Review Article

Ocular Parasitosis Caused by Protozoan Infection during Travel: Focus on Prevention and Treatment

Abstract

International travel is rising quickly worldwide. Many people travel to tropical and subtropical areas, where there has been increasing exposure of travelers to infectious pathogens. Ocular parasitic infections are more prevalent in these geographical areas and they can lead to morbidity and mortality, often due to late or misdiagnosis due to the unfamiliarity of health staff with these diseases. This is an up-to-date comprehensive review article that familiarizes physicians with ocular signs and symptoms, treatment, prevention, and geographic distribution of some parasites associated with travel.

Keywords: *Acanthamoeba, American trypanosomiasis, eye, giardiasis, leishmaniasis, malaria, parasitosis, protozoan infection, toxoplasmosis, travel*

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Introduction

International travel is rising quickly worldwide.[1] In 2015, the number of travelers exceeded 1.2 billion and it is estimated that it may reach 1.6 billion in 2020 in all countries.[2-4] Many of them travel to tropical and subtropical areas and participate in outdoor activities.[3] Travel to such places and these behavioral habits cause increasing exposure to infectious pathogens and travelers can easily acquire and transmit these diseases.[5,6] Ocular infections caused by various parasites in humans are more prevalent in tropical and subtropical geographical areas. These infections can lead to ocular morbidity and mortality largely because of misdiagnosis, often from unfamiliarity of healthcare workers with the disease course.

For identification of the causes of ocular infection, matching general and ocular symptoms and signs with travel history to endemic areas, dietary history, and advances in diagnosis are important.[7] This article familiarizes ophthalmologists and general physicians with some ocular parasites. For each disease, we describe the causative agent, geographic distribution, clinical ocular presentation, diagnostic methods, treatment, and prevention in travelers.

Methods

A literature search was performed using PubMed Medline until 2016. To collect material for this study, a detailed search of the PubMed database was performed using any term related to ophthalmology. The terms were as follows: "eye," "vision," "visual," "optic," "lens," "retina," "uvea," "choroid," "cilia," "cornea," "sclera" AND Giardiasis, Leishmaniasis, Malaria, *Acanthamoeba*, American trypanosomiasis, Toxoplasmosis, AND travel.

Based on this research, the total number of articles accounting for giardiasis was 47, 380 for leishmaniasis, 1362 for malaria, 3988 for *Acanthamoeba*, 232 for American trypanosomiasis, and 4801 for toxoplasmosis. Articles published other than English language, lacking full-length forms, and those published before 1990 (totally 5507 papers) were excluded from this review. Studies in English language emphazing on ocular manifestation of these infections and their associations with travel were subjected (2763). All searches were combined, and we removed duplicate manuscripts and irrelevant articles by reading their titles and abstracts (122 of 2763). The electronic search was classified using the following phrases: travel, ocular infection, ocular parasitic presentation, diagnosis, treatment, and prevention.

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Results

The most important ocular diseases caused by protozoans include giardiasis, leishmaniasis, malaria, *Acanthamoeba*, American trypanosomiasis, and toxoplasmosis. Treatment and prevention recommendation are summarized in Table 1.

Giardiasis

Giardiasis is caused by an enteric flagellated protozoan parasite of the genus *Giardia*. *Giardia* is transmitted through ingestion of cysts in contaminated food or water, or directly through the fecal/oral route.[8]

In one study, the risk of travel-associated giardiasis was estimated at 5.3 per 100,000 travelers with highest incidences in travelers from the Indian Subcontinent, East and West Africa, South and South East Asia, and South and Central America.[9-11] In addition, the highest risk was seen in the youngest age group, with a decreasing risk with higher age.[11] Caucasian ethnicity, long travel time (more than 32 days), traveling to South or South East Asia, afebrile presentation, and presenting with gastrointestinal symptoms were all associated with giardiasis in returned tropical travelers.[12] The peak incidence of giardiasis was shown in travelers returning from South Asia, the Middle East and South America.[13]

Table 1: Recommended treatments and preventions for ocular parasitosis caused by protozoan infection during travel

