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Central nervous system infection by *Angiostrongylus cantonensis* in children: experience from Guangdong, China

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Abstract

Background Angiostrongylus cantonensis (*A. cantonensis*)–induced central nervous system (CNS) infection is a rare parasitic disease. Although global incidence is rising, pediatric cases remain underrecognized. This study aimed to characterize clinical features and evaluate the diagnostic utility of metagenomic next-generation sequencing (mNGS) in children.

Methods We retrospectively analyzed pediatric CNS angiostrongyliasis cases admitted to a national neurology center in Guangdong, China, between 2017 and 2024.

Results A total of 22 pediatric patients were enrolled (median age 1.8 years; male: female = 14:8). Most cases (68.2%) began between June and October; 45.5% had confirmed or probable exposure. Fever was the most common symptom (77.2%), followed by somnolence or lethargy (63.6%) and vomiting (59.1%). No patients reported neck stiffness or hyperesthesia. All patients showed peripheral eosinophilia (median peak 24.0%, IQR 16.0%–36.0%) and cerebrospinal fluid (CSF) pleocytosis. The initial CSF eosinophil percentage exceeded 10% in 10/22 patients (45.5%), and this increased in 7/22 patients (31.8%) during follow-up. Median peak CSF eosinophil percentage was 17.2% at day 18. Among 10 patients tested for CSF cytokines, 90.0% had elevations, with IL-6 being the most common and associated with higher CSF eosinophil percentages. Serum and CSF IgG against *A. cantonensis* were positive in 44.4% and 46.7%, respectively. Metagenomic next-generation sequencing (mNGS) of cerebrospinal fluid was performed in 18 of the 22 patients, and *A. cantonensis* was identified in all tested cases (18/18, 100%), including four who were seronegative. The median mNGS read counts of *A. cantonensis* were 2,453 (IQR 353.5–28,641.75), which were not significantly correlated with CSF eosinophil percentages, white blood count, or protein levels. Brain magnetic resonance imaging abnormalities (81.8%) included leptomeningeal enhancement (45.5%), ventricular enlargement

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(40.9%), and cortical lesions (31.8%). Electroencephalogram was abnormal in 54.5%, mainly showing slowing (50.0%) or epileptiform activity 9.1%. Albendazole was used alone in 13.6% of patients, while 86.4% received combined therapy with corticosteroids. Of the 20 patients with follow-up (median 2.5 months), all recovered clinically and radiologically without relapse or sequelae.

Conclusion Pediatric CNS angiostrongyliasis in Guangdong primarily affects rural children during summer–autumn. Clinical signs may be nonspecific. mNGS outperformed serology, especially in early or seronegative cases. Most patients had favorable short-term outcomes.

Keywords *Angiostrongylus cantonensis*, Angiostrongyliasis, Children, mNGS, CNS

Background

Human angiostrongyliasis is a parasitic disease caused by *Angiostrongylus cantonensis* (*A. cantonensis*), with clinical manifestations varying depending on the organs involved. Central nervous system (CNS) infection caused by *A. cantonensis*, referred to as neuroangiostrongyliasis, is characterized by eosinophilic meningitis or meningoencephalitis due to larval invasion and parasitism within the CNS [1]. Clinical manifestations typically include headache, fever, neck stiffness, nausea, and vomiting. In more severe cases, patients may present with cranial nerve involvement, seizures, coma, or even death [2].

A. cantonensis infection was initially endemic to Southeast Asia and the Pacific Basin, but reported cases have now sharply increased worldwide, with over 30 countries affected, including regions in Africa, South America, the Caribbean, Australia, and Europe [3–6]. China has become one of the most heavily impacted countries in the past decade [7]. In mainland China, Guangdong province is recognized as one of seven endemic regions, with Guangzhou—alongside Wenzhou, Fuzhou, Kunming, and Beijing—accounting for 88.9% of reported cases [7, 8].

Although adults are more commonly affected, pediatric cases are increasingly recognized, especially in regions such as Taiwan, where infections have frequently been linked to exposure to the African giant snail [9–11]. However, pediatric cases remain underreported and insufficiently characterized. The absence of clear epidemiological history and atypical clinical presentations in children pose significant diagnostic challenges [12, 13]. This study retrospectively analyzed pediatric patients with CNS *A. cantonensis* infection treated at Guangzhou Women and Children's Medical Center between May 2017 and December 2024. The aim is to improve awareness among pediatricians and enhance diagnostic and therapeutic management in this population.

Subjects

Pediatric patients younger than 14 years who were diagnosed with CNS angiostrongyliasis and admitted to the Department of Neurology at Guangzhou Women and Children's Medical Center between May 2017 and December 2024 were included in this study. Patient selection was based on the 2023 updated diagnostic criteria for neuroangiostrongyliasis proposed by Graeff-Teixeira et al. [7] Only patients who met the criteria for either probable or confirmed neuroangiostrongyliasis were eligible for inclusion. The diagnosis of probable neuroangiostrongyliasis required the presence of neurological symptoms (e.g., headache), cerebrospinal fluid (CSF) eosinophilia, and at least two minor criteria (e.g., blood eosinophilia, exposure history, or positive serology). The diagnosis of confirmed disease required the detection of larvae in tissue, CSF, or ocular samples, or the identification of parasite DNA. Patients were excluded if they had an alternative confirmed diagnosis explaining their neurological symptoms (e.g., bacterial or viral meningitis, autoimmune encephalitis, or CNS tumors). All eligible cases were identified retrospectively after the study had been initiated, by systematically reviewing the electronic medical records of patients admitted during the study period. The updated 2023 diagnostic criteria were then applied to determine inclusion. All clinical information analyzed in this study was obtained retrospectively from electronic medical records, and no additional procedures, follow-up visits, or laboratory analyses were conducted specifically for this study. The following categories of information were systematically extracted from the electronic medical records: demographic data, clinical manifestations, laboratory investigations (blood and CSF), CSF cytokine panels, serological tests and Metagenomic next-generation sequencing (mNGS) results, radiographic examinations (chest X-ray, chest computed tomography (CT), and brain magnetic resonance imaging (MRI)), electroencephalogram (EEG) findings, and treatment regimens and clinical outcomes. Clinical features of patients, including demographic data, clinical manifestations, laboratory investigations, neuroimaging examination, electroencephalogram (EEG), treatment and outcomes were retrospectively reviewed. This study was approved by the Ethics Committee of Guangzhou Women and Children's Medical Center. Written and signed consent was obtained from the patient's parents or guardians, who also explicitly consented to publish their details, clinical data, and images that could identify them.

