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Review

Eosinophilic meningitis due to *Angiostrongylus cantonensis* in Europe

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ABSTRACT

Objectives: To describe and analyse the epidemiological and clinical characteristics of imported human angiostrongyliasis in Europe.
Methods: A systematic literature review of cases of human angiostrongyliasis in Europe was performed. Seven databases were searched. The epidemiological and clinical characteristics were extracted from included records and simple summary statistics were performed on extracted data.
Results: Twenty-two cases reported between 1988 and 2019 were identified. They were mainly from French Polynesia, Southeast Asia, and the Caribbean Islands. The dominant suspected mode of transmission was ingestion of prawns, shrimp, or salad. For patients with data, 90% had a history of headache, often lasting, and half had paresthesia. Eighty-nine percent had eosinophilia, 93% had cerebrospinal fluid (CSF) eosinophilia, and 92% had elevated CSF protein. Central nervous system (CNS) imaging was normal in most cases. Two-thirds received albendazole or mebendazole treatment, although this is not currently recommended.
Conclusions: We have increased previous numbers to 22 reported cases in total since 1988. Angiostrongyliasis should generally be suspected in patients with a lasting headache who have returned from Southeast Asia, China, the Caribbean Islands, Australia, or French Polynesia, as well as parts of North America and Tenerife, Spain, although one autochthonous case from mainland Europe has also been reported. A dietary history should focus on prawns, shrimp, and salad, whilst also including slugs and snails and other paratenic hosts where relevant. The clinical diagnosis is supported by the presence of blood eosinophilia, CSF eosinophilia, and elevated CSF protein. A definitive laboratory diagnosis should be sought, and CNS imaging should be used to support, not to rule out the diagnosis. The most up-to-date evidence should always be consulted before initiating treatment. Current recommendations include analgesics, corticosteroids, and periodic removal of CSF for symptom relief, while antihelminthic treatment is debated.

Introduction

Angiostrongylus cantonensis is a zoonotic pathogenic nematode with rats as the definitive hosts (Wang et al., 2008). Human infection occurs from deliberate or inadvertent ingestion of third-stage larvae in raw or undercooked intermediate hosts, namely snails or slugs, or via contaminated fomites, e.g., uncooked vegetables. In addition, the ingestion of paratenic hosts such as freshwater shrimps, land crabs, frogs, toads, and monitor lizards can also cause infection (Cowie, 2013). Figure 1 shows the lifecycle, human transmission, and symptoms of *A. cantonensis*.

Upon ingestion, the infective larvae invade the intestinal wall causing enteritis and then enter the bloodstream (Wang et al., 2008; Yii, 1976). The most common site of migration is the central nervous system (CNS), causing the main clinical manifestation of angiostrongyliasis, i.e., eosinophilic meningitis, defined as the presence of more than 10 eosinophils/mm^3 in the cerebrospinal fluid (CSF) and/or at least 10% eosinophils in the total cerebrospinal leukocyte count

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(Wang et al., 2008; Sawanyawisuth and Chotmongkol, 2013; Weller, 2019). Symptoms of this condition range from mild headache to severe, throbbing headache, dizziness, nausea, vomiting, fever, neck stiffness, paresthesia, and stabbing pain in the trunk and limbs aggravated by touch (Wang et al., 2008; Cui et al., 2011). In the majority of patients with eosinophilic meningitis, spontaneous remission occurs without specific treatment, but severe cases resulting in neurological sequelae or even death have been observed (Wang et al., 2008; Yii, 1976; Weller, 2019; Lo Re and Gluckman, 2003). Larval passage through the liver and lungs may cause cough, rhinorrhoea, sore throat, malaise, and fever (Wang et al., 2008; Yii, 1976). A rare complication of *A. cantonensis* infection is ocular angiostrongyliasis, which may present with monocular blurred vision, diplopia, or strabismus after or concurrently with more common symptoms of angiostrongyliasis (Feng et al., 2013; Punyagupta et al., 1975; Sawanyawisuth et al., 2007).

A. cantonensis is a common cause of eosinophilic meningitis inendemic parts of the world, mainly Thailand (incidence as high as 2 per 100 000 population per year) and China, and less so Australia (Barratt et al., 2016). Recent data suggest a geographical expansion of the parasite, resulting in a rapidly increasing incidence of human infection (Barratt et al., 2016). *A. cantonensis* has recently been found in rats in the south-eastern United States (Teem et al., 2013; York et al., 2015; Stockdale-Walden et al., 2015) and in three species of molluscs in north-eastern Tenerife, Spain (Martin-Alonso et al., 2015). The molluscs are part of the natural fauna of Tenerife and can be found in both forests and inhabited areas, posing a potential risk of transmission to humans. Furthermore, two of the mollusc species, *Cornu aspersum* and *Theba pisana*, are native in several parts of Europe (Martin-Alonso et al., 2015).

Previously, the number of cases of imported angiostrongyliasis in Europe has been put at 11 (15 if counting all identified case reports) (Maretic et al., 2009), whilst a recent literature review of foodborne nematodiasis in the European Union identified 12 cases (Serrano-Moliner et al., 2018) (nine European cases according to our definitions, as three were reported from Cuba (Padilla-Docal et al., 2011), please see Methods). However, these reviews were not