Disease/infection	Causative agent	Prevention	Treatment agent	Dosage
Giardiasis	*Giardia lamblia*	Avoidance of contaminated water and foods. Avoidance of recreational water activities and swimming	Tinidazole	2 g orally, single dose
			Nitazoxanide	500 mg orally two times per day for 3 days
			Metronidazole	500 mg orally twice daily or 250 mg orally three times per day; duration 5-7 days
			Albendazole	400 mg orally once daily for 5 days
			Mebendazole	200 mg orally three times per day for 5 days
			Paromomycin	10 mg/kg orally three times per day for 5-10 days
			Furazolidone	100 mg orally four times per day for 7-10 days
			Quinacrine	100 mg orally three times per day for 5 days
Leishmaniasis	*Leishmania* spp.	Protection against sandfly bites, limitation of outdoor activities, wearing protective clothing, use of fans or ventilators, use of bed nets, use of wide-mesh nets with a pyrethroid-containing insecticide, and applying N, N-diethyl-meta-toluamide-containing repellents to uncovered skin	Fluconazole	200 mg orally once daily for 6 weeks
			Ketoconazole	600 mg orally once daily for 28 days
			Miltefosine	2.5 mg/kg (maximum 150 mg) orally in three divided doses for 28 days; if weight is 30-44 kg, use 50 mg orally twice daily
			Sodium stibogluconate	20 mg Sb/kg/day intravenously or intramuscularly for 10-20 days
			Meglumine antimoniate	20 mg Sb/kg/day intravenously or intramuscularly for 10-20 days
			Amphotericin B deoxycholate	0.5-1 mg/kg intravenously dosed daily or every other day for a cumulative total dose of 15-30 mg/kg
			Liposomal amphotericin B (AmBisome)	3 mg/kg intravenously daily for five to seven doses, such as days 1-5, 10
			Pentamidine isethionate	3-4 mg/kg intravenously or intramuscularly every other day for four to seven doses or until healed

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Table 1: Contd...

Disease/infection	Causative agent	Prevention	Treatment agent	Dosage
Malaria	*Plasmodium falciparum*	Most travelers develop malarial disease because they were not aware of personal protection measures and/or chemoprophylactic regimens. All travelers to endemic areas for malaria should be educated about personal and environmental measures on protection against *Anopheles* mosquito bites. These measures included wearing clothing that covers as much skin as possible (long sleeves, long pants, and fully closed shoes with socks), using a repellent containing N, N-diethyl-3-meta-toluamide or picaridin, treating clothing with a pyrethroid in the regions with high risk for malaria, and sleeping under a permethrin-treated bed net in not well-screened or air-conditioned locations	Chloroquine	600 mg base (=1000 mg salt) orally immediately, followed by 300 mg base (=500 mg salt) orally at 6, 24, and 48 h; total dose: 1500 mg base (=2500 mg salt)
			Hydroxychloroquine	620 mg base (=800 mg salt) orally immediately, followed by 310 mg base (=400 mg salt) orally at 6, 24, and 48 h; total dose: 1550 mg base (=2000 mg salt)
			Atovaquone-proguanil	4 adult tabs orally once daily for 3 days
			Quinine plus one of the following: doxycycline, tetracycline, or clindamycin	Quinine: 542 mg base (=650 mg salt) orally three times daily for 3 or 7 days plus one of the following - doxycycline: 100 mg orally twice daily for 7 days, tetracycline: 250 mg orally four times daily for 7 days, clindamycin: 20 mg base/kg/day (up to 1.8 g) orally divided three times daily for 7 days
			Mefloquine	684 mg base (=750 mg salt) orally as initial dose, followed by 456 mg base (=500 mg salt) orally given 6-12 h after initial dose; total dose=1250 mg salt
			Artemisinin	Doses must be adjusted based on the available combination formulation and body weight
Acanthamoeba keratitis	*Acanthamoeba* spp.	Wear, replace, and clean contact lenses and their cases according to the eye care provider and the manufacturer's guidelines. Remove contact lenses before carrying out any activity involving contact with water bodies such as swimming, showering, or using a hot tub. Avoid eye contamination or corneal trauma using adequate eye protection	Chlorhexadine combined with Brolene Other tretments such as propamidine, miconazole, and neomycin also has been successful in only a few instances	Every hour until 2-3 days around the clock, then every hour while awake until 3 days, then tapered to 4 times a day
Chagas' disease	*Trypanosoma cruzi*	Vector control by indoor residual insecticide spraying and improvement of housing to prevent bugs becoming established in cracked walls and thatched roofing. Sugar cane presses and other food preparation facilities should be protected from possible contamination by infected reduviid bugs sleep under a mosquito net and treat bedding with an insecticide to prevent bites	Benznidazole	5-7 mg/kg per day orally in two divided doses for 60 days
			Nifurtimox	8-10 mg/kg per day orally in three or four divided doses for 90-120 days

Contd...

