Severe CNS angiostrongyliasis in a young marine: a case report and literature review

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***Angiostrongylus cantonensis* is the most common cause of eosinophilic meningitis worldwide. Infection typically occurs through ingestion of undercooked molluscs or vegetables contaminated by infective larvae. Endemic regions were previously limited to southeast Asia and the Pacific basin; however, this parasite is seeing an alarming increase in global distribution with reported cases in more than 30 countries, including several states in the USA. Although infection typically results in meningitis, a broad spectrum of CNS involvement and severity is emerging as diagnostic methods (such as real-time PCR) continue to improve diagnosis. In this Grand Round, we report a case of a 20-year-old active duty US marine serving in Okinawa, Japan, afflicted with severe CNS angiostrongyliasis marked by radiculomyelitis with quadriparesis, hyperaesthesia, and urinary retention. We present this case to highlight that no clear guidelines exist for the treatment of severe CNS angiostrongyliasis and provide our consensus recommendation that treatment algorithms include use of dual corticosteroids plus anthelmintics when radicular symptoms are present. In this Grand Round we review the clinical features, epidemiology, advances to diagnostic techniques, and available data on current treatment options for CNS angiostrongyliasis. This diagnosis should be highly considered in the differential diagnosis of a patient presenting with meningeal symptoms, paraesthesia or hyperaesthesia, and CSF eosinophilia so that treatment can be started early, which is particularly important in children, because of their increased risk of severe disease and mortality. We recommend combined therapy with albendazole and prednisolone, with consideration for increased steroid dosing in severe cases.**

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Introduction

Angiostrongylus cantonensis is a parasitic nematode and is the most common cause of eosinophilic meningitis and meningoencephalitis, capable of causing human infection with clinical presentation ranging from mild headache to coma and death.[1] This parasite was first described in rats in southern China in 1935, and the first human infection was documented in Taiwan in 1945.[1–3] Subsequent human cases were mostly reported throughout southeast Asia and numerous Pacific islands, until the more recent increase in worldwide infections, which has highlighted angiostrongyliasis as an emerging disease. The increase in the number of regions documenting infection is presumed to be secondary to the ship-borne disbursement of infected rats (the parasite's definitive host) or invasive snail species (the intermediate host), or to travellers returning from endemic areas.[1,2,4,5]

Low mortality rates are seen in patients with angiostrongyliasis; however, some clinical courses are complicated by severe neurological deficits with protracted recovery despite therapeutic intervention.[3] Of note, treatment effect on clinical outcomes in severe disease remains to be sufficiently studied. In this Grand Round, we present a case of severe CNS angiostrongyliasis that shows the broad spectrum of neurological sequelae seen in this emerging infectious disease. We will also review diagnostic methods, including the newly available quantitative real-time PCR (rtPCR) test, and the current treatment options for severe disease.

Case presentation

A 20-year-old male US marine serving in Okinawa, Japan, presented with bilateral thigh myalgia, dysuria, and constipation. His initial assessment was unremarkable and he was discharged home with 20 mg oral prednisone. 10 days after his initial symptoms he developed headache, neck stiffness, and severe hyperaesthesia. Upon further questioning, he revealed that he had consumed a raw giant African snail (*Achatina fulica*) 2 days before his initial symptom onset. He was then admitted to hospital with the suspected diagnosis of eosinophilic meningitis secondary to *A cantonensis* infection.

The initial lumbar puncture revealed an opening pressure of 22 cm H_2O and a white blood count of 44 cells per µl with 84% lymphocytes and 16% polymorphonuclear leucocytes (figure 1). Eosinophils were not seen; however, Giemsa staining was not done on this specimen. He was initially started on empiric antibiotics, antivirals, and prednisolone (20 mg). He developed quadriparesis, diminished deep tendon reflexes, and urinary retention, with continued hyperaesthesia to light touch. F-wave conduction testing was done for neurological localisation of lesions, with subsequent MRI of the spinal cord that was notable for high intensity areas in the bilateral anterior horn grey matter from cervical to lumbar regions. A repeat lumbar puncture on day 18 after ingestion of the snail revealed a count of 278 cells per µl, with 8% eosinophils (22 cells per µL) and an opening pressure of 42 cm H_2O (figure 1). He was started on albendazole 15 mg/kg per day, methyl prednisolone 1000 mg per day (changed to prednisolone 60 mg per day after 3 days), and 400 mg/kg per day intravenous immunoglobulin for 5 days. He had several lumbar punctures to relieve his continued headaches related to increased opening pressure. Albendazole was suspended

