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To cite this version:
Céline Dard, Eve Tessier, Duc Nguyen, Loïc Epelboin, Dorothée Harrois, et al.. First cases of Angiostrongylus cantonensis infection reported in Martinique, 2002–2017. Parasite, EDP Sciences, 2020, 27, pp.31. 10.1051/parasite/2020032. hal-02904012

HAL Id: hal-02904012
https://hal.archives-ouvertes.fr/hal-02904012
Submitted on 21 Jul 2020

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First cases of *Angiostrongylus cantonensis* infection reported in Martinique, 2002–2017

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Received 5 January 2020, Accepted 28 April 2020, Published online 12 May 2020

Abstract – Neuroangiostrongyliasis is a parasitic disease caused by the accidental ingestion of the nematode *Angiostrongylus cantonensis* in its larval form. Human infection can lead to eosinophilic meningitis, sometimes complicated by life-threatening radiculomyelitis or encephalitis. Although some cases have been reported from other Caribbean Islands, no cases have been diagnosed in Martinique so far. Here, we report the first eight laboratory-confirmed cases of neuroangiostrongyliasis in the island of Martinique, French West Indies, between 1 January 2002 and 31 December 2017. One case was fatal and five resulted in neurological sequelae. The medical community should consider the risk of *A. cantonensis* infection in patients living in or returning from Martinique.

Key words: *Angiostrongylus cantonensis*, Angiostrongyliasis, Eosinophilia, Helminth, Meningitis, Encephalitis, Caribbean, Martinique.

Résumé – Premiers cas d’angiostrongylose à *Angiostrongylus cantonensis* à la Martinique, de 2002 à 2017. L’angiostrongylose neuméningée est une maladie parasitaire causée par l’ingestion accidentelle du nématode *Angiostrongylus cantonensis* sous sa forme larvaire. L’infection humaine peut conduire à une méningite à éosinophiles, pouvant évoluer en radiculomyélite ou encéphalite menaçant le pronostic vital. Bien que des cas aient été rapportés dans d’autres îles des Caraïbes, aucun cas n’avait été diagnostiqué à la Martinique jusqu’à présent. Dans cet article, nous caractérisons les huit premiers cas d’angiostrongylose neuméningée biologiquement diagnostiqués à la Martinique, Antilles françaises, entre le 1er janvier 2002 et le 31 décembre 2017. Un cas s’est révélé mortel et cinq ont engendré des séquelles neurologiques. La communauté médicale doit désormais considérer le risque d’infection à *A. cantonensis* chez les patients vivant ou revenant d’un voyage à la Martinique.

Introduction

*Angiostrongylus cantonensis* is a nematode parasite that is the leading cause of infectious eosinophilic meningitis in humans in tropical and sub-tropical regions [6]. The life cycle involves rats as definitive hosts (mainly *Rattus* spp.) [49], various gastropods as intermediate hosts, and crustaceans [23], fishes and various other species as paratenic hosts [6].

Human infection is accidental, by ingestion of stage 3 larvae (L3) in gastropods or in paratenic hosts [11]. Neuroangiostrongyliasis is commonly a self-limited meningitis syndrome, but a large spectrum of clinical manifestations is possible [5]. Clinical manifestations range from asymptomatic disease and mild headaches to radiculomyelitis and encephalitis that can lead to permanent neurological injury or even death [29]. Most human cases of neuroangiostrongyliasis have been recorded...
in East and Southeast Asia, and the Pacific Basin, but the disease appears to be emerging in Australia [1], South America [13, 32, 44], the United States [3, 21], and some islands of the Caribbean (Cuba, Haiti, Dominican Republic, Jamaica, and Guadeloupe) [12, 19, 42]. Several patients infected with *A. cantonensis* have been diagnosed with neuroangiostroglyiasis – but not reported in the scientific literature – during the last few years on the island of Martinique, a French overseas department in the Lesser Antilles with a population of 371,200 inhabitants as of 1 January 2018 (INSEE census, French National Institute of Statistics and Economic Studies, [https://www.insee.fr](https://www.insee.fr)). The objectives of this study were to estimate the incidence and assess the clinical and biological features of neuroangiostroglyiasis in Martinique.