Methods

Definition

CSF eosinophilia was defined as the presence of more than 10 eosinophils/mm³ and/or eosinophils accounting for ≥ 10% of the total CSF leukocyte count [14]. Peripheral blood eosinophilia was defined as an eosinophil count >0.6 × 10^9/L and/or >4% of the total white blood cell count (WBC) [14]. CSF pleocytosis was defined as a WBC count >15 cells/μL according to the standards of our center. Elevated CSF protein was defined as a protein concentration >0.5 g/L. Low CSF glucose was defined as a glucose concentration < 2.2 mmol/L [15]. Exposure history was categorized according to the 2023 updated diagnostic criteria for neuroangiostrongyliasis [7]. Confirmed exposure referred to ingestion of raw or undercooked high-risk vectors (e.g., snails, slugs, contaminated vegetables), whereas probable exposure was additionally defined in this study to describe less specific but plausible risk scenarios (e.g., playing near ponds, handling fish, or eating cooked shellfish).

Laboratory examination

mNGS was performed on CSF and/or blood samples. CSF (3–4 mL) and blood (2–3 mL) were collected using sterile tubes or cell-free DNA blood collection tubes. DNA extraction was carried out using the QIAamp DNA Micro Kit (QIAGEN, Hilden, Germany) according to the manufacturer's instructions. DNA libraries were constructed with the QIAseq™ Ultralow Input Library Kit for Illumina (QIAGEN, Hilden, Germany), following the manufacturer's instructions. The Qubit fluorometer (Thermo Fisher Scientific, MA, USA) and Agilent 2100 Bioanalyzer (Agilent Technologies, Palo Alto, USA) were utilized to assess the quality and quantity of each library. Only those libraries that met the quality standards were sequenced on the Nextseq 550 platform (Illumina, San Diego, USA), targeting approximately 20 million 75 bp single-end reads per library. For bioinformatics analysis, raw data were filtered to remove adapter sequences, short reads (< 35 bp), low-quality reads (Q < 30), and low-complexity reads. Human reads were excluded by mapping to the human reference genome (hg38). The remaining reads were aligned to Microbial Genome Databases using the Burrows-Wheeler Aligner. Negative controls (NTC, sterile deionized water) and positive controls (known quantities of synthetic fragments) were included in each batch of experiments, following the same wet lab and bioinformatics procedures. For detected bacteria (excluding *Mycobacterium tuberculosis*), fungi (excluding *Cryptococcus*), and parasites, a positive result was considered if the coverage ranked in the top 10 of similar species/genera and was absent in NTC, or if the RPM ratio between the sample and NTC (RPM_{sample}/RPM_{NTC}) was greater than 10 when RPM_{NTC} was not zero. For viruses, *Mycobacterium tuberculosis*, and *Cryptococcus*, a positive mNGS result was indicated by the detection of at least one species-specific read and its absence in NTC, or a RPM_{sample}/RPM_{NTC} ratio greater than 5 when RPM_{NTC} was not zero.

IgG antibodies against parasite were detected in both CSF and serum using a parasite-specific enzyme-linked immunosorbent assay (ELISA) panel (Shenzhen Huakang Biomedical Engineering, Shenzhen, China) including *A. cantonensis*, *Toxoplasma gondii*, *Echinococcus spp.*, *Taenia solium*, *Clonorchis sinensis*, *Sparganum*, *and Schistosoma japonicum*.

CSF cytokine levels, including tumor necrosis factor β (TNF-β), interleukin (IL)-12p70, IL-1β, IL-10, IL-6, tumor necrosis factor α (TNF-α), interferon-γ (IFN-γ), IL-8, IL-4, IL-5, IL-17F, IL-17A, and IL-22 were measured using the Aimplex multiplex flow immunofluorescence assay (QuantoBio, Beijing, China) on a BD FACSCanto II flow cytometer. All procedures were performed by the hospital's clinical laboratory, following previously published protocols [16].

Follow-up

All patients were followed up either by a neurologist in the neurological clinic or by a neurologist via telephone contact.

Statistical analysis

Statistical analyses were performed using SPSS (IBM SPSS Statistics, Version 23.0). Continuous variables that followed a normal distribution were expressed as mean ± standard deviation (SD), as confirmed by normality testing. Continuous variables were presented as median and interquartile range (IQR) due to non-normal distribution. Group comparisons were conducted using the Mann–Whitney U test. Correlations between non-normally distributed quantitative variables were assessed using Spearman's rank correlation coefficient. A two-sided P-value < 0.05 was considered statistically significant. All figures were generated using GraphPad Prism 10.0 (GraphPad Software Inc., USA).

Results

Demographics

A total of 22 patients (male: female = 14:8) were enrolled between 2017 and 2024, including 18 confirmed and 4 probable neuroangiostrongyliasis cases. The median onset age was 1.8 years old (interquartile range [IQR] 1.1-4.0 years). One patient had intellectual disability, and no other relevant comorbidities were identified. The onset of illness predominantly occurred between June and October, accounting for approximately 68.2% (15/22) of cases. The highest incidence was observed in June, comprising 18.2% (4/22) of the total cases, with monthly case

numbers calculated by summing all cases across 2017–2024 (Fig. 1). 72.7% (16/22) of patients lived in rural area (Table 1). A total of 45.5% (10/22) of patients had a confirmed or probable exposure history before disease onset. Three patients had a confirmed exposure history, including ingestion of raw vegetables ($n=1$), ingestion of raw snails ($n=1$), and ingestion of cockroach feces based on traditional folk remedies ($n=1$).Seven patients had a probable exposure history, which included eating cooked crawfish ($n=1$), eating cooked oysters ($n=1$), playing near ponds ($n=1$), eating food picked up from the ground ($n=1$), fishing and handling fish in outdoor freshwater environments ($n=1$), engaging in frequent activities near ditches and grassy areas ($n=1$), and playing with snails, noted in one patient with intellectual disability ($n=1$).

