Characterization of the parasite-induced lesions in the posterior segment of the eye

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Ocular lesions are frequently associated with different parasitic infections. The classes of infection include protozoa, nematodes, cestodes, and ectoparasites. Ocular parasitic infections can manifest in any part of the eye; the disease manifestations are frequently characterized as either posterior or anterior eye disease. Parasite-induced lesions may be due to damage directly caused by the parasite, indirect pathology caused by toxic products or the immune response initiated by infectious parasitism. This review characterized the parasite-induced lesions in the posterior segment of the eye. Prompt diagnosis and early treatment of these lesions can reduce ocular morbidity. The method of the literature search was conducted on PubMed, Elsevier Scopus database, and Google Scholar with no limitation on the year of publication databases. It was limited to English articles published for ocular lesions in clinical studies and was focused on parasitic infections of the eye.

Key words: Ocular lesions, parasitic infections, posterior segment

Ocular lesions caused by different parasites in human are more prevalent in geographical areas where environmental factors and poor sanitary conditions favor the parasitism between man and animals. Dietary history, travel history to endemic areas, clinical features of inflammatory eye diseases, and advances of diagnosis are important to determine the source of infection.[1] Parasitic organisms can infect the eye either by direct introduction through trauma or surgery, by extension from infected adjacent tissues, or by hematogenous dissemination to the eye.[2]

Ophthalmic manifestations of parasitic infections may involve either the anterior or posterior segment of the eye. Posterior segment involvement includes choroiditis, retinichoroiditis, retinal vasculitis, retinal hemorrhage, central retinal vein thrombosis, papilledema, retinal detachment, orbital cysts and optic atrophy that lead to permanent retinal damage and visual loss.[3-5] Establishing the diagnosis of parasitic infections of the eye is accomplished by a combination of the clinical history, clinical examination, and accurate identification of the causative organism. A combination of antiparasitic drugs and surgery is the usual therapeutic approach to most parasitic eye infections.

Protozoa Involving the Posterior Segment of the Eye

Toxoplasmosis

Toxoplasmosis is caused by the protozoan parasite *Toxoplasma gondii*. Infection may be acquired through ingestion

raw infected meat, contaminated vegetables or water, blood transfusion, organ transplantation and congenitally, across the placenta from the mother to the fetus.[6,7] *T. gondii* infects up to a third of the world population[8] and toxoplasmic retinochoroiditis is the most common cause of posterior uveitis.[3]

Toxoplasmic retinochoroiditis occur either immediately or later after the initial infection or in reactivation.[9,10] Recurrent attacks of toxoplasmic retinochoroiditis result from rupture of dormant cysts in the retina and release of viable parasites that induce necrosis and inflammation or hypersensitivity reaction to parasite antigen.[11] Moreover, it was found that *T. gondii* infection induced DNA damage in retinal cells.[12] The intensity of damage to retina and choroid depends on the severity of the infection and the associated inflammatory reaction. Within the retina, lysosomal and other autolytic enzymes released by inflammatory cells predominantly macrophages and lymphocytes are thought to contribute to the pathogenic mechanisms of retinal tissue damage.[13]

Clinical diagnosis of toxoplasmic retinochoroiditis is based upon ophthalmoscopic examination. Typical fundus abnormalities present as the grey-white focus of retinal necrosis with adjacent choroiditis, vasculitis, hemorrhage, and vitreitis [Fig. 1].[14] Active inflammation lasts about 6 weeks, at which time the lesion begin to regress, leaving behind

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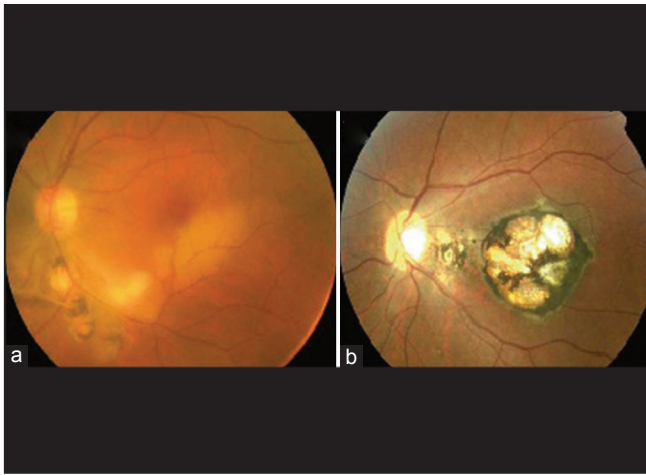
Figure 1: (a) Fundus photograph of the left eye of a patient with ocular toxoplasmosis shows an active focus of retinochoroiditis adjacent to old pigmented scars inferotemporally and an area of retinal whitening along the inferior temporal arcade consistent with a diagnosis of branch retinal artery occlusion. (b) Fundus photograph shows congenital toxoplasmosis involving the macula