**Patients and methods**

**Study design**

A retrospective single-centre observational study was undertaken at the University Hospital of Martinique – the main hospital on the island – spanning the period 1 January 2002 – 31 December 2017.

**Inclusion and exclusion criteria**

The following clinical and biological inclusion criteria were used: (i) neurological symptoms requiring lumbar puncture; (ii) eosinophilic meningoitis defined as the presence of more than 10 eosinophils/mm³ in the cerebrospinal fluid (CSF) or ≥10% of the total CSF leukocyte count [5]; and (iii) detection of anti-*A. cantonensis* immunoglobulins in serum and/or CSF by indirect immunofluorescence assay (IIF) [22] or by western-blot (31-kDa antigen [34]). Patients with eosinophilia in the CSF due to a traumatic lumbar puncture or blood eosinophilia of another aetiology were excluded. Neuroangiostroglyiasis cases were defined as “confirmed” for patients who met the first two inclusion criteria, and with the detection of specific anti-*A. cantonensis* immunoglobulins in serum and/or CSF by western-blot. When *A. cantonensis* serology was found to be positive by IIF only, cases were defined as “probable” because of the low/lack of specificity of this method for nematode infections, in which some cross-reactions can be observed [47,48].

**Data collection**

Demographic data including exposure history, laboratory results (from blood and CSF), clinical presentation, imaging features (brain scan or MRI), and outcomes (recovery, sequelae, and death) were retrospectively collected from the medical charts, according to the legal and ethical guidelines of the French National Committee on Data Protection (CNIL).

**Angiostrongylus cantonensis serology by indirect immunofluorescence assays**

From 2002 to 2010, samples provided for *A. cantonensis* serological testing were sent to the only laboratory performing neuroangiostroglyiasis infection diagnosis in France, including its overseas regions (Laboratory of the Centre Hospitalier de Gonesse, Gonesse, France). An indirect immunofluorescence (IIF) assay was used for the detection of antibodies against *A. cantonensis* antigens, as described in [18]. Due to logistical constraints and availability of certain reagents, patient serodiagnosis in this laboratory ceased in 2010 and no other laboratory then performed the test in France. Subsequent serological analyses were therefore performed in Thailand or Switzerland by western-blot.

**Angiostrongylus cantonensis serology by western-blot**

Western blot assays using antigens derived from *A. cantonensis* adult worms were performed to detect IgG against *A. cantonensis* in either the Department of Parasitology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand, or the Swiss Tropical and Public Health Institute, Basel, Switzerland. The detection of the 31-kDa band confirmed serum positivity as it shows high sensitivity and specificity (>99% for both) for the diagnosis of *A. cantonensis* infections [17].

**Results**

Descriptive results of the clinical presentations, including biological, imaging, and epidemiological features, are shown in Table 1 and statistically analyzed in Table 2. During the 16-year period of the study, four confirmed and four probable cases of neuroangiostroglyiasis were diagnosed in Martinique, among which three were children below 2 years of age, one was an 11-year-old boy, and four were adults aged from 37 to 64 years. The annual incidence rate was 0.14 cases/100,000 inhabitants/year (95% CI [0.04–0.23]) with six of the cases occurring during the rainy season from June to November. All patients were born and lived in Martinique and none reported recent travel. Contact with molluscs was reported in two cases. All five patients older than 2 years of age (Table 1) presented with pre-existing mental disorders (pica syndrome, bipolar disorder, intellectual disability, or autism), which may have promoted the accidental or even deliberate consumption of snails. All cases presented with acute neurological signs and/or symptoms requiring a lumbar puncture: dysfunction of the cranial nerves (highlighted by clinical neurological examination of the 12 pairs of cranial nerves), headaches, axial hypotonia, seizures, radiculargia, and neck stiffness. Clinical examination was difficult for one patient because of autism. During hospitalisation, five patients had fever and three had digestive symptoms (vomiting, abdominal pain, loss of appetite, and/or diarrhoea). Brain imaging was performed for all patients (CT scan or MRI); five presented abnormalities, with abnormal enlargement of the cerebral ventricles or cortical atrophy, and three were normal. Blood eosinophilia at admission was inconsistent, with a median of 1.72 G/L (13% of the WBC count in blood) and a range of 0.49–6.43 G/L (5–31%). Median eosinophilia in the CSF at first lumbar puncture was 74.5% (25% of the WBC count in CSF), with a range of 0–1550/mm³ (4–68%).
Table 1. Description of the probable cases (numbers 1–4) and confirmed cases (numbers 5–8) of *Angiostrongylus cantonensis* infection in Martinique, including clinical, biological, imaging, and epidemiological features.