Table 1: Contd...

Disease/infection	Causative agent	Prevention	Treatment agent	Dosage
Toxoplasmosis	*Toxoplasma gondii*	Pregnant women should not eat undercooked meat to avoid vertical transmission. Steak tartare should be avoided. Barbecued meats should be well grilled or avoided	Pyrimethamine	Oral: 50-75 mg/day for 1-3 weeks depending on patient's tolerance and response, then may reduce dose by 50% and continue for 4-5 weeks; use with a sulfonamide in combination with leucovorin calcium

Extraintestinal manifestations of giardiasis are rarely reported, but in a recent study around 33% of patients affected by giardiasis showed long-term extraintestinal symptoms; hence, these symptoms are not as rare as previously assumed.[14] Ocular complications included iridocyclitis, choroiditis, retinal hemorrhages, salt and pepper degeneration, and severe bilateral anterior uveitis.[15-17] Susceptibility to ocular complications with giardiasis seems higher in smaller children.[18] It has been proposed that salt and pepper degeneration may be a consequence of toxic metabolites produced by the parasites, not direct invasion [Figure 1].[15,19]

Several different treatments for giardiasis have been described; first-line therapy for giardiasis is generally tinidazole and metronidizaole. Metronidazole 500 mg orally twice daily or 250 mg orally three times per day is recommended, for a duration of 5–7 days. Also, it is recommended that for children it should be orally divided three times per day for 5–7 days (maximum 250 mg per dose). Another choice for giardiasis treatment approved by the Food and Drug Administration is nitazoxanide.[20] Third-line therapies for pregnant or refractory cases are paromomycin and quinacrine, respectively.[21]

Prevention and recommendations: Giardiasis

Since the main route of transmission of giardiasis is ingestion of contaminated water and foods, our recommendations to travelers for prevention are consumption of only treated water and cooked foods, especially when traveling to locations with high incidences of the parasite. In addition, recreational water activities and swimming should be performed with caution in suspected water in these locations. Suitable treatment for giardiasis is important for reducing ocular complications.

Leishmaniasis

Leishmaniasis is a tropical parasitic disease caused by obligate intramacrophage protozoans. These parasites are transmitted to humans during blood sucking by female sand flies.[22] Travelers to endemic areas are at risk.[23-30] Ocular findings in cutaneous leishmaniasis indicate a local phenomenon due to the initial site of the bite near the eyelids. Ptosis, cicatricial ectropion or entropion, bilateral lagophthalmia, and chronic ulcerative blepharoconjunctivitis have been described.[31-33] Extension of the infection to lacrimal ducts may cause dacryocystitis.[34]

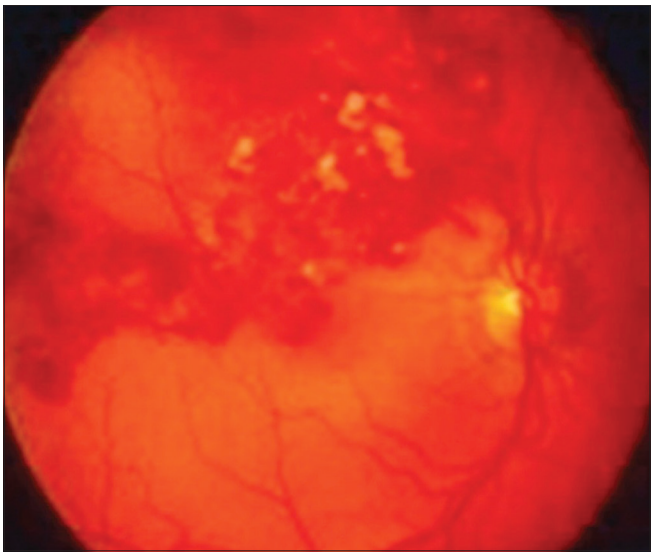

Figure 1: Salt and pepper degeneration of the retina in a child infected with Giardiasis

Ocular manifestations in visceral leishmaniasis, also known as kala-azar, are predominantly retinal vascular abnormalities, including focal retinal whitening, cotton wool spots, and hemorrhages with increased vessel tortuosity.[35] Bilateral, multifocal retinal hemorrhages can be improved by specific antileishmanial therapy.[7,36,37] Treatment is also summarized in Table 1.

