Toxocariasis: Clinical Aspects, Epidemiology, Medical Ecology, and Molecular Aspects

Dickson Despommier*

Department of Environmental Health Sciences and Department of Microbiology, Mailman School of Public Health, Columbia University, New York, New York 10032

INTRODUCTION

Toxocariasis is the clinical term applied to infection in the human host with either *Toxocara canis* or *Toxocara cati*. Both of these are ascarid nematodes in the order Ascaridida, superfamily Ascaridiidea, family Toxocaridae. Their definitive hosts are the domestic dog and cat, in which they live as adults within the lumen of the small intestine. Infection can occur by the host ingesting viable, embryonated eggs from contaminated sources (e.g., soil and earthworms, etc.), or they can acquire the infection in utero (i.e., transplacentally) from the infected mother when she ingests more infective eggs. In contrast, the human host is aberrant with respect to the completion of the life cycle. Infective larvae hatch after ingestion of eggs, but the juvenile stages fail to develop to mature adult worms. Instead, they wander throughout the body for months or up to several years, causing damage to whatever tissue they happen to enter. The ability of a eukaryotic parasite to survive in any mammal for that length of time is unusual. Only a few others have evolved long-term survival strategies; namely, the adult stage of schistosomes live for 10 to 25 years, the first-stage larva of *Trichinella spiralis* lives for the life span of the host, some species of adult filarial nematodes live 10 to 15 years, and the juvenile stage of most species of tapeworms survive for 5 to 10 years. To accomplish this daunting feat, all of these parasites have acquired unique mechanisms for evading the host’s immune system. *Toxocara* spp. are no exception.

The dominant clinical manifestations associated with toxocariasis are classified according to the organs affected. There are two main syndromes: visceral larva migrans (VLM), which encompasses diseases associated with the major organs, and ocular larva migrans (OLM), in which toxocariasis pathological effects on the host are restricted to the eye and the optic nerve. *T. canis* and *T. cati* are distributed worldwide, due to human settlement of nearly all land masses. Our penchant (almost a genetic imperative) for surrounding ourselves with various domestic animals, particularly cats and dogs, has ensured a worldwide distribution for toxocariasis. In addition, many places that remain permanently uninhabited also have robust populations of feral dogs and cats, introduced there during the 17th through the 19th centuries by sea-faring nations, thus facilitating the maintenance of these two ascarid infections on numerous islands throughout the Pacific Ocean basin, including the Galápagos Islands.

Several species of *Toxocara* infecting domestic cats and other felids have been recently identified. *Toxocara malayensis* n. sp. (18) infects domestic cats, while *Toxocara lycus* infects the caracal (30). It is not known whether either of these newly described entities cause human infection resulting in clinical disease, but given the epidemiological pattern established by *T. canis* and *T. cati*, it is likely that at least a portion of the total number of aberrant infections in humans have resulted from exposure to their migrating larvae. This review concentrates on the most prevalent of *Toxocara* species, namely, *T. canis* and *T. cati*.

HISTORY OF DISCOVERY

Human infection with *Toxocara* spp. was first described by Wilder (61) in 1950. He identified a nematode larva of unknown species within a retinal granuloma of a child. In 1952, Beaver and colleagues (4) reported on a similar series of children who presented with high circulating eosinophilia, and suffered from severe, long-term, multisystem disease. From this group of patients, they described most of the clinical features of VLM and, in histopathological sections of tissues ob-

* Mailing address: Department of Environmental Health Sciences, Mailman School of Public Health, Columbia University, 722 W. 168th St., New York, NY 10032. Phone: (212) 781-6670. Fax: (212) 781-1830. E-mail: ddd1@columbia.edu.
tained at biopsy, correctly classified the causative agents as the larva of either *T. canis* or *T. cati*. Since that time, the juveniles of these two parasite species have been detected in a variety of lesions of the eye and throughout the body (31, 59) in patients from all corners of the world. Today, the public health community at-large acknowledges that toxocariasis in all its clinical forms constitutes a major health risk, especially among children exhibiting pica.

