

ONCHOCERCIASIS: AN OVERVIEW

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Summary

Onchocerciasis also known as river blindness and Robles' Disease, is a parasitic disease caused by infection by *Onchocerca volvulus*, a nematode. Onchocerciasis is the world's second-leading infectious cause of blindness. The vast majority of infections occur in sub-Saharan Africa, although cases have also been reported in Yemen and isolated areas of Central and South America. Due to the vector's breeding habitat, the disease is more severe along the major rivers in the northern and central areas of the continent and severity declines in villages farther from rivers. In the present review we have highlighted on epidemiology, mortality/morbidity, history, life cycle of *Onchocerca volvulus*, classification, sign and symptoms, treatment, prevention etc.

Keywords: Nematode, *Onchocerca Volvulus*, River Blindness, Robles' Disease

Introduction

Onchocerciasis is an infection caused by the nematode *Onchocerca volvulus*. Humans acquire onchocerciasis through the bite of *Simulium* blackflies. Because the fly develops and breeds in flowing water, onchocerciasis is commonly found along rivers and is sometimes referred to as river blindness. In the human host, the adult nematodes live in subcutaneous nodules and produce microfilariae, which are found throughout the body but preferentially reside in the skin and eye. Repeated exposures to infected flies increase the number of adult worms and microfilariae in the host. Chronic cutaneous onchocerciasis (onchodermatitis) causes pruritus, a papular rash, scarring and lichenification. Over time, affected skin may begin to sag, leading to terms such as "hanging groin." Patchy depigmentation on the legs leads to a condition known as leopard skin. The term sowda is used to describe severe pruritus with darkening of the skin, often confined to one limb. Chronic ocular onchocerciasis may lead to sclerosing keratitis and iridocyclitis and finally to blindness¹. Onchocerciasis is endemic in Africa, Yemen and in small foci in Central America and South America. The burden of the disease has been reduced by prevention efforts, including control of the fly vector and periodic ivermectin therapy in at-risk individuals. More recently, attention has been focused on *Wolbachia* organisms, which are endosymbiotic bacteria carried by adult worms and microfilariae. Treatment of *Wolbachia* infection has been shown to disrupt microfilariae production by the adult female nematode².

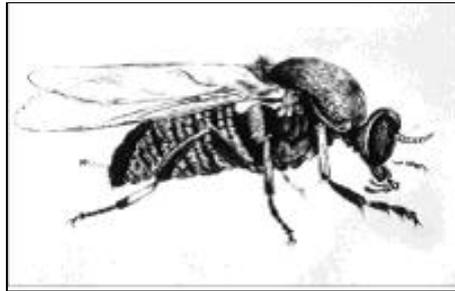


Figure 1: Simulium fly (black fly)

EPIDEMIOLOGY^{3,4}

FREQUENCY

United States

Onchocerciasis is not acquired in the United States. Occasional cases are found in immigrants or travelers from endemic areas. However, symptomatic onchocerciasis usually requires heavy infestations and repeated exposure to the vector fly. Short-term travelers are at little or no risk of the disease. Pruritus, dermatitis and eosinophilia may occur in travelers who stay longer than 3 months in endemic areas of Africa. Symptoms may occur months to years after leaving the endemic area.

International

Currently, onchocerciasis is endemic to 30 African countries, Yemen and in localized foci of 6 Central and South America countries. Globally, approximately 18-36 million individuals have onchocerciasis, 99% of whom reside in Africa. The World Health Organization (WHO) estimates that 750,000 people are blind or have reduced vision as a result of the disease. Since 1975, the WHO, international foundations, nongovernmental organizations and governments have worked cooperatively to reduce the burden of onchocerciasis. Initial efforts focused on insecticide sprays and habitat control to reduce the numbers of black fly vectors. With the introduction of effective treatment, the program became focused on periodic treatment of at-risk persons. Since 1988, ivermectin has been provided free of charge by Merck through the Mectizan Donation Program. By 2002, most affected countries had introduced population-based programs to supply ivermectin at least annually to at-risk individuals. The drug temporarily reduces the microfilarial burden, resulting in reduced morbidity and a reduced number of flies becoming infected when they bite humans. Reports suggest that this has been highly effective in the Americas, where transmission has been interrupted entirely in several areas and ocular disease has been eliminated in 9 of the 13 foci. In Africa, morbidity and transmission have been reduced but not eliminated. This may be due, at least in part, to migration of infected people into new areas, as well as the challenges inherent in educating and motivating large numbers of people. Despite the challenges they face, control programs have had a significant impact. In Africa alone, an estimated 600,000 cases of blindness had been prevented by 2002 and 18 million children were living in risk-free areas. In 2007, 69 million doses of ivermectin were supplied through the Mectizan Donation Program to reduce the burden of onchocerciasis.

