming meat dishes with raw or undercooked meat. In Europe, the actual number of human cases has been relatively low and the most cases (87%) occurred in Romania, Bulgaria, Latvia, Lithuania, and Spain. Argentina is considered the country with largest number of cases in the last years. From 1989 to 2009, domestic pigs were considered the major source of infection. However, during 2010-13, the consumption of game meat was the most cause of infection as noted in countries such as USA and Canada. Although Trichinelliasis is considered as a threat to public health worldwide and *T. spiralis* continues to be the causative agent in most outbreaks, there is a decreased incidence of human cases. The great reduction of trichinelliasis is related to the post-mortem meat inspection mandatory in many countries, along with the development of standards for killing muscle larvae by the freezing, heating or curing of pork and the widely instituted laws requiring the cooking of waste food intended as pig feed [56,57].

Symptoms

The CSF eosinophilia is rare among patients with neurotrichinelliasis. An important symptom cluster for diagnosis is the combination of swelling facial lesions on the lids or the lips, an acute fever, and myalgias. Hemiparesis can also be observed representing the clinical manifestations of meningitis, encephalitis or polyradiculoneuritis. Other symptoms are headache, neck stiffness, deep-tendon abnormal reflexes and behavior disturbances which may last for two weeks, and the recovery is spontaneous [6,58]. Disease severity is influenced by the number of larvae ingested, may presenting respiratory failure, myocarditis and acute adrenal gland failure resulting in death in some cases [59].

Diagnosis

The main criterion for trichinelliasis diagnosis is a history of eating raw or undercooked meat, specially pork meat, and clinical manifestations with blood eosinophilia. CSF is normal in most patients and serology (ELISA or Western Blot) is used to detect antibodies in serum or CSF. Multiplex PCR is also used to detect *Trichinella* DNA. Imaging examination can show multifocal small lesions in the cortex and the white matter. These lesions are believed to represent multifocal ischaemic lesions rather than inflammatory infiltrations of the brain. The diagnosis can be confirmed by the presence of encysted larvae, through muscle biopsy, but is not always conclusive, and the parasite can sometimes be detected in remaining contaminated meat [6,60,61].

Treatment

Albendazole or mebendazole are the anthelminthics of choice to neurotrichinelliasis and corticoids in severe cases can be used. In patients without treatment the mortality can reach 50% [6,62,63].

Prophylaxis

The population of countries with dietary habits including consumption of raw or undercooked meat, especially pork meat, should be informed and the awareness about the risks of infection should be highlighted since the human behavior is the most important determinant in the persistence of trichinelliasis. The meat inspection is essential to prevent and control disease as well as the increasing regulations directed at ensuring the safety of meat and the enhancement of good management practices in farming, especially in areas in which trichinellosis is highly endemic [56,57].

NEUROSCHISTOSOMIASIS

Life Cycle

Schistosoma spp. is blood-dwelling trematodes with sexual dimorphism. The life cycle is complex and evolves human and other mammals as vertebrate hosts and different genus of freshwater snail as invertebrate host. The most important species that cause neuroschistosomiasis are

Schistosoma mansoni, *S. japonicum* and *S. haematobium* [64,65]. *Schistosoma spp*. inhabit different venous in mating pairs. Eggs are deposited in small vessels of the target parasitized organ. The infected individual excretes schistosome eggs in feces (*S. mansoni* and *S. japonicum*) or urine (*S. haematobium*). The eggs not excreted are carried by the bloodstream for other organs. The miracidium releases from eggs inside water and penetrates into the tegument of snail intermediate hosts, and then cercariae are generated by asexual reproduction. After light stimulation, the infective larvae emerge from snail, penetrate into human skin transforming in schistosomulum reaching the blood circulation, and are carried to the portal or vestibule circulation to complete the life cycle. *S. mansoni* migrate to the inferior mesenteric vein, *S. japonicum* to the superior mesenteric vein and *S. haematobium* parasite bladder veins [66].

