Ocular Parasitic Diseases: A Review on Toxocariasis and Diffuse Unilateral Subacute Neuretinitis

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ABSTRACT
Parasitic infections may damage various ocular tissues, thereby causing visual dysfunction. In 1950, Wilder described the first case in which larval forms of nematodal intestinal roundworms (Ascaridoidea: Ascaris, Toxocara, Ancylostoma, Necator, and Strongyloides) were implicated as a cause of intraocular disease. This review focuses on two disorders associated with parasitic infections: ocular toxocariasis and diffuse unilateral subacute neuroretinitis. [J Pediatr Ophthalmol Strabismus 20XX;XX:XX-XX.]

INTRODUCTION
Parasitic infections may produce severe damage to various ocular tissues, thereby causing visual dysfunction. In this review, we will focus on two of these infections, ocular toxocariasis and diffuse unilateral subacute neuroretinitis (DUSN). Although these diseases are not widely distributed worldwide, we believe it is of great value to the general ophthalmologist to be familiar with their different presentations, due to the poor visual prognosis they carry.

OCULAR TOXOCARIASIS
Human infection by Toxocara, a common roundworm that infects dogs and cats, may take one of two forms: visceral larva migrans and ocular toxocariasis.1-5 The characteristics of the infection will depend on the number of parasites, site of infection, migratory behavior, and the host immunological response.6,7

Visceral larva migrans is characterized by generalized systemic involvement due to the migration capabilities of the second stage larvae of Toxocara canis. It typically presents in children from the ages of 6 months to 5 years. The disease is usually self-limited and subclinical; however, fever, pulmonary manifestations, hepatomegaly, eosinophilia, pallor, irritability, anorexia, and malaise can occur.6,7

On the other hand, ocular toxocariasis appears in older patients, with an average age of 7.5 to 8.6 years.7-9 Several studies have revealed Toxocara and other visceral larvae migrans to be the cause of intraocular inflammation in 9.4% of pediatric uveitis.10,11 Rarely does a patient present with both visceral larva migrans and ocular toxoplasmosis at the same time or even at separate intervals.3,6,12

Epidemiology and Life Cycle of T. canis
The adult dog usually acquires the T. canis parasite by ingesting the parasite’s eggs or second stage larvae found in contaminated soil, infected meat, and feces. The larvae form cysts and reactivation of the larvae during gestation can infect the fetal puppies in the uterus. Following birth, the larvae migrate to the puppies’ lungs and then travel up the respiratory tract to the pharynx, where they are swallowed. They then mature to become egg-laying adult worms in the gastrointestinal tract. Approximately 4 weeks after their birth,
worms begin laying eggs. Older dogs can harbor adult worms that do not lay eggs.\textsuperscript{13} \textit{Toxocara} eggs are found in the soil throughout tropical and temperate climate regions. In the United States and Western Europe, soil from parks and public areas has been found to carry a contamination rate of 10% to 30%.\textsuperscript{14} In Venezuela, a 33% contamination rate was found in a metropolitan area.

Humans are primarily infected through the ingestion of soil and food contaminated with \textit{Toxocara} larvae. After the eggs are ingested, they develop into second stage larvae in the small intestine. They then enter the portal circulation, following hematogenous and lymphatic routes to form cysts in tissue structures.\textsuperscript{15} The parasites reach the eye through the retinal, ciliary, and choroidal circulation. Humans are not natural hosts of \textit{Toxocara}, and the parasite cannot mature into an adult worm in the intestine.\textsuperscript{13}

\textbf{Clinical Presentation}

Ocular toxocariasis is typically unilateral. Patients present with unilateral decrease in visual acuity, strabismus, or leukocoria.\textsuperscript{14,16} Cases with bilateral involvement are extremely rare.\textsuperscript{17} Younger children generally do not report visual changes, even if visual acuity is profoundly decreased, and it is common that parents may seek medical attention only when the signs become striking. As such, diminished visual acuity is frequently detected in routine examination.\textsuperscript{14,16} Impairment of visual acuity and leukocoria are the most common presenting manifestations.

Several ocular presentations have been recognized, the most common of which is granulomatous inflammation in the posterior pole or periphery.\textsuperscript{14,18-20} Some patients may present with a more marked chronic inflammation in the retina and the vitreous known as nematode endophthalmitis.\textsuperscript{5,14}

\textbf{Posterior Pole Granuloma.} In the acute stage, retinochoroiditis appears clinically as a hazy, ill-defined white lesion with overlaying inflammatory cells in the vitreous. As the acute inflammatory reaction subsides, the lesion appears as a well-defined elevated mass ranging from one-half to four disc diameters in size.\textsuperscript{14,21} In some cases, traction bands may extend from the lesion to the optic disc or to the macular area. In the case of chronic granulomatous inflammation, large retinal vessels may infiltrate the mass and disappear into its substance, probably representing retinochoroidal anastomosis (Fig. 1).