MORTALITY/MORBIDITY^{5,6}

- Onchocerciasis is the second-leading infectious cause of blindness in the world.
- Skin disease and subcutaneous nodules can be intensely pruritic.
- Long-term onchodermatitis may cause scarring, depigmentation, loss of skin elasticity and disfigurement.
- Although not directly fatal, blindness and skin disease caused by onchocerciasis affect the hosts' ability to assimilate into their societies, perform daily tasks and care for themselves.
- Affected persons often have a low body mass.

- Blindness alone has been estimated to reduce life expectancy by 4-10 years.
- In the West African savanna, up to 10% of villagers may be blind from the disease.

HISTORY^{7,8}

1875	Onchocerciasis, first described in 1875, is caused by a filarial nematode (<i>Onchocerca volvulus</i>), a parasite transmitted by the bite of infected black flies of the genus <i>Simulium</i> . Onchocerciasis is a leading cause of eye disease in Africa
1916	Suramin or Suramin sodium is a medicinal drug developed by Oskar Dressel in 1916. The molecular formula of "suramin sodium" is: C ₅₁ H ₃₄ N ₆ Na ₆ O ₂₃ S ₆ . It is used for treatment of human sleeping sickness, onchocerciasis
1968	It was at the Tunisian capital that WHO and partners held in 1968, the first meeting, ever, for the control onchocerciasis in Africa. That meeting concluded that it was possible to defeat onchocerciasis through control of the black fly vectors
1974	Onchocerciasis; Epidemiological mapping; Mass distribution; Ivermectin Introduction The Onchocerciasis Control Programme in West Africa (OCP) started in 1974. Soon after its beginning, it became evident that the Programme borders were invaded
1975	Ivermectin is a semisynthetic avermectin that was first introduced commercially for veterinary use in 1975. The mechanism of action of this compound rendered it effective against parasites resistant to other antiparasitic agents.
1987	The drug kills <i>Onchocerca microfilariae</i> with almost no serious side-effects and its effects after one oral dose last for approximately a year. In 1987, Merck & Co. announced its decision to provide the drug without cost in whatever quantities were needed
1995	The research effort would guide and support a new regional organization to control onchocerciasis on the rest of the continent. In December 1995, this new umbrella organization, known as the African Programme for Onchocerciasis Control (APOC), was created
1996	APOC's financial assistance to Nigeria beginning in 1996, the Nigerian Onchocerciasis Control Program (NOCP) and its many NGO partners 17, 18 shifted from a strategy of village-based volunteers
2002	All Onchocerciasis Control Programme (OCP) activities in Africa will be phased out on Dec 31, 2002, a date which will signal a landmark in the history of onchocerciasis (river blindness) control in Africa.
2007	Onchocerciasis Elimination Program of the Americas.” Available online. URL: http://www.cartercenter.org/health/river_blindness/oepa.html . Accessed March 22, 2007. World Bank Group. “Global Partnership to Eliminate Onchocerciasis.”
2010	WHITEHOUSE STATION, NJ, Nov 11, 2010 Public health officials at the 20th Inter-American Conference on Onchocerciasis in Antigua, Guatemala, confirmed that more than one-third of all Latin Americans who are the risk of Onchocerciasis

Table 1: History of Onchocerciasis

DISTRIBUTION OF ONCHOCERCIASIS

Onchocerciasis is locally transmitted in thirty countries of Africa, 13 focal areas located in 6 countries (Mexico, Guatemala, Ecuador, Colombia, Venezuela and Brazil) in the Americas and in Yemen in the Middle East. Onchocerciasis in casual travelers is rare; the infection is transmitted in remote rural areas and, unlike malaria, contracting onchocerciasis often requires more than one infectious bite. Thus, risk of infection is greater in adventure travelers, missionaries and Peace Corps and other long-term volunteers who are likely to have more intense or sustained exposure to blackfly bites. Given the low rate of transmission in the Americas, the likelihood is very low that any travelers in this region (even missionaries and long-term volunteers) would ever get infected⁹.

