Ocular Larva Migrans: A Severe Manifestation of an Unseen Epidemic

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Abstract *Toxocara canis* and *Toxocara cati*, which infect dogs and cats respectively, may cause infection in humans with a wide spectrum of clinical symptoms and morbidity. Prevalence studies have suggested more widespread affliction than indicated by level of awareness among clinicians in endemic areas. Transmission in the United States continues with seroprevalence estimates identified as high as 22 % in some low-income communities. Best known for causing hepatitis and pneumonitis associated with the syndrome called visceral larva migrans, toxocariasis can also cause debilitating vision loss via ocular larva migrans and is considered a cause of preventable vision loss. While not a common manifestation of toxocariasis, the severity of this condition and its predilection for affecting children warrants increased attention. Herein, we review current knowledge of ocular larva migrans epidemiology, presentation, diagnosis, and treatment.

Keywords Ocular larva migrans · *Toxocara canis* · *Toxocara cati* · Toxocariasis · Epidemiology · Diagnosis · Treatment · Parasitology · Tropical medicine · Blindness · Retinal detachment · Parasitic infections

Introduction

The roundworm *Toxocara spp*, found in dogs and cats, has severe clinical manifestations in human infection, causing symptoms ranging from chronic cough to hepatitis to seizures

[1, 2]. One particularly serious manifestation is debilitating vision loss, the result of ocular larva migrans (OLM). While not a common manifestation of toxocariasis [3, 4, 5], both the severity of ramifications of OLM and the potential under-reporting, based on seroprevalence studies, make OLM worthy of additional public attention [5, 6].

Toxocariasis in Humans

Dogs and cats shed unembryonated eggs in feces as part of the *Toxocara spp* lifecycle. Eggs take around 3 weeks to embryonate and become infective, after which they can exist for several years in soil [7]. When ingested by humans, or another non-host animal, the eggs hatch and the larvae penetrate the intestinal wall to reach the circulatory system and migrate throughout the body. The *Toxocara* larvae release an excretory-secretory antigen (TES) with high immunogenicity and allergenicity; this is the main stimulator of the human immune response [8].

Humans, typically children, acquire the infection via ingestion of eggs, likely in feces-contaminated soil, but potentially also via unwashed hands or vegetables. Dog ownership and pica (geophagia) have been highly associated with *Toxocara* infection [7, 9]. *T. canis* has an estimated prevalence of 5 % in dogs in the United States based on fecal examination in 44 states [10], and much higher in puppies [11]. Samples of soil taken from parks, playgrounds, and public areas in several locations in North America have shown high rates of soil contamination [7].

Despite some of the limitations in terms of specificity and sensitivity of currently available serological immunodiagnostic assays to indirectly measure human *Toxocara spp* infection, there is some consensus that there is underdiagnosis and under-reporting of this condition. Serological surveys performed in the U.S. in the early 70s demonstrated higher infection rates among socioeconomically disadvantaged black and Hispanic children [2]. Recent seroprevalence studies

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among humans conducted as part of the National Health and Nutrition Examination Survey (NHANES) confirmed previous estimates by identifying *Toxocara* antibodies present nationally in 13.9 % of individuals ≥ 6 years old. Prevalence varied considerably by population group. The survey demonstrated >22 % prevalence among those living below the poverty line (based on the Department of Health and Human Services Poverty guidelines published yearly), more than 21 % prevalence in non-Hispanic blacks, and 17.4 % prevalence in the American Deep South [12]. While these measures of seroprevalence do not equate to either current infection or presence of severe symptoms [8, 11], they provide evidence of a higher infection prevalence than is indicated by the level of awareness of *Toxocara* infection and demonstrate that toxocariasis is most profound in areas and communities of poverty [13]. The prevalence of human toxocariasis in tropical settings is not well known, but it is likely that it is also underreported; its clinical manifestations, leading to severe morbidity and long-term sequelae, place this parasitic infection in the category of a neglected tropical disease.