Figure 2: Retinal features of cerebral malaria, revealing multiple white centered hemorrhages, macular whitening (indicated by black triangles) and orange discoloration of vessels (indicated by the black arrow)

a characteristic macular pigmented scar on the retina.[15] However, atypical lesions also occur, including punctate outer retinitis, neuroretinitis, and papillitis and their toxoplasmic origin may be demonstrated by laboratory testing or by a positive response to specific treatment.[16]
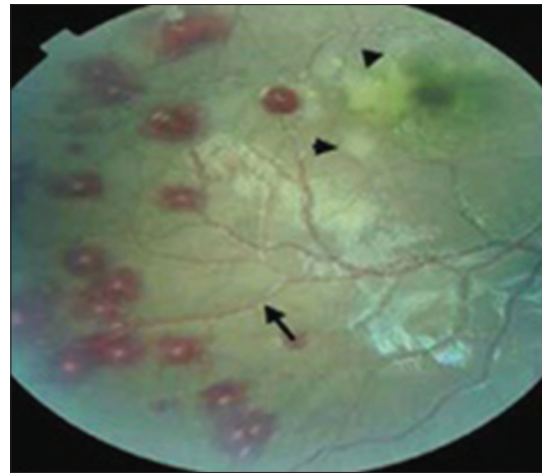
Laboratory diagnosis of toxoplasmosis is based on detection of antibodies and *T. gondii* DNA using polymerase chain reaction (PCR) that support clinical findings.[17] The combination of pyrimethamine and sulfadiazine remains the mainstay for treatment and prophylaxis of toxoplasmosis.[18]

Malaria

Malaria is a mosquito-borne infectious disease caused by intraerythrocytic protozoa of the genus *Plasmodium*. Ocular manifestations associated with malaria were recorded by several investigators.[4,19] Malarial retinopathy consists of four main components: Retinal whitening; vessel discoloration of retinal vessels to orange or white; hemorrhages; and papilledema [Fig. 2].[20] Cotton wool spots are also seen and are distinct from retinal whitening. The vessel changes and pattern of retinal whitening appear to be unique to this disease.[4] The central mechanism causing malarial retinopathy appears to be a microvascular obstruction that strongly supports the sequestration of erythrocytes in small blood vessels.[21] Other eye-related findings include amaurosis fugax, optic neuritis, glaucoma, panuveitis, oculomotor paralysis, and cortical blindness. It is held that retinal hemorrhage is a poor prognostic indicator in cerebral malaria.

The pathogenesis of disease with respect to malaria can generally be traced to problems related to the physical effects of the parasite (microvascular obstruction and hemolysis) and the direct metabolic effects of the parasite (tissue hypoxia and hypoglycemia). In addition, retinal hemorrhage is thought to be a consequence of anemia.[22]

Papilledema and retinal hemorrhages can be visualized with an ordinary direct ophthalmoscope while the retinal whitening and vessel abnormalities that are found in the peripheral retina require indirect ophthalmoscopy.[4] The definitive diagnosis of malaria is made by microscopic identification of the parasite in the blood smear. Several methods can be used alternatively including serological immunoassays, antigen-based rapid diagnostic tests, and molecular amplification methods.[23-25] Treatment of ocular manifestations relies on treating the systemic infection.

