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Nematode infections of the eye: toxocariasis, onchocerciasis, diffuse unilateral subacute neuroretinitis, and cysticercosis

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Ocular toxocariasis may cause a large spectrum of manifestations in the eye, from an asymptomatic posterior granuloma, to total retinal detachment [1]. It represents one of the most common parasitic causes of visual loss throughout the world [2], and it usually affects young children. Other nematodes can cause ocular disease, most of them related to adult large worms. Diffuse unilateral subacute neuroretinitis (DUSN) is a more recently described disorder believed to be caused by smaller nematodes [3,4]. Onchocerciasis and cysticercosis are seen mainly in the developing world.

Toxocariasis

Wilder first recognized nematodes as pathogens in the posterior segment of the eye in 1950. In 1952 Beaver et al described the association of *Toxocara* species with human disease [5]. Toxocariasis is a zoonotic disease caused by the infestation of humans by second-stage larva of the dog nematode *Toxocara canis* or the cat nematode *T cati* [6]. Ocular toxocariasis may affect the eye causing uveitis, posterior and peripheral retinochoroiditis, endophthalmitis, or papillitis, each of which can lead to loss of vision in the affected eye [7].

Epidemiology

Human toxocariasis is probably one of the most widespread zoonotic nematode infections, occurring mainly in areas where the relationship between man, soil, and dog is particularly close [8]. *T canis* is an often encountered canine parasite, affecting dogs, wolves, foxes, and other canidis, whereas *T catis* may be found in domestic cats [9–11]. Human beings are contaminated through ingestion of the ova by geophagia, by eating contaminated foods, or by close contact with puppies. Toxocariasis may manifest itself in the systemic form, visceral larva migrans, or the ocular form, ocular larva migrans. It is rare to see the ocular and visceral forms of the disease at the same time.

Ocular toxocariasis

Clinical features

Toxocara is a well-documented cause of intraocular inflammation in children [11]. Clinical presentation depends on the primary tissue or anatomic site of involvement, which may include the peripheral retina, the vitreous, the posterior pole, or the optic disk. The most common presentation involves peripheral retina and vitreous, occurring separately or together. A hazy white lesion may be seen or in the periphery, often with moderate vitreitis. As the

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inflammation resolves, a peripheral elevated white mass is seen better, and is typically associated with retinal folds extending toward the macula [12,13]. An intraretinal or subretinal mass, or granuloma, is usually seen with the posterior form of disease. Endophthalmitis, with mild or no anterior inflammation, is an uncommon but recognized presentation. Papillitis can also occur, and it is usually caused by an invasion of the optic nerve by the nematode or as an inflammatory response to the organism in another site of the eye. The condition is almost always unilateral and it usually affects children, but also can be seen in adults [7].

Pathogenesis and differential diagnosis

Sprent first described the *T canis* life cycle in 1958 [5]. As mentioned previously, it is a canine roundworm sharing certain characteristics with the feline roundworm *T catis* and with the human roundworm *Ascaris lumbricoides* [5]. Ingested *Toxocara* eggs emerge in the duodenum. The larvae then perforate the intestinal wall, enter the circulation, and can lodge in the eye, most probably by the choroidal blood system. Thereafter the organism can migrate into the subretinal space or vitreous cavity, where it ultimately dies and is encapsulated by an eosinophilic granulomatous inflammatory reaction [4].

Leukocoria is a frequent finding in patients with ocular toxocariasis. The differential diagnosis includes retinoblastoma, endophthalmitis, retinopathy of prematurity, congenital cataracts, persistent hyperplasic primary vitreous, Coats' disease, and various forms of trauma [10,12,13].

Laboratory investigations and therapy

Leukocytosis and hypereosinophilia are present in most patients with visceral larva migrans. Eosinophilia is usually absent in ocular toxocariasis. The presence of larva can be disclosed by tissue biopsy, but because the larvas are rarely able to finish their life cycle in humans, they are not detected on stool analysis. Until the use of the enzyme linked immunosorbent assay (ELISA) test, immunodiagnostic tests lacked sufficient sensitivity and specificity for the diagnosis of ocular toxocariasis. In recent times, however, ELISA has become the main serologic method for detecting visceral larva migrans, and for confirming the clinical suspicion of ocular toxocariasis. ELISA has a reported sensitivity of 78% and a specificity of 92%, but it is known that the sensitivity and specificity of ELISA vary according to the cutoff titer chosen defined as positive [14]. Most of the cases of ocular toxocariasis are diagnosed clinically, but in some patients with opaque media radiologic imaging techniques, such as ultrasonography, ultrasound biomicroscopy, CT, or MRI studies, may be helpful [5,14,15].

Treatment options for *T canis* infection depend on the type and severity of infection. Management of the systemic form of toxocariasis includes the use of systemic anthelmintic agents, antibiotics, or corticosteroids [7]. In patients with ocular toxocariasis, one must have in mind the visual potential of the eye, the amount of active inflammation, and the degree of macular damage. In eyes with active vitreitis, systemic or periocular corticosteroids may represent an important therapeutic tool. Anthelminthics may be used to destroy nematodes and eliminate further migration of the larva, but the parasite may resist such treatment. In some situations, such as to clear vitreous debris, relieve vitreomacular traction, repair tractional and tractional-rhegmatogenous retinal detachments, and remove the posterior hyaloid, posterior vitrectomy can be performed [16–18].

