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Commentary OMICS International

Neurotoxocariais: A Rare or Neglected Disease?

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Commentary

Human toxocariasis is due to the larval stages of the *Ascarids Toxocara canis* (*T. canis*) and probably *Toxocara catis*, common roundworm of dogs and cats respectively. Among the helminthiasis, toxocariasis is one of the most prevalent worldwide, especially in settings where man-soil-dog relationship is particularly close. Even if it tends to be more prevalent in tropical settings, seroprevalence in western countries ranges from 2.4% to 31.0% [1,2].

Humans are infected by the ingestion of embryonated eggs present in contaminated soil or food. When ingested, embryonated eggs, develop into juvenile larvae that crossing the small intestine migrate to any organ through the circulatory system determining a multisystem inflammatory tissue reactions (Figure 1). Visceral larva migrains (VLM) and ocular larva migrans (OLM) are the most common clinical manifestation, even if asymptomatic infection is common [2]. *T. canis* larvae can cross the blood brain barrier invading the central nervous system (CNS) and leading to the cerebral toxocariasis or neurotoxocariasis. Autopsy studies of isolated cases, in fact, have revealed *T. canis* larvae in leptomeninges, gray and white matter of cerebrum, cerebellum, thalamus and spinal cord [3-8]. To date CNS infection in humans is thought to be rare, even if in animal models larvae often migrate to the brain. Neurotoxocariasis can give different neurological disorders such as meningitis, encephalitis, cerebral vasculitis, seizures, headache, but asymptomatic infection are probably common [2]. Neurotoxocariasis is not a frequent diagnosis and it is probably underdiagnosed due to the nonspecific nature of its symptoms (seizures, headache) as well as to the lack of confirmatory diagnostic exams. Diagnosis of neurotoxocariasis, in fact, is based on the detection of high serum and CSF titers of *T. canis* antibodies and neuroimaging. The clinical and radiological improvement, as well as the normalization of the CSF parameters during antihelminthic therapy, supports the diagnosis. Peripheral and CFS eosinophilia can be also present. However diagnostic criteria are not available and the definitive diagnosis can be reached only by histological examination of infected tissue [2]. Enzyme-linked immunosorbent assay (ELISA) with TES-Ag from second stage *T. canis* larvae [9], is the most common serological assay, that however can give antigenic cross reactivity with different nematode infections [10]. Conversely the use of TES-western blot overcomes the possible cross-reaction [11], but is more expensive and rarely available. Concerning the neuroimaging (CT scan and MRI), neurotoxocariasis is mainly characterized by a granulomatous process leading to reversible white matter lesions and single ring-enhancing ("cerebral granuloma") or multiple ring-enhancing lesions as demonstrated in biopsy-confirmed cases reported in literature [12,13]. However, ring-enhancing lesions are one of the most commonly encountered abnormalities that can be caused by a variety of infectious disease, neoplastic, inflammatory, or vascular diseases [14]. In particular, single enhancing lesions (SEL) represent a common diagnostic dilemma in tropical countries where they are generally due to infectious diseases such as neurocysticercosis (NCC) and tuberculosis. In particular, in *T. solium* endemic areas the evidence of SEL at neuroimaging is quite common and, according to the widely accepted diagnostic criteria [15], cerebral granuloma disappearing after albendazole or praziquantel treatment is considered one of a major criterion for the diagnosis of NCC. It should be noted that when a single cysticercus granuloma is present, negative serology is frequent due to a lower sensitivity of the enzyme-linked immunoelectrotransfer blot, considered the gold standard among the serological assays. However, according literature evidences, a SEL disappearing after albendazole treatment [12,13] can be also due to *T. canis*, thus in this scenario a diagnosis of neurotoxocariasis cannot be entirely ruled out. Regarding the treatment of neurotoxocariasis mebendazole, thiabendazole, albendazole, or diethyl carbamazine have been used with different results, even if is there is a lack of well-controlled studies [16].

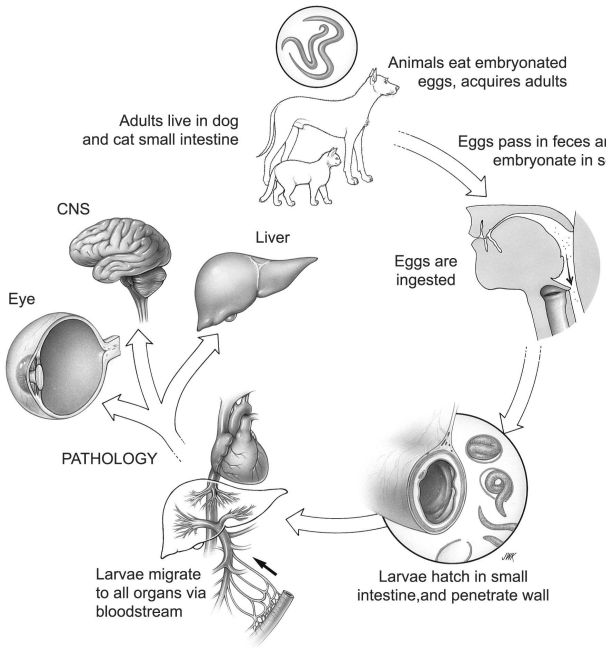

Figure 1: Life cycle of *T. canis* and *T. cati*.

Another unsolved issue is the meaning of the association between toxocara seropositivity and epilepsy consistently reported in literature. Early observations have highlighted a high titers of *T. canis* antibodies among epileptic subjects [17,18]. After these reports, several case-control studies have been carried out in different geographic areas,

often supporting this possible positive association between epilepsy and *T. canis* seropositivity [19-32]. This association was also confirmed by a recent meta-analysis including seven cases-control studies, suggesting a possible increased risk of developing epilepsy among people exposed to *T. canis* infection [32]. Even if seizures have been related to the presence of single or multiple toxocara lesions found in cases described in literature, the epileptogenesis of helminth infections is largely unknown [33-35]. Helminths, in fact, can cause seizures by producing focal lesions, but an antibody-mediated epilpetogenesis cannot be ruled out. As well known, helminths determine a conspicuous immune activation including the production of autoantibodies that, if directed against neuronal antigens, may cause epilepsy [33] From this point of view toxocariasis could also increases the risk of developing epilepsy due to masked mechanisms, despite the absence of detectable focal cerebral granuloma [2].

As matter of the fact, despite toxocariais is considered the most frequent helminthic infection worldwide, neurotoxocariais is largely unknown and diagnosis is rarely sought leading to a possible underestimation of its real burden.

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