Clinical symptoms and signs

The most common initial symptom was fever, observed in 72.7% of patients. During the course of illness, fever, somnolence/lethargy, and vomiting were the predominant symptoms, whereas neurological manifestations such as extremity weakness, hemiplegia, and cranial nerve abnormalities were less frequent (Table 1). No patients reported neck pain or stiffness, diplopia, blurred vision, or coma. Ophthalmic examinations were performed in 77.3% (17/22) of patients, and no remarkable abnormalities were found, including papilledema.

Laboratory findings

Patients were admitted at our hospital within a median of 15 days (IQR 7-23.8 days) after the onset of symptoms. All patients underwent routine blood test upon admission to our hospital. The median initial blood eosinophil counts of total white blood cell (WBC) was 13.5% (IQR 8.5%-17.8%) and all patients had eosinophilia. The eosinophil count as a proportion of total WBC, hereafter referred to as eosinophil percentage. The blood eosinophil percentage in 59.1% (13/22) of patients still increased after the initial test. The median maximal blood eosinophil percentage was 24.0% (IQR 16.0%-36.0%) at a median 21.5 days (IQR 15.0-25.3 days) after onset (more details are shown in Table 1). The median serum IgE was 300.5 IU/L (IQR 49.0-535.0 IU/L) and serum IgE levels were elevated in 72.7% (16/22) of patients.

All patients underwent their first lumbar puncture at a median 17 days (IQR 6.5–23.3 days). The median initial CSF WBC was 369.5×10^6/L (IQR $169.8\text{-}556.8\times10^6$/L) and pleocytosis was observed in all patients. The median initial CSF protein was 0.58 g/L (IQR 0.43–0.67 g/L) and elevated CSF protein was observed in 59.1% (13/22) of patients. The initial CSF glucose was 2.20 ± 0.89 mmol/L and 59.1% (13/22) of patients exhibited low CSF glucose. The median initial CSF eosinophil percentage was 10.0% (IQR 0.0-17.1%). The initial CSF eosinophil percentage higher than 0.0% and higher than 10.0% was seen in 50.0% (11/22) and 45.5% (10/22) of patients, respectively. The CSF eosinophil percentage in 31.8% (7/22) of patients still increased after the initial test, among which the initial CSF eosinophil percentage was 0.0% in three patients and over 10.0% in four patients. Among these 8 patients whose initial CSF eosinophil percentage was 0.0%, 3 patients had the subsequent CSF eosinophil percentage

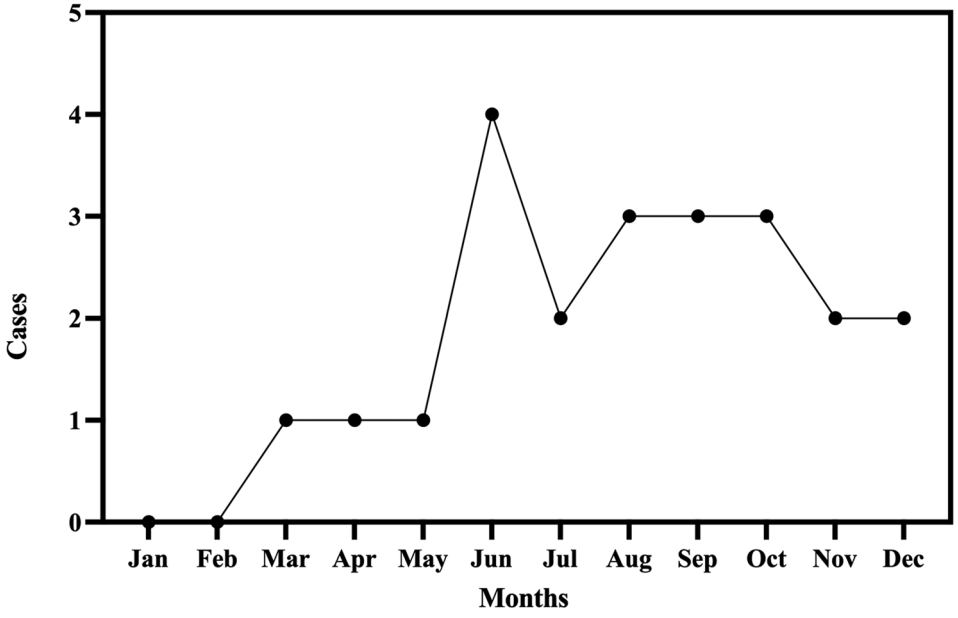

Fig. 1 Monthly distribution of disease onset. The numbers represent the total cases accumulated for each calendar month across the study period (2017–2024)

Table 1 Characteristics of patients

	All patients (*n* = 22)
Demographic characteristics	
Sex(male, n(%))	14(63.6)
Onset age (years, median (IQR))	1.8(1.1-4.0)
Rural life mode(n(%))	16(72.7)
Expose history (n(%))	10(45.5)
Clinical presentation	
Fever (n(%))	16(72.7)
Somnolence or lethargy (n(%))	14(63.6)
Vomiting (n(%))	13(59.1)
Extremity weakness (n(%))	7(31.8)
Headache (n(%))	4(18.2)
Abdominal pain (n(%))	4(18.2)
Skin rash (n(%))	4(18.2)
Diarrhea (n(%))	1(4.5)
Cough (n(%))	1(4.5)
Confusion or impaired consciousness (n(%))	1(4.5)
Hemiplegia	1(4.5)
Cranial nerve abnormalities (n(%))	1(4.5)
Blood laboratory test	
Initial blood eosinophil percentage (%, median (IQR))	13.5(8.5–17.8)
Maximal blood eosinophil percentage (%, median (IQR))	24.0(16.0–36.0)
Final blood eosinophil percentage (%, median (IQR))	3.5(1.8–5.3)
Positive serum *A. cantonensis* serological(n(%))	8(44.4)
CSF characteristics	
Initial CSF WBC (x10^6/L, median (IQR))	369.5 (169.8-556.8)
Initial CSF protein (g/L, median (IQR))	0.58 (0.43–0.67)
Initial CSF Glucose (mmol/L, mean ± SD)	2.20 ± 0.89
Initial CSF eosinophil percentage (%, median (IQR))	10.0 (IQR 0.0-17.1)
Maximal CSF eosinophil percentage (%, median (IQR))	17.2% (0.8%-25.8%)
Final CSF eosinophil percentage (%, median (IQR))	0.0(0.0-0.8)
Positive CSF *A. cantonensis* serological(n(%))	7(46.7)
CSF mNGS *A.cantonensis* identified (n(%))	18(100)
Brain MRI abnormality (n(%))	18(81.8)
Confirmed neuroangiostrongyliasis (n(%))	18(81.8)
Probable neuroangiostrongyliasis (n(%))	4(18.2)
Treatment	
Albendazole alone (n(%))	3(13.6)
Albendazole with corticosteroids (n(%))	19(86.4)