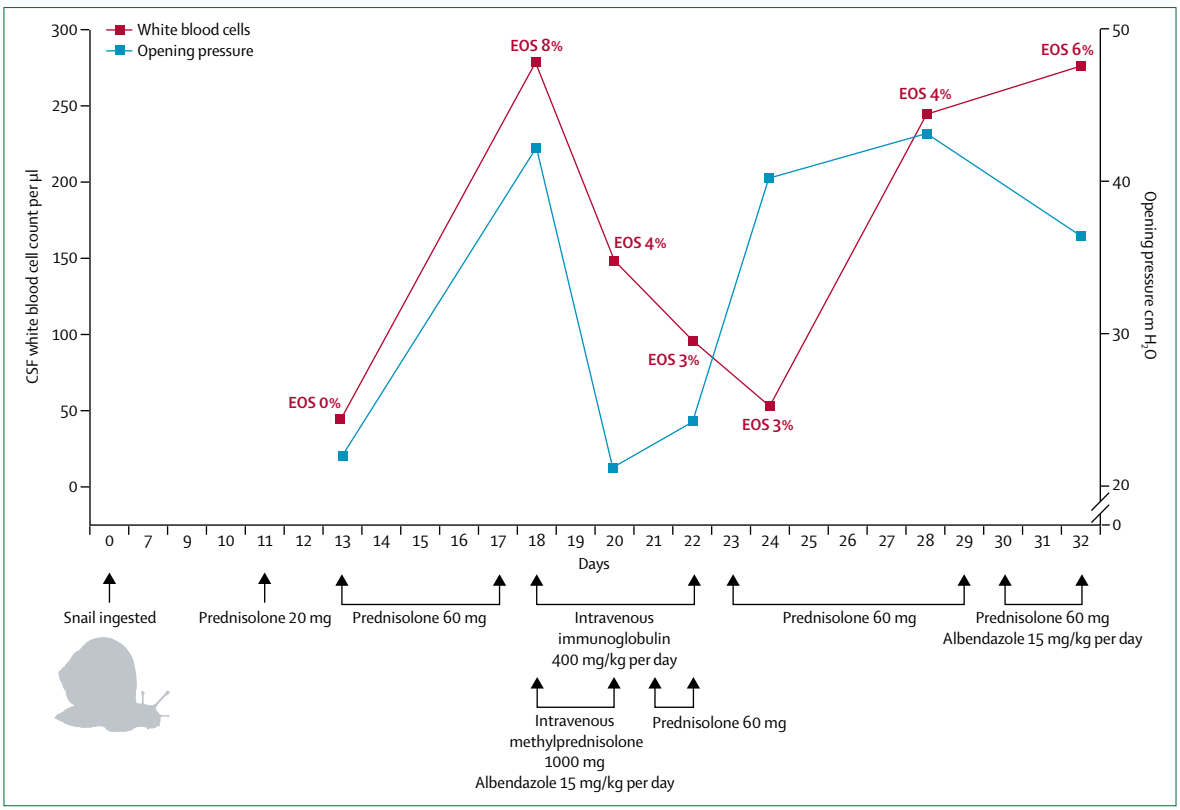

Figure 1: **Time course of treatment methods and lumbar puncture studies**
CSF eosinophilia (red line) and opening pressure measurements (blue line) were obtained serially through repeated lumbar punctures done during clinical treatment. Treatment regimens, including medication administered and duration of therapy relative to days post-snail ingestion, are shown along the X-axis. Results are combined from lumbar punctures done at the Okinawa Chubu Hospital, Okinawa, Japan, and the Naval Medical Center San Diego, San Diego, CA, USA. CSF=cerebrospinal fluid. EOS=percentage eosinophils in CSF white blood cell count.

after day 3 of treatment, because of concern for raised liver enzymes.

26 days after ingestion, he was subsequently transferred to the Naval Medical Center San Diego (San Diego, CA, USA) for continued care. Before military air evacuation he was intubated, owing to his profound weakness and for airway protection, but was extubated shortly after arrival. He continued to display severe quadriparesis with marked hyperaesthesia, requiring large amounts of pain control and sedation with ketamine, dexmedetomidine, and fentanyl. Ophthalmological examination revealed clinically significant papilloedema but no evidence of parasitic invasion. Repeat MRI of the brain and spinal cord was acquired using a 3-Tesla scanner with a protocol optimised using a contrast-enhanced fluid-attenuated inversion recovery (FLAIR) sequence. Within the spine there was persistent confluent abnormal increased signalling of the second thoracic vertebra and patchy enhancement involving the central grey matter of the entire spinal cord, abnormal leptomeningeal enhancement, and diffuse oedema within the paraspinal muscles (figure 2). MRI of the brain was done with high-resolution three-dimensional volumetric sequences and showed new punctate scattered foci of restricted diffusion indicative of acute cerebral ischaemia were present, presumably secondary to an infectious or inflammatory-mediated vasculitic insult. Characteristic linear areas of blooming susceptibility on susceptibility-weighted imaging were present, representing trails of petechial blood products presumably due to the migratory movement of the parasites (figures 2 and 3).

Repeat lumbar punctures continued to display increased opening pressure (figure 1). His liver enzymes improved and he was restarted on a 2-week course of albendazole 15 mg/kg per day, because of increased cerebrospinal fluid (CSF) cell counts and opening pressure. This course was started with concurrent prednisone (60 mg) and he had no further increase in liver enzyme concentrations. Of note, peripheral eosinophilia (11·1%) was first detected 31 days after ingestion. Following the completion of albendazole, he was continued on 50 mg of prednisone, which was tapered down over the course of 10 weeks.

DNA extracted from the CSF on days 13 and 18 after ingestion and analysed with rtPCR using previously published primer sequences[6,7] was negative for *A cantonensis*, but tests done on additional samples collected on day 20 after ingestion were positive. Immunological testing of CSF and serum with ELISA was not readily available in Japan

