Posterior Pole Manifestations of Toxocariasis

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Abstract

Ocular toxocariasis is an uncommon worldwide parasitic infection that affects mostly children and is found in both rural and metropolitan areas. In many parts of the world, parasitic infections of the eye are a major cause of blindness. The diagnosis of toxocariasis is essentially clinical, based on the lesion morphology and supportive laboratory data such as serum ELISA titers and ELISA *Toxocara* titers on aqueous humor; other diagnostic methods are imaging studies including optical coherence tomography (OCT), fluorescein angiography (FA), computed tomography (CT) scan, and ocular ultrasound. Treatment is directed at complications arising from intraocular inflammation and vitreous membrane traction. Early vitrectomy may be of value both diagnostically and therapeutically.

Keywords

Infectious uveitis • Nematode intraocular infections • Ocular toxocariasis • Retinochoroidal granuloma • *Toxocara canis* • *Toxocara cati* • Toxocariasis epidemiology

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Introduction

In many parts of the world, parasitic infections of the eye are a major cause of blindness [1]. Human toxocariasis is probably one of the widest spread zoonotic nematode infections, and it is considered one of the most prevalent helminthiasis in industrialized countries [2, 3]. The nematodes *Toxocara canis* and *Toxocara cati* are parasitic roundworms that infect dogs (toxocariasis), other

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canidae, and cats. Ocular toxocariasis (OT) is an uncommon worldwide infection caused by the nematode larvae of *T. canis*, commonly found in dogs [1].

Nematodes were first recognized as pathogens in the posterior segment of the eye by Wilder in 1950. In 1952, Beaver and associates described the association of *Toxocara* species with human disease [1, 4]. The main source of human infection is considered to be environmental contamination by *Toxocara* spp. eggs, especially in public areas of large urban centers, such as parks and gardens frequented by dogs and cats as well as humans [2, 5]. The epidemiology of toxocariasis in different regions has been studied; an association between the higher frequency of seroreactivity to *T. canis* antibodies in humans and socioeconomic variables, such as educational level, family income, water treatment, and contact with soil, has been observed [2]. It usually affects young children, and it may cause a wide spectrum of ocular disease from an asymptomatic posterior granuloma to total retinal detachment [1, 6]. However, ocular infection appears to be much less common than systemic infection [7].

The objective of this chapter is to describe the posterior pole manifestations of ocular toxocariasis as well as its pathogenesis, epidemiology, diagnosis, and current management.

Pathogenesis and Life Cycle

The first complete description of the *T. canis* life cycle (Fig. 4.1) was provided by Sprent in 1958. This canine roundworm shares certain characteristics with the feline roundworm *T. cati* and with the human roundworm *Ascaris lumbricoides* [1]. Dogs may acquire the intestinal infection in five different ways: (1) by ingestion of infective embryonated eggs with stage 1 larvae encapsulated inside, (2) by ingestion of infective second-stage larvae infesting the meat of a rodent, (3) by ingestion of advance-stage larva from the feces or vomit of prenatally infected pups, (4) by transmammary passage of larvae in milk from a lactating bitch to nursing puppies, and (5) by transplacental migration. In cats, transplacental migration has not been proved [8]. Ingested *Toxocara* eggs, with first- and second-stage larvae emerge in the duodenum, and liberate the third-stage larvae, which perforate the intestinal wall [1, 8]. Once located in the intestinal wall, the larvae pass through the portal circulation and migrate via the liver and heart to alveolar capillaries. In puppies, which are more frequently infected, the larvae are able to complete a migratory and developmental cycle. The worms hatch and migrate through the portal system and undergo transtracheal migration. The third-stage larvae are coughed up and aspirated, and they mature into sexually differentiated forms in the small bowel. If the host is an older puppy or an adult dog, particularly with some immunity acquired from past infection, the larvae do not complete the lung migration. Most puppies acquire the infection prenatally. However, they generally expel the worms before reaching adulthood [8].

In common with other non-canine or non-feline hosts, humans can be paratenic hosts for *T. canis* or *T. cati* and can become infected after the ingestion of infective ova or, less frequently, larvae. Ova hatch in the intestine, releasing the second-stage larvae, which migrate throughout the soft tissues of the body, including the brain, for prolonged periods of time [4]. They are often associated with migratory tracks characterized by hemorrhage, necrosis, and inflammation, with eosinophils predominating. Larvae may become encapsulated within granulomas where they are either destroyed or persist in a viable state for many years. In the eye, where the migration of a single larva can be observed, the inflammatory response can lead to partial or total retinal detachment with visual loss [3]. It appears from histological evidence that it is more likely that larvae travel in blood vessel rather than by burrowing (Fig. 4.2a, b, c). It is probably by transport within blood vessels that the larvae reach the eye [7]. The host immune responses to migrating larvae appear to be directed against the larval excretory-secretory antigens (TES-Ag) [3]. These antigens are