| Case | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |
|------|---|---|---|---|---|---|---|---|
| **Demographic characteristics** | | | | | | | | |
| Year | 2002 | 2002 | 2006 | 2008 | 2013 | 2015 | 2015 | 2015 |
| Season | Dry | Rainy | Rainy | Rainy | Rainy | Dry | Rainy | Rainy |
| Age | 10.5 months | 11 months | 13 months | 37 years | 64 years | 61 years | 58 years | 11.5 years |
| Residential locality | Fort-de-France | Le Lamentin | Cap Ferré, Saint-Anne | Le Diamant | ND | Quartier Morne Etoile, le Lorrain | Quartier Petit Versailles, Saint-Anne | |
| Medical history | None | None | Substance addiction, bipolar Intellectual disability | Diogenes syndrome | Schizophrenia | Autism, stunted growth | | |
| Risky behaviour | Playing on soil | Accidental slug ingestion | Unknown | Undercooked snail consumption | Stays in forest several days | Unknown | Pica disorder | Pica disorder |
| **Clinical presentation** | | | | | | | | |
| Neurological signs and symptoms | Strabismus, cranial nerves VI palsy | Yes | Yes | No | Yes | No | No | Yes |
| Digestive signs and symptoms | Anorexia | None | None | Nausea, vomiting | None | Loss of appetite | None | Loss of appetite, constipation itching |
| Laboratory tests | | | | | | | | |
| CRP (mg/L) | <5 | <5 | <5 | 11.6 | 74 | <5 | <5 | <5 |
| Total WBC count (G/L) | 8.24 | 15.09 | 10.03 | 10.00 | 12.20 | 16.35 | 6.61 | 20.75 |
| Eosinophils in blood G/L (%) | 0.49 (5)/3.23 (26) | 2.23 (14)/3.66 (17) | 0.89 (10)/1.40 (11) | 4.29 (21)/2.76 (13) | 1.98 (36)/6.43 (31) | | | |
| WBC count in CSF 1st LP | 170 | 600 | 0 | 389 | 1040 | 410 | 2280 | 1080 |
| Eosinophils in CSF/mm3(%) | 59 (35)/90 (15) | 0 (0)/220 (38) | 59 (62)/600 (60) | 45 (18) | 1550 (68) | 691 (64) | | |
| Proteinorachia (g/L) | 1.25/0.33 | 1.17/1.10 | 1.71 | 1.71 | 3.70 | 3.4 | | |
| Glycorachia mmol/L | 0.1/1.0 | 2.3/4.3 | 1.0 | 0.9 | | | | |
| Intracranial Hypertension | ND | ND | No | Yes | 37 | No | Yes | ND |
| Angiostrongylus serodiagnosis | Positive (D13, D24, D49) | Negative (D13) | Negative (D38) | Negative (D19) | Positive (D24) | Positive (D24) | Positive (D19) | Positive (D19) |
| Cross-reactions (sera) | Cysticercosis (1/2048e) | None | None | Echinococcus | Toxocara | Toxocara, Filaria, Strongyloides | Toxocara, Strongyloides | Toxocara, Echinococcus, Strongyloides |
| Specific antibodies in CSF | Positive (D12) | Positive (D19, D24) | Positive (D19) | ND | ND | Positive (D19) | Positive (D19) |
| Parasitological examination of faeces | Negative | Negative | Negative | Negative | Negative | Negative | Negative | Negative |
| Brain CT-scan | Subnormal | None | None | Hydrocephalus, ventricular dilatation, myelitis | Normal | Normal | Normal | Normal |
| Brain MRI | Ventricular dilatation | Normal | Normal | | Normal | Ventricular dilatation | Normal | Abnormal (no precisions) |