increased higher than 10%. The median maximal CSF eosinophil percentage was 17.2% (IQR 0.8%- 25.8%) at a median 18 days (IQR 9.8–33.3 days) after onset(Table 1). The maximal CSF eosinophil percentage higher than 0.0% and higher than 10.0% was seen in 63.6% (14/22) and 59.1% (13/22) of patients, respectively.

The initial blood and CSF eosinophil percentage was not correlated (Spearman's rank correlation coefficient, $\rho = 0.105$, $P = 0.164$), as well as the maximal blood and CSF eosinophil percentage (Spearman's rank correlation coefficient, $\rho = -0.180$, $P = 0.424$). The initial CSF eosinophil percentage was not correlated with the initial CSF WBC, protein or glucose (Spearman's rank correlation coefficient, $P > 0.05$).

A total of 45.5% (10/22) of patients underwent CSF cytokine panel examinations. Among these patients, 90.0% (9/10) exhibited elevations in at least one cytokine. The most commonly elevated cytokines were IL-6 (80.0%, 8/10), IL-4 (70.0%, 7/10), IL-10 (70.0%, 7/10), IL-8 (60.0%, 6/10), IL-5 (50.0%, 5/10), IL-17F (50.0%, 5/10), and IL-22 (50.0%, 5/10). Moderate to low frequency elevations were observed in IL-2 (40.0%, 4/10), IFN-γ (40.0%, 4/10), TNF-α (30.0%, 3/10), IL-1β (20.0%, 2/10), TNF-β (20.0%, 2/10), IL-17A (10.0%, 1/10), and IL-12p70 (10.0%, 1/10). The maximal CSF eosinophil percentages were significantly higher in the IL-6–elevated group compared to the non-elevated group (median 19.5%, IQR 11.9–44.3% vs. 0.0%, IQR 0.0–0.0%, $Z = -2.095$, $P = 0.044$; Mann–Whitney U test).No significant difference was observed in peripheral blood eosinophil percentages between the two groups.

A. cantonensis serological and mNGS tests

A total of 18 patients underwent serum IgG antibody testing against parasitic infections using a standardized panel. Among them, 5.6% (1/18) tested negative for all antibodies. Serum *A. cantonensis* IgG positivity was observed in 44.4% (8/18) of patients. Of these, 4 patients showed A. cantonensis IgG positivity only, while another 4 patients had A. cantonensis IgG positivity in combination with other parasite antibodies. The combinations of multiple positivity were as follows: *A. cantonensis* IgG + *Toxoplasma gondii* IgG (1 patient), *A. cantonensis* IgG + *Toxoplasma gondii* IgG + *Sparganum* IgG (1 patient), *A. cantonensis* IgG + *Taenia solium* IgG (1 patient), and *A. cantonensis* IgG + *Clonorchis sinensis* IgG (1 patient).

Among patients without *A. cantonensis* IgG positivity, antibodies against other parasites were detected in 50.0% (9/18) of patients, including *Echinococcus* IgG (1 patient), *Schistosoma japonicum* IgG (1 patient), *Toxoplasma gondii* IgG + *Echinococcus* IgG (3 patients), *Toxoplasma gondii* IgG + *Echinococcus* IgG + *Clonorchis sinensis* IgG (2 patients), *Toxoplasma gondii* IgG + *Taenia solium* IgG (1 patient), and *Toxoplasma gondii* IgG + *Taenia solium* IgG + *Sparganum* IgG (1 patient).

A total of 15 patients underwent CSF IgG antibody testing against parasitic infections using a standardized panel. Among them, 40.0% (6/15) tested negative for all antibodies. CSF *A. cantonensis* IgG positivity was observed in 46.7% (7/15) of patients. Of these, 6 patients showed *A. cantonensis* IgG positivity only, while 1 patient

Table 2 Summary of serological testing and mNGS for *A. cantonensis*

Patient group	CSF mNGS result	Serum *A. cantonensis* antibody test	CSF *A. cantonensis* antibody test	Notes
n = 18 (mNGS performed)	18/18 with *A. cantonensis* detected	14 tested: 6 positive, 8 negative; 4 not tested	11 tested: 5 positive, 6 negative; 7 not tested	4 patients negative for both serum and CSF antibody had *A. cantonensis* detected by mNGS
n = 4 (mNGS not performed)	–	4 tested: 2 positive, 2 negative	4 tested: 1 positive, 3 negative	In 1 serum-positive case, *A. cantonensis* was also detected by mNGS of blood

Table 3 Radiographic and neurophysiological findings in patients

Examination	Performed *n* (%)	Abnormalities *n* (%)	Main findings
Chest X-ray	9(40.9)	7(77.8)	Increased lung markings (*n* = 3, 33.3%), ill-defined opacities (*n* = 4, 44.4%)
Chest CT	13(59.1)	13(100)	Hazy patchy opacities (*n* = 12, 92.3%), nodular high-density shadows (*n* = 4, 30.8%), consolidation (*n* = 1, 7.7%), pulmonary cavity (*n* = 1, 7.7%), mediastinal lymphadenopathy (*n* = 1, 7.7%), calcification (*n* = 1, 7.7%)
Brain MRI	22(100)	18(81.8)	Leptomeningeal enhancement (*n* = 10, 45.5%), ventricular enlargement (*n* = 9, 40.9%), cortical lesions (*n* = 7, 31.8%), cerebellar lesions (*n* = 4, 18.2%), periventricular white matter lesions (*n* = 2, 9.1%), basal ganglia lesions (*n* = 2, 9.1%)
EEG	22(100)	12(54.5)	Slow background (*n* = 11, 50.0%), epileptiform activity (*n* = 2, 9.1%)

had combined positivity for *A. cantonensis* IgG and *Toxoplasma gondii* IgG. Among patients without *A. cantonensis* IgG positivity, antibodies against other parasites were detected in 13.3% (2/15), specifically Toxoplasma gondii IgG positivity in 2 patients.