Onchocerciasis

Onchocerciasis, also named river blindness or Robles disease, is a parasitic disease caused by the microfilariae *Onchocerca volvulus* [19]. *O volvulus* is transmitted by the bite of the black *Simulium* fly, which breeds in rapidly flowing waters. The clinical manifestations of onchocerciasis range from no skin or eye lesions to very severe skin involvement and blindness.

Epidemiology

Onchocerciasis is an endemic disease in Africa and Central America, but pockets of the disease also exist in South America. In Africa, the clinical and epidemiologic characteristics are different from other places. In the savannas, for example, about 40% of the patients fewer than 40 years old develop blindness [20]. Because of the high prevalence of this disease in Africa it has become one of the main causes of blindness worldwide. According to the World Health Organization, onchocerciasis affects at least 18 million people worldwide, and 300,000 are blind from the disease [21]. In Central America, the clinical presentation seems to be the same, but ocular involvement occurs earlier. In Brazil, for example, the disease occurs in the Yanomanis Indians in the north part of the country [22]. In this population, the ocular findings seem to be restricted to the cornea and blindness tends not to occur [23].

Ocular features

The ocular manifestations of onchocerciasis are caused by the presence of dead parasites within the eye. The microfilariae penetrate the eye by the bulbar conjunctiva at the limbus, then invade the cornea, aqueous humor, and iris. They reach the posterior segment by the circulation or ciliar nerves, which supply the peripheral retina and choroid.

Puntate keratitis is often the first manifestation of onchocerciasis, the patient referring only to conjunctival itching. The microfilariae then migrate to the cornea and eventually die causing a corneal opacity referred to as *cracked-ice* or *snowstorm*. In late stages, the corneal lesions turn to scar tissue producing sclerosing keratitis as described by Pacheco-Luna [24]. An iridocyclitis also can be seen and atrophy of the iris may occur. Other complications, such as cataract and glaucoma, also may be present. Chorioretinal lesions typically begin in the periphery with pigmented lesions, sheating of the retinal vessels, and visual field constriction. Optic atrophy tends to occur late in the disorder. Macular edema can also be found.

Diagnosis and therapy

Diagnosis of onchocerciasis is done by the microfilariae or adult worms from skin or subcutaneous nodules obtained by biopsy, or by identification of live microfilariae in the aqueous humor. The first choice to treat this condition is the macrofilaricidal agent ivermectin, which is given as a single oral dose of 150 μmg/kg. Annual ivermectin therapy seems to improve intraocular inflammation [25–27]. Although used routinely, vector control strategies tend to have limited success.

Diffuse unilateral subacute neuroretinitis

Diffuse unilateral subacute neuroretinitis (DUSN) was first described by Gass et al in 1978 [4,28]. It usually affects healthy patients and can be divided into two stages: the early stage, which is characterized by visual loss, vitreitis, papillitis, and clusters of multiple evanescent, gray-white outer retinal lesions; and the late stage, characterized by optic atrophy, retinal artery narrowing, diffuse pigment epithelial degeneration, and an abnormal electroretinogram [29]. DUSN is caused by two as of yet unidentified species of nematode, both of which can cause progressive ocular damage [30–33].

Epidemiology

Initially described in the Southeastern and Midwestern parts of the United States and the Caribbean islands, DUSN has also been reported in other parts of North America, in South America, and in Northwestern Europe [29,30]. In Brazil DUSN is considered an important cause of posterior uveitis in children and young healthy adults [34–37].

Clinical features

Because prompt treatment may prevent visual loss, it is very important that the diagnosis of DUSN be made early. Most patients with DUSN, however, present with advanced disease. The onset is frequently insidious, and patients usually complain of unilateral paracentral or central scotoma, ocular discomfort, or transient obscurations of vision [28]. Patients are usually in good general health. The disease is characterized by unilateral vitreous inflammation, optic disk swelling, and the presence of clusters of gray-white lesions in the deep retina. DUSN is often misdiagnosed as multifocal choroiditis, multiple evanescent white dot syndrome, acute posterior multifocal placoid pigment epitheliopathy, or nonspecific optic neuritis and papillitis. Late stages of the disease include narrowing of the retinal vessels, optic nerve atrophy, and the development of focal or diffuse atrophic changes in the retinal pigment epithelium [37,38]. Recently, some cases of bilateral DUSN have been described in Brazil by de Souza et al [39].

