Angiostrongylus cantonensis (the Rat Lungworm) Infection and Hearing Loss

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62.1 Introduction

Eosinophilic meningitis has an association with infections caused by three major incidental parasites of humans, namely, *Angiostrongylus cantonensis*, *Baylisascaris procyonis*, and *Gnathostoma spinigerum*. Both *A. cantonensis* and *B. procyonis* have a tropism for neural tissues in their usual host as well as in humans. *G. spinigerum* is capable of infecting both the meninges and the regions external to the meninges. When these parasites infect humans, the infection usually progresses only to a certain point, as the parasite remains in the larval form, unable to reproduce or undergo maturation into the adult form. As the larvae enter the nervous system they provoke an eosinophil-dominated inflammatory response which is also reflected in high numbers of eosinophils in the peripheral circulation [1].

A. cantonensis is a species of nematode within the metastrongyloidea superfamily. Cases of eosinophilic meningitis are frequently due to infection with this organism. The common name for *A. cantonensis* is the rat lungworm. Rats are the definitive hosts, whilst snails or slugs are intermediate hosts. Certain other host

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species also transport the parasite. The region of maximum prevalence for infections with *A. cantonensis* is the Asia-Pacific region, although there are sometimes outbreaks or isolated infections in other parts of the world. Currently, nine members of the Angiostrongylus genus are recognised, with the most significant, from the point of view of their ability to produce disease in humans, being A. cantonensis and A. costaricensis [2, 3].

The parasite most likely to produce eosinophilic meningitis is *A. cantonensis* [4, 5]. The larval forms of this pathogen exhibit a preference for inhabiting nervous tissues [6].

62.2 Aetiology

The definitive host species for *A. cantonensis* is the rat. Adult parasitic worms penetrate into the rat's circulatory system and undergo maturation within the bloodstream. Sexual reproduction occurs within the host, leading to the laying of fertilised eggs, which are released into the circulation. These eggs are eventually deposited in the narrow calibre blood vessels within the lungs and they then hatch at this site. The first stage of larval development sees the parasitic larvae penetrate into the airways and pass upwards towards the upper respiratory tract and pharyngeal region. The larval forms are swallowed into the gut, passing through the host and being deposited externally when the rat defaecates. The intermediate host stage then begins. The parasite is ingested by a snail or slug, and enters this organism. If a rat then eats an infected snail or slug, the lifecycle of the parasite is then completed. The parasitic larvae are by now at their third stage. The parasite preferentially migrates to the brain of the rat, where maturation into the young adult occurs. These organisms then re-enter the venous portion of the rat's circulation, being transported to the lungs, which are the site of sexual maturation. The female nematode produces eggs which hatch in the pulmonary tissues. There are some other potential stages in the lifecycle of the parasite. Paratenic hosts (also referred to as transport hosts) are organisms which harbour the parasite but are not crucial for it to complete its lifecycle. They ingest the parasite in larval form from the true intermediate host and are then themselves eaten by the definitive host (i.e. a rat). Paratenic hosts include carnivorous snails, frogs, lizards, prawns, crabs or freshwater shrimps. If vegetable matter is contaminated with snail slime, the parasitic larvae may also be ingested from this source [2, 3, 7].

Human beings are not definitive hosts for *A. cantonensis*, but they may act as incidental host if they ingest parasite-infected intermediate or paratenic species, or snail slime containing parasitic larvae. The behaviour of the parasite in the human resembles that seen in the definitive host. Faecal-oral transmission is a key component. The ingested parasites penetrate the circulation via the mucosal lining of the gut. In the bloodstream, maturation occurs, the adult nematode worms depositing her eggs in the smallest calibre vessels of the pulmonary circulation. Once these eggs hatch, there is larval migration up to the pharynx, causing coughing. The larvae are then ingested once again and progress through the gastrointestinal tract, leaving

the body when the patient defaecates. Intermediate hosts (snails or slugs) ingest the larvae, which are at the first stage of their development. If a rat or human consumes the intermediate host when the larvae have reached the third stage, these larvae can penetrate the circulation and preferentially migrate to the central nervous system. In nervous tissue, the parasite finally assumes its adult form. The adult worms migrate via the veins draining the brain towards the heart, then into the lungs, where full sexual maturity occurs. They are then lodged in the smallest calibre vessels of the pulmonary arterial circulation. The female deposits eggs here.