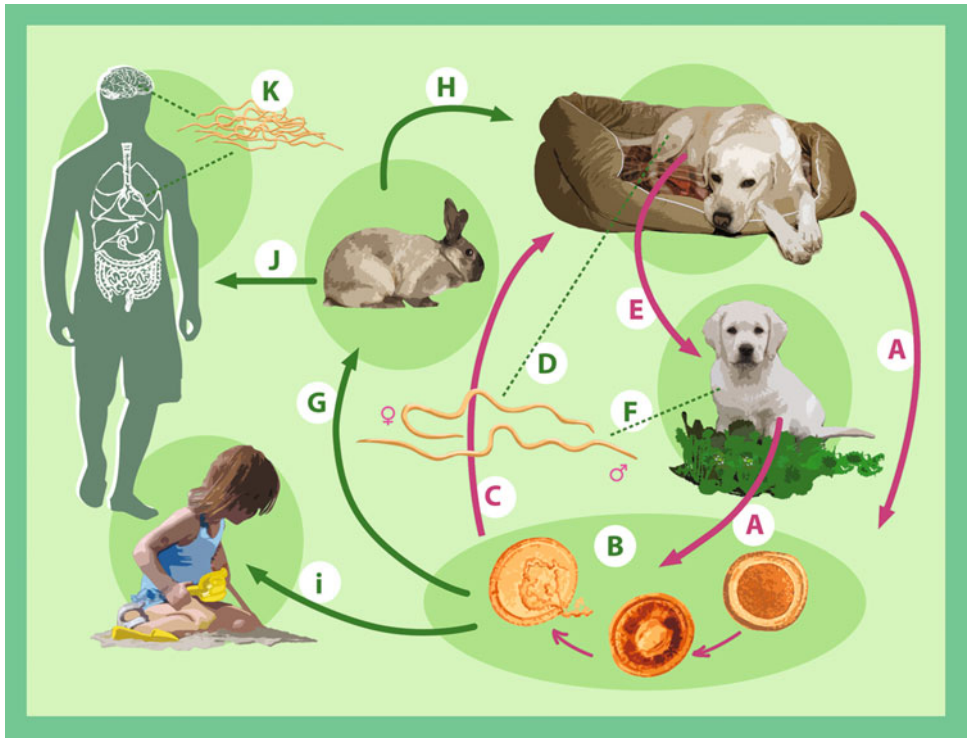

Fig. 4.1 Toxocara life cycle. (*A*) *Toxocara canis* accomplishes its life cycle in dogs, with humans acquiring the infection as accidental hosts. (*B*) Unembryonated eggs are shed in the feces of the definitive host. Eggs embryonate and become infective in the environment. (*C* and *D*) Following ingestion by dogs, the infective eggs hatch and larvae penetrate the gut wall. In younger dogs, the larvae migrate through the lungs, bronchial tree, and esophagus; adult worms develop and oviposit in the small intestine. (*E and F*) In older dogs, patent infections can also occur, but larval encystment in tissues is more common. Encysted stages are reactivated in female dogs during late pregnancy and infect by the transplacental and transmammary routes the puppies, in whose small intestine adult worms become established. Puppies are a major source of environmental egg contamination. (*G*) *Toxocara canis* can also be transmitted through ingestion of paratenic hosts: eggs ingested by small mammals (e.g., rabbits) hatch and larvae penetrate the gut wall and migrate into various tissues where they encyst. (*H*) The life cycle is completed when dogs eat these hosts and the larvae develop into egg-laying adult worms in the small intestine. (*I* and *J*) Humans are accidental hosts who become infected by ingesting infective eggs in contaminated soil or infected paratenic hosts. (*K*) After ingestion, the eggs hatch and larvae penetrate the intestinal wall and are carried by the circulation to a wide variety of tissues (liver, heart, lungs, brain, muscle, eyes). While the larvae do not undergo any further development in these sites, they can cause severe local reactions that are the basis of toxocariasis. The two main clinical presentations of toxocariasis are visceral larva migrans and ocular larva migrans. Diagnosis is usually made by serology or the finding of larvae in biopsy or autopsy specimens

released by larvae from their epicuticle, which is readily sloughed off when bound by specific antibodies [3, 9].

Toxocara larvae secrete and excrete products that are highly immunogenic, which promotes a Th2-type cellular immune response, leading to the production of interleukins 4 and 5 and causing IgE antibody production and eosinophilia [10]. The relative importance of *T. canis* and *T. cati* in causing eye disease has been a matter of debate, and the mechanism by which larvae in tissues are killed and eliminated is not known until now, but there are many hypotheses about it.

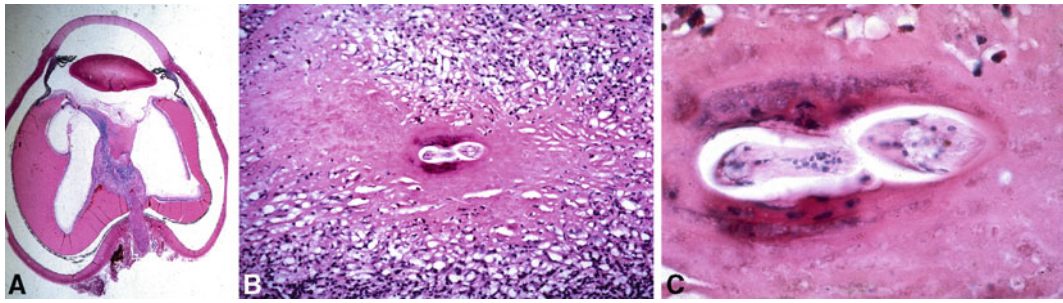

Fig. 4.2 (**a**) Retrolental intravitreal fibroinflammatory mass with retinal detachment. (**b**) Intravitreal mass composed of fibroinflammatory cells with plasma cells, eosinophils, and fibrous tissue surrounding a nematode of *Toxocara canis*. (**c**) Partially well-preserved nematode of *Toxocara canis* (Courtesy of Dario Savino-Zari, M.D.)

Clinical Manifestations

The clinical manifestations of toxocariasis are determined by the size of the *Toxocara* inoculum, frequency of reinfection, organ localization of the larvae, and host response [10, 11]. The spectrum of clinical manifestations varies widely, ranging from predominantly asymptomatic cases to those with severe organ injury [10].

There exist three essential clinical types of human toxocariasis:

1. Visceral larva migrans syndrome (VLM) is due to severe systemic infestation leading to fever, hepatosplenomegaly, pneumonitis, and convulsions. Serum IgE may be elevated, and the blood exhibits substantial eosinophilia and leukocytosis, and affects primarily 1- to 5-year-old children [10, 12].
2. Ocular larva migrans syndrome (OLM) is most commonly seen in otherwise healthy patients, manifesting itself into three clinical types that were classified by Wilkinson and Welch: peripheral inflammatory mass type (Fig. 4.3), posterior pole granuloma type (Figs. 4.4a, b and 4.5a, b), and diffuse nematode endophthalmitis [12–15]. Ocular larva migrans syndrome occurs in children generally older than 8 years of age [10]. These patients have a normal white blood count, normal serum IgE, and show no eosinophilia [12].
3. Covert toxocariasis has been diagnosed in patients who do not fall into the VLM or OLM categories but instead reveal vague symptomatology. Raised levels of *Toxocara* antibodies have been implicated in signs and symptoms, such as hepatomegaly, cough, sleep disturbances, abdominal pain, headaches, and behavioral changes [12].

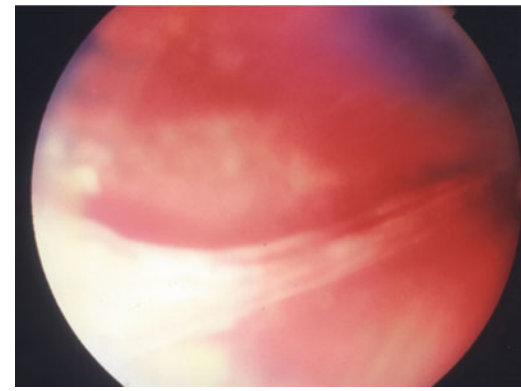

Fig. 4.3 Peripheral inflammatory mass type in a patient with *Toxocara canis*

There are two forms of ocular *Toxocara*, visceral and ocular, that cause an infection with potentially serious consequences for vision [13]. Covert toxocariasis has not been recognized to show ocular manifestations in previous reports.

Probably, the most common presentation of OT is the granuloma found in the posterior pole or at the periphery [13]. There is a high proportion of unilateral ocular infection with mild ocular inflammation in more of 50% of cases, but it may also be a bilateral disease particularly in the

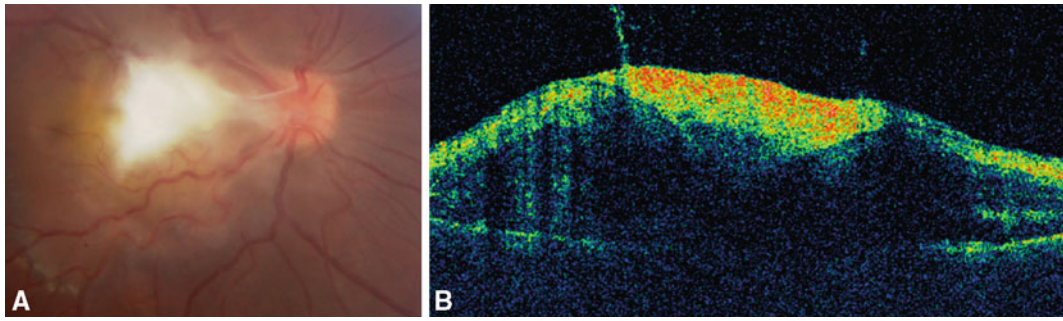

Fig. 4.4 (**a**) Posterior pole granuloma with secondary fibrocellular membranes extending into the optic nerve, vitreous, and surrounding retina in an 8-year-old boy with *Toxocara canis*. (**b**) Optical coherence tomography reveals a characteristic hyper-reflectivity of the internal layers of the retina with tractional macular detachment and posterior shadowing of the choroid

