

Toxocariasis: A Neglected Parasitic Disease with Public Health Importance

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Editorial

Toxocariasis together with Chagas disease, neurocysticercosis, toxoplasmosis and trichomoniasis are considered as the five most important neglected parasitic diseases [1]. Toxocariasis is a helminthic zoonosis mostly caused by two species of the ascarid nematodes *Toxocara canis* and to a lesser extent *T. cati* [2-4]. However, *Toxocaris leonina* belonging to the family Ascarididae can produce mixed infections with both *Toxocara* species in dogs and cats [4]. In addition, it is able to infect humans; therefore it has zoonotic and public health importance [4,5]. *Toxocaris leonina* has been regarded as a causative agent of visceral larval migrans in human beings [5]. *Toxocara canis* and *T. cati* are common roundworms of the small intestine of canids and felids, respectively [4,6]. Toxocariasis carries a major health risk particularly in developing countries [7]. Human toxocariasis tends to be more prevalent in tropical and subtropical countries and rural populations than in temperate, urban and industrialized ones [4,7,8]. In tropical and subtropical regions, the humid climate provides surviving of parasite eggs in soil and this limits the control, preventive and eradication programs [4]. Despite the poor hygiene and inappropriate anthelmintic treatments in dogs in rural settings, environmental contamination with *Toxocara* eggs is common in outdoor parks of urban and suburban settings [4,8,9]. Human beings as paratenic hosts become infected by ingestion of embryonated eggs in soil, from contaminated vegetables and fruits or consuming raw or undercooked meat and viscera of infected paratenic hosts including chicken, calves and lambs [7,10-12].

The causative agents are transmitted among canids and felids via a wide variety of routes including vertical, trans-placental (in dogs), trans-mammary and horizontal transmission [4]. Horizontal transmission occurs through ingestion of the embryonated eggs present in environment or ingestion of larvae in infected organs of paratenic hosts [4,10]. Distribution of toxocariasis is worldwide and is more prevalent in children [13,14]. Having a dog or cat as companion animal at home and close and frequent contact with such animals can predispose particularly children up to the age of 12 years to the ingestion of *Toxocara* eggs [8,13,15]. Poor hygiene, poverty and lack of education can exacerbate the exposure to *Toxocara* spp. [9]. Although toxocariasis has no racial predilection, males are usually more affected than females [16,17].

Visceral and ocular involvement of the disease are called visceral larva migrans (VLM) or visceral toxocariasis and ocular larva migrans (OLM) or ocular toxocariasis, respectively [1,3,18]. Neural larva migrans (NLM) or neurological toxocariasis (NT) and convert or common toxocariasis (CT) are two less severe syndromes predominantly in adults and children, respectively [3,4,8]. The disease may vary from asymptomatic infection to severe lesions in different organs [1,4,8,13]. The symptoms and their severity depends on many factors such as the tissue invaded, number of migrating larvae, sites of

larval migration, and age and immune status of the host [3,8]. In VLM that is mainly diagnosed in young children of less than 8 years of age, the clinical symptoms are usually associated to hepatic and pulmonary migration of the larvae [3,4,10]. Fever, abdominal pain, loss of appetite, vomiting, diarrhea, necrosis of the liver, hepatomegaly with splenomegaly or hepatosplenomegaly, coughing, wheezing, bronchospasm and asthma as well as pneumonia or bronchitis are symptoms related to patients with VLM [4,10]. Moreover, hypergammaglobinemia of immunoglobulin IgG, IgM and IgE have been described in serological tests [10]. Similar to VLM, OLM mostly occurs in children [4]. In OLM, involvement is restricted to eyes and the optic nerves and the clinical symptoms are presented as unilateral impairment accompanying by strabismus [1,8,19]. Such clinical manifestations are initiated by an immune response to the larval migration into the eyes [3,4].