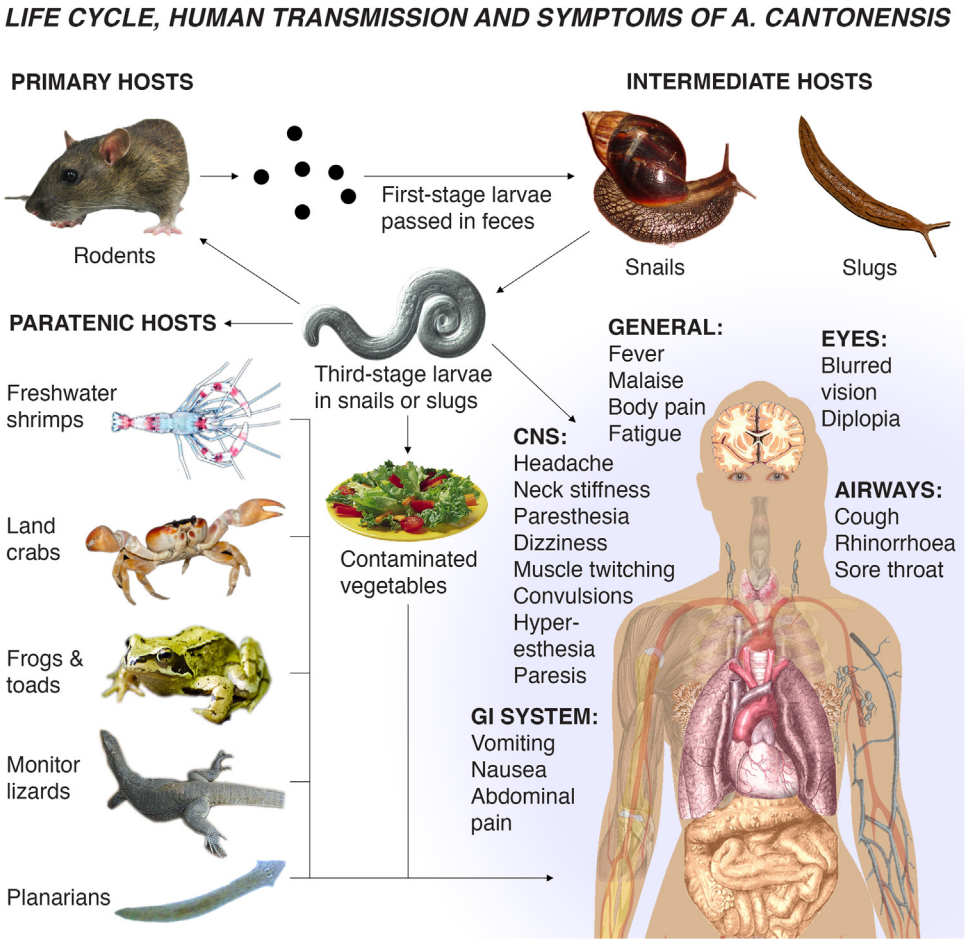

Figure 1. The lifecycle, human transmission, and symptoms of *Angiostrongylus cantonensis*. Rodents, mainly rats, are the primary hosts and ingest third-stage larvae in snails or slugs. The larvae move through the bloodstream to the CNS, where they moult twice to become adult worms. The adult worms then migrate to the pulmonary arteries and lay eggs, which are carried to the capillaries and break into the alveoli where they hatch. The first-stage larvae then migrate through the trachea to be swallowed and shed with the faeces. First-stage larvae are ingested by intermediate hosts (snails and slugs) where they develop into third-stage larvae. Third-stage larvae are transmitted to paratenic hosts (freshwater shrimps, land crabs, frogs, toads, monitor lizards, and planarians) through their ingestion of intermediate hosts. The third-stage larvae can be transmitted to humans through the ingestion of paratenic or intermediate hosts, or via contaminated fomites, e.g., vegetables (Wang et al., 2008; Sawanyawisuth and Chotmongkol, 2013; Lo Re and Gluckman, 2003; Koo et al., 1988). In humans, the larvae invade the intestinal wall causing vomiting, nausea, and abdominal pain and then enter the bloodstream (Wang et al., 2008; Yii, 1976). Most commonly, the larvae migrate to the CNS causing eosinophilic meningitis, with the most common symptoms being headache, neck stiffness, paresthesia, dizziness, pain in the trunk and limbs, muscle twitching, fatigue, convulsions, hyperesthesia, and paresis (Wang et al., 2008; Yii, 1976; Cui et al., 2011). The larvae pass through the bloodstream to the liver and lungs, causing cough, rhinorrhoea, sore throat, malaise, and fever (Wang et al., 2008), and on rare occasions to the eyes causing blurred vision or diplopia (Wang et al., 2008; Feng et al., 2013). (All images used are in the public domain, from https://commons.wikimedia.org, www.publicdomainpictures.net, or www.cdc.gov (CDC-DPDx)).

focused on the sole question of investigating the epidemiological and clinical history with the disease in Europe, and limitations in the databases searched, search strings applied, countries, years, and languages included in these reviews, as well as the details presented on clinical cases and their management, warrant an expanded investigation into the question. A recent global review identified 17 cases in Europe, however with no reported methodology or quantitative analysis performed (Ansdell and Wattanagoon, 2018). With increased globalization and host organisms on the move, an updated overview of the occurrence and characteristics of human angiostrongyliasis in Europe is relevant to identify any potential epidemiological and clinical patterns that may help equip European clinicians so that they are better able to diagnose and manage the disease.

A focused and comprehensive investigation into the epidemiological and clinical characteristics of eosinophilic meningitis caused by *A. cantonensis* in Europe was performed.

Methods

A search was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for systematic review without meta-analysis (Moher et al., 2009); the PubMed, Ovid MEDLINE, Embase, CINAHL Plus, and Cochrane Library databases were searched for reports on humans, in any language. No time restriction was applied. The PubMed search string was: angiostrongylus[tiab] or angiostrongyliasis[tiab] or cantonensis[tiab] or "rat lungworm"[tiab] or angiostrongylus cantonensis[MeSH]. An equivalent search string was used in the other databases, with the same content but Boolean operators changed to comply with database syntax (see Supplementary material Appendix). EndNote software (Clarivate analytics, 2020) was used to compile the records. Citations in included articles were screened for potential relevance.

Inclusion criteria were case reports with title or abstract mentioning eosinophilic meningitis due to *A. cantonensis*. All relevant records that were available through the London School of Hygiene and Tropical Medicine and Odense University Hospital subscriptions were included. Where records were unavailable, an internet search for publicly available copies of the record was conducted, and where this was unsuccessful, the authors were contacted via email and given several months to respond. Reports that were not from Europe, i.e., the patient did not present at a health centre in Europe, were excluded.

The review was performed independently by two authors (F. Federspiel and S. Skovmand) between February and December 2019. Data were first extracted by F. Federspiel and then verified by S. Skovmand during her review. Figure 2 shows an overview of the search strategy results.

The following data were extracted from case reports: country reported from, patient sex, age, travel destination, suspected mode of transmission (i.e., food items ingested), presenting symptoms, clinical presentation, initial workup findings, mode of diagnosis, treatment, and outcome. Laboratory result units were converted into the same SI units to enable comparison. Eosinophilia was defined as an eosinophil granulocyte count of more than 0.6×10^9/l and/or more than 4% of the total white blood cell (WBC) count in peripheral blood (Medscape, 2018; Medscape, 2019). A definitive diagnosis was defined as a laboratory-based confirmation of *A. cantonensis* infection. For clinical outcomes, full recovery was defined as a statement of full remission, recovery, successful treatment, symptom improvement, symptom regression, or similar. Persistent symptoms were defined as symptoms being present $\geq$6 months after presenting at the health centre.