\textbf{Peripheral Granuloma.} Ocular toxocariasis can occur as an acute inflammatory process in the peripheral retina and ciliary body. This may either be preceded by mild acute inflammation in the anterior or posterior segment or the eye may be quiet. The peripheral granuloma appears as a hazy, white, elevated mass in the peripheral fundus. It can be associated with retinal folds that may extend from the peripheral mass to the optic nerve head or to other areas of the fundus. In some cases, the traction may lead to heterotopia of the macula, resulting in severe vision loss. It is likely that many cases of “congenital” retinal folds are acquired peripheral retinal granulomas due to \textit{T. canis} (Fig. 2).
Chronic Endophthalmitis. Another common manifestation of ocular toxocariasis is chronic endophthalmitis (Fig. 3). This is usually associated with cicatricial membrane, retinal detachment, low grade anterior uveitis, and posterior synechiae. The cicatricial membrane begins to form in the peripheral quadrant of the fundus where the most severe inflammation lies and progresses across the posterior surface of the lens. Severe vitritis may also manifest as leukokoria (Fig. 4). A yellow–white mass, usually in the peripheral retina, which may resemble an endophytic retinoblastoma, can be seen through a hazy vitreous. *Toxocara* endophthalmitis does not produce much pain or photophobia and external ocular examination reveals only minimal signs of inflammation, usually with no ciliary flush. Hypopyon may develop in severe cases.

A cicatricial stage is characterized by tractional bands that may pull on the retina and ciliary body. Patients with endophthalmitis are usually younger than patients with posterior pole granuloma.

**Atypical Presentation.** Optic nerve granuloma, papillitis, inflammatory iridal mass, intracorneal larvae, motile larvae in the vitreous and retina, and scleritis may occur. We evaluated two cases that presented with vitreous hemorrhage; after the hemorrhage cleared up, the typical fundus changes of a posterior pole granuloma were detected.

**Differential Diagnosis**

*Toxocara* endophthalmitis may closely resemble an endophytic retinoblastoma. Shields et al. found that 42% of patients with presumed retinoblastoma had pseudoretinoblastoma, and 16% of these had ocular toxocariasis. The clinical features that may help differentiate both entities are: (1) the mean age at presentation for retinoblastoma is 22 to 23 months, whereas for ocular toxocariasis it is 7.5 to 8.9 years; (2) retinoblastoma shows tumor growth; (3) there is a family history; and (4) there is lack of inflammation in retinoblastoma.

Vitreoretinal traction, signs of inflammation, and posterior subcapsular cataracts may be seen in ocular toxocariasis. However, these signs are uncommon in patients with retinoblastoma. Computed tomography and B-scan ultrasonography may show the typical tumor pattern in patients with retinoblastoma, with evidence of calcification within the mass. On the other hand, endophthalmitis secondary to toxocariasis does not commonly demonstrate a tumor pattern.

Additionally, ocular toxocariasis may present with eosinophils in the vitreous or aqueous humor without evidence of malignant cells on histopathologic examination. This may be observed in the presence of normal levels of lactate dehydrogenase and phosphoglucone isomerase. Other entities to be excluded are toxoplasmic retinochoroiditis, pars planitis, retinopathy of prematurity, familial exudative vitreoretinopathy, persistent fetal vasculature, Coats’ disease, and organized vitreous hemorrhage.
Diagnosis

The current gold standard to test for systemic or ocular infection with *T. canis* is the enzyme-linked immunosorbent assay (ELISA), which carries both a sensitivity and specificity rate of approximately 90%. Although the Centers for Disease Control and Prevention considers serum ELISA titers of less than 1:32 to be insignificant for the diagnosis of systemic toxocariasis, other institutions have stated that a serum titer of 1:8, or even lower, is sufficient to support the diagnosis if the patient has signs and symptoms compatible with the disease. However, a positive serum titer cannot be used to definitively confirm the diagnosis of ocular toxocariasis, although the absence of serologic evidence of *Toxocara* presence could reduce the odds of this organism being the cause of ocular disease. Authors have found that 31.8% of affected children without signs of ocular toxocariasis exhibited a serum titer of 1:16 or greater. ELISA testing of intraocular fluids has been demonstrated to be of great value in diagnosing ocular toxocariasis.