Diffuse unilateral subacute neuroretinitis is caused by a solitary nematode of two different sizes migrating in the subretinal space. The smaller nematode, measuring 400 to 700 μm in length, seems to be endemic to the southeastern United States, the Caribbean islands, and Brazil. The larger nematode, measuring 1500 to 2000 μm in length, has been described in the northern Midwestern United States [40]. The identity of the two worms is unknown. *Ancylostoma caninum* and *T canis* have been suggested to represent the smaller nematode [30,31], but the clinical picture and the low rate of serologic evidence of infection with *T canis* seems to make *Toxocara* species an unlikely cause of DUSN [4]. Some patients with DUSN have cutaneous larval migrans, before or concomitant with the answer of ocular symptoms, which has led some authors to suggest *A caninum*. *Baylisascaris procyonis*, a nematode found in the intestinal tract of a raccoon, has been suggested to be the larger nematode. Tropical varieties of *T canis* and *A caninum* have been suggested to cause

DUSN in Brazil based on recent morphologic investigations performed by de Souza EC et al (personal communication, 2001).

Laboratory investigations and therapy

Patients with DUSN usually have a negative systemic evaluation. Atypical presentations should suggest other diagnosis, however, and laboratory tests should be examined as indications. Electroretinography has value, because most patients with DUSN have an abnormal electroretinogram, even if tested early in the course of the disease. Electroretinogram is rarely extinguished completely, which can help differentiate DUSN from the tapetoretinal degenerations [3,41]. Recently, it has been noticed that Goldman perimetry may be useful to evaluate remaining visual field before and after treatment of the disease (de Souza EC, personal communication, 2001).

Therapy is limited in patients with DUSN. If the worm is visualized, laser treatment of the nematode can be highly effective and may improve visual acuity and inflammatory ocular signs, according to Gass [35,42]. The worm can be induced to migrate away from the macula before treatment by directing a bright light on it. The worm may also be surgically removed for identification purposes [31]. Chemotherapy with anthelmintic drugs, such as thiabendazole, may be the only treatment available when a worm cannot be visualized, but success is often difficult to document.

Treatment with corticosteroids has shown transient suppression of the inflammation without altering the final outcome of the disease [34,42]. Patients with retinal complications caused by the inflammation may benefit from surgical intervention in some cases.

Cysticercosis

Cysticercosis is a common cause of ocular inflammation in some developing countries. *Cysticercus cellulosae* is the larvae of *Taenia solium*, and is the most common tapeworm to invade the eye. The ingestion of *T solium* eggs, which occurs when undercooked pork infected with cysticerci is ingested, causes cysticercosis [43]. The soil and the environment are contaminated when sanitation is poor. Usually the eggs develop into larva only when they are ingested by an intermediate host, such as pig, but humans can play this role when eggs are ingested in contaminated food and water [44]. Once larvae penetrate the intestinal wall and gain access to the lymphatics or blood vessels, they can disseminate to various organs, such as the skin, brain, and eye. As mentioned previously, this infestation is prevalent in parts of the developing world where poor hygiene is common, such as Central and South America, India, Southeast Asia, China, and certain parts of Africa [45].

Ocular features, diagnosis, and therapy

Several sites in the eye can be affected, including the subretinal space, the vitreous, the subconjunctival space, the anterior chamber, and the orbit. It seems that larvae use the posterior ciliary arteries to gain access to the subretinal space [46]. Diagnosis is typically made by observing *Cysticercus* within the eye. The larvae can be seen in the vitreous once they cross the retina, leaving a retinochoroidal lesion or scar at the point of exit. ELISA for antibodies to endemic types of *Taenia* may be helpful, and in some cases eosinophils are evidence. Slit lamp examination or B-scan ultrasonography may show movement of living cysts in some cases. Medical treatment of cysticercosis may cause serious visual loss, because the degeneration of the cyst can produce severe inflammation [47]. Surgical removal of intraocular cysts is usually recommended [48]. Vision may be irreversibly affected when the macula is involved.

Summary

Nematode infections of the eye are common in different parts of the world, but some are usually encountered only in developing nations, such as onchocerciasis and cysticercosis. Ocular toxocariasis is a well-known cause of unilateral ocular disease affecting mainly children and young adults, and is usually caused by *T canis*. Prevention of ocular toxocariasis is based on such measures as appropriate health care for dogs and cats, including regular anthelmintic treatments, preventing contamination of the environment with feces, and promoting responsible pet ownership [1,49–51]. Onchocerciasis is caused by infection with the filarial parasite *O volvulus*, and occurs in endemic areas along rivers and streams. In hyperendemic areas almost every person is infected and about half of the population is eventually blinded by onchocerciasis. Because of this, elimination of host-vector contact is very important. DUSN is caused by a motile nematode and is found in the Southeastern and Midwestern United States and in many parts of the world. In Brazil, DUSN is becoming an important cause of posterior

uveitis in children and young healthy adults. The destruction of the worm during the early stages of the disease can prevent progression of the visual loss. It is important to remain aware of this entity, not only in areas where it has been described, but also in regions not yet identified as being endemic [52]. Cysticercosis is caused by the encystment of the larvae of the tapeworm *T solium*, and usually results from ingesting eggs from food, water, or other material contaminated with human feces. Surgical removal of the cyst is usually indicated when possible.

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