The World Health Organization Europe Centralized Information System for Infectious Diseases and the European Centre for Disease Prevention and Control Surveillance Atlas of Infectious Diseases were consulted to capture any further registered cases in Europe;

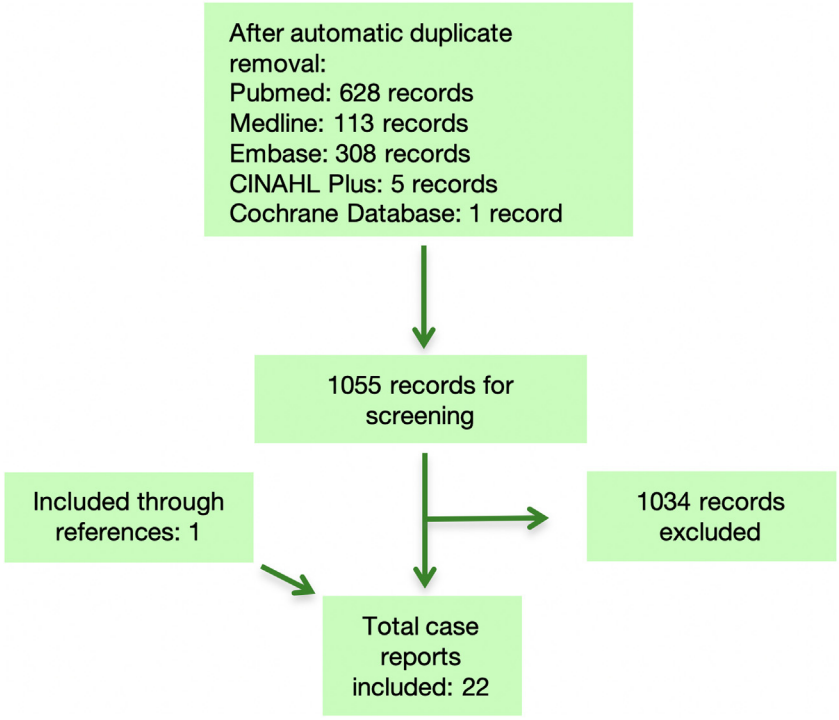

Figure 2. Overview of the search strategy results.

however neither of these databases track *Angiostrongylus* cases (World Health Organization Regional Office for Europe, 2019; European Centre for Disease Prevention and Control, 2019).

Results

Epidemiology

The search returned 1055 records for screening after automatic duplicate removal. From these records, 17 case reports were identified for inclusion, for a total of 22 cases. Three papers were excluded due to lack of access and no response from the authors after contacting them (Bouree et al., 2010; Montseny et al., 1995; Bronstein et al., 1977). Table 1 shows all data extracted from the case reports. There were no disagreements between the two reviewers regarding study inclusion or data extraction. Case reports were published between 1988 and 2019 in English, French, German, and Spanish. Nine cases were reported from France, three from Germany and Switzerland, two from the Netherlands, and one each from Belgium, Croatia, Italy, Spain, and the United Kingdom (Table 2). Eleven patients were female and 11 were male (Table 2). The median age of the patients was 30 years, ranging from 11 months to 54 years (Table 2).

Eight patients had travelled to Tahiti, French Polynesia, and seven of these cases were reported from France (Table 3). Five of the cases were policemen who had returned from a mission in Tahiti and they were all reported in the same case-series (Malvy et al., 2008). Four patients had travelled to Thailand, two each to the Dominican Republic, the Philippines, and Cuba (one was from Cuba and had evidently travelled to Spain), one had travelled to Malaysia and Singapore, one through multiple Latin American and Australasian countries, and one patient from France had no travel history (Nguyen et al., 2017) and was the first case reported as an autochthonous case. The geographical distribution of cases and where infections were acquired are shown in Figure 3. The suspected mode of transmission was ingesting prawns or shrimp for nine patients, particularly freshwater prawns or shrimp, salad for six patients, and snails for one patient (Table 3). A definitive diagnosis was obtained in 57% of patients with data (12/21).

Clinical manifestations

Ninety percent of patients with data on clinical manifestations (18/20) were reported as presenting with a history of headache, often lasting 1–2 weeks before seeking help (Table 4). Fifty percent (10/20) had a history of paresthesia, dysesthesia, or anaesthesia, 30% (6/20) of fever, 20% (4/20) of neck pain, neck stiffness, or meningism, 20% (4/20) of vomiting, and 10% (2/20) of diarrhoea. Data on physical examination was available for 17 cases (Table 4). Neck stiffness was reported in 41% of cases (7/17), fever in 29% (5/17), paresthesia, dysesthesia, or anaesthesia in 24% (4/17), photophobia in 18% (3/17), and 35% (6/17) were reported as having no focal neurological deficits.

Data on initial workup results were available from between seven patients (CT head) and 18 patients (blood eosinophilia) for the different types of tests extracted (Table 5). Eighty-nine percent of patients with data (16/18) had eosinophilia and 93% (13/14) had CSF eosinophilia. Elevated CSF protein was detected in 92% of patients (12/13), and low CSF glucose in 38% (3/8) of patients. Eighteen percent (2/11) of reported magnetic resonance imaging (MRI) scans and no (0/7) computed tomography (CT) scans showed a specific pathology indicative of *A. cantonensis* neuroinfection. (One CT scan showed suspected vascular occlusion compatible with Moyamoya disease, which was, however, not confirmed on a subsequent MRI scan (Brummaier et al., 2019); we have treated this finding as incidental in our analysis.)

Treatments and outcomes

Sixty-five percent (13/20) of patients with data on treatment were treated with albendazole or mebendazole. Sixty percent (12/20) were treated with corticosteroids, 20% (4/20) received therapeutic lumbar punctures (LPs), and 15% (3/20) were treated with ivermectin (Table 6).

Outcome data were available for all 22 patients (Table 6). Seventeen patients (77%) recovered fully. Three patients (14%) had persistent cutaneous symptoms and one patient (5%) had persistent headache. One patient (5%) died, an 11-month-old girl from Cuba reported from Spain, who presented at an advanced clinical stage with fever, generalized paresis, and respiratory distress (Siles Cadilla et al., 1998). The patient was covered broadly with intrathecal β-lactam antibiotics, diphenylhydantoin, corticosteroids, tetramisole, and piperazine, but died 10 days after admission. Diagnosis was made on autopsy, with young and adult *A. cantonensis* worms found in the brain, spinal cord, and lungs.