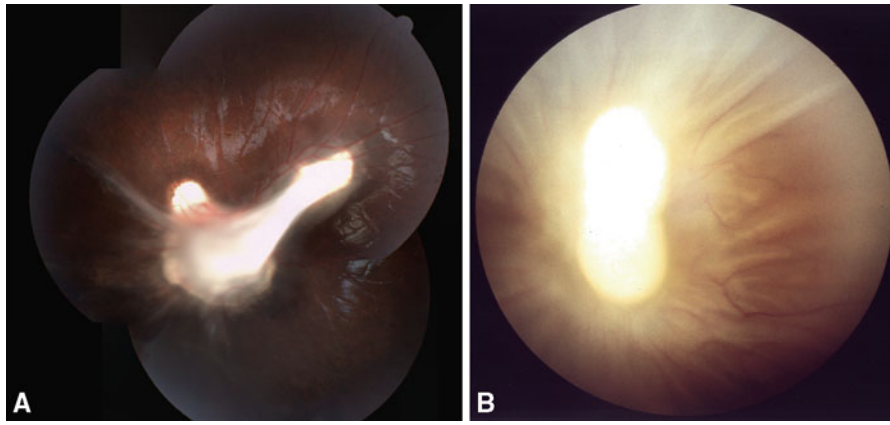

Fig. 4.5 (**a** and **b**) Two patients with posterior pole granuloma and tractional retinal detachment due to *Toxocara canis* (Fig. 4.5a, courtesy of Endalup Reyes, M.D., and Martin A. Serrano, M.D.)

chronic form [14, 16]. In addition, there is recurrence in more of 30% of patients [17]. Some reports have identified that *Toxocara* granuloma was located in the peripheral retina between 50% and 64%, posterior pole granuloma between 25% and 36% of cases [14, 17], and endophthalmitis presentation was identified in less than 25% of cases [17].

Most cases of OT have less than 20/40 of visual acuity (VA) at presentation, with a median VA in eyes with endophthalmitis between 20/200 and 20/400, in eyes with peripheral granuloma a median of 20/70, and in eyes with a posterior pole granuloma a median of 20/50 [17]. The peripheral retina and vitreous sites are the most common; however, those may occur separately or together [1].

A hazy, not well-defined white lesion may be seen in the posterior pole or in the periphery, and different degrees of vitritis may be present. As the inflammation resolves, a peripheral elevated white mass usually is seen, typically associated with retinal folds extending toward the macula [1, 18]. Sometimes, the granuloma presents posteriorly as an intraretinal or subretinal mass (Fig. 4.6a, b). Endophthalmitis usually presents with a quiet external eye with little pain but a severe vitreous inflammation, a mild anterior chamber reaction, and often a secondary cataract [1]. The intraocular inflammation may lead to macular detachment through either direct vitreomacular traction or epiretinal membrane, creating a macular pucker (see Fig. 4.4a). Traction

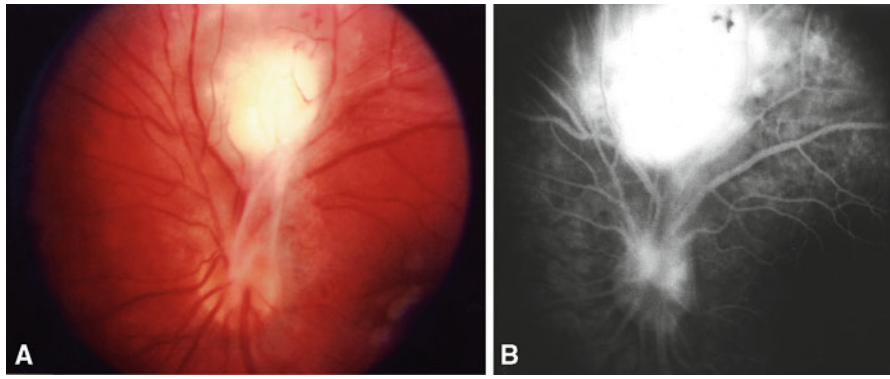

Fig. 4.6 Posterior pole granuloma superior to the optic disk with secondary fibrocellular membranes extending into the optic nerve, vitreous, and surrounding retina in a 10-year-old boy with *Toxocara canis*. (**a**) Color photograph. (**b**) Fluorescein angiogram

also may lead to retinal breaks in atrophic retina, creating a combined tractional-rhegmatogenous detachment [19]. An optic papillitis also can occur, usually because of an invasion of the nerve by the nematode or as an inflammatory response to the organism in another site of the eye [1].

Epidemiology

Uveitis is a common cause of vision loss, accounting for 5–20% of all cases of blindness worldwide [17]. Toxoplasmosis is the most common etiology of infectious posterior uveitis and having OT as one of the less frequent cause [20]. However, the study of the epidemiology of human toxocariasis remains problematic for a number of reasons. First, much of the epidemiology of human toxocariasis is based on serodiagnosis, which has inherent problems, and our understanding of the relationship between exposure and disease remains poor. Second, the lack of standardization of both clinical signs and symptoms and serological testing can introduce variation between studies and make comparisons difficult. Third, randomly selected data at the population level is scarce, and therefore, it is difficult to assess the public health significance of disease in different countries [4].

The prevalence of infection of dogs with adult *Toxocara* worms was reported to be about 25% in Western countries [3, 21], while the rate in cats in France was 30–60% [3]. The prevalence of infection tends to decrease with increasing age of the animal and is lower in well-cared-for pet dogs than in stray or pound dogs. This high prevalence, together with the high fecundity of *Toxocara* and the increasing number of pet animals in Western countries, explains the high level of soil contamination with *Toxocara* eggs in parks, playgrounds, and other public places [3].

Recent studies have demonstrated that soil samples taken from gardens of homes where a clinical case of toxocariasis is found are likely to be contaminated. *Toxocara* eggs have been recovered from salads and other raw vegetables taken from such gardens [3]. Geophagia or soil eating is a specific type of *pica* that increases the risk of toxocariasis, especially in children living in homes with puppies that have not been dewormed. Poor personal hygiene as well as consumption of raw vegetables grown in contaminated kitchen gardens may result in chronic low-dose infections [3].

Toxocara seroprevalences range from 4% to 46% in adults and can be as high as 77.6% in school children [22], and the disease affects females and males with approximately equal frequency [17]. In the United States, the overall prevalence was found to vary between 4.6% and 7.3%, but ranged as high as 10% in the American South and over 30% for socioeconomically disadvantaged African American children. Higher

seroprevalence was also linked to markers of low socioeconomic status, including poverty and crowding and lower educational level for head of household [23, 24]. In 2008, the Centers for Disease Control and Prevention (CDC) in the United States reported on *Toxocara* seroprevalence from the Third National Health and Nutrition Examination Survey (NHANES III), a cross-sectional survey conducted between 1988 and 1994. The survey sampled at higher rates specific minority groups (e.g., non-Hispanic Blacks and Mexican Americans) and age groups (young children and the elderly). Based on a representative sample of just over 20,000 in individuals over the age of 6, the overall seroprevalence was 13.9% [23, 25], suggesting that ten million Americans are infected with *Toxocara.* However, the seroprevalence was found to be considerably higher among non-Hispanic Blacks and people living in poverty.

Based on the number of African Americans living in poverty in the United States, it has been calculated that as many as 2.8 million have toxocariasis, making this disease one of the most common infections among any underrepresented minority groups [23]. In a separate study conducted in the 1990s, high rates of toxocariasis were also found among inner-city Hispanic populations in Bridgeport and New Haven, Connecticut, especially among Puerto Rican immigrants [23, 26]. On the other hand, unlike previous reports in other countries, most patients reported with ocular toxocariasis in Japan are adult, and this prevalence may be due to the changing dietary habit in that country [14].

Diagnosis

The diagnosis of OT is difficult and, in the majority of cases, remains only presumptive. Standard diagnostic methods for ocular *Toxocara* are fundoscopy, imaging, and serologic testing [13].