LIFE CYCLE OF ONCHOCERCA VOLVULUS^{10,11}

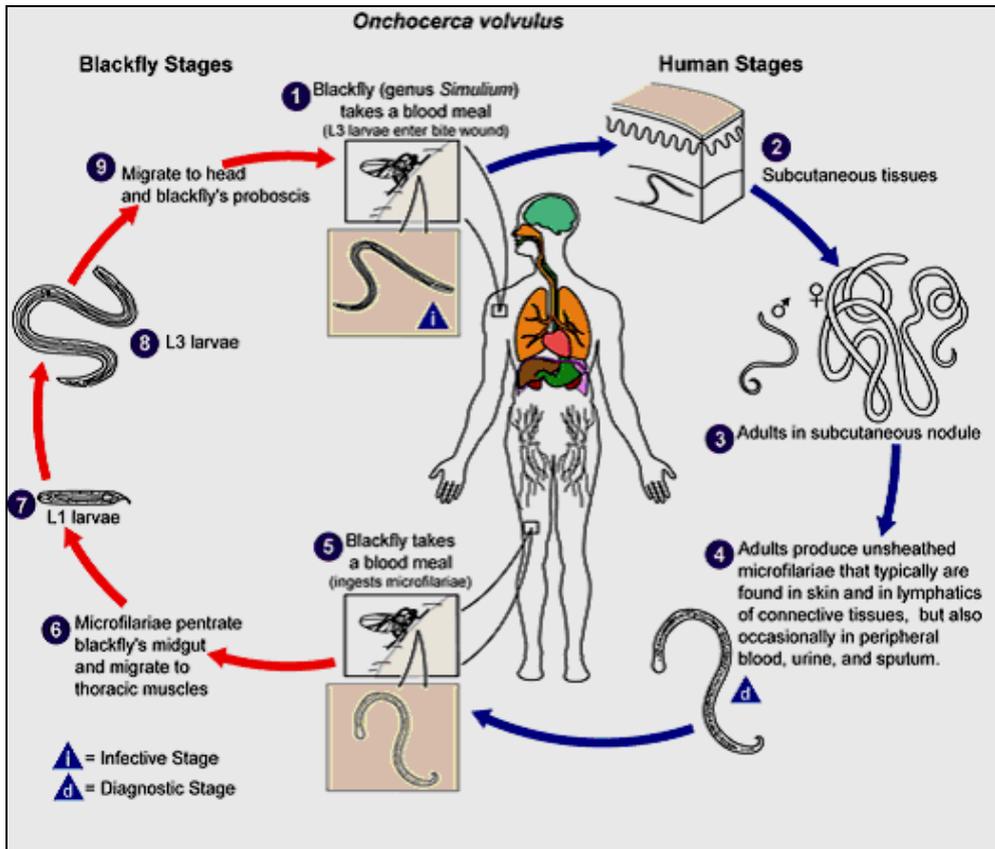


Figure 2: Life Cycle Of Onchocerca volvulus

1. A Simulium female black fly takes a blood meal on an infected human host ingesting microfilaria.
2. The microfilaria enter the gut and thoracic flight muscles of the black fly progressing into the first larval stage.
3. The larvae mature into the second larval stage and moves to the proboscis and into the saliva in its third larval stage. Mature in about 7 days.
4. The black fly takes another blood meal passing the larvae into the next human host's blood.
5. The larvae migrate to the subcutaneous tissue and undergo two more molts. They form nodules as they mature into adult worms over six to twelve months.
6. After maturing, adult male worms mate with female worms in the subcutaneous tissue to produce between 700 and 1,500 microfilaria per day.
7. The microfilaria migrate to the skin during the day and the black flies only feed in the day, so the parasite is in a prime position for the female fly to ingest it. Black flies take blood meals to ingest these microfilaria to restart the cycle.