Discussion

We present a comprehensive overview of human *Angiostrongylus* cases reported from Europe. Our results increase existing numbers for the historical occurrence from respectively nine cases (Serrano-Moliner et al., 2018) (reported as 12 cases, but three of these were reported from Cuba (Padilla-Docal et al., 2011)), 15 cases (Maretic et al., 2009) (reported as 11 cases, but one of these was a case series of five cases (Malvy et al., 2008), all of which we have included), and most recently 17 cases (Ansdell and Wattanagoon, 2018), to our estimate of a minimum 22 cases. This updated case number has allowed for some simple summary statistics, which reveal some key points about the disease in Europe. Whilst reporting bias inevitably limits the implications for clinical practice that can be inferred from these observations – as is always the case for a literature review – one can make certain important inferences that will be helpful for European clinicians managing the disease, most likely for the first time in their lives. These are outlined below.

This study found that about 40% of cases were reported from France, and the majority of these patients had travelled to Tahiti, French Polynesia. This may be due to travel activity between France and French Polynesia, from which the third-most global cases are reported, after China and Thailand (Wang et al., 2008). An autochthonous case was also reported from France. This illustrates the need not to rule out the disease if the eosinophilic meningitis patient does not have a relevant travel history, but a dietary history should be taken, including the consumption of raw or undercooked, imported food items from endemic areas.

The predominant modes of transmission were the ingestion of prawns, shrimp, and salad, while only one patient reportedly had eaten snails. This most likely reflects the dietary habits of Europeans, who do not frequently tend to eat what may be perceived as ‘exotic delicacies’ such as raw snails, whilst the consumption of these is customary among some populations in Thailand and China (Wang et al., 2008). The dietary history should therefore include these four more common food items and should not narrowly focus on the ingestion of exotic delicacies such as snails, which predominate in the literature from endemic countries.

Ninety percent of patients with data were reported as presenting with a headache, often lasting. Half of the patients

Table 1
Identified case reports on human angiostrongyliasis in Europe and data extracted.

Report	Country reported from	Sex	Age (years)	Travel destination	Suspected mode of transmission (food items ingested)	Presenting symptoms	Clinical findings	Initial workup findings	Mode of diagnosis	Treatment	Outcome
Brummaier et al. (2019)	Switzerland	F	33	Thailand	Uncooked freshwater mussels	Headache, nausea, vomiting, diarrhoea, fatigue, feeling of generalized swelling, weakness, insomnia	Afebrile, no focal neurological deficits, no meningism	WBC 6.5 × 10^9/l - eosinophils 0.01 × 10^9/l CSF: - 1067 cells/μl - 25% eosinophils - glucose 2.6 mmol/l - protein 0.54 g/l ↑ CT head: Suspected vascular occlusion in supply area of right MCA compatible with Moyamoya disease (not confirmed on MRI) MRI: No vascular abnormality; a few age-appropriate, non-specific white matter lesions in both hemispheres; no leptomeningeal or nodular enhancing lesions	EITB for *A. cantonensis*-specific IgG antibodies positive	Albendazole 400 mg bid for 3 weeks, prednisone 60 mg/day for 2 weeks	Complete recovery
Nguyen et al. (2017)	France	F	54	None	Not identified, patient only declared eating vegetables and fish bought at local supermarket	Fever and headache 2 weeks	Neck stiffness and photophobia, no focal neurological deficits	WBC 12.1 × 10^9/l ↑ - eosinophils 18% ↑ CSF: - WBC 950/μl ↑ - 56% eosinophils - glucose 2.22 mmol/l ↓ - protein 0.9 g/l ↑ CT head and MRI NAD	WB positive for antibodies against *A. cantonensis* 31-kDa antigen in serum and CSF	Evacuation of CSF, prednisone 1 mg/kg for 1 week, albendazole 800 mg/day for 5 days	Complete regression of symptoms
Lammers et al. (2015)	Netherlands	M	45	Philippines	Fresh fish, prawns, salads and raw vegetables	Headache, painful skin on upper legs	Dysesthesia on upper legs	Eosinophils 1.26 × 10^9/l ↑ CSF: - WBC 1323/μl ↑ -eosinophils <0.001 × 10^9/l - glucose 2.59 mmol/l-protein 1.53 g/l ↑ MRI: Subtle hyperintense left pontine lesion	Experimental real-time PCR on CSF positive for *A. cantonensis*, confirmed by sequencing	Initial viral + bacterial encephalitis regimen followed by albendazole 600 mg bid and prednisolone 20 mg tid (duration NR)	Persisting altered cutaneous sensations
Lammers et al. (2015)	Netherlands	M	49	Philippines	Fresh fish, prawns, salads and raw vegetables	Painful skin area on chest	Dysesthesia on chest	Eosinophils 0.66 × 10^9/l ↑ CSF: - WBC 2442/μl ↑ - no eosinophilia	Experimental real-time PCR on CSF positive for *A. cantonensis*, confirmed by sequencing	Albendazole 600 mg bid and prednisone 20 mg tid (duration NR)	Persisting altered cutaneous sensations
Luessi et al. (2009)	Germany	M	32	Thailand	Raw fish, clams, vegetables and salad	Headache	Afebrile, mild lassitude, no neck stiffness, no neurological deficits	WBC 8.5 × 10^9/l - eosinophils 15.7% ↑ CSF: - WBC 699/μl ↑ - glucose 2.86 mmol/l - protein 0.71 g/l ↑ CT head, MRI and EEG NAD	WB positive for antibodies against *A. cantonensis* 29- and 31-kDa antigens in serum but not in CSF	Albendazole 800 mg/day (duration NR), dexamethasone 12 mg/day for 7 days followed by 6 mg/day for 7 days, repeated therapeutic LPs although no effect on headache	Full remission