Most patients with visceral larva migrans will manifest a leukocytosis and hypereosinophilia. On the other hand, eosinophilia is usually absent in OT. Tissue biopsy can show the presence of larvae, but because the larvae rarely are able to finish their life cycle in human beings, stool analysis will not detect *Toxocara* [1]. In the absence of parasitological evidence of infection, diagnosis of toxocariasis has relied mainly on immunological methods [10, 27]. Thus, the *Toxocara* excreted-secreted antigens (TES) have been applied to different immunological assays. The TES-based enzyme-linked immunosorbent assay (ELISA) for detection of IgG-specific antibodies, in particular, is widely preferred for diagnostic purposes and also for seroepidemiologic surveys [10].

Toxocara is a parasite with the ability to evade the immune system, which could explain the chronicity and persistence of the infection [10]. The ELISA has made immunodiagnosis the main serologic method for detecting visceral larva migrans and for confirming the clinical suspicion of OT [1]. Moreover, measurement of avidity (functional affinity) of specific IgG antibodies seems to be useful to discriminate between chronic and early phases of the infection, as in the case for other infectious diseases. In other words, high avidity IgG antibodies are associated with the chronic phase low avidity (functional affinity) of specific IgG antibodies that are associated with the chronic phase and low avidity IgG with freshly acquired toxocariasis. There are few follow-up studies of toxocariasis patients after chemotherapy, but it has been reported that specific IgG antibody levels remain elevated for many years [10]. In toxocariasis, specific IgM antibodies were reported to occur in both acute and chronic phases, differing from most unrelated infections in which they are transient [10]. Lately, IgA and IgE have been found to be useful for diagnosis and follow-up of toxocariasis.

For VLM and some forms of covert toxocariasis, the sensitivity and specificity of the *Toxocara* ELISA are estimated at 78% and 92%, respectively, at a titer of 1:32 [23]. The sensitivity of the ELISA for OLM, however, is considerably less. The larvae may remain alive within the host for months, and host antibody levels may remain strongly positive for 2 or 3 years or more [23, 25]. Therefore, in the CDC, the presence of antibody titers greater than 1:32 may be considered reflective of active infection [23].

The presence of any level of antibodies in the serum is therefore likely to support the diagnosis of *Toxocara* uveitis if the clinical picture raises this possibility. However, most ophthalmologists consider a serum titer of ≥1:8 to be positive for OT if the patient has clinical features consistent with the diagnosis [7, 28]. On the other hand, the absence of serum antibodies does not rule out the diagnosis [17].

The possibility that *T. cati* might play a part in causing ocular lesions has been raised by Petithory et al., who reported positive ELISA test for *T. cati* in the vitreous of six out of nine patients with OLM, all nine of whom also had positive vitreous *T. canis* ELISA tests [29]. Therefore, testing intraocular fluid for antibodies has also been shown to be helpful in diagnosing toxocariasis. These samples often contain higher levels of antibody than the serum [17, 30]. Taking into account that establishing the diagnosis of OT based on clinical features and serologic results is unreliable, we suggest the addition of *T. canis* and *T. cati* Goldmann-Witmer coefficient (GWC) determination to the diagnostic repertoire in patients with unexplained focal chorioretinitis or vitritis [22]. Cytology of the aqueous or vitreous may play a role in the differentiation between retinoblastoma and *Toxocara* posterior pole granuloma in children. The presence of eosinophils in aqueous or vitreous biopsy specimens also suggests the diagnosis to toxocariasis [31].

Imaging studies, particularly ultrasound examination and computed tomography (CT), are useful. Three ecographic patterns in 11 patients with OT were reported [31, 32]: (1) a solid, highly reflective peripheral mass (located in the temporal periphery in 91%) of patients, (2) a vitreous membrane extending between the posterior pole and the mass, and (3) traction retinal detachment or fold from the posterior pole of the mass (Fig. 4.7). Also described was pseudocystic transformation of the peripheral vitreous on ultrasound biomicroscopy. Intraocular calcification is not uniformly present, but may be seen in eyes with ocular toxocariasis with significant ocular disruption or phthisis [31].

Recently, it was demonstrated that optical coherence tomography (OCT) is useful for the differential diagnosis between *Toxocara* granuloma that have subretinal extension and idiopathic choroidal neovascularization in the active stage. In general, OCT examination demonstrates a *Toxocara* granuloma as a highly reflective mass, protruding above the retinal pigment epithelium, and sometimes surrounded by subretinal fluid (see Fig. 4.4b) [13, 33, 34].

Differential Diagnosis

Patients with OT will often seek treatment because of leukocoria. The differential diagnosis of OT varies with the clinical presentation of the disease. It includes retinoblastoma (RB), retinopathy of prematurity (ROP), congenital cataracts, persistent fetal vasculature, infectious endophthalmitis, various forms of trauma, and the general groups of severe exudative and hemorrhagic retinopathies, which may present a similar clinical picture [1].

As RB is the most common malignant intraocular neoplasm of childhood, it is critically important to distinguish it, particularly the sporadic, unilateral variant, from OT. Factors that may be helpful in making this distinction include the following: (1) mean age at presentation for OT, 7.5–8.9 years, versus for RB, 22–23 months; (2) paucity of inflammatory stigmata in RB; and (3) continuous growth of RB lesions. Furthermore, normal levels of aqueous humor lactate dehydrogenase and phosphoglucose isomerase, the demonstration of eosinophils in vitreous or aqueous aspirates, and absence of malignant cells favor a diagnosis of OT [31].

Infectious endophthalmitis is distinguished by the history of recent trauma or ocular surgery. Acute signs of external inflammation typical for bacterial endophthalmitis are uncharacteristic in toxocariasis. However, a delayed onset with less virulent bacterial or fungal organisms needs to be differentiated. Vitreous or aqueous sampling for microscopic examination and microbiologic studies should provide a definitive diagnosis in these cases. Endogenous endophthalmitis usually occurs in the setting of immunodeficiency and positive blood cultures [8].