mNGS of blood samples was performed in 4 patients. *A. cantonensis* was identified in 3 patients, with 75, 310, and 16,978 unique reads, respectively. In the remaining patient, *Cytomegalovirus* was detected with 4 unique reads.

mNGS of CSF samples was performed in 18 patients, and *A. cantonensis* was identified in all cases (100.0%, 18/18), with a median of 2,453 unique reads (IQR 353.5–28,641.75) (Table 2). One patient, who did not undergo CSF mNGS examination, underwent blood mNGS and *A. cantonensis* was identified with 16,978 unique reads. The other three patients underwent both serum and CSF IgG antibody panel testing for parasitic infections.

CSF mNGS also identified occasional non-*A. cantonensis* pathogens, including *Aspergillus* (34 unique reads) and *Pseudomonas aeruginosa* (5 unique reads) each detected in a separate patient. *Aspergillus versicolor* (19 unique reads) and *Moraxella catarrhalis* (23 unique reads) were co-detected in a single patient. Given the low read counts and the absence of clinical manifestations indicative of active infection, these findings were considered incidental and clinically insignificant. Notably, mNGS successfully identified *A. cantonensis* in four patients who tested negative for both serum and CSF IgG antibodies against *A. cantonensis* (Table 2). The unique read counts in these antibody-negative patients ranged from 147 to 27,664. The unique read counts mapped to *A. cantonensis* were not significantly correlated with initial or maximal CSF eosinophil percentages, initial CSF WBC count, or protein concentration (Spearman's ρ, all $p > 0.05$), but showed a negative correlation with initial CSF glucose levels ($\rho = -0.494$, $p = 0.037$). No significant differences in *A. cantonensis* unique read counts were found between patients with positive versus negative CSF IgG against *A. cantonensis* (Mann-Whitney U test, $Z = -0.379$, $p = 0.705$), serum IgG (Mann-Whitney U test, $Z = -0.388$, $p = 0.698$), or those with versus without elevation in each CSF cytokine included in the panel (Mann-Whitney U test, $P > 0$).

Radiographic and neuroelectrophysiological findings

Radiographic and neuroelectrophysiological findings are summarized in Table 3. Chest imaging frequently revealed abnormalities, predominantly hazy patchy opacities. Brain MRI was abnormal in most patients, with leptomeningeal enhancement, ventricular enlargement, and cortical lesions as the main findings (Fig. 2). EEG abnormalities occurred in 54.5% of patients, including slow background and epileptiform activity.

Treatment and outcome

Albendazole alone was administered to 13.6% (3/22) of patients, while 86.4% (19/22) received combination therapy with albendazole and corticosteroids. Among these, nine patients received dexamethasone at approximately 0.6 mg/kg/day, with treatment duration ranging from 2 to 10 weeks (two patients discontinued prematurely due to early discharge). The remaining ten patients received intravenous methylprednisolone at 2 mg/kg/day, followed by a tapering course of oral prednisone for 1–2 months. Pulse methylprednisolone was generally reserved for patients with more severe disease or those unable to tolerate oral therapy at treatment initiation.

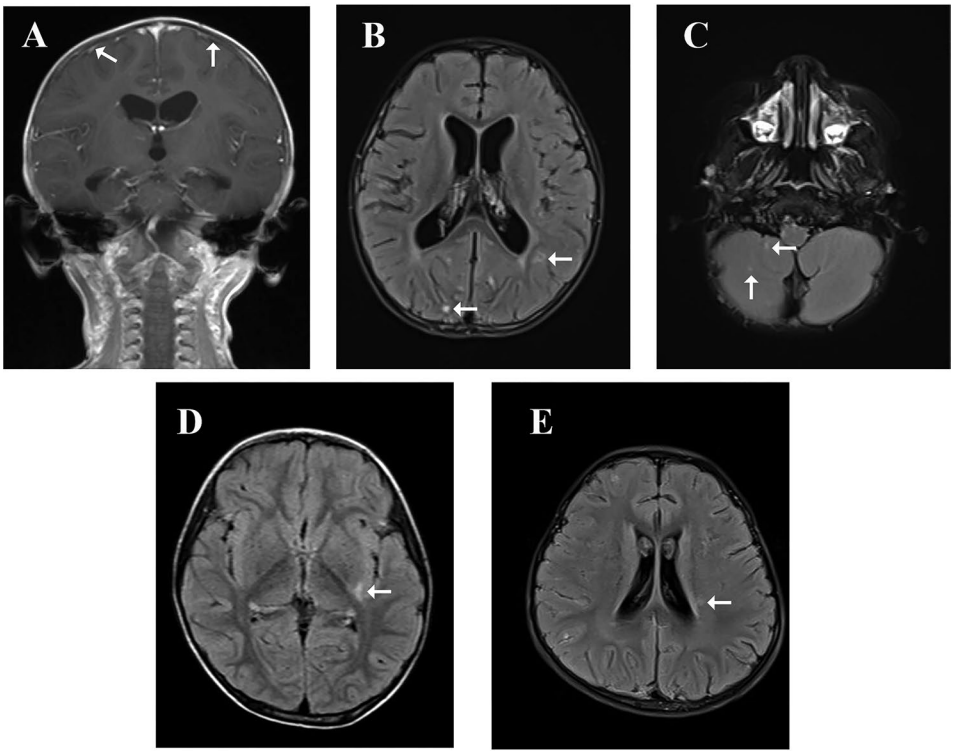

Fig. 2 Brain MRI findings in patients with *A. cantonensis*. (**A**) coronal T1-weighted MRI showing leptomeningeal nodular enhancement after gadolinium injection. (**B**) Axial T2-weighted Flair MRI showing hyperintense lesions in the subcortical and deep white matter of the posterior parieto-occipital region. (**C**) Axial T2-weighted Flair MRI showing hyperintense lesions in cerebellum. (**D**) Axial T2-weighted Flair MRI showing hyperintense lesions in basal ganglia. (**E**) Axial T2-weighted Flair MRI showing hyperintense lesions in white matter around the left lateral ventricle