Epidemiology

Schistosomiasis is the most significant parasitic disease after malaria in the tropics [62]. *S. mansoni* is an endemic in Africa, Caribbean, Middle East countries and South America, *S. haematobium* in Africa and Middle Eastern countries. Moreover, some of these regions there are an overlap of these parasites. *S. japonicum* is an endemic in Japan, Philippines and China [67].

In many underdeveloped countries this disease is a problem to public health. Moreover, poor conditions of hygiene and social-economical factors contribute for the dissemination of the diseases. In the tropics, encephalopathy and myelopathy caused by Schistosoma spp. are misdiagnosed or non-diagnosed. Neuroschistosomias is have been reported in tourists, aid workers and soldiers that were in endemic areas [65,68,69,71].

The prevalence of encephalitis caused by Schistosoma spp. is low. In China, about 1-5% of patients adults hospitalized with schistosomias are presented acute schistosomal encephalopathy. Additionally, the report of cases of this diseases is increasing, mainly in people not previously exposed to parasite [66,70,71].

Symptoms

The acute neurological manifestation, normally occurs in the third week after the systemic symptoms [64], however symptoms can be present from one week to more than two years [72,73].

The more common symptoms are headache raging from intermittent to severe, vomiting, diarrhea, fever, prostration, mental disturbance, hemiparesis, paraplegia, ataxia, seizure, cerebellar syndrome, papilloedema can also occur because of intracranial pressure [58,64,66,74]. Thus, the symptoms caused are tumor-like. The neurological manifestation may be the first signs of the diseases in nonimmune patients [66].

Diagnosis

Detection of eggs in feces or urine happens in more than 40% of patients with neuroschistosomiasis [75]. Neuroimaging as MRI can show inflammatory granulomas in the

cerebral cortex with heterogeneous enhancement of gadolinium contrast, surrounded by edema. CT is also used showing mass lesions with hyper dense lesions. Meanwhile, these findings are non-specific, other parasitic diseases and tumors should be considered in differential diagnosis [65]. The combination of ELISA and IHA has 90% sensitivity and 93% specificity in the diagnosis of neuroschistosomiasis. Besides, the levels of antischistosomal IgG1 in the CSF can aid the diagnosis.

Treatment

In patients with neuroschistosomias is the treatment needs to be immediate to avoid complications and majority, based on clinical diagnosis. There is no consensus regarded the treatment. Usually, corticosteroids, schistosomicidal drugs as praziquanel, and surgery are used [65].

Prophylaxis

The prevention consists of sanitation, education health, identification and treatment of sick individuals and combating snails. Moreover, avoid contact with water suspected be with infected snails.

NEUROCYSTICERCOSIS

Neurocysticercosis is the most common parasitic diseases of the CNS, mainly in areas where pigs and human lives together in unsanitary conditions [1,58]. This diseases has a worldwide distribution and is caused by larval form of *Taenia solium*, the pork tapeworm [58,76].

Life Cycle

Man is the definitive host and develops the adult tapeworm *T. solium* in the small intestine ingesting raw or undercooked pork with cysticercus. Pigs are intermediate host but humans can also play this role. Eggs or proglottis containing mature eggs are released in the environment with human feces. Humans can ingest accidentally these eggs through consumption of food or water contaminated with feces. Pigs become infected eating human feces as well as soil, water or food contaminated. Then, the intermediate host develops the larval stage in tissues as muscles, subcutaneous and /or brain, resulting in cysticercosis. [58,77].

Epidemiology

It is endemic in Latin America, Africa and Asia and this helminth is the major responsible for epilepsy and convulsion in the neurological disease in endemic regions [79]. Human cysticercosis usually occurs in poor areas without sanitation and where pigs are breeding freely with direct contact in human feces.

According to Torgerson and Macpherson [80] (2011), the number of global neurocysticercosis can be over 2 million daily per annum. Additionally, in the Latin America and China the cases have

been estimated at 11-29 million and 3-6 million, respectively [67]. However, the number of cases of neurocysticercosis is growing in non- endemic areas due to migration of people from endemic areas [80].