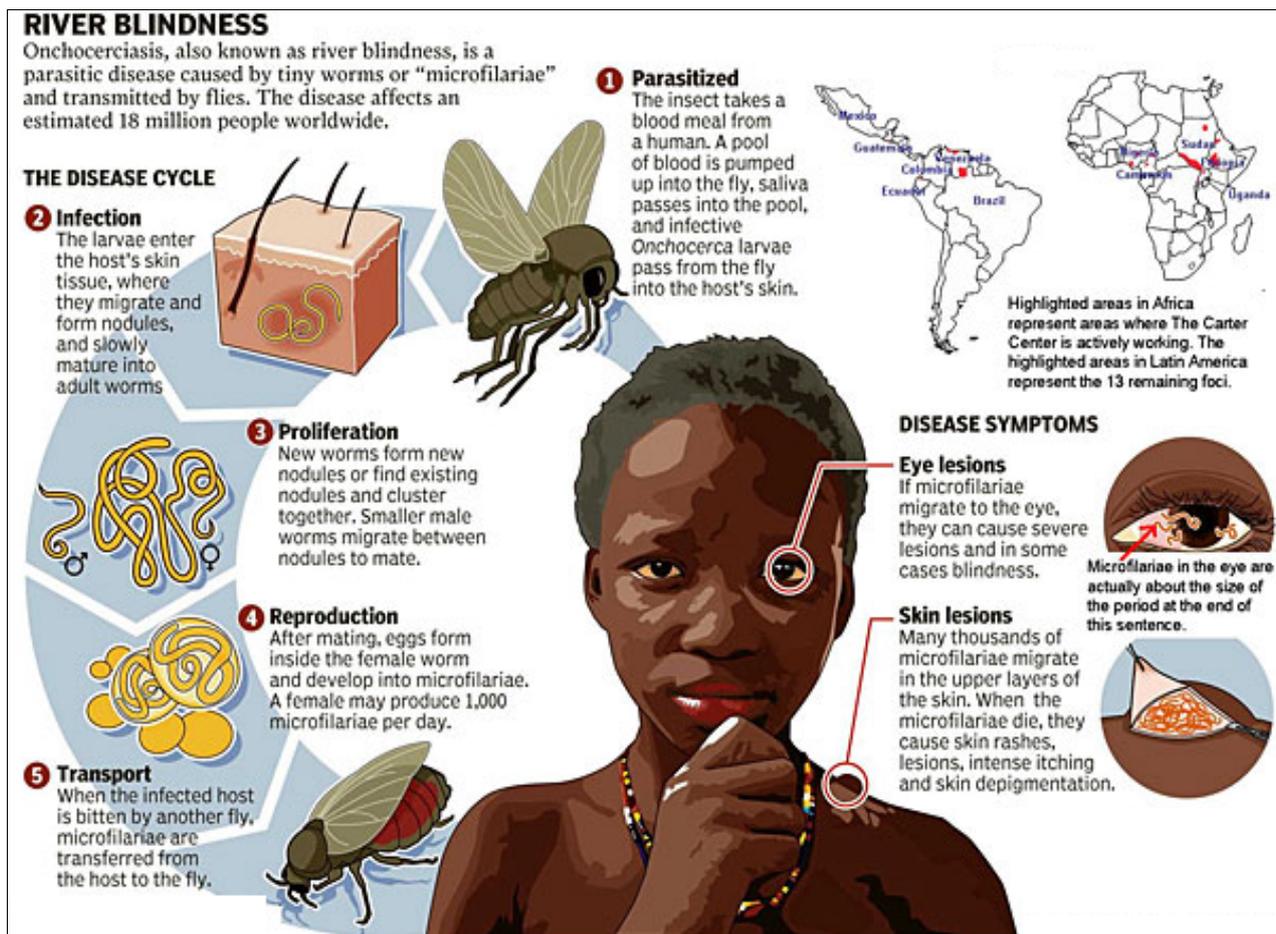


Figure 3: Diagrammatic Explanation of Onchocerciasis RACE

Onchocerciasis does not have a racial predilection. For an unclear reason, the symptoms caused by *O. volvulus* infection appear to differ from region to region. For example, onchodermatitis is more common in forested areas, while blindness is more common in savanna areas. Some evidence has suggested that genetic variation in the host may explain part of this geographic specificity¹².

AGE

Onchocerciasis does not have an age predilection. Children born to mothers with onchocerciasis may be immunotolerant to *O. volvulus* infection, potentially leading to a higher microfilarial burden. Transplacental transmission of microfilariae may occur¹³.

CLASSIFICATION^{14, 15}

Onchocerciasis may be divided into the following phases or types:

Erisipela de la costa	An acute phase characterized by swelling of the face with erythema and itching. Onchocerciasis causes different kinds of skin changes and these changes vary in different geographic regions. This skin change, erisipela de la costa, of acute onchocerciasis is most commonly seen among victims in Central and South America.
Mal morando	A cutaneous condition characterized by inflammation that is accompanied by hyperpigmentation.
Sowda	A cutaneous condition, a localized type of onchocerciasis.
Leopard skin	A term referring to the spotted depigmentation of the skin that may occur with onchocerciasis.