Prevention and recommendation: Leishmaniasis

There is still no available vaccine against leishmaniasis for humans.[38] Travelers to endemic areas must be taught that the only protective methods are those of protection against sandfly bites. These methods include limitation of outdoor activities, especially from sunset to sunrise when sandflies are frequently active; wearing protective clothing; and applying N, N-diethyl-meta-toluamide-containing repellents to uncovered skin. Because of weak flying ability of sandflies, use of fans or ventilators can inhibit their activity. In addition, sleeping in air-conditioned or well-screened areas and indoor spraying is advised.[3] Since the highest activity of sandflies occurs when people are sleeping, the use of bed nets is one of the most important protection methods. The use of wide-mesh nets with a pyrethroid-containing insecticide can decrease sandfly biting rates.[22,39,40] Also, there are some indoor

protection such as some topical products which can be applied to the skin. For example, citronella, linalool, and geraniol candles are some effective essential oils for this propose.[41]

Malaria

Malaria is caused by intraerythrocytic protozoa of different *Plasmodium* species. These parasites are transmitted to humans through the bite of female *Anopheles* mosquitoes.[42]

Malaria remains endemic in 97 countries.[43] The most important cause of travel-related mortality and morbidity is malaria.[44] In general, all travelers going to sub-Saharan Africa are at risk, unless their travel is entirely restricted to high altitudes, such as Mount Kilimanjaro.[45] However, one study showed that the distribution of malaria is expected to shift with future climate changes with higher risks in African highlands, central Europe, and North America.[46] Traveling to Oceania and West Africa is classified as high-risk travel for developing encephalitis due to malaria that requires chemoprophylaxis.[47]

Ocular complications due to malaria disease are divided into two parts: the effects of the parasite on the eye and the ocular side effects of antimalarial drugs. Ocular involvement in malaria can occur in severe cases.[48] Other studies have shown that retinopathy is associated with mortality in children with cerebral malaria.[49] Malarial retinopathy contains of four distinct components: retinal whitening, retinal vessel wall discoloration to orange or white, hemorrhages, and papilledema [Figure 2].[19,50] The characteristic pattern of retinal whitening and vessel changes appears to be exclusive to malaria in a comatose patient, even if the peripheral blood smear is negative for malarial parasites.[51] Amaurosis fugax, optic neuritis, glaucoma, panuveitis, oculomotor paralysis, and cortical blindness have been described in this disease.[19]

In addition, eyes are affected by antimalarial drugs. Early retinopathy from chloroquine or hydroxychloroquine occurs in 10% and 2.7% of users, respectively.[52] Bilateral pigment changes in the retinal pigment epithelium of the macula and bilateral enlarged blind spots have been seen in mefloquine users.[53,54]

Treatment of systemic infection can cause improvements of ocular manifestations. Because severe or complicated cases of malaria can deteriorate suddenly during the early course of treatment, these patients should be admitted to hospital for at least 24 h.[55] Treatment is also summarized in Table 1.

Prevention and recommendation: Malaria

Most travelers develop malarial disease because they were not aware of personal protection measures and/or chemoprophylactic regimens.[56] All travelers to endemic areas for malaria should be educated about personal and environmental measures on protection against *Anopheles* mosquito bites. These measures include wearing clothing that covers as much skin as possible (long sleeves, long pants, and fully closed shoes with socks), using a repellent containing N,N-diethyl-3-meta-toluamide or picaridin, treating clothing with a pyrethroid in the regions with high risk for malaria, and sleeping under a permethrin-treated bed net in not well-screened or air-conditioned locations. Since the activity of the *Anopheles* mosquito is generally between dusk and dawn, limitation of outdoor night activity is advised.[2,57] Chemoprophylaxis is necessary for any person traveling to high-transmission countries, especially in Africa. Multiple regimens for chemoprophylaxis exist and selection of them depends on patient preference, side-effect profile, cost, and drug susceptibility of *Plasmodium* species in the area.[42] Also, there are some important diseases for travelers which are transmitted by mosquitoes. For example, dengue, filariasis, chikungunya, West Nile virus, yellow fever, dirofilariasis, Japanese encephalitis, tularemia, Saint Louis encephalitis, eastern equine encephalitis, western equine encephalitis, Venezuelan equine encephalitis, Ross River fever, La Crosse encephalitis, Zika fever, and Barmah Forest fever.[58]

