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REVIEW

NEUROTOXOCARIASIS: A LITTLE-KNOWN MANIFESTATION OF A NEGLECTED ZOONOSIS

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ABSTRACT

This review covers general aspects of the occurrence of toxocariasis as a parasitic zoonosis, focusing on neurotoxocariasis, a form of human infection that is still poorly understood and under-studied. The main aspects of manifestations resulting from the involvement of the central nervous system (CNS) in experimental animals and humans are discussed, emphasizing the difficulties in establishing a precise laboratory diagnosis of this infection and the existing therapeutic challenges.

KEY WORDS: Neurological infection; neurotoxocarosis; *Toxocara canis*; *Toxocara cati*.

INTRODUCTION

Helminths of the genus *Toxocara* are nematodes of the Ascaridae family. There are 27 known species in the genus *Toxocara*, three of which have zoonotic potential: *Toxocara canis*, *T. cati*, and *T. pteropodis*, whose usual hosts are dogs, cats and bats, respectively, harboring adult worms in their intestines. However, numerous vertebrate species can act as paratenic hosts (primates, rodents, pigs, birds), in which third-stage larvae of the helminth survive for long periods, migrating or encysted in tissues (Strube et al., 2013; Ziegler & Macpherson, 2019). Holland & Hamilton (2013) noted that little is known about the importance of wild animals as paratenic hosts of *Toxocara* spp., with few reports of their occurrence in natural conditions (Dubinský et al., 1995). Nevertheless, many species of rodents, rabbits and other mammals, birds, and even earthworms have been identified as potential paratenic hosts. Humans, when infected by *Toxocara*, also act as paratenic hosts.

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Human infections by *Toxocara* spp. larvae are mostly asymptomatic. It occurs through ingesting embryonated eggs (with L3 larvae), and larvae encysted in the muscles or viscera of paratenic hosts when consumed raw or undercooked (Ma et al., 2017). When present, clinical manifestations can result in visceral, ocular, neurological, and "covert" forms (Lee et al., 2010; Ma et al., 2017; Nicoletti, 2013; Rostami et al., 2019). The severity of the disease depends on the parasitic load, the duration of the larval tissue migration process, the age, immune response, and genetic characteristics of the affected patient (Holland & Hamilton, 2013; Moreira et al., 2014).

Toxocariasis is considered the most common parasitic infection in humans in the USA, especially among the poorer segments of the population (Hotez & Wilkins, 2009). It is also highly prevalent in developing countries, although its importance is underestimated (Holland & Hamilton, 2013; Chen et al., 2018). Recently, toxocariasis has become a focus of international attention, being included among the five most neglected parasitic infections (Cantey et al., 2021). Seroepidemiological surveys conducted in Brazil involving various population segments revealed anti-*Toxocara* antibody prevalence rates ranging from 4.2% to 65%, with many regions showing rates above 20% (Fialho et al., 2020). The accelerating growth in the human population worldwide, particularly in Brazil, alongside the number of dogs and cats kept as pets, favors the increase in the occurrence of toxocariasis in urban areas (Rostami et al., 2019).

This paper will focus on the involvement of the CNS by *Toxocara* larvae, a situation more frequent in adults and less so in children (Deshayes et al., 2016), albeit the occurrence in the latter has been related to circumstances affecting cognitive development (Hotez, 2014).

Toxocara *Larvae in the Central Nervous System*

Toxocara larvae were first reported in the CNS of humans in 1951 by Beautyman & Woolf, who described the presence of ascarid larvae in the thalamus of a child who had died of poliomyelitis. Years later, Beaver (1956) introduced the visceral larva migrans syndrome concept by describing the clinical presentation of children with pulmonary and hepatic alterations, accompanied by other systemic manifestations, but without signs or symptoms of CNS invasion. Liver biopsies in these cases revealed the presence of *Toxocara* larvae.

Experimental studies using mice and rats as models showed a higher larval recovery in the CNS in infections by *T. canis* compared to *T. cati* (Lescano et al., 2013; Janecek et al., 2014; Santos et al., 2015), with *T. cati* larvae showing a preference for muscles, cerebellum, and eyes (Strube et al., 2013; Janecek et al., 2014; Santos et al., 2015). Conversely, experimental

infections in mice demonstrated more significant behavioral changes when caused by *T. canis* larvae than *T. cati* larvae (Janecek et al., 2017).

Animal models for neurotoxocariasis revealed destructive effects of the parasite on brain tissues, with stimulation of biomarkers associated with acute brain injuries. The developed immune response stimulates the production and release of pro-inflammatory cytokines and chemokines that contribute to CNS dysfunction and facilitate the parasite's survival in the host organism (Waindok & Strube, 2019). The evidence of an association between neurotoxocariasis and CNS degeneration was observed by Chou et al. (2017), with amyloid substance accumulation in the hippocampus of mice with cerebral parasitism by *T. canis* larvae.