**LIFE CYCLE**

Ingestion of the embryonated eggs of *Toxocara* (Fig. 1) initiates infection in both the definitive and aberrant host. Children accidentally come into contact with them when they play in sandboxes and on playgrounds contaminated with *Toxocara* eggs. This situation arises from indiscriminate defecation on these sites by cats and dogs that harbor the adult worms. After ingestion, the eggs hatch to release larvae (juveniles) that penetrate the small intestine, enter the circulation, and then are free to wander throughout the body, with the possibility of invading all organs. There is controversy as to whether these are second- or third-stage larvae. In the definitive host, the juvenile parasites go on to complete the life cycle, which, in many ways, resembles that of *Ascaris lumbricoides*, the ascarid infecting humans. Transplacental infection is common in both dogs and cats. In addition, the definitive host can become infected by ingesting embryonated eggs carried by paratenic hosts, such as earthworms, ants, and other soil-dwelling invertebrates. Humans can develop aberrant infections by ingesting these same animals.

**FIG. 1. Life cycle of *T. canis* and *T. cati***
Worms develop to the adult stage (Fig. 2) in the small intestine about 60 to 90 days after the larvae hatch. Mating then ensues, giving rise to nonembryonated eggs (Fig. 3), which become excreted with the fecal mass. Embryonation occurs in the soil within a week or so after deposition (Fig. 4). Incubation periods of longer duration are due to lower temperatures. In northern latitudes, eggs can lie dormant until the temperature rises in spring, triggering embryonation.

CLINICAL ASPECTS

The degree of host damage, and the concomitant elicitation of signs and symptoms, varies with regard to which tissue has been invaded; the liver (20), lungs (27), and central nervous system (CNS) (32), including the eyes (49), appear to be most sensitive. In addition, the number of migrating juveniles and the age of the host are two additional factors important as to whether a given individual’s condition will become elevated above the clinical horizon. Pathological consequences are largely dependent upon the death of the juveniles. Their death heralds the onset of marked delayed-type and immediate-type hypersensitivity responses. Inflammation manifests as eosinophilic granulomas. The immediate hypersensitivity responses to dying and dead larvae in the viscera, including the lungs, liver (Fig. 5), and brain (Fig. 6), produce symptoms characteristic of VLM.

In the eye, migrating third stage larvae can damage the retina, inducing granulomatous reactions (Fig. 7; Fig. 8) leading to impaired sight. In severe cases, the granuloma was responsible for the loss of sight. These pathological manifestations have, in the past, occasionally been misdiagnosed as retinoblastoma (28, 62). Today, with reliable immunodiagnostic reagents and methods, OLM is almost never mistaken for other clinical entities. Epidemiologic evidence suggests that ocular disease tends to occur in the absence of systemic involvement and vice versa, which has led to the proposal that the two manifestations of this infection be reclassified as OLM.
and VLM (19). It is possible that there are strains of *T. canis* with specific tropisms. Alternatively, VLM may reflect the consequences of a host inflammatory response to repeated waves of migrating larvae through the viscera, whereas OLM occurs in individuals who have not been previously sensitized (24).

**CLINICAL SIGNS AND SYMPTOMS**

**VLM**

VLM is mainly a disease of young children (<5 years old) (63). It presents with fever; enlargement and necrosis of the liver (46); enlargement of the spleen; lower respiratory symptoms (particularly bronchospasm, resembling asthma); eosinophilia sometimes approaching 70% (1); and hypergammaglobulinemia of immunoglobulin M (IgM), IgG, and IgE classes. In the last of these instances, symptoms are more pronounced, with increased levels of IgE/anti-IgE immune complexes (39). Myocarditis (44), nephritis (53), and involvement of the CNS have been described. CNS involvement can lead to seizures, neuropsychiatric symptoms, or encephalopathy.

There is an increasing appreciation that more subtle clinical manifestations might also arise as a result of long-term exposure to the migrating juveniles. So-called covert toxocariasis ranges in spectrum from asymptomatic infection to larvae migrating in specific target organs (38, 52, 57). In the lungs, larval migrations may result in asthma (6, 56). *T. canis* has been suggested as an environmental risk factor for asthma among some inner-city populations (42). Similarly, in the brain, *T. canis* has been implicated as one of the causes of so-called idiopathic seizure disorders (9), as well as a cause of functional intestinal disorders (25). One study implicated *Toxocara* as a contributing factor in skin disorders of at least two varieties (prurigo and urticaria) (22), while another presented indirect evidence linking *Toxocara* infection with a form of eosinophilic arthritis (45). In experimental infections in mice, learning behavior and memory are affected, and both appear to be dose and time dependent (8). It is therefore reasonable to speculate that similar phenomena are likely to be at work in long-term infections in humans, as well.