Humans are paratenic hosts, meaning not true hosts, to the *Toxocara* worm, and their lifecycle is not completed in humans. When *Toxocara* eggs are ingested by a human, the eggs hatch in the intestine and the larvae reach the circulatory system, but do not further develop. Instead, they migrate throughout the body and eventually become dormant and encased in tissue. The human host inflammatory immune response, activated by migrating larvae, their active release of TES, and the passive release upon their death, cause the majority of damage to tissues in organs reached by the larvae from the circulatory system [11]. The human physiologic response to infection is mediated primarily by a hypersensitivity response, which can be either immediate or delayed-type. The degree and type of clinical disease manifestations depends on several factors including the strength of the host immune response, the organs invaded, the degree of infection or larva burden, and the frequency of re-infection [2, 14].

There are three main clinical conditions recognized as being caused by *Toxocara* infection: visceral larva migrans (VLM), covert toxocariasis, and ocular larva migrans (OLM) that may occur among socioeconomically disadvantaged populations. These syndromes very rarely occur together, as they represent different degrees and locations of infestation and immune response [15]. VLM occurs with a heavy larva burden and invasion of sensitive organs, namely liver, lungs, and central nervous system, typically manifesting as hepatitis, pneumonitis or seizures if larvae penetrate the central nervous system [11, 16•]. VLM mainly affects young children averaging 6 months to 3 years of age [2]. Covert toxocariasis has relatively unknown prevalence due to its nebulous symptoms such as headache, abdominal pain, cough, fever, and wheezing, but seems to span a wide range of ages and has been linked using serology to decreased lung function over time [12,

16•, 17, 18]. OLM is the least common manifestation of *Toxocara* infection, is more typical of older children and teenagers, and occurs when even a single larva enters the eye. OLM may cause significant visual disability and blindness [8, 9, 19, 20•, 21].

Epidemiology of Ocular *Toxocara* infection

Ocular larva migrans, sometimes referred to as ocular toxocariasis, is an uncommon manifestation of infection with *Toxocara* spp. in humans. Prevalence of OLM is difficult to estimate due to a combination of lack of adequate studies, poor association between clinical OLM disease and serologic prevalence of *Toxocara* antibodies, and lack of awareness of OLM. There have been a few geographically limited prevalence studies in the U.S. over the past 30 years [5, 21], but the largest and most recent indication of prevalence of OLM comes from a national survey of ophthalmologists conducted by the Centers for Disease Control (CDC) in collaboration with the American Academy of Ophthalmology. Results of this survey found 68 reported cases of OLM in the U.S. from September 2009 to September 2010. This survey was limited by low participation (19 %), as well as the likelihood of both under-reporting of less severe clinical disease by providers and higher prevalence of toxocariasis in areas of poverty with less access to healthcare, where cases may go undocumented and untreated. Nevertheless, this important survey provides a starting estimate for assessing the prevalence of ocular toxocariasis by population and location in the U.S. (Table 1). This study demonstrates a significantly higher prevalence of OLM in specific areas. From 2009–2010, there were more cases of OLM reported in the southern states compared to all other regions combined, with the State of Georgia having the highest number of cases. The survey also demonstrates a higher prevalence within urban and suburban communities. Given study limitations noted above and paucity of additional large-scale studies of OLM prevalence, associations between *Toxocara* seroprevalence and prevalence of OLM cannot be concretely determined.

Mechanism of Disease in Ocular Larva Migrans

The unique and subtle presentation of OLM suggests a mechanism of acquiring ocular *Toxocara* infection. Because it typically does not present with other symptoms of toxocariasis and patients are otherwise completely asymptomatic and without elevated WBC or eosinophilia, it is likely that the larva burden is low [8, 15]. With a very low larva burden, the immune system is not sufficiently activated to isolate or disable the larva and it has time to migrate throughout the body until it enters the eye. Those larvae that do not continue to develop into adults can have a lifespan of several years in the human

Table 1 Number and percentage of patients with newly diagnosed OLM by selected characteristics – United States 2009–2010 (N=68)