Visceral leishmaniasis

Leishmaniasis is a tropical infection caused by the protozoan, belonging to the group of *Leishmania* that causes Old World and New World disease. These are typically divided into the cutaneous, mucocutaneous, visceral, viscerotropic, and disseminated disease. Visceral leishmaniasis or kala - azar is a systemic disease caused by *Leishmania donovani* parasite. The concurrent presence of visceral leishmaniasis with ocular involvement has been reported.[26]

Ocular leishmaniasis is a sight-threatening condition that needs to be rapidly recognized and treated to avoid permanent visual loss. It can present with retinichoroiditis, central retinal vein thrombosis, papilledema, and flame-shaped retinal hemorrhages. Retinal changes in visceral leishmaniasis include focal retinal whitening, cotton wool spots, hemorrhages, as well as increased vessel tortuosity.[5] There are few case reports of ocular leishmaniasis. In 2003, in Spain, a patient with the sudden visual loss caused by retinal hemorrhage was presented. On a systemic evaluation, he was found to have visceral leishmaniasis and treated with pentavalent antimonials.[27]

Retinal changes are observed by retinal photography. Laboratory diagnosis of visceral leishmaniasis is made by direct demonstration of organisms on tissue smears or biopsy, culture on Novy-MacNeal-Nicolle medium, the demonstration of the parasite in splenic or bone marrow aspirate where amastigote can be seen or immunodiagnosis by demonstration of parasite antigen.[28] Treatment of choice is pentavalent antimony-containing compounds.[29]

Giardiasis

Giardiasis is the most common waterborne parasitic infection of the human intestine worldwide. The etiological agent,

Giardia duodenalis (syn. *Giardia intestinalis*, *Giardia lamblia*), is a flagellated, binucleated protozoan parasite which infects a wide array of mammalian hosts.[30] *Giardia* is transmitted through the ingestion of cysts in contaminated food or water, or directly via the fecal/oral route. Giardiasis can present with a broad range of clinical manifestations from asymptomatic to acute or chronic diarrheal disease.
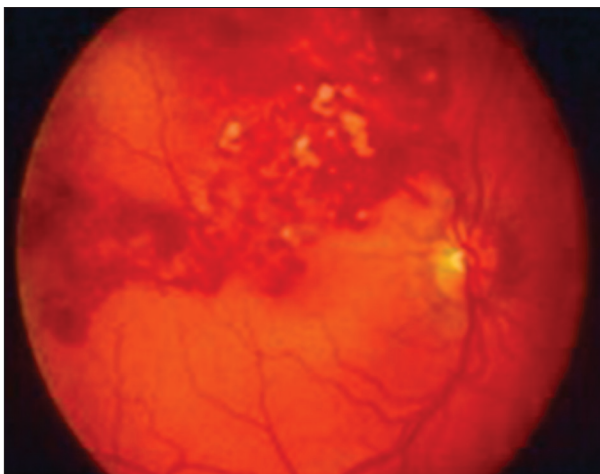
Ocular complications such as iridocyclitis, choroiditis, and retinal hemorrhages have been reported to be associated with giardiasis. Khalifa *et al*.[31] described a "salt and pepper" degeneration (punctuate areas of normal hyperpigmentation on a light yellow pink-retina) involving the retinal pigmented epithelium in children suffering from Giardiasis [Fig. 3]. These lesions are thought to be caused by damage to the cells of the retina, accompanied by the release of pigment granules in retinal layers, where they can be seen as blackish dots.[32] The possibility of direct invasion by the parasite is not thought to be part of the pathogenesis. It has been suggested that the pigmented degeneration may result from toxic metabolites produced by the parasites.[33] Enteric inflammation may lead to uveitis via a triggering agent that crosses intestinal mucosa. Extraintestinal manifestations are considered immunologically mediated, with circulating immune complexes found in patients with ocular involvement.[34] Molecular mimicry and human leukocyte antigen-B27 have also been implicated, whereby antigenic cross-reactivity results in antibody production against host cells.[35]

Finding of *Giardia* cyst stage in the fecal smear or identification of *Giardia* antigen may help support the diagnosis of ocular giardiasis. However, ocular giardiasis is generally made by exclusion and demonstration of improvement in ocular findings following a course of treatment with antigiardial agents.[36] Metronidazole or albendazole is the treatment of choice.