Elephant skin	A term used to describe the thickening of human skin that may be associated with onchocerciasis.
Lizard skin	A term used to describe the thickened, wrinkled skin changes that may result with onchocerciasis.

Table 2: Classification of Onchocerciasis

SIGNS AND SYMPTOMS^{16, 17}

Symptoms of onchocerciasis reflect the developmental stage of the parasite and the degree of immune response by the host. Clinical manifestations are highly variable.

- Symptoms of onchocerciasis do not appear until after the L3 larvae mature into adult worms. On average, symptoms appear between 9 months and 2 years after the initial infecting bite. The interval between acquisition of the parasite and onset of symptoms is sometimes referred to as the prepatent phase.
- Once developed, adult worms cluster in subcutaneous nodules (onchocercomata).
- Generalized pruritus may occur early in the infection and may be severe. A papular rash known as onchodermatitis may be present. Initially, the rash may be transient, but chronic infection over several years may lead to lichenification, loss of skin elasticity, atrophy and/or depigmentation.
- Itchy eyes, redness, or photophobia may be early symptoms of ocular onchocerciasis. Over years, the scarring progresses to cause visual loss and ultimately blindness. Acute optic neuritis is less common but may also cause blindness.
- Weight loss and generalized myalgias may occur.

PHYSICAL

- Skin examination in patients with onchocerciasis may reveal subcutaneous nodules, diffuse onchodermatitis, lymphedema and/or atrophic changes.
 - Onchodermatitis consists of raised papules that are intensely pruritic. Vesicles and pustules may also be present. Scratching may cause secondary infection.
 - In its extreme form, skin atrophy may cause drooping of the inguinal skin, termed hanging groin.
 - In some cases, the skin is dry and resembles ichthyosis.
 - Sowda refers to severe pruritus and darkened skin, usually confined to one limb. It is most commonly described in Yemen but also occurs in Africa.
 - Leopard skin refers to bilateral, symmetric, patchy depigmentation of the shins.
 - Lymphadenopathy may occur.
 - Subcutaneous nodules are firm, nontender and mobile and are several millimeters to centimeters in size. They develop most commonly over bony prominences on the trunk and hip (Africa) or head and shoulders (Americas).
- In the eye, the inflammatory response to dying microfilariae and *Wolbachia* antigens causes punctate keratitis (snowflake opacities). Advanced cases may result in corneal fibrosis or opacification. Slit-lamp examination may reveal microfilariae in the cornea and anterior chamber. Other ocular manifestations include iridocyclitis, glaucoma, chorioiditis and optic atrophy.

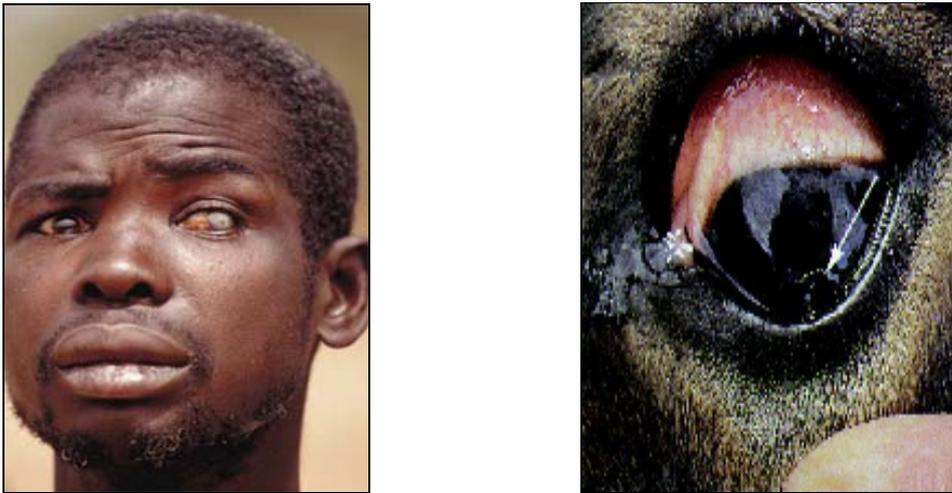


Figure 4: Signs and Symptoms of Onchocerciasis

CAUSES ¹⁷

- *volvulus* is transmitted by the bite of infected *Simulium* flies. The fly bites during daylight hours. *Simulium* flies breed near fast-flowing rivers and streams.
- Ocular symptoms are caused by the inflammatory response invoked by the release of *Wolbachia* antigens when microfilariae die.