Demographic	No of patients	%
Age (yrs) (n=44)		
Median	8.5	
Range	1–60	
Sex (n=43)		
Male	24	56
Female	19	44
Race (n=43)		
White	30	70
Black	8	19
Asian/Pacific Islander	4	9
American Indian	1	2
Ethnicity (n=41)		
Hispanic	7	17
Non-Hispanic	34	83
Region (n=44)		
Northeast	6	14
Midwest	5	11
South	25	57
West	8	18
Environment (n=40)		
Urban	12	30
Rural	7	18
Suburban	16	40
Mixed	5	12
Pet ownership (n=33)	21	64
Type of pet (n=21)		
Dog	9	43
Cat	6	29
Dog and cat	5	24
Unknown	1	5
Health insurance coverage (n=43)		
Private	18	42
Medicare	16	37
Medicaid	0	
Uninsured	3	8
Unknown	6	14

(Taken from Reference 20: Lum FC, Hoskins HD, Moorthy RS, Read RW, Starr MC, Jones JL, et al. Ocular Toxocariasis – United States, 2009–2010. MMWR 2011;60:734–736)

body [2]. It is possible that children with OLM have had a very small number of larvae in their systems for a longer period of time, for example due to repeated small-dose inoculation [22]. The small larva burden would fail to incite immune response while providing more time for chance ocular migration and older age on presentation. The unilateral nature and the fact that OLM typically occurs in children slightly older than those typically afflicted with VLM support this concept.

Ocular larva migrans is typically caused by migration of *Toxocara spp* larvae through the choroidal and retinal vessels into the posterior segment of the eye, or occasionally through the optic nerve via the central nervous system [23, 24]. There is no evidence in the literature that anything particularly draws *Toxocara* larvae to the eye in humans. Models of OLM in monkeys have attempted to discover whether there is a predilection of the larvae for the eye, but at this point, inoculation in any location besides the brain and the eye itself yields rare and unpredictable intraocular infection. Models inoculating the carotid artery, the stomach, periocular tissue, and systemic inoculation have all shown rare ocular infection [22]. Mongolian gerbil models seem to demonstrate some predilection for the eye, given the high prevalence of ocular lesions after infection with low larva burden [25], but this mechanism is yet unknown and has not been demonstrated in either humans or other animal models.

Even with intraocular injection, considerable variation exists in response to ocular presence of *Toxocara* larvae. One model using cynomolgus monkeys with intravitreal injection of viable, embryonated *Toxocara* larvae demonstrated several interesting findings supporting this variability [22]. First, not all intraocular larvae incited an immune response, and viable larvae were found in the vitreous, retina, and optic nerve up to 9 months after inoculation, without inflammatory response. This demonstrates large variability in the immune response to intraocular larvae. It remains unclear whether this variation is due to differences in larval activity and toxin release or specific immune characteristics of the host. Second, while several larvae did incite immune response in the form of acute inflammatory granuloma or chronic fibrotic granuloma, the surrounded larvae did not appear to be necrotic, and several larvae demonstrated ability to move through ocular tissue and leave the site of reaction. Third, when examined 3 days after inoculation, no reaction was seen in any of the eyes, showing that brief occupation of the eye may not incite immune response. Finally, while dead larvae caused little reaction, *Toxocara* proteins intravitreally injected stimulated severe retinal vasculitis. These results, though just a model of infection in humans, suggest considerable variability in response to intraocular infection by *Toxocara* larvae.

Clinical Findings in Ocular Larva Migrans

OLM typically occurs as the sole manifestation of toxocariasis in individuals with no antecedent history symptoms, though may rarely be accompanied by symptoms of covert toxocariasis, such as wheezing, or symptoms of VLM [9, 11]. Typical presentation of OLM is unilateral in the majority of cases and most commonly affects older children than those afflicted by VLM [3•, 4, 9, 11]. Most cases of OLM are otherwise asymptomatic, have a normal WBC and no eosinophilia, and can have negative serology [2, 4, 8, 15].