Symptoms

Patients with neurocysticercosis develop encephalitis if occur inflammation pressure around the cyst or multiple simultaneous lesions in the granular stage [1]. It is more common in young women and children [81,82]. The clinical manifestation depends on the host immunity to parasite, location and number of cysts. Most symptoms are resulted from direct inflammatory process to cyst degeneration [83]. The manifestation includes headache, vomiting, sensory deficits, cerebellar ataxia, involuntary movements, dementia and seizures.

Hydrocephalus or/and seizures occurs frequently due to the site of infection in neurological region, usually in the brain and the subaracnoid space [84].

Diagnosis

The diagnosis of neurocysticercosis is complex due to the non-specificity of some imaging findings symptoms and signs; moreover, serological tests have low specificity and sensibility. CT and MRI are used as gold standard; it can show the scolex within the vesicle that is pathognomonic of neurocysticercosis). Immunodiagnostic methods as indirect haemagglutination, ELISA, complement fixation, and enzyme linked immune Electro Transfer Blot Assay **(EITB)** are available to detect antibodies [83]. Histological investigation confirms the diagnosis, although the procedure is limited.

Treatment

The treatment is based on natural history and pathogenesis of the disease. The use of antihelminthics drugs is controversial depending on the cysts burden, captivity and viability, however cysticidal therapy with albendazole or praziquantel with steroids has shown affectiviness [85]. Depending on the case, neurosurgical intervention should be considered [83].

Prophylaxis

Sanitary disposal of human feces, control of cisticercosis on inspection of porks, detection and treatment of infected people to prevent the parasite dispersion. Do not consume vegetables that have not been properly sanitized and drink filtrate water and present good practices of hygiene. Tourists that visit endemic area should be informed.

ECHINOCOCCOSIS

Human cystic echinococcosisis caused by the presence of larval stage of four different species of the tapeworm *Echicoccocus* genus. The most frequent infection in human is caused by *Echinococcus granulosus* [86] that can cause cerebral cystic echinococcosis (cystic hydatidosis).

Life Cycle

Canids as dogs, foxes and coyotes are the definitive host and develop the adult worm in the small intestine. Herbivores such as sheep and cattle are the intermediate host and human is the accidental host. The definitive host eliminates eggs that are ingested by the intermediate host. Human become infected eating food or handling soil or dog excrement contaminated by eggs. Canids are infected by eating herbivores organs containing cysts [87].

Liver and lungs are the most common organs affected by the cysts but can affect any organs, including the nervous system [86].

Epidemiology

Echinococcosis is endemic in some countries of Africa, Europe, Southeast Asia, Middle East and several countries of Latin America. The epidemiology of the disease is influenced by cultural, economic, agricultural, educational and medical factors and considered a public health problem [88].

The frequency occurrence of hydatic cysts in other organs outside liver and lung is 10%, and among these 1-3% in the CNS [89,90]. This zoonosis is self-limiting but possibly fatal.

Symptoms

The symptoms caused by hydatic cysts in the CNS depend on the site of infection. Usually, the cysts are situated within the ventricles, subarachnoid space or parenchyma. Headache, hemiparesis, vomiting, epilepsy, mental changes, irritability and psychotic syndromes have also been reported [90]. Seizures can occur [91] but is rarer when compared with neurocysticercosis.

Diagnosis

Neuroimaging produced by CT scans, MRI, ultrasonography and/or chest X-ray is the most frequent tool used in the diagnosis. Additionally, serological tests are used to detect antibodies against *E. granulosus* in the serum or CSF. PCR is also used and when possible histological investigations may confirm the diagnosis [58,92].

Treatment

The mainstay of treatment for CNS hydatic cysts is surgical removal and the choice drug is albendazole. The pharmacotherapy is indicated in some occasion before or after surgery [93].

Prophylaxis

Establishment of control program by the government in endemic areas, reducing the prevalence of the parasite in definitive and intermediate host. Do not feed dogs with raw infected viscera, discard carcasses properly and guide dog owner about the parasite transmission.

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