IMPACT OF ONCHOCERCIASIS ¹⁷

Onchocerciasis is the second leading infectious cause of blindness and can cause debilitating and disfiguring skin disease. However, the worldwide burden of onchocerciasis has been considerably reduced as the result of very successful disease control programs led by the World Health Organization (WHO). These programs are based on control of the blackfly population and/or mass administration to affected communities of an oral drug called ivermectin (MectizanTM), that is donated by Merck & Co., Inc. As a result of these programs, millions of people are at greatly reduced risk of debilitating itching, disfigurement and blindness caused by onchocerciasis. Unfortunately, many people still do not have access to prevention and treatment measures.

DIAGNOSIS ¹⁷

- Pathological diagnosis
 - Traditionally, a diagnosis of onchocerciasis requires demonstration of microfilariae in a skin-snip biopsy sample (see Procedures). This technique yields high specificity (100%) in experienced hands but low sensitivity (20%-50%) in early stages of infection.
 - The diagnosis may also be made by direct examination of surgical specimens obtained by excision of nodules.
- Immunodiagnosis
 - Antibody detection does not distinguish between active and past infections. Various antibodies have been tested, as follows:
 - ◇ Ov16 card test: Antibodies against this antigen have been shown to yield high sensitivity (approximately 80%) and specificity (approximately 85%) and may yield positive results in early infections when skin-snip results are negative. Capillary blood samples are collected by finger prick. The immunochromatographic card test is used to detect the presence of immunoglobulin G4 (IgG4) antibodies to recombinant Ov16 antigen.
 - ◇ Recombinant hybrid proteins (OvH2 and OvH3): This test is based on hybrid proteins of two separate *Onchocerca* proteins (Ov20 and Ov33). High sensitivity (>95%) and specificity

(>95%) has been described in this enzyme-linked immunoassay (ELISA)-based antibody detection test.

- ◇ An ELISA-based test using a cocktail of 3 antigens (Ov7, Ov11, Ov16) has also been used to detect antibodies. A comparison study showed that a mixture of these 3 proteins yielded a sensitivity of approximately 97% and a specificity 100%, superior to those of the recombinant Ov16 card test.
- ◇ Testing for a low-molecular-weight antigen fraction of female *O. volvulus* parasite yields sensitivity and specificity similar to those of skin-snip testing.
- Antigen detection: Oncho-27 antigens have been studied in the diagnosis of *Onchocerca* infections. The advantage of this test is that it uses urine or tears for testing. In a study of 456 patients in a hyperendemic area of Cameroon, this technique yielded a sensitivity and specificity of 100%.
- Nucleic acid amplification tests: Polymerase chain reaction (PCR) using material from skin-snips or skin scratches provides high sensitivity and specificity, superior to older methods.^[26, 31] However, the limited availability of technical expertise, as well as the high cost of the test, restricts its use in resource-limited settings.

Imaging Studies

- Ultrasonography may reveal nonpalpable nodules, although this is not useful as a screening test. Ultrasonography of an adult worm in a nodule reveals a homogeneous echogenic area containing echodense particles with a lateral acoustic shadow.

Other Tests

- Diethylcarbamazine (DEC) patch test: Based on the principle of Mazzotti reaction, topical application of DEC in a cream base (DEC patch) elicits localized cutaneous reactions (pruritus, maculopapular eruptions, dermal edema) in response to dying microfilariae.^[27] Earlier studies reported varying degree of sensitivity (30%-92%) in patients with positive skin-snip results. Severe cutaneous reactions may require steroid therapy or hospitalization. Higher concentrations of DEC and longer patch times increase the sensitivity. However, false-positive reactions may occur in patients with other filarial diseases such as *Loa loa* infection.

TREATMENT^{18, 19}

Medical Care

Because most of the pathogenesis of onchocerciasis is secondary to microfilariae, the goal of therapy is to eliminate the microfilarial stage of disease to improve symptoms, to prevent progression of eye lesions and to interrupt disease transmission.

