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CASE REPORT

THE FIRST CASE OF *Angiostrongylus cantonensis* EOSINOPHILIC MENINGITIS DIAGNOSED IN THE CITY OF SÃO PAULO, BRAZIL

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SUMMARY

Introduction: *Angiostrongylus cantonensis* is a natural parasite found in lung arteries of rats, which in humans may cause eosinophilic meningitis. **Objective:** To report the first case of eosinophilic meningitis caused by *Angiostrongylus cantonensis* in the city of São Paulo, Brazil. **Case report:** A male patient, 11 years old, living in the southern area of São Paulo, was admitted to the Pediatric Emergency Department with ongoing headaches for three days, but no fever or any other complaint. The presence of snails and rodents was reported in the peridomicile. The child was awake, lucid, oriented; muscular strength preserved, isochoric, photo reagent pupils and terminal nuchal rigidity - Glasgow Coma Scale (GCS) = 15. The laboratory tests showed a mild leukocytosis with 1736 eosinophils/mm³ and the CSF analysis disclosed 160 leukocytes/mm³ with 36% of eosinophils. The bacterial culture was negative. Computed Cerebral Tomography showed no alterations. The RT-PCR assay for detecting *Angiostrongylus cantonensis* larvae and DNA was negative. ELISA antibodies for IgG anti-*A. cantonensis* was negative in serum and undetermined in CSF and samples collected five days after the onset of symptoms. Seroconversion was observed in the sample collected 135 days later. **Conclusion:** the epidemiological and clinical data, the CSF alterations with eosinophilia and the seroconversion strongly suggest *Angiostrongylus cantonensis* eosinophilic meningitis.

KEYWORDS: *Angiostrongylus cantonensis;* Eosinophilic meningitis; CSF eosinophilia.

INTRODUCTION

Angiostrongyliasis is an infection which is caused by a nematode with two medically important species: *Angiostrongylus cantonensis* (*A. cantonensis*) and *Angiostrongylus costaricensis* (*A. costaricensis*). These nematodes belong to the superfamily *Metastrongyloidea*[2].

Angiostrongylus cantonesis is a parasite which primarily affects rat lungs. Mature forms reside in the pulmonary artery of rats where females lay their eggs. First stage larvae hatch from the eggs, migrate to the pharynx, are swallowed and eventually reach the feces through the gastrointestinal tract[2].

These nematodes have a vast array of intermediate hosts such as several land and water snails. The intermediate hosts eat the feces of rodents infected by these first stage larvae, which after two changes develop into third stage larvae; the infecting form of the parasite[2].

Third stage larvae ingested by the human host penetrate the gastrointestinal tract vessels and migrate via the bloodstream to the central nervous system. There, larvae develop into young worms that die frequently and rapidly, failing to complete their biological cycle. A predominantly eosinophilic inflammatory response then occurs in the meninges as well as in encephalic and medullary tissue. Although many cases are self-limiting, neurological sequelae may occur and death has also been reported[22].

Both humans and rodents may be infected by the ingestion of molluscs, live or poorly cooked snails or paratenic hosts such as crabs and infected shrimps. Raw foods such as fruit and vegetables contaminated with secretions of molluscs infected with *A. cantonensis* are another source of infection[15].

From an epidemiological perspective, human infections are most commonly diagnosed in Southeast Asia, mainly in Thailand and Malaysia as well as Hawaii, Indonesia, the Philippines, Japan, Papua New Guinea, Hong Kong, Singapore, Taiwan and South Korea[25].

Dissemination of the parasite to other areas of the world is a result of globalization, with the intercontinental migration by ship of rodents infected with this nematode[7].

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The first case of human infection in North America was reported in 1995 in a child who had eaten a snail[18].

In Brazil, *A. cantonensis* was identified by CALDEIRA *et al.*[1] in 2007 as the etiological agent of two human cases of eosinoplilic meningitis in Cariacica and Vila Velha in the state of Espírito Santo[1], and in 2009 another case of eosinophilic meningitis was reported in Pernambuco (LIMA *et al.,* 2009)[13].

In the state of São Paulo, five cases of *A. cantonensis* eosinophilic meningitis had been reported until September 2010 - four of them on the southern coast of the state in Mongaguá, which involved infected subjects of the same family, and another one in the city of São Paulo, which is the focus of the present report[3].

CASE REPORT

An 11-year-old male patient born and living in the southern area of the city of São Paulo (SP), with no report of recent travel, was admitted to the Pediatric Emergency Department in September 2010 with a history of headaches for seven days which had worsened over the last three days, but with no fever. Blurred vision when symptoms started and a rash 20 days prior to the onset of symptoms were also reported. During the physical exam the child was awake, acyanotic, anicteric, hydrated; not pale, spatial-temporal oriented; responding to verbal stimuli; with muscular strength preserved; isochoric and photo reagent pupils and with mild terminal nuchal rigidity. GCS = 15. Cerebral Tomography presented no alterations.