The larvae are surrounded firstly by an eosinophilic abscess and eventually a granulomatous reaction [4,19]. Major consequences of OLM may firstly be blindness and secondary glaucoma [3,4]. Convert toxocariasis in children is characterized by fever, headache, anorexia, behavioral and sleep disturbances, cough, abdominal pain, hepatomegaly, nausea and vomiting [9]. Common toxocariasis in adults is associated with weakness, pruritus, rash, abdominal pain and pulmonary symptoms [4]. In cases of VLM, the larvae may disseminate via the bloodstream to anywhere in the host body such as the central nervous system (CNS) and occasionally peripheral nervous system and localize there; therefore causing neurological lesions and dysfunctions [16,20]. Involvement of the CNS leading to neurotoxocariasis is uncommon with few cases reported in the literature [3,21]. Migration of larvae of *Toxocara* spp. to the CNS in most instances is not associated with clinical central nervous signs. However, rarely it may result in a variety of neurological disorders including meningo-encephalitis, myelitis, cerebral vasculitis, seizure and optic neuritis or combined presentations [3,9,19,22]. Pathological disorders such as demyelination, focal malacia and inflammatory cells infiltration especially eosinophils, lymphocytes, plasma cells and macrophages has also been described [23]. The cerebral lesions are mostly located in the white matter [3]. Following these manifestations, the patients complain about headache, weakness, confusion, epileptic seizure, neuropsychological disturbances, depression, sensory disturbances, reduced long and short term memory and probably cognitive and behavioral disorders [3,17,23]. Moreover, ataxia, dullness, rigor, tremor, paralysis, para-paresis, tetra-paresis, as well as urinary retention have been reported [3,23]. Toxocariasis has been suggested as an important risk factor for epilepsy, a chronic neurological disorder and therefore considerable attention has been directed toward the probable role of *T. canis* infection in epilepsy [9,21].

It seems the damages to the affected organs and CNS is due to the inflammatory reactions induced by the larvae [16,24]. The larvae produce glycosylated proteins inducing production of IL-5 and CD4- $\text{Th}2$ response which eventually promote vascular adhesion and eosinophilic infiltration [16,25]. Eosinophilia is a common finding in blood and/or the cerebrospinal fluid (CSF) of toxocariasis cases [16,22,26]. It has been shown that in cerebral *T. canis* infections, the release of cytokines such as interleukin (IL) 5 and interferon γ (IFN- γ) and inducible nitric oxide synthase (iNOS) is induced [22,24,26]. Various cells in the CNS including neurons, astrocytes, oligodendrocytes and microglia possess receptors of these cytokine [24,26]. The presence of IL-5 in the CNS can lead to the infiltration of eosinophils and subsequent degranulation of these cells results in the release of toxic mediators causing destruction of surrounding cells [22,26]. Intense release of cationic proteins from the eosinophil granules that are toxic to endothelial cells has been reported as a possible cause of these lesions [25]. It has been demonstrated that iNOS exerts deleterious effects on the murine brain during infection with *T. canis* [24,26]. On the other hand, the up-regulation of IFN- γ in the CNS can result in activation of macrophages and microglia increasing nitric oxide production and subsequent tissue damage [23,26].

However, *T. canis* in most instances is regarded as the main cause of human toxocariasis [3,8], nonetheless, the risk of the disease caused by *T. cati* should not be underestimated or ignored. Therefore, the infection risk for humans with *T. cati* should be considered at least as high as that with *T. canis* so that cats are more likely to contaminate places like gardens due to their defecation habits [23].