Two patients were lost to follow-up after discharge, as their families chose to discontinue treatment for personal reasons before completing the full therapeutic course. Among the remaining 20 patients who completed treatment, clinical symptoms improved and brain MRI lesions showed resolution. The CSF eosinophil percentage was dynamically monitored through follow-up. Based on the longitudinal patterns observed, patients were categorized into four distinct groups. Three patients (13.6%, 3/22) exhibited a fluctuating decline, characterized by an overall decreasing trend in CSF eosinophil percentage with intermittent rises during the decline (Fig. 3A). Two patients (9.1%, 2/22) showed a gradual decline, characterized by a steady decrease in eosinophil percentage throughout follow-up (Fig. 3B). Seven patients (31.8%, 7/22) demonstrated an initial rise then decline, showing an early increase in eosinophil percentage followed by a gradual decrease over time (Fig. 3C). One patient (4.5%, 1/22) showed a gradual increase, with a steady rise in eosinophil percentage across follow-up, and the final eosinophil percentage was 10% and refused repeat repeat CSF examination after that (Fig. 3D). Nine patients (40.9%, 9/22) maintained persistently low (< 10%) eosinophil percentages at all measured time points (Fig. 3E). Patients underwent their final routine blood test and lumbar puncture at a mean of 91.9 ± 53.5 days after onset. The median peripheral eosinophil percentage was 3.5% (IQR 1.8–5.3%), significantly lower than both the initial and peak values (Wilcoxon signed-rank test, $P < 0.05$). Similarly, the median CSF eosinophil percentage was 0.0% (IQR 0.0–0.8%), also significantly lower than the initial and maximal CSF values ($P < 0.05$). Following discharge, two patients were lost to follow-up, while 20 patients were monitored for a median of 2.5 months (IQR 1.0–19.9 months) with no reported sequelae or relapse.

Discussion

This retrospective study reviewed 22 pediatric cases of CNS *A. cantonensis* infection diagnosed at a single tertiary hospital in Guangzhou, Guangdong Province, between May 2017 and December 2024. To our knowledge, this is among the largest single-center pediatric cohorts reported in mainland China to date, and provides important insights into the clinical features, diagnostic approaches, treatment strategies, and short-term outcomes in children with this rare parasitic CNS infection.

In our study, there was a male predominance (14 males vs. 8 females), and 16 of 22 patients resided in rural areas, consistent with previous reports. For example, Bénédicte Melot et al. reported 92 cases of eosinophilic meningitis in New Caledonia, with 63% male and nearly 80% from rural areas [17]. Sawanyawisuth et al. similarly found a

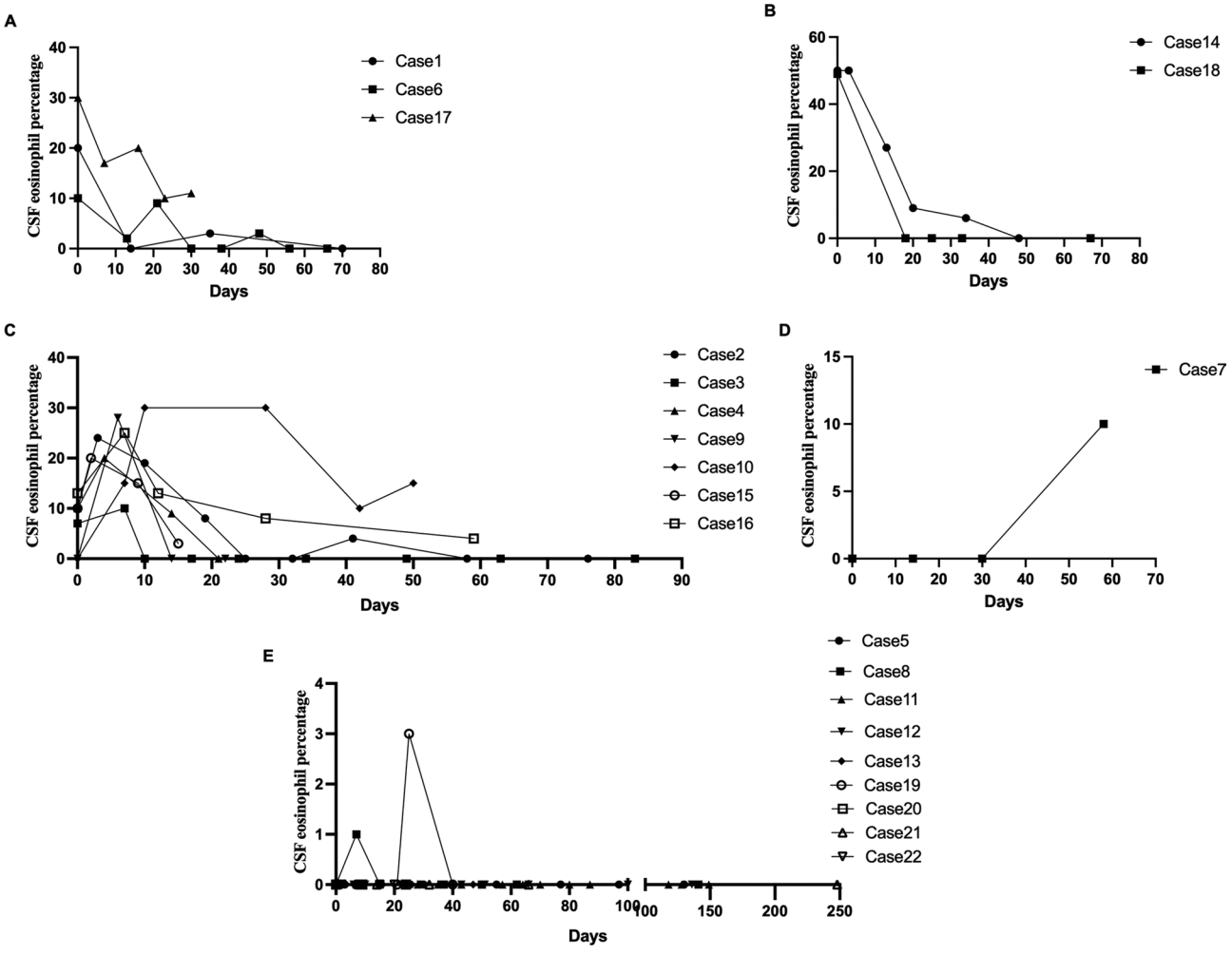

Fig. 3 Dynamic patterns of CSF eosinophil percentage across 22 patients. (**A**) Fluctuating decline pattern observed in three patients. (**B**) Gradual decline pattern observed in two patients. (**C**) Initial rise followed by decline observed in seven patients. (**D**) Gradual increase pattern observed in one patient. (**E**) Persistently low levels (within 10%) observed in nine patients. Note: Day 0 corresponds to the time of the first lumbar puncture