Maretic et al. (2009)	Croatia	M	47	Malaysia and Singapore	Vegetables, salads, shrimp (although believed from saltwater)	Fever, headache, vomiting, constipation, paresthesia, difficulty urinating	Increased muscle tone, tremor, decreased deep tendon reflexes, urinary retention, saddle anaesthesia	WBC 11.5 × 10^9/l ↑ - eosinophils 2% CSF: - 320 cells/μl ↑ - eosinophils 6.5%	Antibodies against *A. cantonensis* 31-kDa antigen detected in serum and CSF	4 therapeutic LPs	Urinary retention persisted for 38 days, mild headache and paresthesia persisted for about a half year
Malvy et al. (2008)	France	M	36	Tahiti, French Polynesia	Raw freshwater prawns	Headache, asthenia, neck stiffness, photophobia, numbness, paresthesia, hyperesthesia, anorexia, weight loss	Normal neurological exam, febrile	WBC 7.2 × 10^9/l - eosinophils 25.0% ↑ CSF: - WBC 1400/μl ↑ - eosinophils 35% ↑ - protein 1.33 g/l ↑	Clinical, not definitive	"3-day course of ivermectin at the daily dosage of 200 μg/kg for 2 weeks", oral prednisolone tapered over 10 days	Initial improvement, relapse at 6 months, then full remission after repeated treatment
Malvy et al. (2008)	France	M	28	Tahiti, French Polynesia	Raw freshwater prawns	Headache[a], fatigue, anorexia, gastric injury	NR	WBC 7.8 × 10^9/l - eosinophils 48.7% ↑	Clinical, not definitive	Albendazole 800 mg/day for 14 days	Recovery
Malvy et al. (2008)	France	M	28	Tahiti, French Polynesia	Raw freshwater prawns	Headache[a]	NR	WBC 6.4 × 10^9/l - eosinophils 12.4% ↑	Clinical, not definitive	Albendazole 800 mg/day for 14 days	Recovery
Malvy et al. (2008)	France	M	36	Tahiti, French Polynesia	Raw freshwater prawns	Headache[a]	NR	WBC 5.9 × 10^9/l - eosinophils 12.0% ↑	Clinical, not definitive	Albendazole 800 mg/day for 14 days	Recovery
Malvy et al. (2008)	France	M	26	Tahiti, French Polynesia	Raw freshwater prawns	Headache[a]	NR	WBC 6.5 × 10^9/l - eosinophils 11.2% ↑	Clinical, not definitive	Albendazole 800 mg/day for 14 days	Recovery
Ali et al. (2008)	Belgium	F	22	Costa Rica, Ecuador, Chile, Argentina, Fiji, Australia	Sashimi, ceviche and salad	In Australia: Headache, diarrhoea, malaise, subfebrile In Belgium (about a month later): Headache, paresthesia of left hemithorax, radicular pain, general malaise, adynamia	In Australia: No nuchal rigidity In Belgium (about a month later): physical and neurological exam NAD	In Australia: Eosinophils 14% ↑ In Belgium (about a month later): CSF: - WBC 342/μl ↑ - eosinophils 40% ↑ - glucose 2.55 mmol/l - protein 0.76 g/l ↑ MRI NAD	WB revealed antibodies against *A. cantonensis* in serum; EIA positive for anti-*Angiostrongylus* IgG after 6 months	Methylprednisolone tapered from 64 mg/day to 16 mg/day over 2 weeks, later albendazole 800 mg/day (duration NR) + methylprednisolone tapered from 32 mg/day to 16 mg/day over 2 weeks	Full remission
Kirsch et al. (2008)	Germany	F	36	Thailand	NR	Headache, fatigue, recurrent slight fever	Meningism only	Eosinophils 12% ↑ CSF: - 200–300 WBC/μl↑ - eosinophilic predominance - protein 0.55 g/l ↑ MRI and EEG NAD	WB positive for antibodies against *A. cantonensis* 31-kDa antigen; ELISA for toxocariasis positive; as no contact with dogs or cats and no CNS involvement beyond meningism → Conclusion: *Toxocara* cross-reaction, and angiostrongyliasis most likely diagnosis	Albendazole 400 mg bid for 3 weeks, prednisolone 60 mg/day for 1 week, then tapered	Rapid improvement upon prednisolone tapering
Jones et al. (2007)	United Kingdom	F	30	Thailand	Snails in a salad	Headache, meningism, fever	Temp. 38.0 °C, neck stiffness, photophobia	WBC 10.1 × 10^9/l - eosinophils 1.35 × 10^9/l ↑ CSF: - 626 WBC/μl ↑ - significant eosinophilia - protein 0.55 g/l ↑ CT head NAD, MRI: Multiple hyperintense white matter lesions	Serum and CSF analysis	Tuberculous meningitis regimen; ivermectin when readmitted, and later dexamethasone	Symptom improvement and normalization of CSF and MRI findings

Table 1 (*Continued*)

Report	Country reported from	Sex	Age (years)	Travel destination	Suspected mode of transmission (food items ingested)	Presenting symptoms	Clinical findings	Initial workup findings	Mode of diagnosis	Treatment	Outcome
Leone et al. (2007)	Italy	M	30	Santo Domingo, Dominican Republic	Freshwater shrimps	Headache, fever 37.6 °C, vomiting, neck pain, generalized paresthesias	Tachycardic, pale, feverish, neck stiffness	WBC 8.85 × 10^9/l - eosinophils 14% ↑ CSF: - 500 cells/μl ↑ - (glucose 0.46 g/dl)[c] - protein 1.29 g/l ↑ CT head and MRI NAD	Clinical diagnosis	Viral + bacterial meningitis regimen, steroids added for 4 days; later treated with mebendazole 400 mg, but discontinued after 1st dose due to accentuation of symptoms; switched to prednisolone 60 mg/day for 2 weeks	Persisting facial paresthesia at 1-month follow-up
Rau et al. (2006)	Germany	F	27	Dominican Republic	Noodles with crab or crayfish	3 weeks severe, wandering dysesthesia and headache	Fever 38.2 °C, slight neck stiffness, paresthesia of right elbow and thigh	WBC 5.6 × 10^9/l - eosinophils 12.3% ↑ IgE 157 IE/ml ↑ CSF: - 110 cells/μl ↑ - 50% eosinophils ↑ - glucose 1.55 mmol/l ↓ - protein 1.09 g/l MRI: several small, unspecific subcortical lesions	Clinical diagnosis supported by nematode antibodies in CSF	Oral albendazole 2 × 400 mg/day and prednisolone 1 mg/kg/day for a total of 4 weeks	Complete remission
Bartschi et al. (2004)	Switzerland	F	26	Cuba	NR	Headache, generalized hyperesthesia, vomiting	No fever; neck stiffness, no focal neurology	Eosinophils 16% ↑ CSF: - 502 cells/μl ↑ - 23% eosinophils ↑ MRI NAD	Positive ELISA against filaria antibodies in serum, but negative IFA; WB on serum showed IgG antibodies reacting with four *A. cantonensis*-specific antigenic bands	2 therapeutic LPs + analgesics	Symptom resolution over 3 weeks
de Roux-Serratrice et al. (2002)	France	M	16	Tahiti, French Polynesia	NR	Headache, neck pain, paresthesia of upper limbs, diplopia	Fever 38 °C, neck stiffness, left cranial nerve VI paralysis, ptosis, kinetic cerebellar syndrome, bilateral papillary oedema	Eosinophils 0.7 × 10^9/l ↑ CSF: - WBC 409/μl ↑ - eosinophils 28% ↑ - (glucose 2.6 g/l)[c] - protein 0.53 g/l ↑ CT head and MRI NAD, EEG abnormal	Antibodies against *A. cantonensis* in blood and CSF	Ivermectin 6 mg/day for 2 days; 2nd LP reduced headache	Slow improvement over 2 months
Siles Cadilla et al. (1998)	Spain	F	11 months	From Cuba	NR	Fever and generalized pareses	Hypotonia, hyporeflexia, involuntary movements of lower extremities, no meningeal signs; respiratory distress	WBC 15.1 × 10^9/l ↑ - eosinophils 20% ↑ CSF: - 160 cells/μl ↑ - glucose 3.55 mmol/l - protein 0.2 g/l EEG abnormal *Ascaris lumbricoides* and *Trichuris trichiura* eggs found in stool	Young and adult *A. cantonensis* worms found in autopsy of brain, spinal cord, and lungs	Intrathecal β-lactam antibiotics, diphenylhydantoin, corticosteroids, tetramisole, and piperazine	Progressive deterioration, patient died 10 days after admission
Thobois et al. (1996)	France	F	25	Tahiti, French Polynesia	Raw fish	Fever 38 °C, headache, photophobia, electrical pain in left calf, vomiting	Normal clinical examination	WBC NAD - eosinophils 7.2% CSF: - 305 WBC/μl ↑ - 37% eosinophils ↑ - glucose 2.2 mmol/l ↓ - protein 0.55 g/l ↑ CT head NAD	Clinical diagnosis	Symptom relief from 1st LP, no other treatment described	Progressive improvement over 2 months