In *Rattus norvegicus* experimentally infected with 500 *T. canis* eggs, Lescano et al. (2004) found larvae in the brain from the fifth day post-infection, with the highest larval count present between the 15th and 60th days. A similar distribution was observed by Llanes et al. (2019), although the recovery of larvae in the brain was lower in this experiment. In the case of BALB/c mice infection, Kim et al. (2024) noted the presence of *T. canis* larvae in the brain from the first week post-infection, with no significant variation in the number of larvae until the fifth week, when the experiment was concluded. Interestingly, Kolbeková et al. (2011), studying the distribution of *T. canis* larvae in BALB/c mice after reinfection, observed that larvae are found earlier in the CNS than in primary infection. Experimental studies in other paratenic hosts also found varying quantities of *T. canis* larvae in the brain (Taira et al., 2003; Sasmal et al., 2008).

When Santos et al. (2009) conducted experimental infections in *R. norvegicus* with *T. cati* eggs, they obtained different results, with few larvae reaching brain tissues. The same pattern of *T. canis* and *T. cati* larval distribution was found in a new experiment conducted by the same group, confirming the predominance of *T. canis* larvae in cerebral parasitism (Lescano et al., 2013). Conversely, Janecek et al. (2014) showed that *T. cati* larvae clearly prefer migrating to the cerebellum. Another noteworthy aspect is the ocular parasitism in experimental infections by *T. cati*, especially when gerbils are used as a model (Strube et al., 2013).

Several authors have experimentally studied the occurrence of behavioral changes in rodents infected by *Toxocara* spp. as a result of CNS involvement. Memory deficits and exploratory behavior changes were observed, as well as behavioral alterations that could facilitate the predation of infected rodents, increasing the likelihood of *T. canis* transmission to its usual hosts (Cox & Holland, 2001; Chieffi et al., 2009, 2010; Janecek et al., 2017). Janecek et al. (2017) report more intense behavioral changes in mice experimentally infected with *T. canis* compared to those infected with *T. cati*. There are indications that genetic and immune response influences cerebral

infection due to differences observed in inbred and outbred mice (Cox & Holland, 2001).

Paradoxically, it was observed that *R. norvegicus* experimentally co-infected with *T. canis* and *Toxoplasma gondii* exhibited behavior similar to the non-infected control group, while animals infected with only one of the species showed significant behavioral changes (Queiroz et al., 2013; Corrêa et al., 2014). In other experimental models, modulation of the response in rodents co-infected with *T. gondii* and other parasites was also observed (Kloetzel et al., 1977; Dubey, 1982).

Neurotoxocariasis in Humans

Although the parasitism of the brain and other nervous structures by *Toxocara* spp. larvae are common in experimental animals, CNS lesions in humans are rare and poorly understood (Deshayes et al., 2016; Meliou et al., 2020). Compiling the existing literature, Fan et al. (2015) found 86 cases of neurotoxocariasis: 24 (28%) with brain lesions and 62 (72%) with spinal cord involvement. However, since 1966 there have been reports linking the occurrence of seizures and the presence of positive serological reactions for anti-*Toxocara* antibodies in humans (Woodruff et al., 1966; Arpino et al., 1990; Kamuyu et al., 2014), and there are references to the association between epilepsy and toxocariasis (Quattrocchi et al., 2012; Luna et al., 2018), as well as associations with psychiatric conditions such as schizophrenia, cognitive deficits, and other psychological alterations. However, it is not possible to categorically affirm a cause-and-effect relationship between these alterations and *Toxocara* infection (Marmor et al., 1987; Fortenberry et al., 1991; Nelson et al., 1996; Richartz & Buchkremer, 2002; Jarosz et al., 2010; Mostafa El-Sayed & Ismail, 2012; Quattrocchi et al., 2012; Walsh & Haseeb, 2012; Khademvatan et al., 2014; Erickson et al., 2015; Fan et al., 2015; Rostami et al., 2019). Recently, in Iran (Sahebi et al., 2024), a case-control study found no statistically significant association between schizophrenia and *Toxocara* infection.

Clinical Presentation and Diagnosis of Neurotoxocariasis

The clinical presentation can be oligosymptomatic or even asymptomatic, and often, the clinical signs go unnoticed (Fan et al., 2015). When symptomatic, neurotoxocariasis can manifest as meningitis, encephalitis, myelitis, vasculitis, optic neuritis, and sometimes behavioral changes (Vidal et al., 2003; Bachli et al., 2004; Moreira-Silva et al., 2004; Eberhardt et al., 2005; Ural et al., 2016; Abir et al., 2017; Sánchez et al., 2018; Meliou et al., 2020). Myelitis, as an isolated sign, is a frequent manifestation of CNS toxocariasis (Fukae et al., 2012; Waindok and Strube, 2019; Axelerad et al., 2021).