The most common presenting clinical findings include strabismus, diminished vision, photophobia, leukocoria, vitritis, ocular injection, and pain (Table 2) [3•, 4, 11, 20•, 21]. Based on one study of patient data spanning 19 years, presenting vision loss from OLM was most commonly associated with vitritis, cystoid macular edema, and traction retinal macular detachment [21]. Though the larva is not known to invade the optic nerve, there are reports of atrophy of the optic nerve head due to intraocular larvae [11], which based on animal models are thought to enter via the central nervous system rather than retinal vessels [24]. The degree of disability from OLM varies. Patients can present with vision loss ranging from 20/40 to hand movements [3•]. Infection may also be subclinical and only diagnosed on routine eye exam [9].

Diagnosis, Treatment and Outcome of Ocular Larva Migrants

Due to the typically low larva burden, OLM is difficult to diagnosis, and many cases remain presumed toxocariasis

Table 2 Number and percentage of patients with newly diagnosed OLM by signs and symptoms present at examination – United States 2009–2010 (N=68)

Clinical Feature	Number	%
Signs (n=32)		
Subretinal granulomatous mass/scar Vitritis	20	65
Vitritis	16	55
Scotoma	10	50
Posterior pole granuloma	13	42
Peripheral granuloma with traction bands	12	39
Active chorioretinitis	11	34
Retinal detachment	9	28
Strabismus	8	27
Anterior uveitis	8	25
Leukocoria	4	15
Diffuse nematode endophthalmitis	2	6
Symptoms (n=37)		
Vision loss	25	83
Permanent	17	68
Temporary	7	28
Unknown	1	<1
Floaters	13	38
Eye redness	12	32
Photophobia	10	27
Eye pain	7	19

(Taken from Reference 20: Lum FC, Hoskins HD, Moorthy RS, Read RW, Starr MC, Jones JL, et al. Ocular Toxocariasis – United States, 2009–2010. MMWR 2011;60:734–736)

without validating serology or visualization of larvae [9, 14]. Ophthalmic examination and identification of typical features is important in the diagnosis of OLM [2]. Diagnosis therefore depends on a combination of fundoscopy, serology, and histopathologic identification of larvae of surgically obtained specimens.

The mainstay of medical treatment is a combination of glucocorticoids, antihelminthic therapy; many cases require vitrectomy depending on the severity and mechanism of damage. Because intra-ocular inflammation is the main cause of damage and visual impairment via inflammation-induced tissue injury and secondary membrane formation, treatment for OLM focuses primarily on controlling inflammation with steroids. Topical or periocular corticosteroids are used. Prednisone may be added at 0.5–1 mg/kg/day for systemic steroid treatment in cases of severe inflammation [14, 15, 26]. Antihelminthic treatment can also be used in OLM, particularly with concomitant extra-ocular toxocariasis symptoms. Recommended antihelminthic agents include diethylcarbamazine and albendazole; the latter crosses the blood–brain barrier and has shown potential for larvacidal activity in host tissues [15, 27]. Surgery, laser, or cryotherapy is considered for some cases of OLM. Treatment with an antihelminthic agent and high dose steroids has shown to be effective treatment in cases with *Toxocara*-associated uveitis with no remissions, but return of full vision does not appear common from literature, most likely due to structural changes [15, 26]. Outcome and residual visual deficits after treatment for OLM thus vary considerably, but full return of vision is unlikely and visual improvement is not guaranteed with any treatment modality.

Conclusion

Ocular Larva Migrants is a severely debilitating manifestation of *Toxocara* infection that, though rare, is difficult to prevent, diagnose, and treat. While new technologies or techniques for diagnosis and treatment are needed to improve outcome in late-detected infections, the largest gains in combating OLM will come from increased public and medical community awareness of the condition in the U.S. and also in other settings. Better public awareness could also increase parasite control in pets and animals nationally. Increased public and parental awareness could help reduce the amount of larvae in environments most utilized by children, such as playgrounds, via improved pet regulations, monitoring of children, or treatment of soil/sand in those areas. And most importantly, better awareness among physicians, pediatricians, optometrists, and ophthalmologists could result in earlier diagnosis of ocular manifestations of *Toxocara* in children, leading to earlier treatment and prevention of severe vision loss.

Compliance with Ethics Guidelines

Conflict of Interest Anna Quinn Hare and Carlos Franco-Paredes declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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