Whilst the parasite inhabits the brain, particularly the subarachnoid space, it triggers a powerful inflammatory response by the host, with eosinophils predominating. This is manifested as acute eosinophilic meningitis. If the parasitic load is high, there will be other sites of inflammation in the patient, resulting in different clinical pictures, namely radiculitis, neuropathies of the cranial nerves, myelitis, encephalopathy and coma. In some cases, mortality of the host ensues. However, since the nematode itself perishes within the brain of patients, whatever the clinical outcome, there is no direct human-to-human transmission [8]. Generally speaking, the infection incubates for between 1 and 3 weeks, but in some cases, the incubation may last up to 6 weeks [2].

62.3 Epidemiology

The principal areas where cases of eosinophilic meningitis secondary to infection with A. cantonensis present are located is Southeast Asia, especially Thailand and Malaysia. Cases also occur in the south of Vietnam and across the Pacific region, such as Indonesia, the Philippines, Taiwan, China, Japan, Papua New Guinea, Hawaii, and some of the small islands which are abundant in this region. The range inhabited by *A. cantonensis* has been extended by ships on which infected rats have been carried, such that cases have been recorded in African and South American countries, Australia, Cuba, Puerto Rico, and on other Caribbean islands [6, 9–15]. The continental United States has also witnessed cases, beginning in New Orleans, then extending into Louisiana and the states of the Southeast more generally [16]. Isolated cases have also been reported from European countries and parts of the USA remote from Louisiana. In some cases, there was a history of travel to an endemic area, but in others no such connection was established [6, 16, 17].

As described above, the lifecycle of *A. cantonensis* is relatively complex. The cycle starts when the adult nematode lays its eggs in the pulmonary artery of the definitive host, the rat [18]. Larvae emerge, which move towards the pharyngeal region, then pass down through the length of the gut, emerging when the rat defaecates. The third larval stage occurs within the intermediate host, a snail or slug. They enter the intermediate host when the snail ingests the larvae within the rat stool. This invertebrate host may then be eaten by another rat, at which point the nematode larvae penetrate into the central nervous system. Here, maturation into the adult occurs. The adults re-enter the circulation, entering the pulmonary vasculature, where again the cycle begins.

A human host may be infected if a person eats uncooked or insufficiently cooked snails or slugs harbouring third stage nematode larvae [19]. Infected larvae may also be found on vegetable matter that has not been cooked [20]. The larvae, as described above, may also be ingested if a paratenic host is eaten. Examples of paratenic hosts eaten by humans include crabs, freshwater shrimps or centipedes [21]. When humans are the incidental host, the parasite still exhibits a tropism for the nervous, or occasionally, pulmonary tissues, but is unable to lay its eggs, so the infection does not pass on from the human.

The average incubation period for rat lungworm infection is from 1 to 3 weeks, but the reported range is from 1 day to above 6 weeks [22].

For children, playing in the dirt in countries where the parasite is endemic represents the main risk. There is also a risk from eating some local delicacies in endemic regions (such as raw caterpillars) [23]. However, even in those regions where *A. cantonensis* has endemic status, it is unusual for outbreaks to occur. The literature contains a report of an outbreak of eosinophilic meningitis secondary to *A. cantonensis*, acquired as a result of travel to Jamaica [1, 11].

62.4 Clinical Features

The larval forms of *A. cantonensis* exhibit tropism for the brain or the eye. Nervous system involvement manifests from 2 days to 5 weeks after infection begins. The usual presentation is as short-lasting meningitis. A somewhat less frequent presentation is with severe disease of the central nervous system and roots of the nerves [5, 24, 25]. The most frequent symptom at case presentation, manifested in above 90% of cases, is an extremely severe headache, generally localised to the frontal or occipital regions or both temples. When a lumbar puncture is performed, the severity of the headache usually decreases. It is common to find that the initial CSF pressure is raised [26].

Patients frequently exhibit nuchal rigidity, complain of nausea and vomiting and experience paraesthesiae. Pyrexia may not occur [27]. A study reporting on an outbreak affecting 12 patients found that three quarters of cases featured paraesthesia or hyperaesthesia affecting the limbs and/or truncal region [11]. In some cases, there is persistence of paraesthetic or hyperaesthetic symptoms beyond the point where resolution of other symptoms has already taken place. In 4–9% of cases, the extraocular muscles or the nerves supplying the face are paralysed, although the paralysis typically is not permanent [28–32]. Mortality seldom occurs [33]. A study which looked at the outcomes in 484 patients presenting with eosinophilic meningitis discovered that a fatal outcome occurred in fewer than 0.5% of patients [34].

The central nervous system is more frequently affected than the eyes, although the larvae may invade the vitreous humour. If this occurs, the patients may complain of blurred vision in one eye, but there may be no signs of meningitis [1, 35, 36].