Treatment

The treatment of ocular toxocariasis depends primarily on the extent of inflammation at presentation and the secondary structural changes in the vitreous and retina that are associated with the disease. In most cases of severe nematode endophthalmitis, numerous complications ensue that frequently result in total blindness in the involved eye. Therefore, prompt treatment is justified in such cases.

**Medical Treatment.** With ocular toxocariasis, the objective of treatment is to reduce inflammation to prevent the formation of membranes that can consequently affect intraocular structures. Periocular and systemic steroids (0.5 to 1 mg/kg prednisone daily) are the mainstays of therapy for eyes with active vitritis. Cycloplegic agents should be employed when signs of anterior segment involvement are present. There have been reports of clinical improvements of ocular toxocariasis treated with antihelmintic agents thiabendazole (25 mg/kg twice daily for 5 days with a maximum of 3 g per day), albendazole (800 mg twice daily for 6 days), or mebendazole (100 to 200 mg twice daily for 5 days). Although it has been proposed that antihelmintic treatment may initiate an intraocular inflammation due to a hypersensitivity response to dead larvae, clinical and experimental evidence indicate that this is not the case. The ultimate utility of antihelmintic therapy remains equivocal.

**Surgical Treatment.** Surgery is reserved for post-inflammatory complications such as persistent vitreous opacification, retinal detachment, and epiretinal membrane formation with vitreomacular or optic nerve traction (Fig. 5). The most common indication for surgical intervention in ocular toxocariasis is retinal detachment. Retinal detachment has been performed in 71% to 88% of ocular toxocariasis cases, with visual improvement in most patients.

**DIFFUSE UNILATERAL SUBACUTE NEURORETINITIS**

DUSN was first described by Gass et al. and Gass and Scelfo in 1978. They described 29 patients between the ages of 5 and 22 years with severe visual loss in one eye, vitritis, mild papillitis, and recurrent crops of evanescent, gray–white lesions affecting the outer retina and pigment epithelium. These lesions are usually followed by progressive loss of visual field, optic atrophy, narrowing of the major retinal vessels, diffuse and focal depigmentation of retinal pigment epithelium throughout the fundus, and a moderate to marked reduction of the b-wave amplitude on multifocal electroretinogram. Previously, this condition was termed “unilateral wipe-out syndrome.”

DUSN is most prevalent in the southeastern United States and the Caribbean, although some cases have been reported in many sections of the United States, Canada, the northern part of South America, Europe, and China.

In the United States, DUSN is probably caused by at least two different nematodes. The smaller one, *Ancylostoma caninum*, measures between 400 and 1,000 µm in length and has a diameter of approximately one-twentieth of its length. It is mainly found in the southeastern United States, the Caribbean, and the northern part of South America. A larger nematode, *Baylisascaris procyonis*, 1,500 to 2,000 µm long, is responsible for DUSN in the northern-midwestern United States and in some parts of Brazil.

**Clinical Manifestations**

Ocular findings in DUSN have been well described by Gass et al. Most patients are young and healthy, with ages ranging from 11 to 65 years (the mean age being 24 years) at the time of the ini-
For the most part, it is a unilateral condition; although uncommon, bilateral cases have been described.\textsuperscript{37,39,40} Many patients, particularly children, may be asymptomatic and visual loss is usually discovered on routine eye examination. Other patients may present with acute onset of multiple, and rapidly changing, central or paracentral scotomata, photopsias, or unilateral vision loss.\textsuperscript{34,35,44-46} In the early stages, inflammation in the anterior segment is uncommon, although keratic precipitates and hypopyon were observed and reported in one patient.\textsuperscript{34,35} Visual acuity may be reduced moderately if the condition is detected early, but it is usually markedly decreased at the time of presentation. The fundus changes, which are the most prominent feature of this syndrome, have been divided into early and late.\textsuperscript{34,35}

The onset of DUSN is subtle and progressive.\textsuperscript{34,35} Patients in the early stages of the disease may present with low vision in the affected eye, mild to moderate vitritis, optic disc swelling, and recurrent crops of evanescent, multifocal, gray–white lesions at the level of the outer retina (Fig. 6). The lesions are typically clustered in one segment of the fundus, and successive crops of these lesions may recur in close proximity to previously affected areas.

The nematode, which often assumes an S-shape or coiled position, should be sought out in the vicinity of the active lesions. In the absence of these white lesions, no other markers exist for the location of the worm. Nematodes propel themselves by a series of slow coiling and uncoiling movements, or by slithering, snake-like movements. The examining light seems to stimulate movement in the nematode and causes it to move deeper into the subretinal space.