Experimental infections in mice have also shed some light as to the effects of VLM on the overall pattern of immune responses. Inbred C3H/HeN mice infected with *T. canis* juveniles had altered patterns of cytokine responses that were presumed
to favor the survival of the parasite. Both IL-12 and tumor necrosis factor alpha were significantly lowered in the infected group compared to controls (26). IL-5 was associated with resistance to *Nippostrongylus brasiliensis* but had no effect against the migrating larvae of *T. canis* (11).

Protective immunity is slow to develop, if it develops at all. This is primarily due to factors most likely related to the ability of the juvenile to periodically change its antigenic signal. Data supporting this speculation will be given more attention below.

**OLM**

OLM usually occurs in children 5 to 10 years old and typically presents as unilateral vision impairment that is sometimes accompanied by strabismus (12). The most serious consequence of the infection is invasion of the retina, leading to granuloma formation, which occurs typically peripherally or in the posterior pole. These granulomas drag the retina and create a distortion, heteropia, or detachment of the macula (54). The degree of visual acuity impairment depends on the specific area involved, and blindness is common. OLM can also cause diffuse endophthalmitis or papillitis; secondary glaucoma can follow. In at least one rare instance following long-term infection with *Toxocara*, a choroidal neovascular membrane formed after presenting earlier as chorioretinitis (37).

**DIAGNOSIS**

Any pediatric patient with an unexplained febrile illness and eosinophilia should be suspected of having VLM. Hepatosplenomegaly and evidence of multisystem disease and history of pica make the diagnosis of VLM more likely. Similarly, OLM should be suspected in any child with unilateral vision loss and strabismus. Diagnostic tests for VLM are primarily immunological (50). The precipitin test is subject to cross-reactions with common antigens of the larvae and blood group substance A. The enzyme-linked immunosorbent assay (ELISA), which employs antigens secreted by the second-stage larva, has sufficient specificity to be the best indirect test for diagnosing this infection. Recombinant antigens have been produced from the second-stage larvae of *T. canis* that promises to add even greater specificity to an already-reliable test (approximately 92%) employing ELISA. The ELISA has a reasonably high degree of sensitivity, as well (approximately 78%), at a titer greater than 1:32 (51).

Other indicators of infection include hypergammaglobulinemia and an elevated isohemagglutinin titer. Thus, a constellation of clinical disease described above, a history of pica, eosinophilia, and positive serology, strongly point to the diagnosis. Liver biopsy may reveal a granuloma surrounding a larva, but a successful diagnosis using this approach is fortuitous at best and not recommended.

OLM is diagnosed primarily on the basis of clinical criteria during an ophthalmologic examination. The immunodiagnostic tests used for VLM are not as reliable for OLM. In one study, only 45% of patients with clinically diagnosed OLM had titers higher than 1:32 (51).

**TREATMENT**

Albendazole is the treatment of choice for toxocariasis. Patients receiving a 5-day treatment course of albendazole (10 mg/kg of body weight/day in two divided doses) improved relative to patients who received treatment with the older anthelmintic drug thiabendazole (55). A dose of 400 mg of albendazole twice a day for 5 days is the currently recommended therapy (21). Because the other commonly used benzimidazole, mebendazole, is poorly absorbed outside the gastrointestinal tract, this agent is a second-line treatment, although some success has been reported in patients who ingest 1 g or more for a 21-day course (21). Symptomatic treatment, including administration of corticosteroids, has been helpful for suppressing the intense allergic manifestations of the infection. OLM is treated by surgery (vitrectomy), anthelmintic chemotherapy, and/or corticosteroids (12, 54).

**EPIDEMIOLOGY**

*T. canis* and *T. cati*, as alluded to, are unfortunately all too common parasites of most domestic and peri-domestic dogs and cats, particularly young ones. Even those sold through reliable kennels and pet shops may harbor adult worms. This is because, as stated in the section dealing with its life cycle, puppies and kittens acquire *Toxocara* juveniles transplacentally from the infected mother. Therefore, having a litter of puppies in the home has been identified as a significant risk factor (35). As expected, children with pica are at higher risk of ingesting embryonated eggs from soil than those not exhibiting this behavior. Growing up in a poor neighborhood is associated with a higher rate of seropositivity for toxocariasis than is being raised in middle-income bracket housing.