Because the clinical signs and symptoms of toxocariasis are non-specific, definitive diagnosis of the disease is a challenge. On the other hand, since poly-parasitism is common in tropical countries, diagnosis of VLM and CT cases is difficult. Generally, diagnosis of toxocariasis cases is based on history, clinical signs, various imaging techniques such as ultrasound, computed tomography (CT) and magnetic resonance imaging (MRI), biopsy and subsequent histopathological examination [8,18]. Beside serological techniques such as the indirect enzyme-linked immunosorbent assay (ELISA) on the basis of the excretory-secretory antigens of the third-stage larvae (L3) of *T. canis*, immunohistochemistry and molecular-based methods such as PCR can be helpful [8,13,18]. Although the diagnostic tests for VLM are immunological, they may not be reliable for OLM [10]. In OLM cases, ophthalmologic examination should be noted [4,10]. In the VLM cases, multiple oval hypoechoic lesions in the liver in sonographic examination and multifocal hepatic lesions present in the images from CT or MRI can be helpful in diagnosis [4]. Detection of the anti-*T. canis* antibodies in vitreous or aqueous humor is helpful in confirming early diagnosis of the OLM patients [4,10]. In addition, ocular ultrasound, fluorescein angiography, CT and optical coherence tomography can be useful [4]. Diagnosis of NT patients is usually based on high serum titers of *Toxocara* spp. antibodies, anti-*T. canis* antibodies in the CSF and eosinophilia in the CSF and/or blood, and close contact with dogs and cats [4,22]. In addition, the clinical and CT or MR imaging findings as well as the normalization of the CSF parameters during treatment can support and confirm the early diagnosis [16,22]. Multifocal, circumscribed granulomatous lesions in CNS with strong contrast enhancement or a combination of circumscribed and diffuse changes in chronic cases may be non-specific MR imaging findings [4,22]. Angiography may confirm cerebral vasculitis in the NT cases [22]. In the NT cases, a list of

diseases that can infect the CNS should be provided to make a differential diagnosis [4].

Severity and location of the lesions are important factors in selecting a suitable drug in toxocariasis treatment [1,3,4]. Albendazole is the choice for the treatment of toxocariasis in patients affected with VLM, CT or NT, and potent larvicides such as thiabendazole and diethylcarbamazine can also be effective in inhibiting larval migration [3,4,8]. Mebendazole is the second-line treatment for toxocariasis, whereas its gastrointestinal absorption is poor [10]. In addition, because the chronic inflammatory reactions by infiltration of eosinophils, lymphocytes, plasma cells and macrophages are more common than abscess formation in the CNS, corticosteroids are thought to be efficient as symptomatic treatment [19]. Treatment of the OLM cases is based on delicate ophthalmic procedures or even vitrectomy, anthelmintic chemotherapy and corticosteroids [4,10].

Wide ranges of the definitive and paratenic hosts and multiplicity of the transmission routes of *Toxocara* species complicate the control, prevention and eradication of the parasite [4]. The high prevalence of the causative parasite in dogs and cats and also difficulties in preventing environmental contamination and human infection highlight its great importance as a zoonosis. Considering the high prevalence of toxocariasis in children, it is necessary to pay attention to the education of children and also the public. Proper cooking of foods can prevent the accidental ingestion of eggs. It should be noted that viable larvae of *T. canis* as well as *T. cati* have been found in meat even after prolonged periods of freezing [7,23]. Good hygiene practices should be encouraged and proper strategies should be designed and applied to prevent transmission of *Toxocara* spp.. Furthermore, probable relationship between toxocariasis and the global burden of epilepsy should be noted in establishing preventive measures. The importance of toxocariasis and persistent of the infective *Toxocara* larvae in meat should not be considered as neglected as previously thought. It should be added that veterinarians play an important role in combating the spread of *Toxocara* infection in places where a large number of dogs and cats are accompanied with pet owners. Regular stool examination and frequent chemotherapy of pets with albendazole or mebendazole can be effective in reducing the eggs number deposited in soil, therefore controlling the disease. In addition, control programs such as reducing the number of pet animals or limiting contacts of small children with them appear to be helpful. Control of the spread of feces of dogs and cats can help in controlling toxocariasis infection. Unfortunately, there is no vaccine available and an appropriate specific control program and development of proper vaccines against this zoonotic disease remain a challenge. Rapid identification and diagnosis of the larvae in paratenic hosts such as humans and development of an effective vaccine are essentials and basic requirement in designing any control program.

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