\textbf{Figure 5.} (A) \textit{Toxocara} peripheral granuloma with traction fibrotic band extending to the optic nerve. (B) Fundus photograph of the same patient 6 weeks after pars plana vitrectomy.

\textbf{Figure 6.} Early stage of diffuse unilateral subacute neuroretinitis. Note the vitritis, optic disc swelling, and crops of multifocal gray–white lesions.
where the clinician may lose the opportunity to identify it. In such cases, the light stimulus should be discontinued for the organism to reemerge from the deeper structures.\textsuperscript{34-36,43,47}

Occasionally, perivenous retinal exudation and sheathing may be observed. In addition, cystoid macular edema, intraretinal and subretinal hemorrhages, retinal exudation, and neovascularization may present during the early stages of the disease.\textsuperscript{34}

Over a period of weeks to months, late manifestations begin to appear.\textsuperscript{36} Diffuse and focal depigmentation of the retinal pigment epithelium is seen. This is usually less prominent in the central area. Gradual narrowing of the retinal vessels and an increase in pallor of the optic nerve will frequently result in an afferent pupillary defect (Fig. 7). In general, the degree of optic disc pallor and retinal vessel narrowing parallel that of central visual loss, but striking exceptions do occur.\textsuperscript{34,35}

Fluorescein angiography will reveal hypofluorescent lesions that turn hyperfluorescent in the late stages of the test. Dye leakage occurs at the optic nerve level; active lesions and petaloid hyperfluorescence are observed in cases of cystoid macular edema. In more advanced stages of the disease, fluorescein angiography may reveal multiple hyperfluorescent lesions due to window defects secondary to retinal pigment epithelium alterations together with a delay in retinal circulation time.\textsuperscript{35}

The clinical evaluation of 78 patients in Venezuela\textsuperscript{39} showed the typical funduscopic late changes described by Gass et al.\textsuperscript{36} The mean age of these patients was 16.7 years; the presenting visual acuity was 20/400 or worse in 69 patients (84.1%). Additionally, a subretinal nematode was identified in 33 eyes (40.2%). All of the nematodes were small, measuring approximately 400 µm in length.

**Diagnosis**

As mentioned, patients with DUSN suffer progressive vision loss and seek medical attention in the late stages of the disease. Consequently, the clinician should focus on the early recognition of this syndrome because treatment may prevent further deterioration of visual function and may even result in visual improvement.\textsuperscript{34,35} In patients with suspected DUSN, we first suggest an evaluation using indirect ophthalmoscopy with a 20-diopter lens (or in some cases a 14-diopter lens) to locate the crops of evanescent white lesions and to attempt to locate the nematode around these areas. Subsequent biomicroscopy in that area with a 78-diopter lens allows the examiner to definitely identify the nematode.\textsuperscript{34,36} In the absence of white lesions, a careful biomicroscopic search of the entire fundus is necessary to find the worm, and multiple patient visits may be required. It is also possible to identify the parasite by careful examination of fundus photographs that include the suspicious areas.

Fluorescein angiography is not helpful in locating the nematode.\textsuperscript{36} Scanning laser ophthalmoscopy using a blue light can help locate the worm due to the provided advantage of enhancing contrast, improving visualization, and recording a videography of the worms’ movements.\textsuperscript{48}

Multifocal electroretinogram is subnormal in the affected eye during all stages of the disease, with b-wave being more affected than a-wave.\textsuperscript{36} Serologic studies, stool examination, and peripheral blood smears are of little value in diagnosing DUSN.\textsuperscript{10,37} *Toxocara* and *B. procyonis* antibody titers have been proposed as diagnostic tools to try to identify the disease.\textsuperscript{49} No serologic test is currently available for *Ancylostoma caninum*. Because of the possibility of commonly shared antigens by different nematodes or seropositivity unrelated to the actual infecting nematode, interpretation of serologic testing may be subject to error.\textsuperscript{48}

**Etiology and Pathogenesis**

There is no consensus regarding the identification of the subretinal nematode frequently found in DUSN. Reports suggest *B. procyonis, A. caninum,*
Dirofilaria, and a larval form of *T. canis* as possible infectious agents involved in DUSN. However, the larval form of *T. canis* is smaller than the worm that causes DUSN and there is a lack of serologic evidence to support the mentioned reports. In addition, funduscopic manifestations are different than those associated with other forms of ocular toxocariasis and the high prevalence of *T. canis* does not correlate with the scant number of DUSN cases reported.