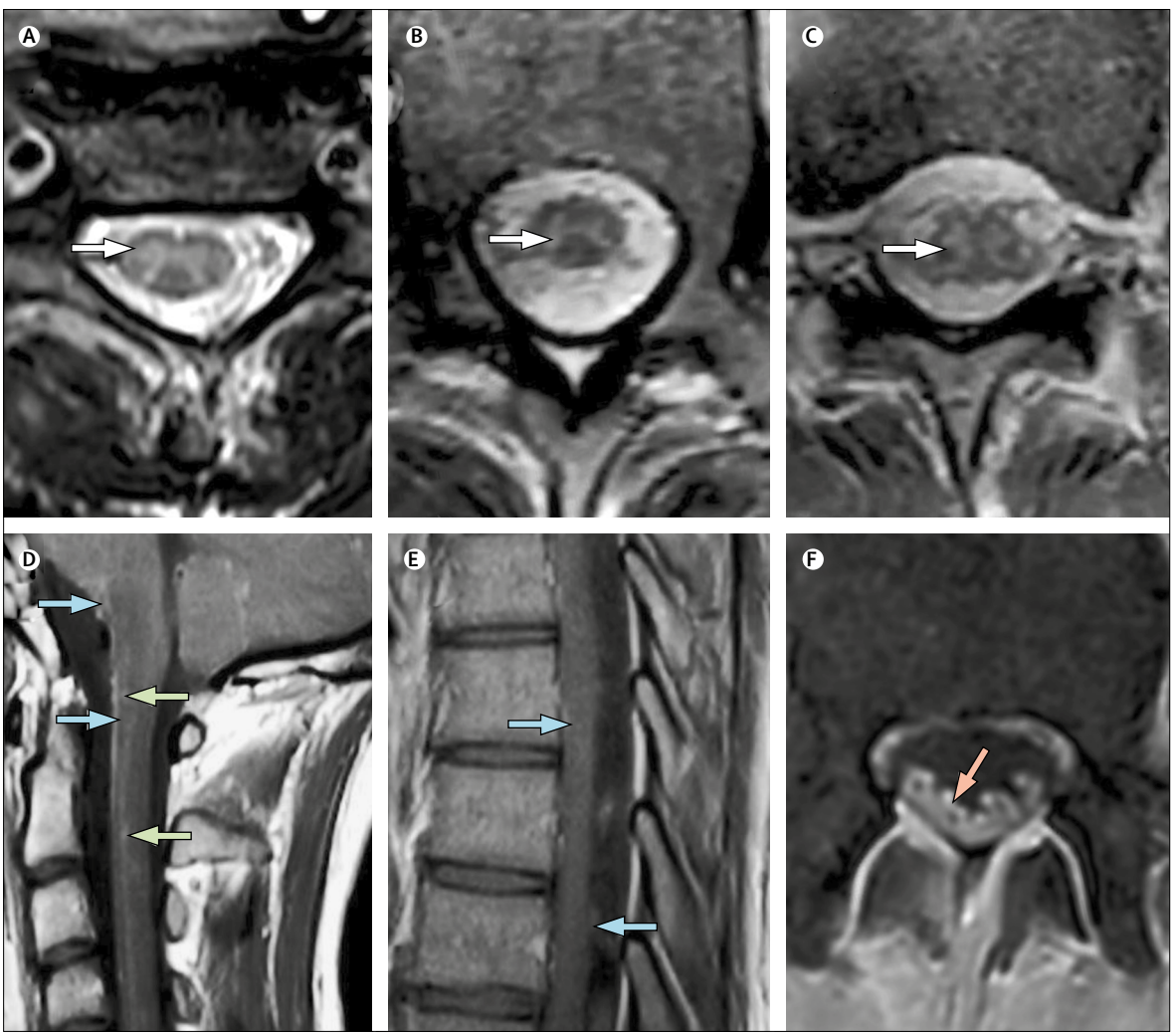

Figure 2: **MRI of the spinal cord indicates meningomyelitis consistent with severe angiostrongylus infection**
Axial T2 sequences of spine at the cervical (A), mid-thoracic (B), and conus medullaris (C) levels show abnormally increased T2 signal of the central grey matter (white arrows), indicating myelitis. Magnified sagittal T1 post contrast sequences of the upper cervical and mid thoracic spine highlight abnormal lepmeningeal enhancement of the cord with so-called sugar coating or zuckerguss appearance of leptomeninges (blue arrows) in conjunction with areas of abnormal central cord enhancement (green arrows) indicative of meningomyelitis (D,E). Axial T1 post-contrast of the cauda equina shows diffuse abnormal nerve root enhancement (orange arrow; F).

and gave negative results for samples obtained during the patient's treatment in a US hospital, 28 days after ingestion. However, testing was done under non-standard conditions using dried adult worms on CSF versus serum, which results in decreased sensitivity.[6–8] Given the known ingestion of *A fulica* in an endemic area, testing for other parasites, such as *Gnathostoma spinigerum*, was not undertaken.

The patient was discharged to an acute neurological rehabilitation centre, where urinary retention improved by 6 weeks after ingestion of the snail and ambulation returned around 8 weeks after ingestion. He continued to have erectile dysfunction and clinically significant allodynia 6 months later and required an extensive narcotic regimen for pain control. At 1-year follow-up he had continued urinary hesitancy and had subsequently developed central obstructive sleep apnoea. His neuropathic pain had shown substantial improvement but to date he still has intermittent pain described as a painful sunburn, predominantly in his lower extremities. He continues to take pregabalin 300 mg twice a day and duloxetine 60 mg per day. He is also being treated with intermittent ketamine infusions every 1–3 months. He has been treated with anywhere from 45 mg to 112 mg of ketamine over 1–3 hours, which has provided substantial long-term relief.

Epidemiology of *A cantonensis* infection

A cantonensis has a proclivity for tropical climates with the incidence of infections higher in the spring and summer corresponding to rainy seasons.[4,9–11] Owing to