(Continued on next page)
and the maximum values during hospitalisation were 373.5 (54.5%), with a range of 45–1550/μL (18–68%). Most patients were treated with albendazole [35] and/or corticosteroids [18]. Clinical outcomes ranged from rapid recovery without sequelae for two patients to neurological sequelae manifested as strabismus and intellectual disability for five patients. One case was fatal for a 58-year-old man. Diagnosis was made by anti-A. cantonensis antibody detection in sera for seven patients and confirmed positive in CSF for five of them. One patient only showed detectable anti-A. cantonensis antibodies in the CSF. Serological analysis was negative for two patients nine days after admission, but positive 19–38 days after admission.

Discussion

This study reports the first eight laboratory-confirmed cases of neuroangiostrongyliasis in Martinique, which occurred between 2002 and 2017, thus extending the range of the Caribbean islands with proven human cases of neuroangiostrongyliasis [12, 20, 44]. Given the potential lethality of neuroangiostrongyliasis, the medical community should therefore strongly consider the possibility of this infection in patients living in or returning from Martinique with eosinophilic meningitis.

In this study, neuroangiostrongyliasis cases occurred in two distinct epidemiological situations: three in infants less than 2 years old and five in patients over 11 years with mental disabilities. The mode of transmission in infants was linked to poor eating behaviour. In particular, pica syndrome may favour infection through the ingestion of gastropods usually not consumed as food in Martinique. No case was reported following consumption of raw paratenic hosts like shrimp, which is in contrast to the main source of infection in French Polynesia [35]. In our study, the diagnosis was initially unclear for all the patients and other kinds of helminthiases were initially suspected, as Martinique had never been reported as an endemic region for A. cantonensis. All but one of the patients were therefore treated with anti-helmintic drugs, although the efficacy and safety of albendazole or mebendazole for neuroangiostrongyliasis treatment remains controversial because of theoretical concerns that they may worsen the inflammatory response to dead and dying worms [5]. The four cases diagnosed after 2013 were also treated with corticosteroids, postulated to provide relief by reducing inflammation and thereby intracranial pressure and headache intensity [9, 43].

Comparison of the incidence of human neuroangiostrongyliasis in Martinique with neighbouring Caribbean Islands is straightforward. Indeed, cases were mainly reported in travellers returning from the Caribbean and it is likely that numerous autochthonous cases have not been reported in the scientific literature. Most Caribbean cases were reported in Cuba with several dozen cases since the 1980s [2, 36], mainly in the cities of Havana and Villa Clara [15, 16, 28, 37], and one case in a Swiss traveller returning from Cuba [7]. In Guadeloupe – another French West Indies island – four autochthonous cases were diagnosed (to our knowledge) between 1999 and 2017 in young children who may have been in contact with infected molluscs ([12] and unpublished data), corresponding to an annual incidence rate of 0.053 cases per inhabitant per year (95% CI [0.001–0.105]), close to that of Martinique. For the Dominican Republic, two suspected cases were reported in travellers returning to Europe [24, 41]. For Jamaica, twelve cases were diagnosed in adult travellers returning from Jamaica [38, 42], seven in autochthonous young children [19, 26] and one ocular case in a young woman [30]. No human cases have been reported in Grenada, the Bahamas, Haiti, and Puerto Rico, although A. cantonensis has been found in the environment on these islands [44]. It is noteworthy that the disease is also expanding in North and South America, in particular in the