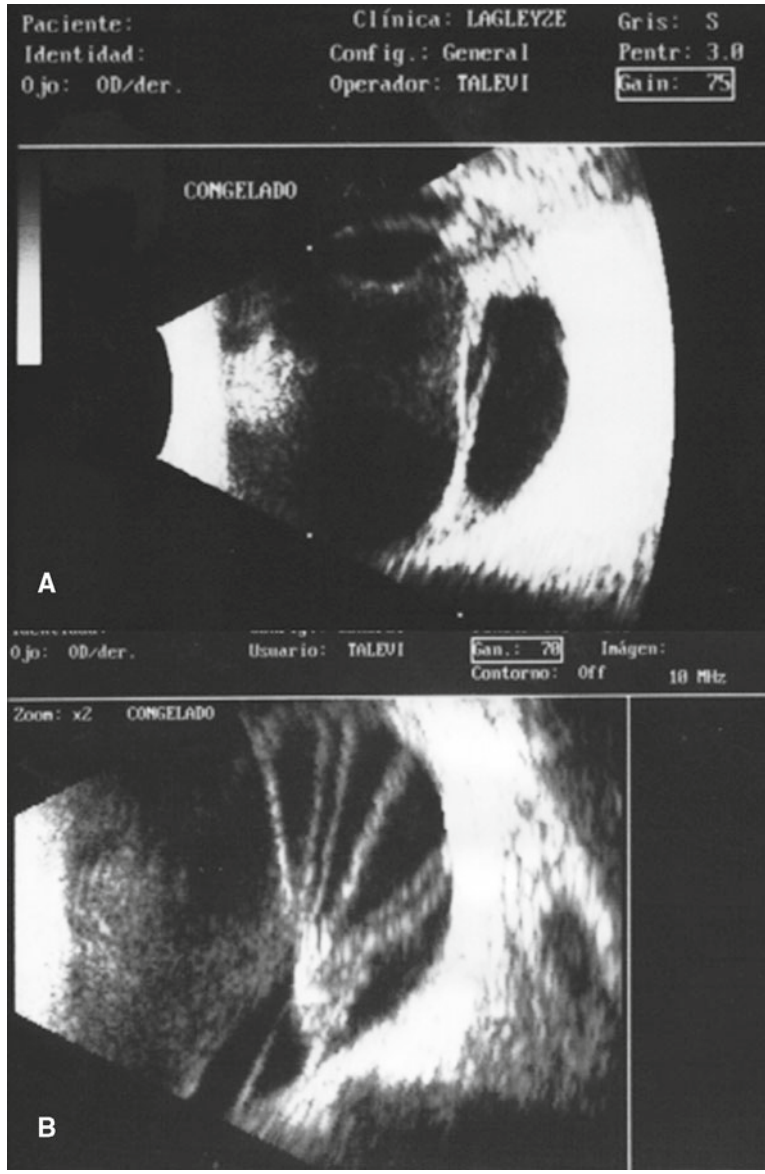

Fig. 4.7 Two different cases demonstrating the ultrasound characteristics of advanced ocular toxocariasis. (**a**) A solid, highly reflective peripheral mass and a vitreous membrane extending between the posterior pole and the mass. (**b**) A tractional retinal detachment at the posterior pole from the mass (Courtesy of Guillermo Talevi, M.D., and Carina Tallano, M.D.)

Differentiation between active toxoplasmic retinochoroiditis and toxocariasis may be difficult, particularly when severe vitritis is present. Serologic studies for toxoplasmosis should provide the diagnosis information [8].

Other pediatric conditions such as ROP, familial exudative vitreoretinopathy (FEVR), persistent fetal vasculature, and Coats' disease usually present neonatally or in early infancy and lack the signs of inflammation of the posterior segment. Retinopathy of prematurity is bilateral, encountered in infants with a history of prematurity and low birth weight, and characterized by proliferative changes and membrane formation.

Persistent fetal vasculature is congenital, unilateral, and associated with micro-ophthalmia. The characteristic morphology includes that of a fibrovascular stalk from the disk to the posterior lens surface, forming a retrolental fibrovascular mass causing ciliary body traction. Coats' disease is a unilateral condition occurring almost exclusively in young males. This is characterized by a white, fibrotic subretinal mass in the posterior pole due to chronic subretinal lipid deposition. There are typical peripheral vascular telangiectasia and lipid exudation with an absence of epiretinal membrane formation [8].

Management

Specific treatment varies greatly depending on the severity of the disease process. The management of the systemic form of toxocariasis includes the use of anthelmintic agents, antibiotics, or steroids [1, 28]. In patients with OT, the visual potential of the eye, the amount of active inflammation, and the macular damage must be considered. Therapy is directed at the inflammatory response to prevent inflammation-induced tissue injury and secondary membrane formation. The inflammation is treated with corticosteroids, either topically or periocularly. Systemic prednisone administered at a rate of 0.5–1 mg/kg/day may be added.

Anthelmintics have been used to destroy viable nematodes and eliminate further migration of the larvae, but the parasites may persist despite treatment [1]. Though numerous anthelmintics have been tested in animal models, controlled randomized studies have rarely been conducted in humans [3]. Magnaval and Glickman have recommended that all cases of VLM should be treated with anthelmintics; they showed similar efficacies of mebendazole (57%), diethylcarbamazine (57%), albendazole (53%), and thiabendazole (47–50%), but moderate efficacy of ivermectin for the treatment of human toxocariasis [3, 12]. Thiabendazole shows negligible larvicidal effects in mice and has a problem in safety, since adverse effects and liver dysfunction occur with a high incidence. In a controlled study, Stürchler et al. reported that albendazole showed a better efficacy for the treatment of OLM when compared to thiabendazole, with milder side effects [35]. In addition, albendazole crosses the blood-brain barrier and has a proven potential for destroying larval stages of *Toxocara spp*. located in the tissues of the paratenic and final host [12]. Diethylcarbamazine, if available, is probably more effective than albendazole; however, its association with gastrointestinal upset and leukopenia (especially in immunocompromised persons) must be borne in mind [4].

Treatment with anthelmintics can lead to severe hypersensitivity reactions caused by dying larvae [36]. Significant allergic or inflammatory reactions can be suppressed with systemic or local corticosteroids. There is no risk of enhancing the infection, as the larvae cannot multiply [12]. Thiabendazole is recommended to be given orally every day in doses of 25–50 mg/kg/day for 7 days, mebendazole's best therapeutic schedule is 20–25 mg/kg/day for 3 weeks, and albendazole is recommended at 10 mg/kg/day for 5 days [3]. Selection of specific drugs depends on several factors, including the physician's previous experience in treating toxocariasis and whether they are locally licensed and available for use. Clearly, there is a need to standardize treatment, where possible, and to adopt a scoring system to quantify clinical severity so that treatment efficacy can be assessed [4].

Peripheral granulomas may be treated with other modalities that include laser photocoagulation; however, any laser procedure may incite an extensive inflammatory response in a uveitic eye [3, 19], and for this reason, combination with steroid therapy to reduce the inflammatory response should be considered. Ocular granulomas can be treated with cryotherapy as well [3, 37]; in children, this procedure is performed under general anesthesia associated to peribulbar anesthesia for intraoperative and postoperative pain control. Cryotherapy is applied directly to the areas of exudation at the pars plana using a double freeze-thaw technique, and periocular steroids should be

administered after the procedure. In cases of residual activity, cryotherapy may be repeated in 3–4 months [19].

Visual loss may result not only from submacular granuloma itself. Intraocular inflammation may lead to macular detachment through either direct vitreomacular traction or epiretinal membrane (ERM), creating a macular pucker that can be demonstrated by OCT (see Fig. 4.4) [19, 38]. Traction also may lead to retinal breaks in atrophic retina, creating a combined tractional-rhegmatogenous detachment as previously stated. A pars plana vitrectomy (PPV) may be beneficial for patients who have not had a satisfactory response to medical treatment or for those who have marked vitreous fibrosis and tractional complications [19, 39]. The fibrous membranes located between the peripheral granuloma and the optic disk usually have extensions into the underlying retina and need to be carefully lifted off from the retinal surface before they can be severed. These membranes usually remain tightly adherent to the optic disk and the peripheral granuloma. They often need to be circumcised rather than delaminated or peeled. Granulomas seem to be an intimal part of the retina; therefore, attempts to extirpate the retinal granuloma usually are unsuccessful and may cause undesirable complications. Therefore, the granulomas are left in place [19, 40].

The results of modern vitreoretinal surgery, in which epiretinal as well as subretinal components of the granuloma are removed by PPV and retinotomy techniques, are reported to provide achievement of macular or complete retinal reattachment in rates up to 100% and 83%, respectively [41]. Additionally, visual improvement after PPV is obtained in 50–66% of cases in some reports [6, 41–43]. Preoperative VA and the presence of tractional retinal folds through the macula affect visual outcome [41, 42]. Even in eyes with chronic tractional retinal detachment, intense anti-inflammatory and orthoptic treatment following surgery can provide ambulatory vision. Pars plana vitrectomy in some cases can also provide diagnostic clues [41].