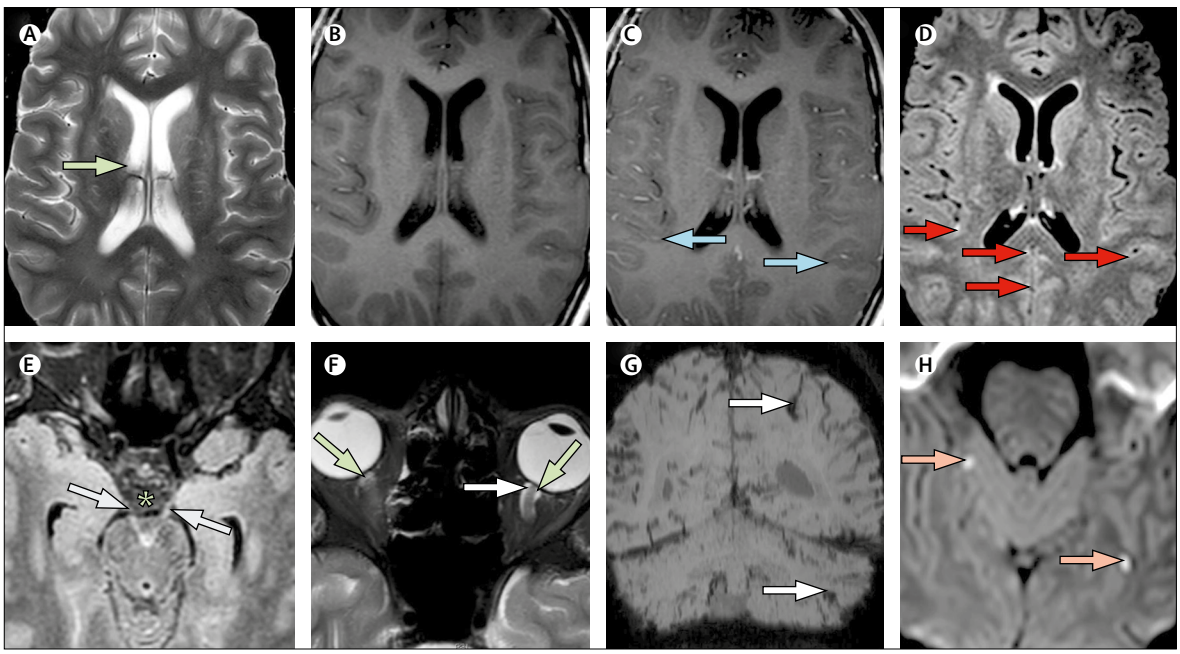

Figure 3: **MRI of the brain reveals extensive disease involvement in severe angiostrongylus infection**
Axial T2 image of the brain shows enlarged lateral ventricles (green arrow) out of proportion to the sulci (A) in conjunction with dilatation of the optic nerve sleeves (white arrow) and flattening of the lamina cribrosa (green arrows; F) implying raised intracranial pressure with resultant hydrocephalus and papilloedema. Axial T1 pre-contrast (B) and T1 post-contrast images (C) show areas of abnormal leptomeningeal enhancement, which are difficult to discern from normal background of pial vasculature. The highly sensitive T2 fluid-attenuated inversion recovery post-contrast sequence shows the overall extent of disease (red arrows; D). Magnified T2 fluid-attenuated inversion recovery post-contrast at the interpeduncular cistern shows abnormal enhancement of the oculomotor nerves (white arrows) as well as non-suppression of CSF signal in the suprasellar cistern (asterisk; E). Coronal susceptibility-weighted imaging highlights focal tract-like areas of abnormal blooming susceptibility, thought to represent haemorrhagic migratory tracks (G). Diffusion-weighted imaging shows punctate areas of restricted diffusion indicating ischaemic changes, mediated by direct cytotoxic insult from the parasite or secondary to an inflammatory response to the primary infection (H).

the relative rarity of disease, little data exist regarding global incidence; however, the annual incidence of angiostrongyliasis in Thailand, where case reports are most numerous, was about 0·2–0·3 per 100 000, based on data from 2005–09.[12] Data from Taiwan before 1990 indicated infection occurred most frequently in children younger than 10 years in this region; however, current data is similar to global incidence demographics indicating infection occurs most commonly in adults aged 20–40 years.[2,9] Mortality has been reported at 1·5–5%;[10,11] however, when encephalitis is present mortality can be as high as 79–91%.[13,14]

For the **US Department of Agriculture Animal and Plant Health Inspection Service** see https://www.aphis.usda.gov/aphis/home/

Since the first reported human infection in Taiwan in 1945, endemic regions had previously been limited to southeast Asia and the Pacific basin with 46% of the approximately 2900 worldwide cases reported through 2011 occurring in Thailand.[2,3] To date, however, a substantial increase in the global distribution of reported cases has occurred, including reports from more than 30 countries throughout Africa, South America, the Caribbean, Australia, and Europe, as well as the USA, where most cases have occurred in Hawaii (figure 4).[1,5,19,20] In 2007, infections with *A cantonensis* became a reportable disease to the Hawaii Government and 86 cases have been documented to date, including an outbreak in Maui in 2017.[21] The first report of *A cantonensis* in North America was the identification of worms in rat species in 1986–87 in New Orleans (LA, USA),[22] where subsequently the first human case in the continental USA was noted in 1993.[23] The parasite is now considered endemic to the Gulf Coast region, with three recent cases documented in children in Houston, TX, USA. Notably, increased documentation of infection in southeastern US wildlife and non-human primates suggests continued bicoastal expansion of the parasite in the USA.[15,16,20,24–27] The larval burden in and geographic location of intermediate and paratenic host species is detailed elsewhere.[5] Current efforts at eradication of the invasive giant African snail are underway; however, an expanded intermediate host reservoir[24] will probably hamper efforts at containing the spread of *A cantonensis* without an increased public health initiative.

Clinical features of CNS angiostrongyliasis

Eosinophilic meningitis is only one of the neurological manifestations caused by *A cantonensis*, which includes meningoencephalitis, radiculomyelitis, cranial nerve involvement and ocular disease manifesting as uveitis, retinitis, haemorrhage, or optic neuritis.[28–33] We thus use the broader term of CNS angiostrongyliasis to more appropriately encompass this clinical spectrum. There is additional heterogeneity in the incubation period, with