## Table 1. (Continued)

| Management & outcome | Treatment | Hospitalization time (days) | Clinical outcome, sequelae | Observation time (days) |
|----------------------|-----------|-----------------------------|---------------------------|------------------------|
|                      | Thiabendazole, albendazole Subtractive LP Albendazole, prednisone Subtractive LP Albendazole, prednisone Subtractive LP Albendazole + MPS Albendazole + MPS Subtractive LP | 55 15 34 19 49 66 + 90 days of physiotherapy | 20 16 |

**Abbreviations:** CSF, cerebrospinal fluid; CT-scan, computerised tomography scan; CRP, C-reactive protein; Dx, day x after admission to hospital; LP, lumbar puncture; MPS, methylprednisolone; ND, not determined.

Normal values: CRP: <5 mg/L; protein level in CSF: 0.15–0.40 g/L; glucose level in CSF: 2.8–4.5 mmol/L; intracranial tension: <20.

a. Serology performed by indirect immunofluorescence in the Medical Center of Gonesse, France.
b. Serology performed by western-blot analysis in the Department of Parasitology, Faculty of Medicine Siriraj Hospital, Mahidol University Bangkok, Thailand.
c. Serology performed by western-blot analysis in the Swiss Tropical and Public Health Institute, Basel, Switzerland.
Table 2. Characteristics of the eight patients with eosinophilic meningitis caused by *Angiostrongylus cantonensis*.

| Characteristic                                      | Result                        |
|-----------------------------------------------------|-------------------------------|
| **Demographic characteristics**                    |                               |
| Age (years)                                         | 24.3 [0.87–63.6]              |
| Sex (male)                                          | 6 (75%)                       |
| Rainy season                                        | 6 (75%)                       |
| Exposure risk                                       |                               |
| Reported contact with snails                        | 2 (25%)                       |
| Previous mental disorders                           | 5 (63%)                       |
| **Clinical picture**                                |                               |
| Fever (>38 °C)                                      | 5 (63%)                       |
| Digestive signs and symptoms                        | 3 (38%)                       |
| Neurological signs and symptoms                     | 8 (100%)                      |
| Headaches                                           | 2 (25%)                       |
| Neck stiffness                                      | 1 (13%)                       |
| Dysfunction of cranial nerves                       | 3 (38%)                       |
| Seizure                                             | 2 (25%)                       |
| Axial hypotonia, hemiparesia                        | 2 (25%)                       |
| Radiculalgia                                        | 1 (13%)                       |
| Coma                                                | 2 (25%)                       |
| **Brain imaging**                                   |                               |
| Normal                                              | 3 (38%)                       |
| Enlargement of cerebral ventricles                  | 3 (38%)                       |
| Cortical atrophy                                    | 1 (13%)                       |
| **Laboratory results**                              |                               |
| In blood                                            |                               |
| C-reactive protein > 5 mg/L                         | 2 (25%)                       |
| Total WBC count (G/L)                               | 10.0 [6.61–20.75]             |
| Blood eosinophilia at admission (G/L)               | 1.72 [0.49–6.43]              |
| Blood eosinophilia at admission (% of WBC)          | 12.5 [5–31]                   |
| Max blood eosinophilia during hospitalisation (G/L) | 2.99 [0.89–6.43]              |
| Max blood eosinophilia during hospitalisation (% of WBC) | 23.5 [10–36]               |
| A. cantonensis positive serodiagnosis               | 7 (88%)                       |
| In CSF                                              |                               |
| Eosinophilia in CSF at first LP (/mm³)               | 74.5 [0–1550]                 |
| Eosinophilia in CSF at first LP (% of WBC)          | 25.0 [0–68]                   |
| CSF glucose at first LP (mmol/L)                    | 2.81 [0.1–4.3]                |
| Protein level in CSF at first LP (g/L)              | 1.14 [0.33–1.71]              |
| Protein level > 0.45 g/L at first LP                | 7 (88%)                       |
| Presence of antibodies in CSF (among those tested)  | 6 (100%)                      |
| **Management**                                      |                               |
| Length of hospital stay (days)                      | 27 [15–66]                    |
| Subtractive LP                                      | 5 (63%)                       |
| Corticosteroids                                     | 5 (63%)                       |
| Anthelmintic therapy                                | 7 (88%)                       |
| Outcome                                             |                               |
| One year recovery                                   | 2 (25%)                       |
| One year neurological sequelae                      | 5 (63%)                       |
| One year mortality                                  | 1 (13%)                       |