male predominance in pediatric cases in Thailand [13]. The median onset age in our cohort was 1.8 years (IQR 1.1–4.0), notably younger than that reported in Thailand (median 12 years) and Taiwan (majority between 3 and 9 years) [13, 18]. Most cases in our series (68.2%) occurred between June and October, overlapping with the local rainy and typhoon season, consistent with seasonal patterns reported in Taiwan [19].

Compared to adults, pediatric cases of eosinophilic meningitis caused by *A. cantonensis* often lack a clear exposure history, which increases diagnostic difficulty. In our study, only three patients had a confirmed exposure history, while seven patients were found to have probable exposure after detailed inquiry into their daily activities and diet. These probable exposures included subtle and easily overlooked unhygienic behaviors, such as playing near ponds, picking up food from the ground, or frequenting ditches and grassy areas—activities that are often difficult to elicit during routine history taking. This highlights the need to consider such possibilities during clinical evaluation and to reinforce hygienic practices in endemic regions.

The clinical manifestations of angiostrongyliasis largely depend on the number of invading larvae as well as their location and movement within the nervous system [6]. Typical symptoms include headache, fever, neck stiffness, nausea, and vomiting, while severe cases may progress to cranial nerve palsies, seizures, coma, or death [2]. Compared with adults, children more often present with fever and gastrointestinal symptoms but less frequently with headache, neck stiffness, or paresthesia [2]. However, headache and neck stiffness are less frequent in children, while paresthesia and hyperesthesia are rarely reported [2, 13, 18, 20]. In our study, fever was the most common symptom (77.2%), followed by somnolence/lethargy (63.6%) and vomiting. Headache occurred in 18.2% of patients, while neck stiffness and hyperesthesia were absent. Given the high prevalence of fever, *A. cantonensis*

infection should be considered in pediatric patients with unexplained fever, particularly in endemic regions [12]. Somnolence or lethargy was observed in 63.6% of our patients, a rate notably higher than that reported in previous studies (20.7%). This discrepancy may be due to the younger age of patients in our cohort, many of whom may have difficulty expressing symptoms verbally, while lethargy is more easily noticed by caregivers. The high rate of lethargy, compared to previous studies, may reflect younger age and caregiver-observed symptoms. No patients developed coma or died. These findings suggest that pediatric *A. cantonensis* infection may present with milder disease in our cohort, possibly due to lower larval burden, but remains clinically nonspecific and difficult to distinguish from other CNS infections [2, 13, 21, 22].

Typical CSF findings in eosinophilic meningitis include elevated protein levels with normal or decreased glucose concentrations [2, 22]. Previous studies have shown that eosinophilic pleocytosis in the CSF is detected at the time of initial lumbar puncture in only about half of the patients, and peripheral blood eosinophilia is observed in less than half at disease onset [2]. The presence of eosinophils in the CSF—a key diagnostic clue—is frequently delayed in relation to symptom onset, complicating early diagnosis. In our study, 45.5% (10/22) of patients had a CSF eosinophil percentage exceeding 10% at the initial lumbar puncture, whereas 59.1% (13/22) exceeded this threshold at any point during the disease course. The median maximal CSF eosinophil proportion was 17.2% (IQR 0.8–25.8%), typically occurring at a median of 18 days (IQR 9.8–33.3 days) after symptom onset. Although all patients presented with peripheral eosinophilia and CSF pleocytosis, there was no correlation between blood eosinophil percentage and CSF eosinophil proportion, nor between total CSF WBC count and CSF eosinophil percentage. While we adopted the conventional definition of CSF eosinophilia as ≥ 10% of total leukocytes [14], we acknowledge that this threshold remains debated. Some studies have reported patients with severe manifestations but CSF eosinophils < 10% [23], and recent guidelines highlight that treatment may be justified based on strong clinical suspicion and exposure history even when strict criteria are not met [24]. Furthermore, Graeff-Teixeira et al. emphasized the lack of consensus and suggested that any eosinophils in the CSF could be considered abnormal [7]. In our series, 40.9% of patients never reached the 10% threshold, supporting the notion that reliance on this cut-off alone may delay diagnosis and treatment, and consistent with previous reports indicating that normal CSF eosinophil counts do not exclude *A. cantonensis* infection [2, 6, 25]. Peak CSF and peripheral eosinophil levels have been reported to occur 25–35 days after larval ingestion, highlighting the importance of repeated CSF and peripheral evaluations when initial results are inconclusive [2].

The definitive diagnosis of *A. cantonensis* infection relies on the detection of larvae in the CSF, intraocular structures, brain tissue, spinal canal, or pulmonary arteries during autopsy. However, even in severe cases, the detection rate of larvae remains low [1, 9]. In our study, no larvae were detected in the CSF, fundus, or chest imaging. Currently, immunodiagnosis is mainly based on ELISA combined with immunoblot or dot immunogold filtration assays targeting 29–31 kDa glycoprotein antigens of *A. cantonensis* [2]. Although ELISA is widely used and highly reproducible, its value in early infection is limited because antibody production may not appear until 10–30 days after infection [6, 26, 27]. Moreover, specificity depends on antigen preparation: crude extracts are prone to cross-reactivity, while the 31 kDa glycoprotein is more reliable, though cross-reactivity with other helminths (e.g., trichinellosis, trichuriasis, opisthorchiasis) has been reported [28]. In our cohort, several patients showed combined antibody positivity. While these findings may reflect serological cross-reactivity, they could also represent past exposure. However, given the young age of our patients (< 2 years), past exposure is less likely, supporting the interpretation that cross-reactivity is a potential limitation of serological testing.