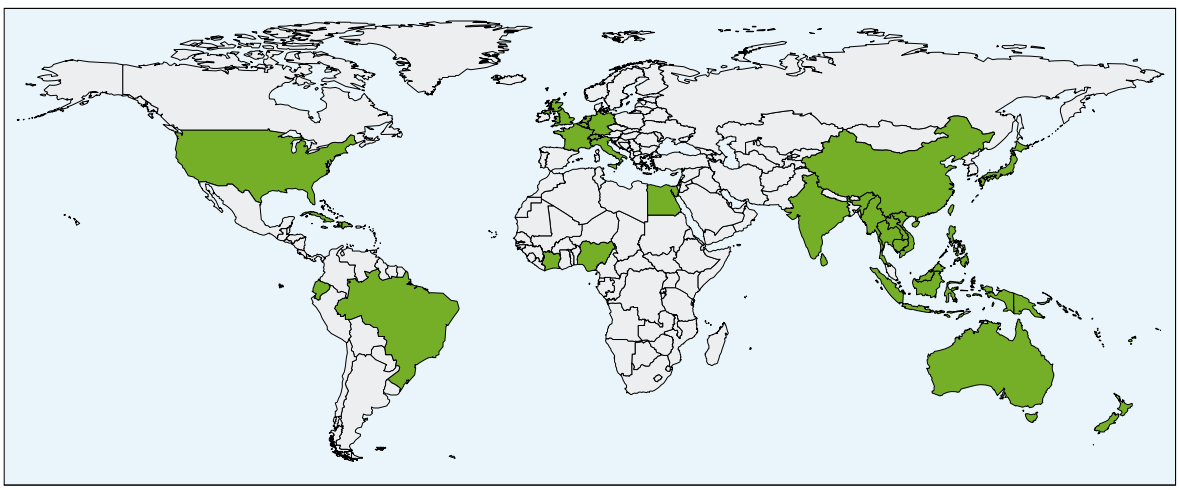

Figure 4: **Countries in which *Angiostrongylus cantonensis* has been reported**
Shaded countries are those in which *A cantonensis* has been detected in naturally infected hosts or human infection has been identified either as epidemic infection or sporadic cases not believed to have been acquired abroad. *A cantonensis* is not necessarily endemic to the entirety of shaded regions.[1,2,3,5,15-18]

symptoms reported 1 day to several months post-infection.[2] The disease presentation is detailed in figure 5 as a collective of the largest case series to date, and further detail is provided in the appendix.

Radiculomyelitis characterised by severe nerve pain, motor weakness and paralysis, and urinary dysfunction is rare in CNS angiostrongyliasis and has been more typically associated with infection by *G spinigerum*, which is characteristically accompanied by CNS haemorrhage.[2,3,5,30,31,36,37] Wide variability in the clinical spectrum of CNS angiostrongyliasis presentation exists between individual outbreaks (figure 5). Therefore, whether this heterogeneity is a manifestation of the theoretically unique patterns of larvae migration in individual cases or whether severe disease is associated with patient age or correlated to the quantity of inoculum present in each outbreak is unclear.

For example, children have a higher mortality and are more likely to have a more severe illness than adults, with a relatively higher proportion presenting with meningoencephalitis and to suffer prolonged neurological sequelae.[29,35,38] In children, the development of more severe symptoms, including paresis, bulbar signs, and coma, has been shown to correspond with an age of less than 5 years and a large larval burden noted at autopsy.[38]

Life cycle and pathogenesis of *A cantonensis*

Also known as the rat lungworm, *A cantonensis* parasites complete their life cycle in rats, which serve as the definitive host. In rats, ingested neurotropic third-stage (L3) larvae mature to the sub-adult stage in the CNS, and subsequently migrate to the right ventricle and pulmonary artery, where they complete their maturation. This process occurs without causing CNS abnormalities in the rats. Mature worms lay their eggs, which hatch into L1 larvae, which penetrate the alveoli, migrate up the trachea, and are swallowed.[1,2] The larvae are released in rat faeces and are subject to ingestion by the molluscan intermediate host. Snails represent the most common intermediate host harbouring L3 larvae, but they can also be found in shrimp, frogs, or monitor lizards. Human infection occurs after ingestion of these hosts in raw or undercooked snails, or through ingestion of small slugs or juvenile larvae overlooked in unwashed salads or raw vegetable juice.[1,13,17–19] Despite speculation, shedding of larvae in molluscan mucus secretions is low and unlikely to represent an additional mode of transmission.[39] After ingestion by human beings, the larvae penetrate the intestinal wall and migrate through the blood and reach the CNS in 2–3 days, where they mature to the subadult stage. However, unlike in rats, they are largely unable to re-enter systemic circulation, eventually dying in 1–2 months in brain tissue.[1,40,41] Given the infection in human beings largely remains confined to the CNS,[1,4,5] patients are unlikely to infect others.

The clinical diseases caused by the presence of L3–L5 larvae in the CNS includes meningitis, meningoencephalitis, and radiculomyelitis.[1] In angiostrongyliasis, both the direct movement through the brain by the worms and the secondary reactive inflammation to this process appear to lead to neurological damage.[1] Necropsy evaluation of infected patients revealed both microscopically visible tortuous non-haemorrhagic tracks typically filled with gitter cells and larger haemorrhagic tracks with surrounding neutrophils throughout the brain parenchyma and spinal cord. Tracks were surrounded by degenerating neurons, as well as oedematous vessels with perivascular infiltrates of lymphocytes and eosinophils, and additional granuloma formation and Charcot-Leyden crystals around dead worms, with numerous vascular lesions and haematomas.[42]

Experimental *A cantonensis* infection in mice, a nonpermissive host like human beings, results in brain