Nematodes Infections Involving the Posterior Segment of the Eye

Toxocariasis

Toxocara canis and *Toxocara cati*, which infect dogs and cats respectively, may cause infection in humans with a wide spectrum of clinical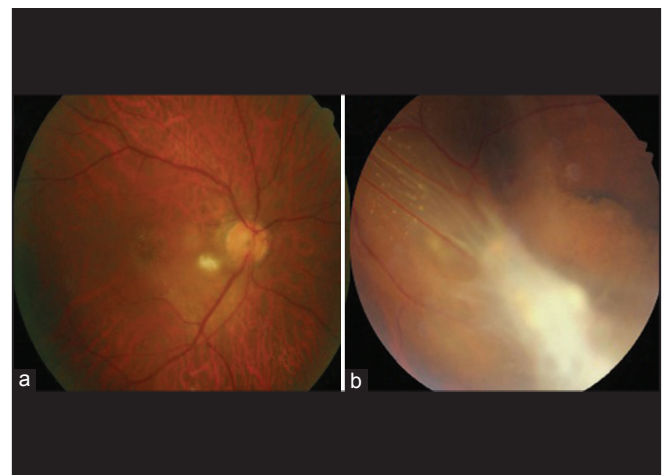 symptoms and morbidity. Humans, typically children, acquire the infection by ingestion of the embryonated eggs usually from contaminated raw vegetables or infected raw meat, and or contaminated water. Dog ownership and pica (geophagia) have been highly associated with *Toxocara* infection.[37,38]

Ocular larva migrans is typically caused by migration of *Toxocara* larvae through the choroidal and retinal vessels into the posterior segment of the eye, or occasionally through the optic nerve via the central nervous system.[39,40] Ocular toxocariasis is unilateral disease in 90% of patients, which typically presents as retinal granuloma, a yellowish or whitish inflammatory mass in the posterior pole or peripheral retina. Granuloma itself or other comorbid conditions such as an epiretinal membrane, macular edema, and retinal detachment can lead to permanent retinal damage and visual loss [Fig. 4].[41]

Diagnosis of ocular toxocariasis depends on a combination of the clinical diagnosis through the identification of typical features by fundoscopy, the finding of specific antibodies in the aqueous humor, and histopathologic identification of dead larvae in the center of eosinophilic granuloma of surgically obtained specimens. The method of choice for routine diagnosis is the enzyme-linked immunosorbent assay (ELISA) using the excretory-secretory antigens of infective larvae of *T. canis*.[38,42] Imaging modalities can provide additional information in many patients.[43] Optical coherence tomography of posterior granulomas usually demonstrates a highly reflective mass located above retinal pigment epithelium.

Ocular toxocariasis can be treated medically or surgically, depending on the severity of intraocular inflammation and comorbid conditions. Medical therapy with a systemic or topical corticosteroid is effective to reduce intraocular inflammation and may reduce vitreous opacification and membrane formation, but it has limited efficacy to resolve structural complications in the retina. Antihelminthic treatment by albendazole, diethylcarbamazine can also be used, particularly with concomitant extra-ocular toxocariasis symptoms. Surgical removal or laser photocoagulation and

Figure 3: Typical salt and pepper appearance of the retina in a child infected with *Giardia lamblia*

Figure 4: Fundus photographs of retinal granuloma in patients with ocular toxocariasis. (a) Posterior pole granuloma appears as an oval, white lesion in the posterior pole of the retina. (b) Peripheral granuloma presents with an amorphous whitish mass with tractional membrane and retinal detachment

cryotherapy can be used to destroy ocular granulomas. The successful surgical outcome was achieved in patients with epiretinal membrane, vitreous opacity, and retinal detachment by providing structural modification, i.e., membrane peeling, removing vitreous opacification, or retinal reattachment that result in stability or improvement in visual function.[41,42,44]

Oncocerciasis

Onchocerciasis, also known as river blindness, is an insect-borne disease, caused by a nematode worm, *Onchorcerca volvulus*. It is the second leading infectious cause of blindness. Ocular onchocerciasis is characterized either as posterior or anterior eye disease that correlate with the location of microfilariae. The predominant ocular findings are punctate keratitis, sclerosing keratitis, iridocyclitis, retinichoroiditis, and optic atrophy.[45] Retinichoroiditis is due to the presence or migration of microfilariae in these layers of the eye as well as the host's response to the migration. The lesions usually involve both eyes and typically appear as focal areas of depigmentation with atrophy of the retinal pigment epithelium [Fig. 5].[14] Subretinal fibrosis may occur in advanced lesions. In addition, peripapillary chorioretinitis can result in optic nerve dysfunction secondary to optic nerve edema and optic neuritis, leading to optic atrophy and eventually blindness.[46,47] Induction of posterior ocular onchocerciasis is thought to involve autoimmune responses and cross-reactive proteins. *O. volvulus* protein was found to be cross-reactive with a 44-kDa human retinal protein.[48,49]