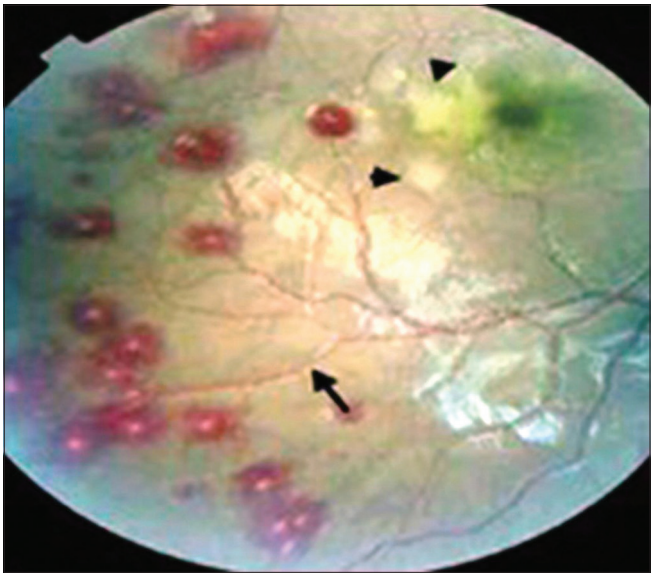

Figure 2: Malaria rethinopathy, showed multiple white centered hemorrhages, macular whitening (black triangles) and vessel wall discoloration to orange (black arrow)

Acanthamoeba

Acanthamoeba species are ubiquitous protozoa that have been isolated from various natural environments such as sea water, fresh water lakes, soil, hot spring resorts, bottled water, and air.[59]

Acanthamoeba keratitis (AK) is a severe infection of the cornea that can cause vision loss in some cases. Decreased vision in AK results from corneal ulceration and scarring. Keratitis frequently occurs in immunocompetent contact lens wearers. Contact lens hygiene is very important, but infection has been seen with some commercially available

multipurpose solutions, suggesting these solutions are ineffective against *Acanthamoeba*.[60-62] Corneal trauma has been considered to be a risk factor of AK in non-contact lens wearers. Other documented causes include swimming and showering with contact lenses *in situ*, exposure to contaminated water or soil, and corneal trauma. Some studies showed that AK was more prevalent during warmer seasons, especially during the summer,[63-66] but others revealed no significant seasonal differences.[67] This difference is perhaps due to more swimming and showering in summer.

The majority of symptoms reported in AK are nonspecific, including pain, eye redness, blurred vision, and photophobia. Early signs of AK include an epitheliopathy with punctate keratopathy and pseudodendrites [Figure 3a]. Ring infiltrate and perineuritis are specific signs in AK and present in only around 50% of patients [Figure 3b].[68-70] Clinical outcomes of AK are poor; the most severely infected eyes require keratoplasty or removal of the affected eye.[70,71]

Treatment of amebic keratitis is difficult and disappointing. Long-term topical application of agents such as propamidine, miconazole, and neomycin has been successful in only a few instances.[7] Treatment is also summarized in Table 1.

Prevention and recommendation: Acanthamoeba

Since diagnosis and treatment is difficult in AK, prevention is more effective. These include the following: (1) wear, replace, and clean contact lenses and their cases according to the eye care provider and the manufacturer's guidelines; (2) remove contact lenses before carrying out any activity involving contact with water bodies such as swimming, showering, or using a hot tub; and (3) avoid eye contamination or corneal trauma using adequate eye protection.[72]

American trypanosomiasis (Chagas' disease)

American trypanosomiasis, also known as kissing bugs and Chagas disease, is only seen on the American continent or among subjects who travel to rural areas of South and Central America. *Trypanosoma cruzi*, the causative parasite, is transmitted through the bite of reduviid bugs. The reservoir is in humans and domestic mammals, along with armadillos and opossums. Oral transmission through food or sugar cane juice contaminated by infected bugs may occur. Vertical transmission and infection through blood transfusion are important routes of infection and can take place in nonendemic areas.[7,73,74]