Most cases of neurotoxocariasis affecting the brain or spinal cord are caused by *T. canis*; in the case of *T. cati* infection, the parasite is more frequently located in the cerebellum (Cardillo et al., 2009; Janecek et al., 2014). Despite the small number of described cases of neurotoxocariasis, there is currently an increase in reports and interest in its occurrence due to the improvement of diagnostic techniques (Costa Barra et al., 1996; Magnaval et al., 1997; Vidal et al., 2003; Moreira-Silva et al., 2004; Kazek et al., 2006; Kinčeková et al., 2008; Scheid et al., 2008; Salvador et al., 2010; Fukae et al., 2012; Ural et al., 2016; Abir et al., 2017; Sánchez et al., 2018; Raissi et al., 2021).

The diagnosis of human infection by *Toxocara* spp. is based on a series of circumstances that must be considered collectively: clinical and epidemiological suspicion, laboratory data including serological and imaging tests, elevated levels of eosinophilia and IgE (Auer & Walochnik, 2020). The detection of IgG subclasses can be useful for the diagnosis of toxocariasis: IgG_2 has high sensitivity but lower specificity; IgG_4, in turn, has higher specificity and is useful for monitoring larval viability before and after treatment (Fillaux & Magnaval, 2013). Organ biopsy with the finding of the larva would be a definitive test, especially if immunohistochemical techniques are used to accurately identify parasitic antigens (De Brito et al., 1994). However, it is an invasive examination that depends on specialized collection and is rarely used.

In the case of neurotoxocariasis, in addition to the search for anti-*Toxocara* antibodies and the presence of blood and cerebrospinal fluid eosinophilia, clinical and radiological improvement after anti-helminthic treatment is important (Finsterer & Auer, 2007; Deshayes et al., 2016; Nicoletti, 2020). The presence of eosinophils in blood or cerebrospinal fluid and elevated IgE levels, while important indicators of CNS infection by *Toxocara* larvae, cannot be considered decisive factors, as they are not always observed (Sánchez et al., 2018). It is possible to visualize CNS lesions caused by *Toxocara* larvae using contrast-enhanced tomography; however, the best imaging technique for diagnosis and post-treatment evaluation is magnetic resonance imaging (Ruttinger & Hadidi, 1991).

Several drugs have been tested for the treatment of toxocariasis; however, none have yet been found to guarantee a complete cure for the infection, both in experimental models and when used in the treatment of humans (Othman, 2012). Benzimidazole anti-helminthics have shown potential in reducing parasitic load and symptoms in experimental models and clinical case treatment but did not result in a complete parasitological cure (Abo-Shehada & Herbert, 1984; Carrillo & Barriga, 1987; Bardon et al., 1995; Lescano et al., 2005).

Other drugs tested, such as ivermectin and nitazoxanide, did not show better results (Vieira et al., 1993; Lescano et al., 2015). The regimen represented by the administration of albendazole (400mg/twice a day/ 5 days) has been recommended for the treatment of toxocariasis (Hotez & Wilkins,

2009); on the other hand, Magnaval et al. (2022) recommend maintaining the administration of albendazole for 14 days. For neurotoxocariasis, Eberhardt et al. (2005) also recommend the use of albendazole due to its low toxicity and good penetration into the nervous tissue, accompanied by the administration of corticosteroids to reduce the inflammatory process resulting from larval degeneration, as well as possible hypersensitivity reactions (Goffette et al., 2000).

Toxocariasis is a parasitic zoonosis with a cosmopolitan distribution, especially in tropical and subtropical regions and low socioeconomic populations, mainly affecting children (Walsh & Haseeb, 2014). Although three species of the genus *Toxocara* (*T. canis*, *T. cati*, and *T. pteropodis*) exhibit zoonotic behavior, only *T. canis* and *T. cati* are significant as agents of infections in humans (Ziegler & Macpherson, 2019).

Despite its high frequency of occurrence, toxocariasis is considered a neglected zoonosis due to difficulties in establishing a precise laboratory diagnosis and the lack of awareness among primary healthcare physicians (Parise et al., 2014).

Neurotoxocariasis, the most neglected form of human involvement, deserves greater attention due to its potential to cause morbidity in humans, its association with behavioral changes in experimental animals and humans, and the possibility, not yet proven, of being related to neurodegenerative processes.

CONFLICTS OF INTEREST

The authors declare that there are no conflicts of interest to disclose

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