Slit lamp examination can be used to visualize the ocular findings associated with onchocerciasis. However, typically nematodes are not visualized, and the classic lesions in the setting of an appropriate history and antecedent skin findings can lead to the correct diagnosis. Serology can also be used to detect exposure to *O. volvulus* with high sensitivity and specificity. ELISA and western blot techniques have been used to quantitatively detect antibodies to *O. volvulus* antigens in the skin, tears, and urine. It has shown that a serum antibody test card using recombinant antigens was successfully used to detect *O. volvulus*-specific IgG4.[50] A positive IgG4 result indicates active infection. Antigen detection dipstick assays, PCR, ultrasound of the nodules, and sclerocorneal biopsy have also been suggested to confirm the diagnosis.[51]

Ivermectin is the most acceptable drug used for mass treatment of onchocerciasis. It has been shown to delay the development of optic atrophy and reduce the visual field loss.[45,52] Moreover, chorioretinal lesions may be treated surgically by vitrectomies or laser photocoagulation.

## Cestodes Involving the Posterior Segment of the Eye

Ocular cysticercosis

Human cysticercosis is a parasitic infection caused by *Cysticercus cellulosae* larvae of *Taenia solium* (pork tapeworm). It is acquired by ingestion of contaminated food containing ova of *T. solium*. Human cysticercosis mainly affects the central nervous system causing focal neurological deficit and signs of increased intracranial pressure. Ocular involvement is well recognized and includes orbital intraocular, subretinal, and optic nerve lesions.[53,54] Cysticercus larva found its way to the eye through the posterior ciliary artery and enter the subretinal space at the retina and reach the vitrious humor as a free floating cyst [Fig. 6].[14] Intraocular cysticercosis in posterior segment usually presents with reduction of vision, seeing floaters, subretinal cysts, and associated retinal detachment. The cysticercus lesion gradually increases in size, and may lead to blindness. It can even mimic with retinoblastoma.[55] When the intact cyst remains viable, it evokes a little or no inflammatory response. Once the cyst ruptures, an antigenic toxic material leaks from the cyst and induces an inflammatory reaction, such as vitritis, uveitis, and sometimes endophthalmitis.

While cysticercosis may be detected by clinical examination, imaging studies may be useful in some situations. In one case report, a B-scan revealed a subretinal subchoroidal cyst with a thick wall containing well defined intracystic echogenic entities representing scolices, and associated retinal detachment.[56] In addition, magnetic resonance imaging (MRI) of the orbit[57] and supporting investigations such as serology (ELISA, immunoblot) was found to be confirming the suspicion for cysticercosis.
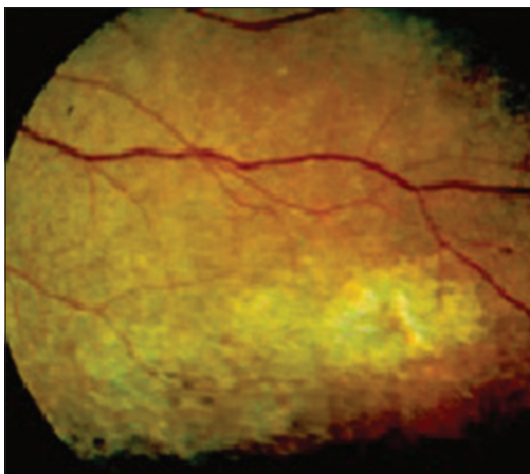
Figure 5: Fundus photograph of a patient with onchocerciasis shows peripheral chorioretinal changes with pigment dispersion and focal areas of atrophy
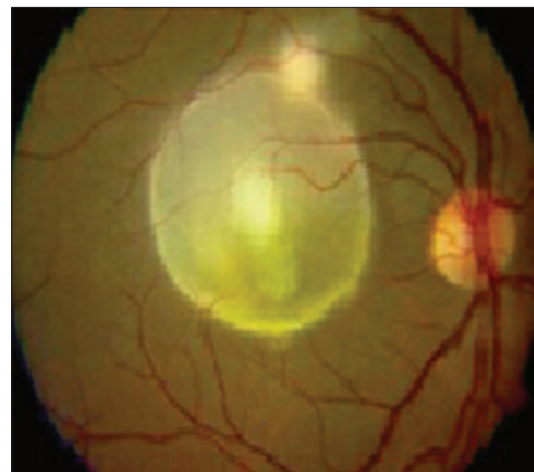
Figure 6: Fundus photograph in a patient with cysticercosis shows a live submacular translucent cyst with clear media