62.5 History and Physical Examination

The clinical presentation in cases of infection with *A. cantonensis* result from the vigorous inflammation triggered by the parasites, which is triggered by their death. The most frequently occurring clinical syndrome to result from infection with *A. cantonensis* is eosinophilic meningitis. The most common symptoms are headache, nuchal rigidity, nausea and vomiting. Paraesthetic or hyperaesthetic symptoms may persist for a number of weeks. Although eosinophilic encephalitis occurs rarely, it is life-threatening, since treatment is generally too late. Invasion of the eyes by the parasite may present as feeling there is something in the eye, when the anterior chamber is involved, and vision is blurred, if the vitreous humour is the site of invasion [37–39].

The central nervous system manifestations include a headache of high severity of a type the patient has not previously experienced, coupled with paraesthetic symptoms, including burning, tingling sensations or being overly sensitive to touch. The headache is not relieved by NSAID treatment. A distinctive feature of the presentation is a shifting paraesthesia. This tends to follow a track along the truncal region and limbs, although it does not correspond to the distribution of specific nerves or dermatomes. There may occur a palsy of the abducens or facial nerves. For unclear reasons urinary retention may also occur. The gut is generally affected before the onset of clear symptoms of neurological involvement. The incubation period is typically from 1 to 3 weeks, but may be extended up to 6 weeks after inoculation. At this initial stage, there may be poorly localised abdominodynia, nausea and vomiting. These symptoms are triggered by invasion of the parasite through the lining of the gut. Neurological symptoms begin when the larval parasite has invaded the brain via the circulatory system. Since it takes a minimum of 1 week for the parasite to enter the brain via the bloodstream, there may potentially be a period during which symptoms do not occur, if the gastrointestinal symptoms quickly resolve. Vomiting may also be triggered by irritation of the meninges. There may also be other symptoms of a more general kind, such as loss of energy, mild pyrexia, insomnia or confusion. Paediatric cases generally manifest gastrointestinal disturbance more prominently than symptoms indicating nervous system involvement. When examining the patient physically, the abdominal and neurological examination require extra focus [2].

62.6 Diagnosis

In the majority of cases, diagnosing nervous system infection with *A. cantonensis* depends on an appropriate clinical history and examination, CSF analysis indicating raised eosinophils and a history revealing potential contact with the infective larval forms of the parasite [1].

CSF analysis should show raised numbers of eosinophils. There is generally a degree of cloudiness to the CSF, but not to the extent where frank turbidity or xanthochromia are observable. The white cell count is in the range 20–5000 cells per

cubic millimeter, typically between 150–2000 cells per cubic millimetre. The eosinophils generally represent between 20 and 70 per cent of the total white cells. In 95% of cases, eosinophils will account for at least 10% of CSF leucocytes [28–31]. The protein level is also generally high, whilst the glucose level is either normal or very slightly above normal [28–31].

There is adequate sensitivity for amplification of *A. cantonensis* DNA by polymerase chain reaction on samples of CSF [40]. Two studies which reported on cases of eosinophilic meningitis found a sensitivity of 67% for detection of parasite DNA in CSF taken from patients with eosinophilic meningitis [40, 41]. Potentially, sensitivity for detection of pathogenic DNA has now risen, thanks to the newer techniques now in use [42, 43].

Another diagnostic test of potential value is ELISA (enzyme-linked immunosorbent assay) [44]. The latest immunoassay techniques have the sensitivity to distinguish between eosinophilic meningitis secondary to *A. cantonensis* and that due to *Gnathostoma* infection [45, 46]. There is still, nonetheless, restricted availability of the latest techniques.

A small number of case reports detail the way next-generation molecular sequencing has been employed to analyse CSF samples [47, 48].

Diagnosis of eosinophilic meningitis secondary to *A. cantonensis* does not call for isolation of the parasite. In any case, this has rarely proven possible except where fatality has occurred [1].

Venous eosinophilia is generally seen in conjunction with the raised numbers of eosinophils in the CSF. For most cases, eosinophils account for more than 3% of the white cells. There is no direct correlation between eosinophil levels in the circulation and in the CSF, nor does the blood level reflect the clinical condition of the patient [1].

62.6.1 Radiological Investigations

There are few features of note on CT imaging, however, the fact that there are no foci of disease does help to differentiate cases of eosinophilic meningitis secondary to *A. cantonensis* from those due to *Gnathostoma* or *Taenia solium* [49]. When magnetic resonance imaging is performed, the signal from the globus pallidus and cerebral peduncle may be heightened on T1 weighting. If T1 weighting is used together with gadolinium enhancement, the leptomeninges are enhanced, the ventricles appear enlarged and there are points within the cerebrum and cerebellum with an abnormally enhanced character. T2 weighting shows hyperintense signals [50–52].