Controversies and Perspectives

It is difficult to establish the diagnosis of OT based on clinical manifestations solely because ocular symptoms may be diverse and inflammatory signs such as redness and pain are not always present. The diagnosis of OT is often made coincidentally in eyes without inflammation, for instance, during an evaluation for strabismus, in cases of decreased vision, or while undergoing a routine examination [22]. Biopsies are rarely performed, and infection is undetectable in clinically asymptomatic cases. Thus, the sensitivity and specificity of serological tests must be improved.

Although *T. canis* is a parasite of dogs, it can be difficult to distinguish from *T. cati*, a similar parasite of cats; therefore, exposure to both dogs and cats is considered relevant to the condition, and the children are often described to be geophagic [17]. Because *T. canis* is much more prevalent in puppies than in adult dogs, the standardized uveitis questionnaire completed by all patients must ask about exposure to puppies (or kittens) instead of adult animals [17]. The possibility that *T. cati* might play a part in causing ocular lesions has been raised by Petithory et al. who reported positive ELISA tests for *T. cati* in the vitreous of six out of nine patients with OLM, all nine of whom also had positive vitreous *T. canis* ELISA tests [7, 29]. However, it has been reported that standard ELISA tests use the antigen prepared from *T. canis* and show a high cross-reactivity between *T. canis* and *T. cati* [44].

The detection of specific anti-*Toxocara* IgG by ELISA does not appear to be useful for monitoring therapy. When ELISA antibody titers were compared between treated and untreated children, the kinetics of specific anti-*Toxocara* IgG was not affected by anthelmintic treatment. Conversely, the specific anti-*Toxocara* IgE serum concentration does seem to decrease significantly posttreatment if it is markedly elevated prior to therapy, especially in atopic patients [3]. *Toxocara* antibody titers can remain positive in the absence of disease, and eosinophilia can take more than 2 years to decline to normal values.

ELISA has offered the best compromise until now with native proteins, but sensitivity and specificity are dictated by the manufacturer's choice of target antigens and the quality control and quality assurance in place [4]. On the other hand, the absence of serum antibodies does not rule out the diagnosis [17]. Therefore, it has been suggested that sera should be tested at dilutions as low as 1:2 and not 1:8 as much of physician use [22]. Additionally, Magnaval et al. noted that eosinophil counts were useful markers in a post-treatment follow-up study (except for ocular patients) [3].

Testing intraocular fluids for antibodies has also been shown to be helpful in diagnosing toxocariasis. These samples often contain higher levels of antibody than the serum [17]. Also, these intraocular fluids might play a role in the differentiation between RB and *Toxocara* posterior pole granuloma in children. However, the decision to perform paracentesis should be made reluctantly, attributable to the risk of spreading malignant cells in case of RB [22].

For the surgical treatment, Werner et al. have recommended that the removal of all components of a *Toxocara* granuloma can be successful in treating OT and is possible with PPV and subretinal surgical techniques [39]. However, another report suggests that the posterior subretinal granuloma should not always be removed in eyes with OT [38].

The role of *Toxocara* infection in asthma is unclear. A notable association between asthma and recurrent bronchitis and *Toxocara* seropositivity was found in children aged between 4 and 12 years in the Netherlands; and in a mouse model, *Toxocara* was found to provoke airway inflammation. However, other human studies in the United States failed to corroborate the association between asthma and *Toxocara* seropositivity [4, 26].

While the NHANES studies indicate that toxocariasis continues to persist and is underrecognized as a health problem, a full appreciation of the US and global burden of disease caused by toxocariasis demands improved serodiagnostic tools. In the United States, the enzyme immunoassay testing is not widely available because of the limited capacity for parasitic disease diagnosis and the limited availability of antigen made from *T. canis* larvae. In addition, the existing assays have a low sensitivity for detecting ocular larva migrans; therefore, some true cases remain undiagnosed and the approximations of national seroprevalence are underestimated [23]. A role for IgE antibody detection, particularly for posttreatment follow-up, has already been identified, and the role of other bodily fluids, such as ocular fluids, for serology requires further investigation.

Further studies to improve diagnostic testing, treatment strategies, patient management, and expand epidemiologic surveillance should be conducted in parallel with control and prevention efforts. These include periodic deworming of dogs and hand washing to prevent fecal oral contact, and case detection and treatment with anthelmintic (preferably albendazole). Better communication between clinicians and diagnostic laboratories is required so that time-course serostudies can be performed and investigations into antibody and antigen kinetics before, during, and after treatment can be undertaken and evaluated. Given the high prevalence of toxocariasis in areas of poor urban and rural hygiene, improved sanitation and access to clean water may also have important roles.

Currently, the best serodiagnostic options are using the IgG TES-ELISA as a screening test (with confirmation by IgE TES-ELISA) and TES-WB. Increased specificity can be achieved by using an IgG4 TES-ELISA, and IgG4 TES-WB could also be useful because it might provide further discrimination after IgG TES-ELISA screening. Better insight into the significance of minor antibody isotypes can be provided by increasing TES coating concentration, although its usefulness could be outweighed in regions where polyparasitism is endemic [4].

The differential diagnosis of OT is largely based on clinical characteristics, a history of prodromal visual and systemic symptoms, signs of inflammation, size and location of lesions, and including the course of the disease process. Optical coherence tomography has become a valuable ancillary diagnostic tool and can

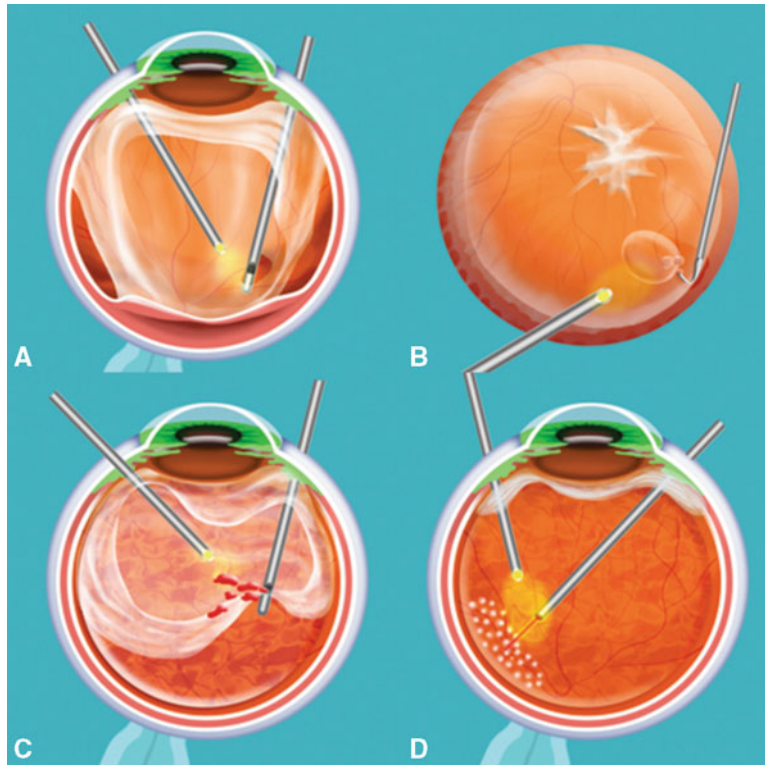

Fig. 4.8 Artist's representation of surgical technique. (**a**) After a core central vitrectomy, a hole is then made in the midperipheral posterior hyaloid. (**b**) Perfluorocarbon liquid (PCL) is injected to mechanically and slowly separate the posterior hyaloid from the retina. A viscodissector attached to a 5-mL syringe filled with PCL to separate membranes from the underlying retina. (**c**) Once all the epiretinal tissues have been separated from the retina, vitrectomy is completed. (**d**) Endolaser is applied under PCL (shown). An air-fluid and an air-silicone oil exchange are performed to finish the case (not shown)

provide useful information on the morphological features associated to the disease. Cross-sectional OCT images may increase understanding of the pathophysiology of presumed subretinal *Toxocara* granulomas and help in the clinical management of the retinal complications related to this disease [13]. The *Toxocara* larva commonly migrates across the retina, and with the actual use of the OCT, Suzuki et al. [45] have reported that the *Toxocara* larva most likely migrate in the nerve fiber layer in a case of posterior pole *Toxocara* granuloma, and Higashide et al. [33] demonstrated by OCT that the granuloma was located in the subretinal space and resembled choroidal neovascularization. Perhaps the pathology of a lesion migrating in the retinal surface is quite different from that of a subretinal lesion.