Vuadens and Regli (1995)[b]	Switzerland	F	46	Tahiti, French Polynesia	No access to full text	No access to full text	CSF: - eosinophilia	Clinical diagnosis	No access to full text	Spontaneous improvement
Scemama et al. (1988)[b]	France	F	14 months	No access to full text	No access to full text	Severe infection with radiculo-encephalomyelitis	"Lesions concerned the nevraxe [neuroaxis] and especially the spinal cord"	No access to full text	No access to full text	Spontaneous improvement

bid, twice daily; CSF, cerebrospinal fluid; CT, computed tomography; EEG, electroencephalogram; EIA, enzyme immunoassay; EITB, enzyme-linked immunoelectrotransfer blot; F, female; IFA, indirect immunofluorescence assay; LP, lumbar puncture; M, male; MCA, middle cerebral artery; MRI, magnetic resonance imaging; NAD, no abnormality detected; tid, three times daily; NR, not reported; WB, Western blot; WBC, white blood cell count.

[a] These patients also had either neck pain, paresthesia, or hyperesthesia as per the case definition used. Four out of the five patients from the study had fatigue.

[b] Only access to the abstract.

[c] Presumed error in units, omitted from analysis.

Table 2
Country reported from, sex, and age of cases.

	Number of reports with data	Number	%
Case report country	22		
France		9	40.9
Germany		3	13.6
Netherlands		2	9.1
Switzerland		3	13.6
Belgium		1	4.5
Croatia		1	4.5
Italy		1	4.5
Spain		1	4.5
United Kingdom		1	4.5
Sex	22		
Female		11	50.0
Male		11	50.0
		Median	Range
Age (years)	22	30	11 months to 54 years

Table 3
Travel destination and suspected mode of transmission for cases.

	Number of reports with data	Number	%
Travel destination	21		
Tahiti, French Polynesia		8	38.1
Thailand		4	19.0
Cuba		2	9.5
Dominican Republic		2	9.5
Philippines		2	9.5
Malaysia and Singapore		1	4.8
Multiple Latin American and Australasian countries		1	4.8
None		1	4.8
Suspected mode of transmission (food items ingested)	16		
Prawns/shrimp		9	56.3
Freshwater prawns/shrimp		6	37.5
Salad		6	37.5
Snails		1	6.3

with data had a history of paresthesia, dysesthesia, or anaesthesia, and about 40% had neck stiffness on examination. This is comparable to the frequencies described in the general literature, and the same can broadly be said for the remaining symptoms and signs extracted (Wang et al., 2008). While we did not perform formal statistical comparisons due to the size and nature of the dataset and absence of a comparison group from endemic countries, our findings do not show any indication that European travel-related cases should present any differently than patients in endemic countries. We therefore follow the literature and recommend the history and examination of adult patients include the most common symptoms and signs of headache, neck stiffness, paresthesia, vomiting, fever, nausea, and blurred vision or diplopia, as identified in descending order of reported global frequency by Wang et al. in 2008 (the presentation may be different in children, with headache, nausea and vomiting, somnolence, and fever being the predominating symptoms, followed by neck stiffness, abdominal pain, and paresthesia) (Wang et al., 2008).

Our findings regarding workup indicate that a clinical diagnosis is supported by the presence of blood eosinophilia, CSF eosinophilia, and elevated CSF protein, as is the case in the general literature (Wang et al., 2008; Yii, 1976; Punyagupta et al., 1975). Cerebral CT scans did not show any specific lesions indicative of *A. cantonensis* neuroinfection, while such were identified in two out of 11 MRI scans reported. Again, this is reflective of the available