Outdoor parks in urban and suburban settings are, in most cases, highly contaminated with embryonated eggs of *T. canis* and *T. cati*, since it is in this environment that people routinely walk their pets (7, 17, 36, 41, 47). Burgeoning populations of urban, semiwild cats and dogs represent a growing problem in many tropical and subtropical regions and most likely contrib-
ute in a major way to the maintenance of high levels of *Toxocara* eggs in the environment (48). It should be added that an increased incidence of rabies is also associated with urban and suburban cohorts of abandoned dogs. Adult patients institutionalized for mental retardation are also at high risk (23).

Preventing the indiscriminate deposition of dog and cat feces in play areas frequented by children appears to be the best control strategy for limiting infection in adolescent populations in large urban centers. In one study in Japan, placing clear vinyl plastic covers over sandboxes at night seemed to effectively discourage pets from using them as fecal dump zones. In addition, during the summer months, temperatures within the sand often rose above 45°C, a condition created by covering them over at night. The authors speculated that this might render the play area safe for use with respect to *Toxocara* (60). Routine treatment of nonferal dogs and cats with ivermectin, mebendazole, or other related benzimidazoles is another available measure which may prove effective in certain settings to limit the spread of this resilient group of parasites. Some cities have solved the dilemma associated with the use of sandboxes by eliminating them from municipal parks and playgrounds.

Veterinarians continue to play an important role in combating the spread of *Toxocara* infection in situations where they see large numbers of dogs and cats that are brought to them by pet owners. Recommending regular stool examinations and the frequent use of chemotherapeutic agents such as mebendazole has proven effective in controlling infection.

**MEDICAL ECOLOGY**

The physical environment plays a crucial role in maintaining and distributing the infective eggs of *T. canis* and *T. cati*, although this subject remains underappreciated. Nonetheless, developing effective control programs may require that this aspect be known in much greater detail. Infectiveascarid eggs of all species can last for months to years outside the host under optimal conditions, due solely to a resistant outer shell composed of ascarosides. This acellular layer enables eggs to withstand various harsh chemicals (e.g., high concentrations of formalin and various inorganic acids), extreme temperature changes, and various degrees of moisture. Future strategies for reducing the number of infectious eggs in soil must find novel ways of breaching the egg shell barrier that protects the immature worm from its external environment.

Earthworms and small mammals play a role in dispersing eggs from a point source. As Darwin pointed out in his essay “On the Formation Of Vegetable Mould through the Action of Worms with Observations on Their Habits” (10), earthworms dump huge quantities of processed (i.e., partially digested) soil onto the surface of the ground, bringing it from depths as great as 2 ft. Viable eggs become incorporated into their fecal pellets and are then subject to random distribution throughout the local area by rain events and wind. Peridomestic mammals, such as dogs, cats, squirrels, and chipmunks, play a role similar to that of earthworms, albeit less efficient, in the dispersal of embryonated eggs (14). Birds that feed primarily on the ground (e.g., pigeons, starlings, and sparrows) can serve as paratenic hosts, carrying eggs from place to place on their feet and beaks, and may be responsible for depositing eggs in places far from the original source.

Another mechanism for egg dispersal is drinking water. In one study, public beaches adjacent to municipal drinking water supplies just outside the city limits of Moscow, Russia, were implicated as a source of contamination (5). The authors speculated that by allowing dogs and cats free access to these recreational areas, this increased the likelihood that eggs of *Toxocara* would enter the water column of the lake. Bathers frequently and inadvertently drink water while wading and swimming, allowing for the possibility of ingesting infective eggs. In addition, this scenario also could lead to eggs contaminating tap water.

Some elements of soil, saprophytic fungi for example (*Pae
cilomyces lilacinus* and *Pae
cilomyces marquandii*), have been shown under controlled conditions to have larvicidal activity against the juvenile worm within its egg’s shell (3). However interesting these findings may be, however, it should be cautioned that their application to the control of *Toxocara* eggs in soil may prove intractably difficult, due to the high degree of unpredictability regarding the behavior of species of any kind that are introduced into new environments (15).

**MOLECULAR ASPECTS**

Nematodes in the genus *Toxocara* are distant relatives of the free-living, soil (and laboratory)-dwelling roundworm *Caenorhabditis elegans*. The latter is the only member of the phylum Nematoda whose entire genomic DNA sequence has been determined (see Nobel Prizes in Medicine and Physiology, 2002). It contains 19,099 genes (7a) and is 97 Mb in size. The genome of *T. canis* is approximately the same size as that of *A. lumbrico
des*, which is about three times larger than that of *C. elegans* (3 × 10⁸ bp) (33). *T. canis* has 18 chromosomes, compared to 24 for *Ascaris*.