Pars plana vitrectomy is the choice of treatment to manage the inflammatory complications of OT and also has been considered as a tool of diagnosis, including in cases with chronic disease [41]. Recently, Arévalo and Garcia-Amaris [19] have described a new surgical dissection technique called "En bloc perfluorodissection" that facilitates removal of ERMs and the posterior hyaloid. It is performed by injecting perfluorocarbon liquid (PCL) between the retina and the posterior hyaloid to separate both the posterior hyaloid and epiretinal tissues from the subjacent retina. This technique has demonstrated to be useful during vitrectomy in eyes with tractional retinal detachment and severe OT (Figs. 4.8 and 4.9). Other advantages include retinal stability at the time of vitreous removal, better visualization of vitreous and intraocular structures, rapid retinal reattachment,

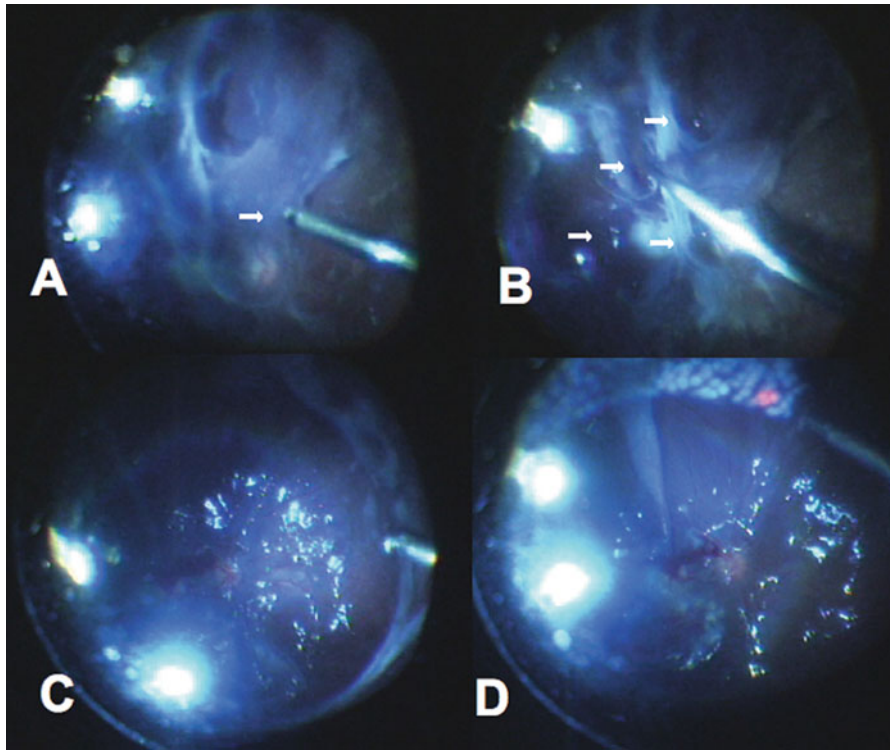

Fig. 4.9 En bloc perfluorodissection performed in a case of tractional retinal detachment in ocular toxocariasis. (**a**) After a core central vitrectomy, a hole is then made in the midperipheral posterior hyaloid (*arrow*). (**b**) Perfluorocarbon liquid (PCL) is injected to mechanically and slowly separate the posterior hyaloid from the retina (*arrows*). A viscodisector attached to a 5 mL syringe filled with PCL is used to separate all the epiretinal tissues from the retina. (**c**) Once all the epiretinal tissues have been separated from the retina, vitrectomy is completed. (**d**) Endolaser is applied under PCL (shown). An air-fluid and an air-silicone exchange are performed to finish the case (not shown)

less blood in the vitreous cavity, subretinal fluid resolution, blood confinement, and easier dissection of ERMs.

Focal Points

Ocular toxocariasis is an uncommon worldwide ocular infection that affects mostly children. It is found in both rural and metropolitan areas. The most common route of infection is the ingestion of soil contaminated with *Toxocara* larva. In most cases, the course of the disease is mild, but the spectrum of clinical manifestations and severity is broad, and the potential for uniocular blindness due to this entity is well recognized. Consequently, to improve the prognosis, visual acuity screening in day-care centers and in schools may be critical to detect this disease in its early stages.

The diagnosis of toxocariasis is essentially clinical, based on the lesion morphology and supportive laboratory data and imaging studies. Differentiation of OT from RB is critical. To avoid unnecessary enucleation of eyes with OT, it is imperative to establish an adequate correlation between the clinical findings and diagnostic methods including serum ELISA titers, radiologic evaluation by ultrasound, and CT scan, and also OCT could be a useful tool. It is of particular importance to perform ELISA *Toxocara* titers on aqueous and/or vitreous humor when the clinical diagnosis is not clear or when the serum ELISA is inconclusive.

Treatment is directed at complications arising from intraocular inflammation and vitreous membrane traction. Early vitrectomy may be of value both diagnostically and therapeutically. Early therapeutic vitrectomy is recommended based on the beneficial results obtained in several series of patients. If an early vitrectomy is performed, then analysis of ELISA titers and cytology of the vitreous humor should be performed for diagnostic purposes.