Laboratory tests: hemoglobin = 14.1 g/dL; hematocrit = 42.5%; leukocytes = 12.400/µL; bands = 1%; segs = 39%; eosinophils = 14%; basophils = 1%; lymphcytes = 40%; monocytes = 5%; platelets = 393000/mm^3; C-reactive protein = 0.05 mg/dL.

Cerebral spinal fluid (CSF) after lumbar puncture performed in the sitting position showed: volume 6 mL; by visual method - opalescent color and aspect. After centrifugation - clear colorless aspect. Total cytology: leukocytes 160/mm^3; red blood cells 0/mm^3. Cytology: neutrophils = 5%; lymphocytes = 50%; eosinophils = 36%; monocytes = 9%; protein = 42 mg/dL; Pandy's test = negative; glucose = 54 mg/dL; chloride = 679 mg/dL; lactate = 16.2 mg/dL.

Bacterioscopy of CSF by Gram stain indicated an absence of bacterial microbiota. CSF bacterial culture was negative at 96 hours. Detection of bacterial antigens by latex agglutination tested negative for *Neisseria meningitidis* type ACY W 135; *Neisseria meningitidis B*, *Escherichia coli*, *Haemophilus influenza*, *Streptococcus pneumoniae* and *Streptococcus B*.

Due to the significant increase of eosinophils in CSF and blood, further clinical, epidemiological and laboratory investigations were conducted.

Family members pointed out the presence of rodents and snails in the peridomicile.

Sorological results showed Enzyme-Linked Immunosorbent Assay (ELISA) for anti-*cysticercus*, anti-*toxocara canis*, anti-schistosomiasis antibodies was negative. Also, ELISA IgG and IgM antibodies to *herpes simplex virus* (HSV) type 1 and type 2 and the hemaglutination assay for *syphilis* were negative.

The direct detection of *Angiostrongylus catonensis* larvae and DNA by Real Time Polymerase Chain Reaction (RT-PCR) in the CSF sample collected five days after the onset of symptoms were negative.

The detection of anti-*Angiostrongylus cantonensis* immunoglobulins (IgG) in serum determined by ELISA was negative and undetermined in CSF in samples collected five days after the onset of symptoms. However, seroconversion was observed in the sample collected 135 days after the onset of symptoms. In order to do this, the antibody detection assay, using the *A. cantonensis* antigen from young female crude extract, Akita strain, which has a sensitivity of 88% and a specificity of 78%, was performed by the Laboratory of Molecular Parasitology, Institute of Biomedical Research of the Pontifical Catholic University of Rio Grande do Sul.

Parasitological stool examination using the Ritchie and Hoffman protocol was negative.

Treatment consisted of intravenous hydration and symptom relief for 24 hours.

Once he was feeling better, the patient was discharged and submitted to outpatient follow-up, and nitazoxanide 7.5 mg/kg, b.i.d. for three days, was used for the empirical treatment.

The patient presented with the gradual resolution of headaches, which receded in seven days.

The Epidemiological Surveillance of the State of São Paulo was notified of the case.

DISCUSSION

We hereby report a case of *Angiostrongylus cantonensis* eosinophilic meningitis, which as far as we know is the first one to be diagnosed in the city of São Paulo.

Epidemiological history coupled with clinical data, alterations in hematological and cerebrospinal fluid dynamics as well as the seroconversion observed in the sample collected 135 days after the onset of symptoms all reinforce the diagnosis of *A. cantonensis* eosinophilic meningitis.

As far as epidemiological data are concerned however, we cannot ascertain for sure how the child acquired the infection, but some aspects must be taken into consideration.

A malacological investigation was carried out in the surrounding areas where the patient resided in a gated neighborhood in the extreme southern area of the city, in a region belonging to the district of Guarapiranga, São Paulo. The presence of snails and rodents in the areas surrounding the patient's residence corroborates this theory since MOTA *et al.,* 2011[16] found *Sarasinula linguaeformis* naturally infected with *A. cantonensis* stage three (L3) in a residential area of Parque Fernanda, a neighborhood in the southern region of the city of São Paulo, SP, Brazil[17].

Eosinophils are not usually present in cerebrospinal fluid. In literature, the presence of 10 or more eosinophils/mL in the cerebrospinal fluid or eosinophilia higher than 10% of the total leukocyte count indicates eosinophilic meningitis[8]. Most cases involving infections in the Central Nervous System (CNS) are caused by helminths[4]. Among helminths, zoonotic infection by *A. cantonensis* is the main cause[24].