**Abbreviations:** CSF, cerebrospinal fluid; LP, lumbar puncture; WBC, white blood cell.

Descriptive results are presented as n (%) and as median (min–max).

United States [27], Brazil [32], and some other South American countries [13, 44]. In this study, most cases occurred during the rainy season, during which snails abound, particularly the giant African snail, *Lissachatina fulica*, which was introduced to Martinique in 1989 [31] and is known elsewhere to act as an intermediate host of *A. cantonensis*. In Guadeloupe, *A. cantonensis* infection in *A. fulica* was 32.4% in 2014 [12]. No doubt other snail and slug species could also act as hosts as there are close to 90 non-marine mollusc species in Martinique [14, 23]. Numerous rodents have also been reported as potential definitive hosts of *A. cantonensis* worldwide [49]. Two species of rats, *Rattus norvegicus* (brown rat) and *Rattus rattus* (black rat), have been present in the territory since the late 18th century and probably play the role of definitive host of *A. cantonensis* in Martinique as they are the only rodent species in Martinique other than the mouse *Mus musculus*. No study has evaluated infection of rats with *A. cantonensis* in Martinique. In neighbouring Grenada [8, 10], Puerto Rico [4], Dominican Republic [45], Haiti [40], Jamaica [46], and Cuba [2], the proportion of infected *Rattus* spp. varies from 23.4% to 60.0% [2, 8], while the parasite appears to be absent in rats in Barbados [25].

Neuroangiostrongyliasis cases in Martinique seem particularly severe relative to other case-series reported in China and South-East Asia, with a higher mortality and sequelae rate. However, given the low number of cases, this must be confirmed as the number of neuroangiostrongyliasis cases increases in Martinique.

All cases were diagnosed by anti-*A. cantonensis* immunoglobulin detection in serum and/or CSF. Diagnosis was not performed by PCR as it was not available in Martinique or metropolitan France at the time of initial diagnosis [33] and no remaining CSF samples were available in our biobanks. In fact, molecular detection of *A. cantonensis* in CSF was developed in the early 2010s [48] and was only recently validated for clinical use [39]. The recent availability of a specific *A. cantonensis* PCR test in the French departments of South America and the Caribbean should improve the diagnosis of this disease in this region and encourage local authorities to undertake epidemiological studies on the intermediate and paratenic hosts and reservoirs, which should broaden our understanding of disease transmission in Martinique.

**Acknowledgements.** We thank the physicians of the University Hospital of Martinique, including medical and clinical biologists, paediatricians, and neurologists for the initial diagnoses of neuroangiostrongyliasis. We thank the Direction de la Recherche Clinique et de l’Innovation (DRCI) of Martinique and the Parasitology-Mycology Laboratory of the University Hospital of Grenoble Alpes for their collaboration to the project “Angiostrongylus Research in French Antilles and Guiana”. We thank Dr. E. Vandemeulebroecke (Laboratory of Parasitology of the Hospital Centre of Gonesse, France) and Dr. Beatrice Nickel and Dr. Hanspeter Marti at the Swiss Tropical and Public Health Institute, Basel, Switzerland, for performing the serological analyses.

**Conflict of interest**

The authors declare that they have no conflict of interest.

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