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References

1. Sabrosa NA, de Souza EC. Nematode infections of the eye: toxocariasis and diffuse unilateral subacute neuroretinitis. Curr Opin Ophthalmol. 2001;12:450–4.
2. Santarém VA, Franco Eda C, Kozuki FT, Fini D, Prestes-Carneiro LE. Environmental contamination by *Toxocara* spp. eggs in a rural settlement in Brazil. Rev Inst Med Trop Sao Paulo. 2008;50:279–81.
3. Magnaval JF, Glickman LT, Dorchies P, Morassin B. Highlights of human toxocariasis. Korean J Parasitol. 2001;39:1–11.
4. Smith H, Holland C, Taylor M, Magnaval JF, Schantz P, Maizels R. How common is human toxocariasis? Towards standardizing our knowledge. Trends Parasitol. 2009;25:182–8.
5. Acha P, Szyfres B. Zoonosis y enfermedades transmissibles al hombre y a los animales. 2nd ed. Washington, DC: Organización Panamericana de la Salud; 1986.
6. Amin HI, McDonald HR, Han DP, Jaffe GJ, Johnson MW, Lewis H, Lopez PF, Mieler WF, Neuwirth J, Sternberg Jr P, Werner JC, Ai E, Johnson RN. Vitrectomy update for macular traction in ocular toxocariasis. Retina. 2000;20:80–5.
7. Taylor MR. The epidemiology of ocular toxocariasis. J Helminthol. 2001;75:109–18.
8. Foster CS, Vitale AT. Diagnosis and treatment of uveitis. 1st ed. Philadelphia: WB Saunders; 2002. p. 428–36.
9. Page AP, Rudin W, Fluri E, Blaxter ML, Maizels RM. *Toxocara canis*: a labile antigenic surface coat overlying the epicuticle of infective larvae. Exp Parasitol. 1992;75:72–86.
10. Elefant GR, Shimizu SH, Sanchez MC, Jacob CM, Ferreira AW. A serological follow-up of toxocariasis patients after chemotherapy based on the detection of IgG, IgA, and IgE antibodies by enzyme-linked immunosorbent assay. J Clin Lab Anal. 2006;20:164–72.
11. Pawlowski Z. Toxocariasis in humans: clinical expression and treatment dilemma. J Helminthol. 2001;75:299–305.
12. Barisani-Asenbauer T, Maca SM, Hauff W, Kaminski SL, Domanovits H, Theyer I, Auer H. Treatment of ocular toxocariasis with albendazole. J Ocul Pharmacol Ther. 2001;17:287–94.
13. do Lago A, Andrade R, Muccioli C, Belfort Jr R. Optical coherence tomography in presumed subretinal *Toxocara* granuloma: case report. Arq Bras Oftalmol. 2006;69:403–5.
14. Yokoi K, Goto H, Sakai J, Usui M. Clinical features of ocular toxocariasis in Japan. Ocul Immunol Inflamm. 2003;11:269–75.
15. Wilkinson CP, Welch RB. Intraocular toxocara. Am J Ophthalmol. 1971;71:921–30.
16. Benitez del Castillo JM, Herreros G, Guillen JL, Fenoy S, Bañares A, Garcia J. Bilateral ocular toxocariasis demonstrated by aqueous humor enzyme-linked immunosorbent assay. Am J Ophthalmol. 1995;119:514–6.
17. Stewart JM, Cubillan LD, Cunningham Jr ET. Prevalence, clinical features, and causes of vision loss among patients with ocular toxocariasis. Retina. 2005;25:1005–13.
18. Monshizadeh R, Ashrafzadeh MT, Rumelt S. Choroidal neovascular membrane: a late complication of inactive *Toxocara* chorioretinitis. Retina. 2000;20:219–20.
19. Arevalo JF, Garcia-Amaris RA. The role of vitreoretinal surgery in children with uveitis. Int Ophthalmol Clin. 2008;48:153–72.
20. Nagpal A, Leigh JF, Acharya NR. Epidemiology of uveitis in children. Int Ophthalmol Clin. 2008;48: 1–7.
21. Barriga OO. A critical look at the importance, prevalence and control of toxocariasis and the possibilities of immunological control. Vet Parasitol. 1988;29:195–234.
22. de Visser L, Rothova A, de Boer JH, van Loon AM, Kerkhoff FT, Canninga-van Dijk MR, Weersink AY, de Groot-Mijnes JD. Diagnosis of ocular toxocariasis by establishing intraocular antibody production. Am J Ophthalmol. 2008;145:369–74.
23. Hotez PJ, Wilkins PP. Toxocariasis: America's most common neglected infection of poverty and a helminthiasis of global importance? PLoS Negl Trop Dis. 2009;3:e400.
24. Herrmann N, Glickman LT, Schantz PM, Weston MG, Domanski LM. Seroprevalence of zoonotic toxocariasis in the United States: 1971–1973. Am J Epidemiol. 1985;122:890–6.
25. Jones JL, Kruszon-Moran D, Won K, Wilson M, Schantz PM. *Toxoplasma gondii* and *Toxocara* spp. co-infection. Am J Trop Med Hyg. 2008;78:35–9.
26. Sharghi N, Schantz PM, Caramico L, Ballas K, Teague BA, Hotez PJ. Environmental exposure to *Toxocara* as a possible risk factor for asthma: a clinic-based case–control study. Clin Infect Dis. 2001;32:E111–6.

27. Glickman LT, Schantz PM. Epidemiology and pathogenesis of zoonotic toxocariasis. Epidemiol Rev. 1981;3:230–50.
28. Shields JA. Ocular toxocariasis. A review. Surv Ophthalmol. 1984;28:361–81.
29. Petithory JC, Chaumeil C, Liotet S, Rousseau M, Bisognani AC. Immunological studies on ocular larva migrans. In: Lewis JW, Maizels RM, editors. Toxocara and toxocariasis: clinical, epidemiological and molecular perspectives. London: Institute of Biology/The British Society for Parasitology; 1993. p. 81–9.
30. Magnaval JF, Malard L, Morassin B, Fabre R. Immunodiagnosis of ocular toxocariasis using Western-blot for the detection of specific anti-*Toxocara* IgG and CAP for the measurement of specific anti-*Toxocara* IgE. J Helminthol. 2002;76:335–9.
31. Vitale AT, Foster CS. Uveitis affecting infants and children: infectious causes. In: Hartnett ME, Trese M, Capone Jr A, Bronya JBK, Scott MS, editors. Pediatric retina. Philadelphia: Williams & Wilkins; 2005. p. 250–89.
32. Wan WL, Cano MR, Pince KJ, Green RL. Echographic characteristics of ocular toxocariasis. Ophthalmology. 1991;98:28–32.
33. Higashide T, Akao N, Shirao E, Shirao Y. Optical coherence tomographic and angiographic findings of a case with subretinal *toxocara* granuloma. Am J Ophthalmol. 2003;136:188–90.
34. Fukuchi T, Takahashi K, Ida H, Sho K, Matsumura M. Staging of idiopathic choroidal neovascularization by optical coherence tomography. Graefes Arch Clin Exp Ophthalmol. 2001;239:424–9.
35. Stürchler D, Schubarth P, Gualzata M, Gottstein B, Oettli A. Thiabendazole vs. albendazole in treatment of toxocariasis: a clinical trial. Ann Trop Med Parasitol. 1989;83:473–8.
36. Byers B, Kimura SJ. Uveitis after death of a larva in the vitreous cavity. Am J Ophthalmol. 1974;77:63–6.
37. Zygulska-Mach H, Krukar-Baster K, Ziobrowski S. Ocular toxocariasis in children and youth. Doc Ophthalmol. 1993;84:145154.
38. Shimizu Y, Imai M, Fukasawa A, Iijima H. Premacular membrane peeling without removal of subretinal granuloma in an eye with ocular toxocariasis. Acta Ophthalmol Scand. 2005;83:395–6.
39. Werner JC, Ross RD, Green WR, Watts JC. Pars plana vitrectomy and subretinal surgery for ocular toxocariasis. Arch Ophthalmol. 1999;117:532–4.
40. Erb MH, Kuppermann BD. Surgical approaches to uveitis. In: Hartnett ME, Trese M, Capone Jr A, Bronya JBK, Scott MS, editors. Pediatric retina. Philadelphia: Williams & Wilkins; 2005. p. 445–66.
41. Acar N, Kapran Z, Utine CA, Büyükbabani N. Pars plana vitrectomy revealed *Toxocara canis* organism. Int Ophthalmol. 2007;27:277–80.
42. Small KW, McCuen 2nd BW, De Juan Jr E, Machemer R. Surgical management of retinal traction caused by toxocariasis. Am J Ophthalmol. 1989;108:10–4.
43. Rodríguez A. Early pars plana vitrectomy in chronic endophthalmitis of toxocariasis. Graefes Arch Clin Exp Ophthalmol. 1986;224:218–20.
44. Sakai R, Kawashima H, Shibui H, Kamata K, Kambara C, Matsuoka H. *Toxocara cati*-induced ocular Toxocariasis. Arch Ophthalmol. 1998;116:1686–7.
45. Suzuki T, Joko T, Akao N, Ohashi Y. Following the migration of a *Toxocara* larva in the retina by optical coherence tomography and fluorescein angiography. Jpn J Ophthalmol. 2005;49:159–61.