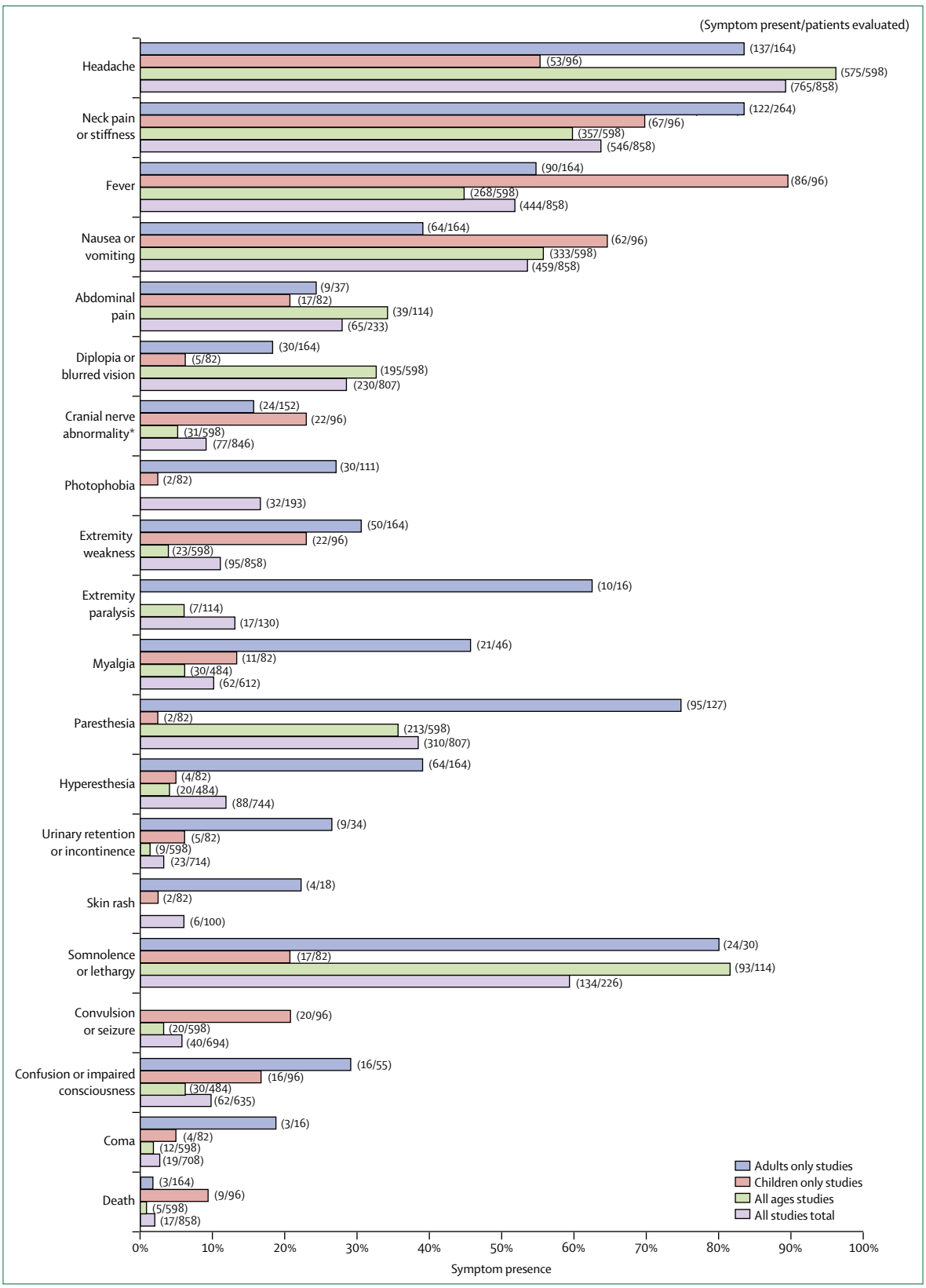

Figure 5: **Frequency of clinical manifestations in nine series of patients with CNS angiostrongyliasis**

Studies differed in the parameters evaluated, which is reflected in differing numbers listed in parentheses for patients evaluated. Five studies included >95% adults and are labelled as adults only.[10,13,19,28,34] Two studies involved only children,[29,35] and two had mixed age groups;[32,33] however, one[33] had >70% children. Hyperaesthesia recorded in one study[32] is probably lower than the true occurrence, because a clear distinction between paraesthesia and hyperaesthesia was not made. Additional data is in the appendix. *Cranial nerve abnormality includes facial palsies or abnormalities in extraocular muscles.

injury and neurological symptoms that are more severe than in rats and reveals potential cellular mechanisms underlying clinical disease. CNS histology of infected rats demonstrated no appreciable cellular reactions around the worms, whereas significant leucocyte infiltration of predominantly neutrophils and eosinophils was noted in mice and correlated to increased intracranial worm degeneration and eosinophil degranulation.[43] Eosinophils contribute to both helminth toxicity and neurotoxicity during *A cantonensis* infection in non-permissive hosts[44] and enhance a T helper 2 cell-mediated cytokine response.[5] In addition, experimentally-infected mice displayed increased activities of proteolytic enzymes matrix metalloproteinase-9 and plasminogen activator, which correlated with increased CSF eosinophilia and albumin levels, thus potentially underlying the blood-CNS barrier breakdown during development of eosinophilic meningitis,[43] as well as increased neuronal death in infected rats.[45]

Laboratory diagnosis

Eosinophilic meningitis is defined as the presence of ten or more eosinophils per µL or eosinophilia of at least 10% in the CSF.[46] CSF generally appears clear or turbid with raised protein levels and normal or slightly reduced glucose concentrations,[46,47] which is in contrast with the non-traumatic bloody or xanthochromic CSF typically found in gnathostomiasis.[8,41,46,47] In addition to the wide spectrum of clinical presentation, detection of CSF eosinophilia often follows an incongruent timeline to symptom onset making diagnostic assessment challenging. Previous case reports have shown that although infected patients displayed eosinophilia at some point during their course, CSF eosinophilia was noted in only half of initial lumbar punctures, with initial blood draws that indicated peripheral eosinophilia in less than half of patients at disease onset.[36] The lower number of eosinophils noted in our patient cannot be used to rule out the diagnosis of CNS angiostrongyliasis,[10,48] and numbers were potentially affected by prednisone administration before admission. Peak CSF and peripheral eosinophil concentrations have been reported at 25–35 days after ingestion.[36] Identification of larvae on microscopy of CSF or in the eye chamber remains the gold standard for definitive diagnosis of CNS angiostrongyliasis, although these findings are rare, even in the most severe cases.[2,11,49] An increased likelihood of recovering larvae in samples has been postulated to occur when lumbar puncture is done after the patient has remained in a seated position for more than an hour; however, this position compromises opening pressure measurements.[18,50,51]