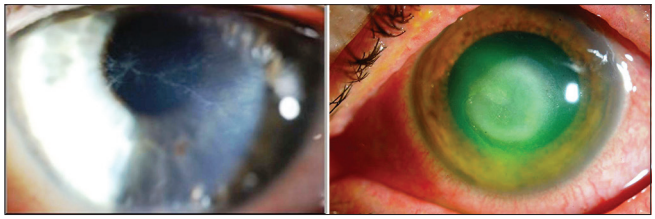

Figure 3: (a) Clinical finding of *Acanthamoeba keratitis*: A. pseudodendrites keratitis. (b) ring infiltrate

Acute infection is rarely symptomatic. Some patients may complain of edema around the bite site or around the eye (Romanna's sign), associated with fever and lymphadenopathy. In the chronic stage, the parasite will infiltrate to other organs, including cardiac conducting tissue, cardiac muscle, and smooth muscle of the gastrointestinal tract.[74,75]

Two medications are available for treatment of American trypanosomiasis, including nifurtimox and benznidazole. Therapy is usually extended for a period of months, and parasitologic cure rates are somewhat disappointing. Both medications carry a long list of significant side effects. Supportive therapy, including surgery where necessary, is given as required for management of related complications. Treatment is also summarized in Table 1.

Prevention and recommendation: American trypanosomiasis

There are very little data regarding prevention of South American trypanosomiasis in travelers. The mainstay of control of the disease is vector control by indoor residual insecticide spraying and improvement of housing to prevent bugs becoming established in cracked walls and thatched roofing.[75] Sugar cane presses and other food preparation facilities should be protected from possible contamination by infected reduviid bugs.

Travelers who are expecting to spend time in rural forested areas, particularly if living or sleeping in local accommodations, should be advised that this will increase their bite risk. It is advisable for travelers in such locations to sleep under a mosquito net and treat bedding with an insecticide to prevent bites.[75]

Toxoplasmosis

Toxoplasma gondii is a protozoan parasite, the lifecycle of which passes through cats. It represents the commonest cause of uveitis worldwide. Human infection occurs through ingestion of food or water contaminated with cat feces. Toxoplasmosis may be acquired at any age but most commonly during childhood.[76]

Humans become infected by this parasite when eating undercooked infected meat and by contamination with cysts following handling of cat litter trays.

Some patients may present with a glandular fever-like systemic febrile illness with adenopathy. Most cases of adult infection will not present with eye signs, but those that do usually present with a focal necrotizing retinitis occasionally associated with vascular occlusion.[77]

The immunocompromized patients and neonates who have been exposed transplacentally by a mother's acute infection are at particularly high risk for ocular complications.

Acute infection in newborns and patients infected with HIV may lead to an intense necrotizing chorioretinitis. More commonly, however, chorioretinitis is the result of necrotizing inflammation following the rupture of an older, slowly growing cyst, thus releasing bradyzoites. Ocular symptoms in the patient with congenital ocular toxoplasmosis may include strabismus, nystagmus, and blindness.[7] Acute, acquired toxoplasmosis is associated with scotoma, photophobia, and loss of central vision due to macular involvement. Oculomotor nerve involvement may result in ptosis.

First-line therapy of chorioretinitis in toxoplasmosis includes the use of pyrimethamine with sulfadiazine and folinic acid to prevent bone marrow toxicity.[78]

In addition, clindamycin and azithromycin are commonly used as first-line treatments. Therapy should continue for 1–2 weeks beyond the resolution of symptoms.[7] Treatment is also summarized in Table 1.

Prevention and recommendation: Toxoplasmosis

Since serious consequences may arise if a pregnant woman is infected for the first time during travel, pregnant women should not eat undercooked meat to avoid vertical transmission. In France, steak tartare should be avoided. Barbecued meats should be well grilled or avoided.

Conclusions

Many travel-related eye diseases are preventable by education of health behaviors, using precautionary measures and taking chemoprophylactic medications or appropriate vaccinations for some diseases. The physicians in both endemic and nonendemic areas should become familiar with their clinical presentation and treatment strategies for earlier diagnosis of ocular lesions caused by parasitic infections to reduce costly, inappropriate laboratory evaluations, delayed or ineffective treatments, and severe complications including severe vision loss.

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Conflicts of interest

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