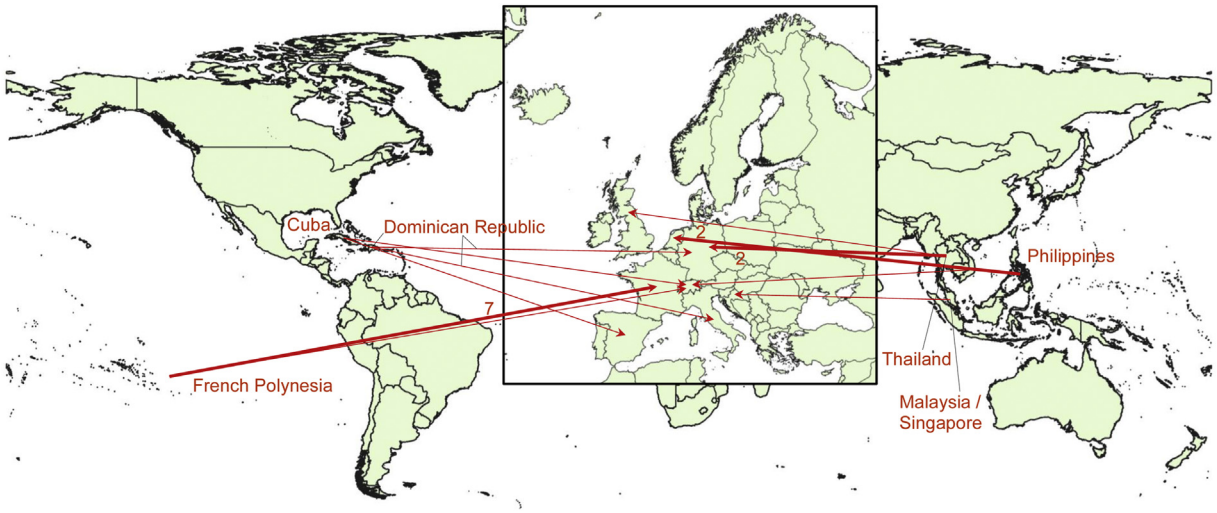

Figure 3. Map showing to which countries infections were imported and where these were acquired. A thick line indicates multiple cases imported from the same country (number of cases shown). One case is not displayed (Belgium (Ali et al., 2008)), as the patient's travel history was extensive.

Table 4
Presenting symptoms and clinical findings for cases.

	Number of reports with data	Number	%
Presenting symptoms	20		
Headache		18	90.0
Paresthesia/dysesthesia/anaesthesia		10	50.0
Fever		6	30.0
Neck pain/neck stiffness/meningism		4	20.0
Vomiting		4	20.0
Diarrhoea		2	10.0
Clinical findings	17		
Neck stiffness		7	41.2
Fever		5	29.4
Paresthesia/dysesthesia/ anaesthesia		4	23.5
Photophobia		3	17.6
No focal neurological deficits		6	35.3

Table 5
Initial workup findings and number and percentage of cases where a definitive diagnosis was obtained.

Initial workup findings	Number of reports with data	Median	Range
WBCs ($\times 10^9$/l)	13	7.8	5.6–15.1
Eosinophils (%)	17	13.37	0.002–48.7
Eosinophils ($\times 10^9$/l)	16	1.0	0.01–3.8
CSF WBCs/cells (/μl)	16	501	110–2442
CSF eosinophils (%)	9	35	7–56
CSF eosinophils (/μl)	9	115	21–532
CSF glucose (mmol/l)	8	2.6	1.55–3.6
CSF protein (g/l)	13	0.7	0.20–1.53
		Number	%
Eosinophilia (number positive)	18	16	89
CSF eosinophilia (number positive)	14	13	93
CSF low glucose (number positive)	8	3	38
CSF elevated protein (number positive)	13	12	92
CT head (number showing lesions)	7	0	0
MRI (number showing lesions)	11	2	18
Definitive diagnosis obtained	21	12	57

CSF, cerebrospinal fluid; CT, computed tomography; MRI, magnetic resonance imaging; WBC, white blood cell count.

Table 6
Treatments and outcomes for cases.

	Number of reports with data	Number	%
Treatment	20		
Albendazole or mebendazole		13	65.0
Ivermectin		3	15.0
Corticosteroids		12	60.0
Therapeutic LPs		4	20.0
Outcome	22		
Full remission		17	77.3
Persistent (≥6 months after presenting at health centre) cutaneous symptoms		3	13.6
Persistent (≥6 months after presenting at health centre) headache		1	4.5
Death		1	4.5

LP, lumbar puncture.

literature, with both cerebral CT and MRI scans frequently being normal or revealing non-specific findings (Tsai et al., 2003; Jin et al., 2008). When lesions are found, some authors find a predilection towards the globus pallidus and cerebral peduncles (Tsai et al., 2003), while others do not (Jin et al., 2008). One of the patients with positive MRI in our review indeed had a lesion in the left pontine tegmentum (part of the left cerebral peduncle) (Lammers et al., 2015), while the other had lesions in the deep white matter and the corpus callosum (Jones et al., 2007). As suggested by the literature, neuroimaging, particularly MRI, should be seen as supportive and not a decisive means of diagnosis (Wang et al., 2008; Tsai et al., 2003; Jin et al., 2008).

Generally speaking, the diagnosis of angiostrongyliasis is challenging: worms are only found in CSF in 2–11% of cases (Punyagupta et al., 1975; Hidelaratchi et al., 2005), and serology analyses are not widely available (Weller, 2019), thus requiring treatment based on a presumptive clinical diagnosis (Wang et al., 2008). In our study, however, a definitive diagnosis was obtained in more than half of the cases. The microbiological diagnosis of angiostrongyliasis requires specialized laboratory capacity. The relatively high diagnostic frequency observed in our study may reflect better access to such capacity in Europe. In most parts of Europe, microbiological diagnosis may be logistically cumbersome and time-consuming, requiring international transportation of laboratory specimens and cross-institutional collaboration.

Table 7
Causes of eosinophilic meningitis (Sawanyawisuth and Chotmongkol, 2013; Weller, 2019; Lo Re and Gluckman, 2003; Punyagupta et al., 1975; Jaroonvesama, 1988; Weller and Liu, 1993). Adapted from Ali et al. (2008), Sawanyawisuth and Chotmongkol (2013), and Lo Re and Gluckman (2003).

Infection	Malignancy	Drugs	Autoimmune diseases and vasculitis	Others
Parasites: *Angiostrongylus cantonensis* *Gnathostoma spinigerum* *Baylisascaris procyonis* *Taenia solium* (neurocysticercosis) *Strongyloides stercoralis* *Toxocara sp* *Loa loa* *Meningonema peruzzi* *Trichinella spiralis* *Echinococcus granulosus* *Schistosoma sp* *Fasciola hepatica* *Paragonimus sp* *Myiasis* Bacteria: *Mycobacterium tuberculosis* *Treponema pallidum* Viruses Fungi: *Coccidioides immitis*	• Glioblastoma • Hodgkin lymphoma • Non-Hodgkin lymphoma • Eosinophilic leukaemia • Undifferentiated myeloproliferative disorders • Leukaemia • Meningeal carcinomatosis • Paraneoplasia	• Ibuprofen • Ciprofloxacin • Intraventricular: gentamicin, vancomycin • Trimethoprim–sulfamethoxazole • Iophendylate dye	• Post-vaccination encephalitis • Systemic lupus erythematosus • Sarcoidosis • Periarteritis nodosa • Eosinophilic granuloma	• Ventriculoperitoneal shunts • Idiopathic hypereosinophilic syndrome

Several confirmatory diagnostic tools are, however, available at reference laboratories, including mainly immunodiagnostic assays targeting a 31-kDa antigen and molecular assays (Wilkins et al. (2013)). A presumptive diagnosis is based on clinical presentation, the presence of eosinophilia in the CSF, and a history of possible exposure to infective *A. cantonensis* larvae in endemic areas (Wang et al., 2008; Weller, 2019), and a laboratory-based confirmation should be sought whenever possible. In terms of the differential diagnosis, Table 7 displays the most common causes of eosinophilic meningitis (Sawanyawisuth and Chotmongkol, 2013; Weller, 2019; Lo Re and Gluckman, 2003; Punyagupta et al., 1975; Jaroonvesama, 1988; Weller and Liu, 1993).