*A. caninum*, which is a common nematode parasite that infects dogs, is suspected of causing DUSN because it frequently results in cutaneous larval migrans that may later manifest signs of DUSN. The worm can survive for months and even years without changing form and its infective larva measures approximately 650 µm. This better corresponds to the entity described in DUSN. Scanning electron microscopy of a nematode excised from a case of DUSN by means of an eye wall biopsy was compatible with, but not diagnostic for, *A. caninum*.

*B. procyonis* is an intestinal nematode that infects raccoons and skunks. The larva measures between 300 and 2,000 µm, and it has been proposed as the larger nematode responsible for DUSN. Nevertheless, infrequent exposure to raccoons or skunks and the absence of central nervous system involvement make *B. procyonis* a highly unlikely pathogen in DUSN.

The pathogenesis of DUSN appears to involve a mechanical, inflammatory, and toxic assault on the outer retina. A local toxic effect in the outer retina is caused by products left in the worm’s wake, and a more diffuse toxic reaction affecting both the inner and outer retinal tissues ensues. Histopathologic study of an eye believed to be affected by DUSN revealed nongranulomatous vitritis and retinitis. It also showed retinal and optic nerve perivasculitis, extensive degeneration of the posterior retina, mild optic atrophy, mild degenerative changes in the retinal pigment epithelium, and a low-grade, patchy, non-granulomatous choroiditis.

**Differential Diagnosis**

The condition most likely to be mistaken for DUSN is multiple evanescent white-dot syndrome (MEWDS), although in the early stages DUSN may resemble toxoplasmosis, cytomegalovirus, and bacterial abscesses. MEWDS can be distinguished from DUSN by an accompanying history of flu-like symptoms, photophobia, wreath-like hyperfluorescent dots on fluorescein angiography, blind spot enlargement, multiple gray or whitish outer retinal lesions, and decreased electroretinogram recordings. Visual acuity may even return to normal levels in some cases after several weeks or months. On fluorescein angiography, the white lesions in DUSN block the fluorescence in the early phase, whereas in MEWDS the lesions are hyperfluorescent in the early stages of the angiogram. Rarely, one can mistake DUSN for sarcoidosis, presumed ocular histoplasmosis syndrome, and multifocal choroiditis due to the appearance of focal chorioretinal scars scattered throughout the fundus. The absence of

![Figure 8. (A) Late stage of diffuse unilateral subacute neuroretinitis. Note the parasite around the retinal vessel (arrow). (B) Fundus photograph of the same patient after retinal photocoagulation of the parasite.](image-url)
optic atrophy, vitritis, vessel attenuation, and the presence of normal-looking retinal pigment epithelium between punched-out lesions is more likely to be encountered in DUSN. Eyes with central retinal artery occlusion may show some characteristics that look like DUSN. Also, the late stages of DUSN may be confused with retinitis pigmentosa, secondary bone-spicules migration, and posterior subcapsular opacification, but unilaterality is characteristic of a feature of DUSN. Trauma may exhibit some DUSN characteristics such as retinal pigment epithelial changes and optic atrophy.

Treatment

Photocoagulation of the parasite when visible, using 200 to 500 µm, 0.2 to 0.5 second of thermal laser application, is the treatment of choice (Fig. 8), although visual acuity does not significantly improve unless the worm is killed soon after onset of visual loss. Photocoagulation does not cause exacerbation of inflammation and results in prompt and permanent inactivation of the disease; however, the search for the nematode can become a time-consuming and frustrating task. Several oral antihelmintic medications, such as thiabendazole and diethylcarbavazine, have been used in an effort to treat this disease. However, most of the studies reported that only the subretinal worms were killed, probably due to inadequate ocular penetration of the drugs. Hence, it has been suggested that if the worm cannot be found in a patient with a high suspicion of DUSN, a scatter pattern of laser burns in the vicinity of the multifocal active lesions can be performed to alter the blood–retinal barrier prior to administration of the oral medication.

Recently, several studies have demonstrated albendazole as a safe and beneficial treatment modality for these patients. Our group published the results of the use of oral albendazole in 6 patients with DUSN, following a 10-day regimen at 200 mg orally 3 times daily. The nematode was killed and was slowly reabsorbed in three cases. Adverse effects of short-term albendazole treatment were rare.

Findings such as bilateral DUSN and the presence of a nematode in a patient who had undergone successful photocoagulation have been described. In light of such reports, we recommend a course of systemic therapy for all patients with DUSN.

CONCLUSION

Ocular toxocariasis and DUSN may produce severe damage to the intraocular structures, causing significant visual impairment. Although these diseases are not well distributed worldwide due to their poor visual prognosis, it is of great importance that physicians be aware of the variety of clinical forms in an effort to achieve an early diagnosis and treatment.

REFERENCES