TSENG *et al.,* 2011[23], show a prevalence of headaches in the cases studied. Furthermore, they also report the presence of fever (68%), hypertesia (30%), nuchal rigidity (17%), nausea and vomiting (16%), disorders of consciousness (9%), abdominal pain (9%), extraocular muscle palsy (4%) and facial palsy (1%)[23].

Identification of *A. cantonensis* larvae occurs in only 1.9% of patients with angiostrongyliasis[12]. Therefore, immunological assays are used as tools to confirm a presumptive diagnosis, including the Immunofluorescent antibody test (IFA)[11], Immunoenzyme staining test (IEST)[5] and ELISA[27].

With regard to imaging tests, computed tomography cannot distinguish *A. cantonensis eosinophilic meningitis* from that caused by other parasites such as gnathostomiasis or neurocysticercosis[9].

On the other hand, the use of magnetic resonance imaging to investigate *A. cantonensis* eosinophilic meningitis shows a diffuse increase in the hyperintense signal of the subcortical white matter of bilateral cerebral and cerebellar hemispheres on T2-weighted images, probably due to the presence of granuloma as a response to the antigens released by the death of the parasite[6].

There are different points of view concerning the benefits of treating infections caused by *A. cantonensis*, but in the beginning treatment consists of support measures to relieve headaches and prevent volume depletion caused by the vomiting[19].

WANG *et al.*, 1999[26], did not observe a decrease in the duration of symptoms with the use of corticosteroids, whether used alone or alongside antihelminthic drugs, but they reported a significant decrease in headaches after lumbar puncture[26].

Based on their experience, LIN *et al.,* 2003[14] and LI *et al.,* 2008[10] reported an improvement in headaches, thus recommending the use of antihelminthic drugs, mainly in cases of severe infection by *A. cantonensis*. However, TSENG *et al.*, 2011[23], reported that no decrease in the duration of the disease was observed with the use of corticosteroids, either alone or alongside antihelminthic drugs[23].

With regard to the empirical use of nitazoxanide, there is no scientific evidence about its therapeutic benefits reported in the literature.

Regarding differential diagnosis, toxocariasis, neuroschistosomiasis and cysticercosis are the second most important causes of eosinophilic meningitis in Brazil. Other causes of eosinophilia in cerebrospinal fluid have been mentioned, including bacterial infections (syphilis and tuberculosis), viral infections (Coxsackie), fungal infections (coccidiodomycosis) and by other helminths (hydatid, strongyloidiasis, filariasis, trichinellosis), inflammatory diseases (rheumatoid arthritis), neoplasia (Hodgkin), the use of drugs and contrast agents or prosthesis[20].

Angiostrongyliasis is an emerging infection, and since *Metastrongylidae* can infect various molluscs, the risk of dissemination to many areas of the country and the world is very high[1,13,15,21]. Therefore, this infection calls for continued surveillance and the implementation of diagnostic techniques and preventive measures.

The present report aims to inform health care professionals about the first case of *Angiostrongylus cantonensis* eosinophilic meningitis diagnosed in the city of São Paulo, Brazil.

RESUMO

Primeiro caso de meningite eosinofílica diagnosticado na cidade de São Paulo, SP, Brasil

Introdução: *Angiostrongylus cantonensis* é um parasito natural das artérias de pulmões de ratos, que pode causar, em humanos, meningite eosinofílica. **Objetivo:** Relatar o primeiro caso de meningite eosinofílica causado por *A. cantonensis* na cidade de São Paulo, Brasil. **Relato de caso:** Paciente do sexo masculino, 11 anos, residente na zona sul de São Paulo, foi admitido no serviço de emergência pediátrica com história de cefaléia há três dias, sem febre ou outras queixas. Relato de presença de moluscos e roedores no peridomicílio. Ao exame físico, criança desperta acianótica, anictérica, hidratada; lúcido, orientado; força muscular preservada, isocórica, pupilas fotorreagentes e rigidez de nuca terminal - Glasgow Coma Scale = 15. Exames laboratoriais indicaram leve leucocitose com 1736 eosinófilos/mm³ e a análise do líquor revelou a presença de 160 leucócitos/mm³ com 36% de eosinófilos. Cultura para bactérias negativa. Tomografia cerebral sem alterações. Pesquisa direta de larvas e de DNA por PCR-RT para *Angiostrongylus cantonensis* foi negativa. ELISA para anticorpos IgG anti-*A. cantonensis* negativo no soro e indeterminado no líquor nas amostras coletadas após cinco dias do início dos sintomas. Soroconversão observada na amostra coletada após 135 dias. **Conclusão:** A história epidemiológica, dados clínicos, alterações liquóricas com presença de eosinofilia e a soroconversão sugerem fortemente o diagnóstico de meningite eosinofílica por *A. cantonensis*.

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