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## Author manuscript

*Neurol Sci.* Author manuscript; available in PMC 2020 November 06.

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Published in final edited form as:

*Neurol Sci.* 2020 January ; 41(1): 239–241. doi:10.1007/s10072-019-04017-9.

## Lack of evidence for *Toxocara* infection in Italian myelitis patients

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### Abstract

Acute myelitis is a common neurological manifestation due to different causes, but in about 15–30% of cases its etiology remains unknown (idiopathic myelitis). Myelitis represents the most common manifestation of neurotoxocariasis, the infection of the human nervous system by larvae of the nematode *Toxocara* spp.; however, despite the high seroprevalence worldwide, its contribution to the burden of disease has not been assessed. We evaluated the presence of antibodies against *Toxocara* spp. in cerebrospinal fluid (CSF) from a sample of 28 patients with a diagnosis of idiopathic myelitis ( $N=20$ ) or encephalomyelitis ( $N=8$ ) who attended the Neurological Unit of the University Hospital of Catania, Sicily. Antibodies against *Toxocara* spp. were measured using a multiplex bead-based assay and *Toxocara* immunoblot using *Toxocara canis* excretory secretory antigens. All samples tested negative for the presence of anti-*T. canis* IgG antibodies. In this series, we found no evidence of a contribution of neurotoxocariasis to the burden of myelitis.

### Keywords

*Toxocara canis*; Neurotoxocariasis; Myelitis; Neglected tropical diseases

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**Ethical approval** The authors certify that they comply with the Principles of Ethical Publishing.

**Informed consent** Informed consent was obtained from all individual participants included in the study.

**Conflict of interest** The authors declare that they have no conflicts of interest.

## Introduction

Acute myelitis represent a large group of disorders characterized by spinal cord involvement due to different etiologies [1]. Among the infective causes, some parasites (*Taenia solium*, *Schistosoma* spp., *Gnathostoma* spp., *Angiostrongylus cantonensis*, *Toxocara* spp.) can also cause acute myelitis even if rarely reported [1].

Human toxocariasis is caused by the larval stages of *Toxocara canis*, humans become infected by ingesting *Toxocara* eggs by direct contact with dogs or by the ingestion of contaminated food or soil. Visceral larva migrans (VLM) and ocular larva migrans are the most common clinical manifestations [2]. However, *Toxocara* larvae can cross the blood-brain barrier leading to neurotoxocariasis (NT). The clinical presentation consists of a wide spectrum of neurological manifestations such as meningitis, encephalitis, myelitis, and cerebral vasculitis, but asymptomatic infection is common [3]. Myelitis represents the most common manifestation of NT, accounting for about 70% of all the cases reported in literature [3, 4]. Usually, NT is diagnosed on the basis of a high titer of anti-*Toxocara* antibodies in the cerebrospinal fluid (CSF) or in serum, neuroimages, eosinophilia in serum or CSF, and clinical and radiological improvement after anthelmintic therapy. A definitive diagnosis of NT is obtained by histological confirmation, which is seldom available; thus, diagnosis is often presumptive [3].

In order to evaluate the possible etiological role of *Toxocara* spp., we evaluated the presence of antibodies anti-*Toxocara* spp. in CSF in cases of idiopathic acute myelitis and encephalomyelitis.

## Materials and methods

We retrospectively identified patients who attended the neurology unit of AOU Policlinico-Vittorio Emanuele of the city of Catania, Sicily, who were discharged with a diagnosis of unspecified or idiopathic myelitis or encephalomyelitis from 2010 to 2018.

We included in the present study only patients with idiopathic myelitis or encephalomyelitis for whom a CSF sample was stored and available for the analysis. CSF samples, previously stored at  $-80^{\circ}\text{C}$ , were sent to the Centers of Disease Control and Prevention (CDC) in Atlanta, GA, where antibodies of *Toxocara* spp. were detected by using a multiplex bead-based assay and an immunoblot based on *Toxocara canis* excretory secretory antigens.

At the time of the admission, patients signed an informed consent allowing further use of the samples for diagnostic or research purposes. The study was approved by the Ethic committee of the AOU Policlinico-Vittorio Emanuele of Catania.

## Results

We identified 28 patients (18 men, 64.2%; mean age at onset of  $48.4 \pm 18.7$  years) discharged with a diagnosis of idiopathic myelitis or encephalomyelitis between 2010 and 2018 for whom a CSF sample was available for further analysis. Of these, 20 were classified as idiopathic myelitis and eight as encephalomyelitis.