62.7 Auditory Impairment

There are differences in how nervous stem infections with *A. cantonensis* present in adult and paediatric patients [5]. In 95% of adults the presenting symptom of neuroangiostrongyliasis is a headache of high severity [53, 54]. The pain is typically perceived throughout the head and lacks any focus. It is often described as feeling like the head is exploding. The usual duration is between 1 and 7 days [55]. Some 40% of patients exhibit nuchal rigidity, which is an indicator of more severe disease [53, 56]. In around 40% of patients, paraesthesiae are reported, usually with a duration of no more than 14 days [30]. Paraesthetic sensations include numbness, pruritus or feeling as if there were worms moving under the skin. Vomiting occurs in 38% of cases and nausea in 28%, in conjunction with a headache. Problems with vision, including double vision, is noted in between 38 and 92% of patients [57]. Pyrexia is observed in 32% of adults with neuroangiostrongyliasis, but only 10% have pyrexia of high grade (i.e. between 38 and 39 °C) [54]. Palsies affecting the abducens and facial nerves are uncommon, as are auditory impairment, gastrointestinal obstruction, or indications that the spine is affected [5, 55, 58, 59].

In paediatric cases of eosinophilic meningitis secondary to infection with *A. cantonensis*, nausea and vomiting are considerably more frequent, being seen in 82% of cases. Pyrexia occurs in 80% of children, 80% exhibit sleepiness, 76% are constipated, 40% suffer abdominodynia, there is weakness of the extremities in 20% and seizures or twitching are more liable to be observed than in adult cases [54]. Furthermore, more than half of paediatric cases present with projectile vomiting, but this typically ceases in less than a week [30]. In comparison with adult cases, paediatric cases have a decreased incidence of paraesthetic symptoms or nuchal rigidity [5, 57].

It is difficult to account for the mechanisms underlying these symptoms, since neither the extent of central nervous injury caused by the migrating parasite nor the immune system response to the presence of living or complete parasitic larvae correspond in severity to the symptoms observed. The immune response is less than might be expected [60, 61]. However, it is clear that the dead (as opposed to living) parasites do mainly account for the eosinophil-dominated immune response. The presence of dead parasites triggers the increased expression of certain inflammatory signalling molecules (both cytokines and chemokines) which act to recruit and attract eosinophils to an area, namely interleukins 5, 12 and 33, as well as eotaxin (CCL11). T helper 2 cells orchestrate this response [62–65]. The resulting inflow of cellular immune mediators and fluid into the brain causes the CSF tension to rise, triggering headache [5, 30, 34].

62.8 Treatment

How severe and how long neuroangiostrongyliasis lasts depends on the number of parasites present in the host. The majority of cases resolve with conservative/supportive treatment alone. The therapeutic aim is to lessen the degree of irritation to the meninges and lessen the CSF tension by draining CSF, whilst offering palliative treatment of headaches. The use of corticosteroids in the form of prednisolone or dexamethasone, with the aim of damping immune reactivity has been shown to lessen the time for which headache occurs and decrease the need for CSF to be repeatedly removed by lumbar puncture [66]. In the past, it was advised that anti-helminthic agents were best avoided, as they may trigger massive release of parasite antigens, causing a more severe inflammatory response by the host immune system. However, it has since been demonstrated that anti-helminthic agents can be safely employed for this purpose and should be potentially employed if the parasitic burden is high. Nonetheless, no additional benefit has been shown to result from adding anti-helminthic agents to corticosteroids [67, 68].

Parasitic invasion of the eyes has a frequency of 1%, when the literature describing cases of *A. cantonensis* is considered as a whole. This invasion is into either the anterior or posterior chamber of the eye. Precisely how this invasion occurs has never been established, but one likely mechanism is for the larvae to migrate along the retinal artery lying adjacent to the optic nerve and its sheath. Generally a single parasitic larva is involved. The associated symptoms are blurring of vision, loss of vision and ocular discomfort. Most such patients also have eosinophilic meningitis. If the larva has penetrated the eye, it needs to be destroyed using a laser and then removed by surgical means [2].

No body has yet published guidelines for the management of neuroangiostrongyliasis. The following recommendations are, however, supported by the evidence base. Real-time PCR DNA amplification can be undertaken on CSF to confirm the presence of *A. cantonensis*. If the initial PCR is negative but clinical suspicion remains high, the lumbar puncture should be repeated and PCR undertaken once again. It is not recommended that serology be undertaken for specific immunoglobulins, either in CSF or blood.

Therapeutic measures should include administration of corticosteroids to lessen the severity of the immune reaction to dead or dying parasites. Albendazole is suitable as an anti-helminthic, but should not be administered without accompanying steroids. In patients with diabetes mellitus, there needs to be careful adjustment of the blood glucose during treatment [2].

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