Molecular diagnostic techniques such as PCR and mNGS have emerged as valuable tools for early detection and confirmation of *A. cantonensis* infection. mNGS is an unbiased, high-throughput sequencing approach that enables parallel detection of nucleic acids from a broad range of pathogens without requiring prior knowledge of the causative organism [10, 29–31]. In contrast, conventional molecular assays such as internal transcribed spacer (ITS)-based PCR and the *A. cantonensis*-specific AcanR3990 PCR are highly sensitive and specific but rely on targeted amplification of known loci, limiting their utility when the pathogen is unexpected or when atypical presentations occur [32, 33].In our series, mNGS identified *A. cantonensis* in 100% (18/18) of tested CSF samples, including four patients negative for serum and CSF IgG, underscoring its superior sensitivity. Non-*A. cantonensis* sequences were occasionally detected but were incidental and clinically irrelevant. Notably, read counts did not correlate with CSF eosinophils, WBC count, or protein, suggesting that mNGS can reliably detect infection irrespective of inflammatory markers and may be particularly valuable in seronegative or atypical pediatric cases.

A. cantonensis–induced CNS inflammation is characterized by vascular changes, massive eosinophilic infiltration, and granulomatous inflammation surrounding dead larvae, all contributing to elevated intracranial pressure [34]. In our study, brain MRI abnormalities

were observed in 81.8% of patients. The most common findings included leptomeningeal enhancement, ventricular enlargement, and cortical lesions as well as cerebellar lesions, consistent with previous reports describing involvement of the cerebrum, cerebellum, and meninges in 45%–69% of patients [35]. This classification highlights the heterogeneity of imaging presentations, though none are specific to *A. cantonensis* infection. Although these findings are nonspecific, they are clinically useful for assessing severity, guiding management, and predicting prognosis in severe cases such as infarction, hemorrhage, or myelitis [2]. MRI changes related to *A. cantonensis* infection have often been reported as reversible, with many intracranial lesions resolving after treatment in case series and reports [6, 34]. However, long-term sequelae have also been described [36].

According to Neuroangiostrongyliasis: Updated Provisional Guidelines for Diagnosis and Case Definitions published in 2023, treatment for probable or confirmed neuroangiostrongyliasis used albendazole (15 mg/kg/day divided bid for 14 days) or other benzimidazole drugs combined with corticosteroids [7]. In clinical practice, combination therapy with albendazole and corticosteroids is commonly used [37]. Albendazole exerts antiparasitic effects by killing larvae, thereby reducing inflammation, improving symptoms, and shortening disease duration [2]. It is generally recommended for use within three weeks of infection onset; administration beyond this period may exacerbate disease severity [2, 6, 38]. Corticosteroids help alleviate immune-mediated inflammation and intracranial hypertension caused by larval disintegration. Corticosteroids may also enhance albendazole bioavailability by increasing its concentration in target tissues [39]. In our study, most patients (86.4%) received combined therapy with albendazole and corticosteroids, including dexamethasone or intravenous methylprednisolone followed by a tapering course of oral prednisone. Treatment regimens were tailored according to clinical status and CSF findings. Although *A. cantonensis* larvae usually die spontaneously within 1–2 months, patients with severe symptoms may require longer treatment courses [9, 40]. Dynamic monitoring of CSF eosinophil percentages provided additional information on the host inflammatory response, with diverse trajectories (decline, fluctuation, or persistently low levels). These patterns may reflect differences in disease severity, treatment timing, or host immunity, and could help identify patients who may need extended therapy. Further studies are warranted to validate the prognostic utility of eosinophil kinetics in neuroangiostrongyliasis.

Reported mortality rates for *A. cantonensis* infection range from 1.5% to 5%, but may reach 79%–91% in cases with encephalitis [1, 13, 25, 41]. Pediatric patients with *A. cantonensis* infection have been reported to experience higher mortality, greater disease severity, and a higher incidence of long-term neurological sequelae [19, 21, 26]. In our study, however, no deaths or persistent sequelae were observed, even in patients with parenchymal brain lesions. During follow-up (median 2.5 months, IQR 1.0–19.9), all 20 evaluable patients showed recovery without relapse or neurological complications, accompanied by marked reductions in peripheral and CSF eosinophil percentages at follow-up.

We acknowledge that the relatively small sample size limits the statistical power of our analyses. In addition, multiple comparisons were performed, which may increase the likelihood of type I error. Therefore, the findings should be interpreted with caution and considered exploratory.

Conclusions

Pediatric CNS angiostrongyliasis in Guangdong primarily affects rural children during summer–autumn. Clinical signs may be nonspecific. mNGS outperformed serology, particularly in seronegative or clinically suspected cases.

Abbreviations

A. cantonensis	*Angiostrongylus cantonensis*
CNS	Central nervous system
CSF	Cerebrospinal fluid
CT	Computed tomography
EEG	Electroencephalography
mNGS	Metagenomic next-generation sequencing
MRI	Magnetic resonance imaging
WBC	White blood cell

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Author contributions

Haixia Zhu, Wenlin Wu and Yanping Ran study concept, acquisition of data and draft the manuscript. Jiahao Cai, Wenxiao Wu, Yuan Zhao, and Yiru Zeng acquisition of data. Chi Hou, Yang Tian, Huiling Shen and Yani Zhang analysis of data and interpretation. Bingwei Peng, Kelu Zheng interpretation of data. Yuanyuan Gao and Xiaojing Li study concept, study design, and critical revision of manuscript for intellectual content. All authors gave final approval of the version to be published.

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Data availability

No new sequencing datasets were generated or analysed during the current study. Pathogen identification was performed based on alignment with publicly available reference databases. Therefore, there are no datasets available for deposition.

Declarations

Ethics approval and consent to participate

This study was approved by the Ethics Committee of Guangzhou Women and Children's Medical Center and was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from the patient's parents or guardians, who also explicitly consented to the publication of clinical details and images that could potentially identify the patient.

Competing interests
The authors declare no competing interests.

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