Currently, the accepted clinical practice for immunodiagnosis uses serum or CSF through combined ELISA and immunoblot analysis or dot immunogold filtration assay primarily targeting a purified 29 kDa and 31 kDa glycoprotein antigen of *A cantonensis*.[12,52–54] Studies have shown that serum antibodies are detected more often and at higher concentrations than CSF antibodies and prove to be the more sensitive immunodiagnostic choice;[10,48,51] however, serum antibodies are not typically noted until convalescence of the disease.[36] Experimental studies in rabbits and mice infected with *A cantonensis* have shown that the peak antibody response does not occur until 4 weeks after infection.[55,56] A newer focus of diagnostic testing is rtPCR on DNA extracted from CSF samples. The median time from symptom onset to positive CSF rtPCR is 21 days, by comparison with 27 days for serum antibody detection, with a specificity of 100%.[7] Sensitivity of the test is lower, with a false negative of 22%.[7] This technique is only validated for human diagnostics through the US Centers for Disease Control and Prevention and the Hawaii Department of Health, and is expected to expand in use for rapid diagnosis.

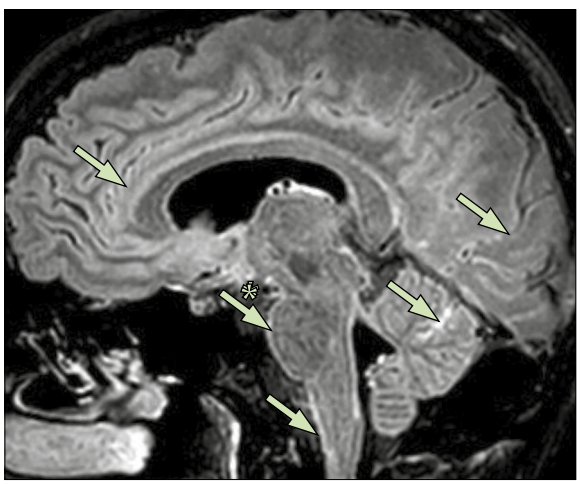

Figure 6: **MRI brain, midline sagittal plane**

Sagittal T2 fluid-attenuated inversion recovery post-contrast shows diffuse abnormal leptomeningeal enhancement involving the cerebrum, cerebellar folia, and brainstem (green arrows) and non-suppression of CSF signal (asterisk)

Imaging

Data for the diagnostic utility of imaging modalities for CNS angiostrongyliasis are scarce. Most studies suggest imaging of the brain is normal; however, findings are diverse, non-specific, and dynamic among cases with CNS lesions seen on MRI.[57–59] Multiple enhancing brain nodules and leptomeningeal enhancement have been observed (figure 6).[57,58] Longitudinal repeat MRI assessment in one study of five patients with *A cantonensis* myelomeningoencephalitis found lesions were most prominent on MRI in the 5th to 8th week after symptom onset, although new lesions were notably seen even after 8 weeks.[57] Additionally, MRI T1-weighted signal intensity in patients with *A cantonensis* infection showed a significant positive correlation with headache severity, as well as CSF and serum eosinophilia.[60] It remains unclear, however, what impact imaging protocol variability confers on diagnosis.

Contrast-enhanced FLAIR sequences are more sensitive and specific compared with post-contrast T1-weighted image sequencing for detection of most abnormal leptomeningeal processes.[61] Moreover, advances in technology for susceptibility-weighted MRI sequences allow for more sensitive detection of blood degradation products[62] and subsequently better detection and visualisation of the subcortical parenchymal haemorrhagic tracts of the migrating parasite.[63] Of note, imaging showing myelitis and cerebral haemorrhage in CNS angiostrongyliasis is limited to case reports and this pattern is more characteristically seen on imaging in CNS *G spinigerum* infection.[56,59,64–66] Gnathostomiasis infection confers an increased likelihood of permanent neurological damage or fatality.[65] Therefore, although the use of imaging is not of diagnostic value in CNS angiostrongyliasis, MRI assessment for cerebral haemorrhage and characterisation of spinal cord involvement can provide the most utility in assessing disease severity and predicting overall clinical course and prognosis.

Treatment

To date, no standard of care treatment regimen for CNS angiostrongyliasis exists. Without treatment, the lifecycle of *A cantonensis* dictates that most worms will die in the CNS within 1–2 months.[40] Observation and supportive care alone with analgesics and therapeutic lumbar punctures might therefore be sufficient for patients with clinically mild disease. For those patients with more severe disease in whom treatment is considered, these treatment plans have largely consisted of corticosteroid therapy with or without addition of anthelmintic agents.[28] Corticosteroids are currently used as the mainstay of treatment on the basis of a randomised, controlled trial that indicated that prednisolone (60 mg per day for 2 weeks) compared with placebo was associated with a shortened median time to headache resolution, and with less individuals requiring repeat lumbar punctures.[67] However, the use of headache as the only primary outcome measure for infection response to therapy was a noted limitation.[67] The effect of corticosteroid use on radiculomyelitis has not been directly evaluated. However, several large case series do indicate that, although headache and fever resolve early, paraesthesia and hyperalgesia resolve slowly,[13,29,33,68] but the association of this resolution to treatment response remains to be directly studied.