Clinical characteristics are shown in Table 1. Sensory deficits were the most common manifestation occurring in 21 (75.0%) patients, followed by motor impairment recorded in 15 (53.6%) patients, and sphincter dysfunction in 14 (50.0%) patients. In contrast-enhanced MRI, the mean number of spinal metameres involved was  $2.4 \pm 2.4$  ranging from 1 to 10, even if the majority presented 1 to 3 metameres involved (15 patients, 53.5%). Cervical and dorsal regions represented the most common localization recorded in 17 and 14 patients, respectively. Contrast enhancement was found in 11 patients (45.8%). The majority of patients (19, 67.9%) were treated with high dosage of corticosteroids while five did not receive any treatment. Complete recovery was recorded in almost all patients (22, 78.6%). None of these patients presented IgG antibodies against *Toxocara* spp. in CSF multiplex bead-based assay or immunoblot.

## Discussion

We investigated the presence of antibodies against *Toxocara* spp. in patients with idiopathic myelitis and encephalomyelitis in an attempt to evaluate the possible role of NT. Toxocariasis is one of the most prevalent helminthiases worldwide, especially in settings where human-soil-dog contact is particularly common [5]. Despite the high *Toxocara* seroprevalence, NT is rarely taken into account in clinical settings and it is rarely diagnosed. As a matter of fact, diagnosis of NT is a challenge because there is no distinct clinical syndrome, imaging studies are not specific, and serology has low specificity and sensitivity. The standard serological test is an ELISA based on secretory-excretory antigens (TES) from *T. canis* larvae of the second stage [6]. This assay has a sensitivity of 78% and a specificity of 92%, but cross-reactions with other nematode infections reduce its specificity, particularly in tropical areas [6]. The use of fractionated native TES in the western blot (WB) assay overcomes the issues with cross-reactions, but WB is rarely available [7]. Since the presence of serum antibodies does not necessarily imply CNS involvement, CSF analysis is an essential requirement to support the diagnosis of NT. MRI of spinal toxocariasis is characterized by hyperintensity on T2 and FLAIR sequences with focal nodular enhancement after gadolinium injection, findings similar to those reported in other inflammatory conditions [3]. Histological confirmation has only been reported in a few cases so the diagnosis of NT is usually only presumptive [3].

Since 1956 to date, approximately 100 cases of NT have been described [3, 4] and isolated myelitis represents the most common presentation, occurring in 70 cases. Nonetheless, the majority of *Toxocara* myelites (about 80%) were reported in three different case series [8–10], and overall, about 60% of the published cases were diagnosed in Korea and Japan, while only a few in western countries (four from Europe, one from the USA, and one from Canada) [3]. Actually out of these 70 cases of myelitis, the diagnosis has been confirmed by biopsy just in one patient, while for 31 patients (44.3%), the diagnosis was based only on ELISA seropositivity (confirmed by WB only in 9 patients); thus, it was only presumptive [3].

As reported, exposure to *T. canis* is also common in western countries [2], but the exact prevalence of CNS involvement in toxocariasis is still unknown and information on the impact of NT is lacking. Even if the large majority of myelites and encephalomyelites

encountered in clinical practice usually have a post-infectious or post-vaccination etiology [11], regardless of our negative result, we cannot exclude, in agreement with literature data [3], that also *T. canis* may have a role. Finally, our series was collated in a referral center and as such they may not be representative of all patients with myelitis. However, the lack of seropositive cases in this small series suggests that myelitis due to *Toxocara* is not a frequent condition in Catania province.

## Funding information

This research was funded by the Department of Medical and Surgical Sciences and Advanced Technologies “G.F. Ingrassia,” University of Catania, Italy (Piano Triennale di Sviluppo delle Attività di Ricerca Scientifica del Dipartimento 2016-18).

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**Table 1**

Demographic and clinical characteristics

<b>Idiopathic myelitis and encephalomyelitis (N = 28)</b>	
Sex (M)	18 (64.3)
Age at onset (mean $\pm$ SD)	48.4 $\pm$ 18.7
Spinal metameres (mean $\pm$ SD)	2.4 $\pm$ 2.4
Cervical lesions (%)	17 (60.1)
Thoracic lesions (%)	14 (50.0)
Cognitive symptoms (%)	4 (14.3)
Motor impairment (%)	15 (53.6)
Sensory deficit (%)	21 (75.0)
Sphincter dysfunction (%)	14 (50.0)
Blood eosinophilia (%)	2(7.1)
Pleocytosis (%)	7 (25.0)