Investigations into the molecular biology of *Toxocara* have mainly focused on the secreted proteins of the migrating juvenile stages. These proteins have proven useful in immunodiagnosis of VLM, and OLM. Speculation favors these same proteins in aiding the worm regarding its capacity to evade potentially protective immune responses. This idea derives from the fact that the juvenile stage wanders about the tissues for months to years without apparent interference from the host. Presumably, the worms eventually die of old age. The fact that many of the excretory-secretory proteins from the juvenile stages constitute a family of at least six highly antigenic mucins (13) associated with the cuticular surface reinforces this concept (29). Secreted mucins temporarily coat the surface of the worm (43) and are shed into the host periodically (2). It is thought that this shedding behavior represents an attempt on the part of the parasite to confuse the host’s immune system, leaving behind it a trail of slime, not unlike that of a snail (34). In this model, the worm periodically switches its secreted antigenic identity, thus avoiding harm.

Many other novel coding regions for other expressed proteins of the resting (dauer) larva have also been reported, including those encoding four different C-type lectins, five varieties of superoxide dismutase, phosphatidylethanolamine binding protein, prohibin, olfactomedin, aquaporin, three unique venom allergen/ASP homologues, and an asparaginyl endopeptidase. Functions for these gene products await further investigation. Another interesting group of proteins has been...
described from various stages of *T. canis* and may help explain the mechanism employed by the parasite to migrate through host tissues. Cathepsin-z-like protease genes have been cloned and their cDNAs have been sequenced, identifying a cysteine protease coding region expressed both in the adult and infective larva (16).

Molecular vaccines could prove useful in aiding in the control of infection in domestic dogs and cats. The search so far has identified the myosins of *Toxocara* as potential candidates (40). Several fragments of myosin proved highly antigenic when used in combination in the ELISA for IgG antibodies resulting from naturally occurring infections. In that study, over 85% of the patients previously diagnosed with VLM were positive. To date, however, no molecular vaccines have been described.

Ascarid nematodes are well-known for their ability to induce strong allergic responses, and laboratory investigators working with *Ascaris* spp. have frequently had to cease research on them solely for this reason. Allergens have been partially characterized from *Ascaris* spp. and constitute a group of lipid-binding polypeptides expressed as a large aggregate polypeptide referred to as nematode polypeptide allergens (64). The parent nematode polypeptide allergen molecule is typically secreted as a large polymer and then undergoes digestion at regular intervals along its length, producing a series of polypeptides of ca. 15 kDa. Each of these smaller molecules is structurally related to one of two subgroups, A or B. It is these smaller subunits of the parent molecule that induce allergic responses in a wide variety of mammalian hosts. A group of polypeptide allergens have been identified from *T. canis*, designated TBA-1 (65), and are similar in structure to those already described in *Ascaris*.

**CONCLUDING REMARKS**

Toxocariasis remains a problem throughout the world, inducing multisystem disease in young people. Overcrowding and the inevitable cohabitation of our peridomestic environment by dogs and cats reinforces the transmission cycle in an already-dismal situation in many regions. Public parks and playgrounds have become zones of disease acquisition, not at all fitting their original purpose. At the present time, control programs aimed at reducing the number of domestic animals, or, at the very least, limiting their access to areas frequented by small children, appear to be effective in a few cases. Control of the spread of dog feces, and to a lesser extent cat feces, also helps limit exposure. Regular treatment of pets with benzimidazoles helps reduce worm burdens and limits the number of eggs deposited in soil. However, for the most part, these hearty nematodes appear to be more than holding their own. What is needed in terms of future control programs is the development of radically new approaches, such as effective molecular or DNA-based vaccines that offer the possibility of lifelong protection. Oral baits laced with vaccine would be ideal for dealing with semiwild dog and cat populations, an approach similar to ones that already exist for the large-scale control of rabies in wild animal populations. To augment vaccine development, rapid, highly sensitive and specific diagnostic tests employing recombinant, antigenic peptides that can be executed in the field are essential elements needed to formulate any future control program. Finally, more effective single-dose treatment regimens with safer (over-the-counter?) drugs for pediatric patients would help limit the time of illness, provided of course that adequate medical infrastructure is already in place. Killing *Toxocara* eggs in contaminated soils is seen by most epidemiologists as a nearly impossible task, but if such a strategy could be found and safely implemented, vast numbers of acres of now potentially dangerous city landscape could be rendered *Toxocara*-free.

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