The treatment of CNS angiostrongyliasis is debated. Eighty percent of the cases reviewed herein received antihelminthictreatment and only 20% received therapeutic LPs. However, most cases of angiostrongyliasis are self-limiting (Wang et al., 2008; Weller, 2019), and some authors recommend a conservative treatment regimen with analgesics, corticosteroids, and periodic removal of CSF for the relief of symptoms due to elevated intracranial pressure, without the addition of antihelminthics (Wang et al., 2008; Weller, 2019; Centers for Disease Control and Prevention, 2019a). Prednisolone has been shown to reduce the occurrence of persistent headache and lower the need for repeat LP for symptomatic relief (Chotmongkol et al., 2000), and adding albendazole to corticosteroid treatment has in one study shown no alleviation of headache (Chotmongkol et al., 2009), while exacerbation of neurological symptoms due to antihelminthic treatment of eosinophilic meningitis has been described (Hidelaratchi et al., 2005). On the other hand, some studies report a positive effect of benzimidazole treatment in reducing the duration of headache and recommend a combination antihelminthic and corticosteroid treatment (Chotmongkol et al., 2006; Diao et al., 2011; Jitpimolmard et al., 2007); however some of the studies reporting benefits of benzimidazoles lack control arms (Centers for Disease Control and Prevention, 2019a; Chotmongkol et al., 2006). Generally, the literature is characterized by small sample sizes (Wang et al., 2008; Centers for Disease Control and Prevention, 2019a), and whether the combination regime is superior to corticosteroid treatment alone and/or repeated LPs remains unanswered.

The main recommendation to be made regarding treatment is for today's clinicians to consult the most up-to-date clinical evidence before initiating treatment.

In terms of patient outcomes, our findings reflect the generally relatively good prognosis of the disease (Wang et al., 2008; Weller, 2019). Regarding the one fatal case identified in which adult worms were recovered from the patient (Siles Cadilla et al., 1998), humans are considered dead-end hosts for *A. cantonensis*. Larvae occasionally mature into fourth- and fifth-stage larvae, but not into reproductive adulthood (Sonakul, 1978; Nitidandhaprabhas et al., 1975; Centers for Disease Control and Prevention, 2019b). As in the included case (Siles Cadilla et al., 1998) and other non-European reports (Prociv and Turner, 2018; Cooke-Yarborough et al., 1999; Kuberski et al., 1979), the recovery of adult worms from human patients has, however, been described. Whether this is due to incorrect staging or the assumption that worms cannot mature into adulthood in human hosts being incorrect remains unknown.

Globally, the total number of reported human angiostrongyliasis cases has been estimated at 2827 (Wang et al., 2008) (2008 estimate), but the extent of human angiostrongyliasis is thought to be much larger due to underreporting (Wang et al., 2008; Kliks and Palumbo, 1992). The majority of cases are found in Thailand (47%) and China (27%) (Wang et al., 2008). The remaining cases have been documented in other parts of Southeast Asia, the Caribbean Islands, USA (mainly Hawaii), Japan, Australia, and the Pacific Islands (Wang et al., 2008). In spite of our expansion of previous estimates of the historical incidence in Europe, this study confirms that angiostrongyliasis is still exceedingly rare on this continent, even when factoring in likely underreporting and the potential incompleteness of this review. In spite of this, increased travel activity, migration, and international trade have led not only to an increased risk among travellers and migrants, but also to the spread of the parasite across continents via hosts who are accidentally dispersed through these activities (Barratt et al., 2016). Therefore, the situation may change with time, and European clinicians should be prepared to encounter this disease both now and in the future.

Study limitations

We did not perform a dedicated grey literature search. However, all included articles were screened for relevant citations, and the absence of language restrictions and search strategy across five major databases and two major European communicable disease

surveillance systems, in accordance with PRISMA guidelines, should have mitigated the risk of overlooking relevant case reports. As for all other literature reviews, this study is subject to underreporting. This is likely to have affected the findings due to the rarity and diagnostically challenging nature of the disease, and our final number of 22 cases reported should be interpreted as a lower bound of the true occurrence. The issue of underreporting cannot be mitigated with the chosen methodology; the statistical findings, however, do compare well with the existing literature, indicating that underreporting may at least not have skewed the statistical findings substantially.

A standard quality assessment of included studies was not conducted, as we did not examine full journal articles, but simply case reports without methods and results sections. An overall quality limitation was that a definitive diagnosis only was obtained in 57% of cases, which may have resulted in false-positives being included in the summary statistics. The summary statistics were conducted on relatively limited data material, but neither did we perform any formal statistical testing, which would have been unwarranted given the population size and the ad hoc nature of assembling a dataset from existing case reports, with the biases that ensue.

Conclusions

We identified 22 reported cases in total since the first case report in 1988, which is an increase from previous estimates. We have discussed key components to be included in the history-taking and workup for suspected cases. *A. cantonensis* has been established in molluscs in Tenerife, Spain, posing a potential risk to travellers and residents. Furthermore, the disease has been reported autochthonously in Europe, and one should not rule out the disease if the eosinophilic meningitis patient does not have a relevant travel history; instead, the ingestion of imported food items from endemic areas, for example, should be explored.

Definitive diagnosis of the disease should be sought with help from specialized laboratories, which may involve transnational collaboration. As this may take time, treatment may need to be initiated based on a strong clinical suspicion. However, as most cases are self-limiting, one should consider the severity of disease in the patient before initiating treatment. The most up-to-date evidence should always be consulted before initiating treatment, and at the time of writing, analgesics, corticosteroids, and periodic removal of CSF for symptom relief are recommended, while antihelminthic treatment is debated.

Finally, human angiostrongyliasis is rare and challenging to diagnose, but with increased travel, migration, and international trade, European clinicians should be prepared to encounter the disease, and we hope that the information provided in this article has contributed to this.

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Ethical approval

No ethical approval was required for this literature review.

Conflict of interest

None.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.ijid.2020.01.012.

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