Treatment of CNS angiostrongyliasis with anthelmintic drugs has been controversial. Several studies have indicated that these drugs relieve symptoms and reduce disease duration. However, theoretical concern remains that neurological symptoms can become acutely exacerbated[2] secondary to a heightened T-helper-2 cell-mediated immune response to the release of intracellular contents from dying worms.[1,5,33,49] To date, however, very little evidence showing this deleterious effect exists, mostly limited to a few case reports that describe the use of anthelmintics as monotherapy.[68–70] In the only prospective, randomised, double-blind, placebo-controlled study evaluating the use of albendazole monotherapy,[71] the treatment group had significantly shorter mean duration of headaches, but not fewer persistent headaches at 2 weeks overall than the control group. Furthermore, although no direct measures of acute heightened disease severity were assessed as direct outcomes, the study reported no significant side-effects attributable to albendazole treatment.[71]

Animal studies provide more insight into the efficacy of anthelmintic agents in CNS angiostrongyliasis. Rabbits, another non-permissive host with CNS disease similar to human beings, experimentally infected with *A cantonensis* displayed increased pathological changes on brain MRI with delayed albendazole monotherapy starting 15 days after infection; however, no changes on brain MRI were observed when treatment was started before 15 days after infection.[72] A similar study in mice showed complete elimination of larvae in the brains of those treated with 10 mg/kg per day of albendazole for 2 weeks if given within 15 days after infection.[73] Post-mortem brain examination of controls revealed damage presumed secondary to migrating larvae and parasite degradation products inciting an inflammatory response. No pathological changes were noted in mice treated within 15 days. Another study in mice showed a direct correlation between the degree of brain inflammation and number of larvae recovered, and that combined treatment with albendazole and thalidomide administered within the first 2 weeks of infection led to both fewer worms available for recovery and decreased severity of meningitis.[74] Anthelmintics did not cause direct harm if administered after 15 days,[74] but the larvicidal activity might be diminished once larvae have reached the L4 stage, emphasising the need for early treatment initiation.

Although the combination of corticosteroids and anthelmintics has been a common strategy to treat CNS angiostrongyliasis,[2,28] several studies have indicated no additional benefit to treating with both therapies compared with corticosteroids alone.[40,75,76] Dual therapy, however, was associated with no increase in serious side-effects.[28,29,33,49] Moreover, these studies are also limited by the use of headache as the primary outcome measure. Given the current paucity of data to suggest actual harm by addition of anthelmintics and of objective clinical response to steroids alone in our patient (figure 1), we suggest treatment of severe CNS angiostrongyliasis should include a 2-week course of albendazole at 15 mg/kg per day in twice daily divided doses, in addition to prednisolone 60 mg/kg for at least a 2-week course. Future studies are needed to assess therapy efficacy on outcomes associated with more severe disease, including radiculomyelitis, and the continued study of the molecular biology of the parasite with respect to understanding virulence factors and points of susceptibility to direct development of more effective therapies is warranted.[5]

Search strategy and selection criteria

We identified references for this Grand Round through searches of EMBASE, Medline (PubMed), and Google Scholar with language limited to English-only articles published from database inception until February, 2018, using the terms: "Angiostrongylus cantonensis", "angiostrongyliasis", "human angiostrongyliasis", and "eosinophilic meningitis." These terms were then combined with the following terms: "drug effects", "drug therapy", "adverse effects", "antihelminthics", "anthelmintics", "albendazole", "corticosteroids", "prednisolone", "prednisone", "methylprednisolone", "methylprednisone", "real-time PCR (or polymerase chain reaction), "diagnosis", "microbiology", "cerebrospinal fluid", "diagnostic imaging", and "MRI (or magnetic resonance imaging)." We also reviewed the US CDC website for reported disease occurrences and US Department of Agriculture Animal and Plant Health Inspection Service website data, as well as searching recent news articles regarding recent outbreaks, in addition to direct correspondence with CDC parasitology staff.

Supportive and adjuvant long-term care

The published literature on supportive care for chronic symptom management during recovery from CNS angiostrongyliasis is scarce. There are no clear guidelines for management of additional disease sequelae, including prolonged severe pain and hyperalgesia. First-line therapies of paracetemol or non-steroidal anti-inflammatory drugs are often inadequate or relatively contraindicated with concomitant corticosteroid use.[40,49] Our patient required a combination of opioids and anaesthetics, including ketamine and dexmedetomidine, throughout hospitalisation, followed by a 10-week steroid taper after discharge. He remained on ketamine in addition to pregabalin and duloxetine for continued hyperaesthesia at 6 months after discharge. Given that radicular symptoms might persist for months,[3,13,28,33,34,77,78] patients who have severe CNS angiostrongyliasis can require a long-term multimodal care strategy. Case-specific considerations include urinary retention, which might require long-term bladder catheterisation, and weakness or immobility, requiring intense rehabilitation.

Conclusion

We report a case of severe eosinophilic meningitis secondary to parasitic infection with *A cantonensis* after ingestion of a raw snail. This patient contributes to the growing number of reported cases of meningitis caused by *A cantonensis* and highlights the complication of radiculomyelitis, defined here under the broader term of CNS angiostrongyliasis. This diagnosis should be highly considered in the differential diagnosis of a patient presenting with meningeal symptoms, para-esthesia or hyperaesthesia, and CSF eosinophilia so that treatment can be started early, which is particularly important in children, because of their increased risk of severe disease and mortality. We recommend combined therapy with albendazole and prednisolone, with consideration for increased steroid dosing in severe cases. rtPCR is increasingly recognised as the diagnostic method of choice; however, when it is not available, ELISA of serum is preferred. The dissemination of this parasite and potential for disease severity make early recognition and accurate detection paramount for patient outcomes, and emphasises the importance of a public health role to provide education and awareness of disease risk factors to individuals in endemic areas or travelling internationally to prevent further transmission.

Contributors

LM did the scientific literature search, contributed to data collection and analysis, co-wrote and edited the manuscript, and did primary figure development. SFE did the scientific literature search, contributed to data collection and analysis, co-wrote and edited the manuscript, and contributed to figure development. DL and MB assisted in the literature search, data collection, interpretation, and writing. JY and MC contributed to data collection, interpretation, figure development, and writing. MM and MN summarised the patient history and contributed to data analysis and interpretation. KO contributed to data collection. TQ assisted in data collection, interpretation, and editing. CV assisted in the data collection, interpretation, figure layout, writing, and editing the manuscript.

Declaration of interests

We declare no competing interests.

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