Initial medical treatment of intraocular cysticercosis with antihelminthic drugs like albendazole or praziquantel has not proven to be particularly useful. Consequently, surgical removal of the parasite is the treatment of choice.[58] The identification is confirmed by histological examination. It is possible to carry out mitochondrial DNA analysis on histopathologic sections.[59]

Ocular hydatid cysts

Hydatid disease is caused by larvae of the dwarf tapeworm of dog (*Echinococcus granulosus*). The oncospheres that hatch from ingested eggs penetrate the intestine and can then be carried, via the portal and systemic circulations, to almost any organ of the body, where they may develop into hydatid cysts.[60] Orbital hydatid cysts cause 1–2% of all hydatid lesions.[61] Usually, orbital hydatid cysts are located in retrobulbar tissues, either within the muscle cone (up to 60%) or outside in the superolateral or superomedial angles. The orbital hydatid cyst is generally unilateral. Most affected are children and young adults.[62] Orbital hydatid cysts usually present in the form of slowly progressing painless unilateral proptosis.[61] The most common presenting clinical symptoms and signs are nonpulsatile, nontender proptosis, visual disturbances, disc swelling, diplopia, chemosis, eyelid edema, and conjunctivitis.[63] Loss of vision is probably related to optic nerve dysfunction secondary to the pressure effects caused by the large size of the cyst.[62]

Diagnosis of orbital hydatid cyst is by computed tomography and MRI. The only definite treatment for orbital hydatid cyst is surgical removal without rupture. Postoperative treatment with albendazole is of great importance if there is spillage intraoperatively to prevent secondary dissemination with local recurrence.[62]

Ocular coenurosis

Coenurosis is caused by infection with *Coenurus cerebralis*, the larval stage of the canine tapeworm *Taenia multiceps* species. Human infection results from accidental ingestion of eggs in contaminated food or water. Eggs hatch, lodge into subcutaneous tissue, eyes or brain, and coenuri develop over approximately 90 days.[64] It is suggested that the larvae enter the eye by way of ciliary arteries or direct inoculation to the conjunctiva. Coenurus can develop in the vitreous humor and may affect retina and choroid. The degree of damage to vision depends on the size of the coenurus and the extent of choroidoretinal lesions. The ophthalmic findings related to severe optic neuritis and/or early stage neuroretinitis that attributed to direct stimulation during larval migration from capillaries radiating the optic disc, or immune pathological reactions or toxic reaction.[65]

The onset of inflammatory responses results in a red and painful eye, followed by the development of glaucoma, retinal fibrosis, and ultimately blindness as the final result of the infection. Diagnosis of ocular coenurosis can only be achieved by surgical removal. The anthelminthic albendazole and corticosteroids are often used to treat ocular lesions.[66]

Internal Ophthalmomyiasis

Ophthalmomyiasis is an ocular invasion by parasitic larvae (maggots) of certain flies in the order *Diptera*.[67] It affects humans either directly by laying eggs or depositing larvae on the conjunctiva or the eyeball, or indirectly, through dirty hands or the bites of infected insects. Internal posterior ophthalmomyiasis is characterized by a different clinical course from asymptomatic ophthalmomyiasis, with accidental discovery to a sudden loss of vision due to severe uveitis and retinal detachment. In the subretinal space, larvae can grow to up to 3–5 mm.[68] Subretinal tracks are a recognized manifestation of posterior segment internal ophthalmomyiasis leading to vision abnormalities, which initially prompted the patient to seek medical evaluation. Subretinal tracks are usually unilateral, but bilateral subretinal tracks were also reported.[69,70]

Early recognition of this condition, when tumors and other conditions remain suspect, may preclude unnecessary invasive surgical procedures, including enucleation.[69] Ophthalmoscopy of the affected eye disclosed characteristic subretinal depigmented linear tracks and a larva within the vitreous. On ultrasound scan, a mobile foreign structure was detected.[68] The treatment of choice is laser photocoagulation or vitrectomy with larva removal and intraocular steroids.[71]

Conclusion

Better awareness among optometrists and ophthalmologists could result in earlier diagnosis of ocular lesions induced by the parasitic infection, leading to earlier treatment and prevention of severe vision loss.

Conflicts of interest

There are no conflicts of interest.

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