- Ivermectin is considered to be the drug of choice as a microfilaricidal agent.
 - Repeated dosing at intervals of 3–12 months is recommended for at least 10-12 years.
 - More frequent dosing is reserved for patients who experience frequent symptomatic recurrences.
 - Ivermectin is usually well-tolerated. Dying microfilaria may result in pruritus and adenopathy (Mazzotti reaction), leading to angioedema in rare cases. Ocular inflammation may also be triggered by dying microfilariae. To minimize this in individuals with microfilariae observed during slit-lamp examination, some experts recommend using a short course of prednisone (2-3 d) along with ivermectin. More frequent dosing with ivermectin (every 3 mo instead of every 12 mo) may reduce inflammatory complications because it does

not permit microfilarial numbers to build, thus reducing the number of dead organisms after treatment.

- Concomitant infection with *L loa* should be ruled out, as ivermectin may precipitate toxic encephalopathy in these patients.
- Ivermectin has little effect on adult worms. It reduces the burden of microfilaria and the risk of complications but does not cure the disease.
- Targeting endosymbiotic *Wolbachia* species has emerged as an exciting new approach in the control of onchocerciasis. Studies of doxycycline therapy (100–200 mg/d for 6 wk) have shown great promise. Doxycycline interrupts microfilarial embryogenesis, dramatically decreasing or eliminating microfilaria for at least 18 months after treatment. The drug has modest activity against adult worms, reducing numbers by approximately 50%-60%. Investigators have also studied rifampin and azithromycin, but early results appear to be inferior to those of doxycycline.

Surgical Care

Nodulectomy can result in cure only if excision eliminates all adult worms. Thus, this is not a practical choice in patients with multiple nodules or in patients in whom nodules are not clinically evident.

MEDICATION SUMMARY¹⁹

Treatment involves microfilaricidal or macrofilaricidal agents. No known nontoxic macrofilaricidal agent is available to kill adult worms.

Antiparasitics

These agents inhibit growth and proliferation of parasites.

➤ Ivermectin (Mectizan, Stromectol)

- Drug of choice for onchocerciasis. Derived from the soil actinomycete *Streptomyces avermitilis*. Metabolized in liver and excreted in feces over 12 d. Plasma half-life is 18 h. Its activity is the result of increased nerve and muscle cell permeability to chloride channels, leading to hyperpolarization and paralysis due to the drug's high affinity binding to glutamate-gated and gamma aminobutyric acid-gated chloride ion channels.

➤ Diethylcarbamazine (Hetrazan)

- Diethylcarbamazine (DEC) is never used in the treatment of onchocerciasis. DEC is rarely used for diagnostic purposes, when low test doses are given and patients are observed for the Mazzotti reaction, which, in mild cases, results in pruritus, dermal edema, maculopapular eruptions, lymphadenopathy and fever and, in severe cases, results in meningismus, severe prostration and/or death. The mechanism of action of DEC is secondary to direct effect on microfilariae by causing organelle damage and apoptosis.

Antibiotics

Empiric antimicrobial therapy must be comprehensive and should cover all likely pathogens in the context of the clinical setting.

➤ Doxycycline (Bio-Tab, Doryx, Doxy, Periostat, Vibramycin, Vibra-Tabs)

- May be used to reduce or eliminate the endosymbiotic bacteria *Wolbachia*. This disrupts production of microfilariae by the adult female worm

PREVENTION²⁰

- Travelers to endemic area can avoid onchocerciasis by avoiding vector contact with protective clothing and repellants.
- Population-based prevention strategies in some of the endemic areas of Africa and South America are based on elimination of blackfly vector and regular (every 6-12 mo) mass ivermectin treatment of affected individuals.

COMPLICATIONS²¹

- Ocular complications of onchocerciasis include blindness secondary to keratitis, pannus formation and corneal fibrosis. Posterior segment complications include chorioretinitis, intraretinal deposits, open-angle glaucoma and optic atrophy.
- Cutaneous complications of onchocerciasis include skin atrophy, depigmentation and sowda (chronic papular dermatitis limited to one limb). A loss of skin elasticity (hanging groin) may also occur.
- Hematologic and immunologic complications of onchocerciasis include chronic lymphadenopathy.

PROGNOSIS²²

- Some eye manifestations and dermatitis resolve in patients undergoing ivermectin treatment every 6-12 months for the lifetime of the adult worm (approximately 12 y).
- Blindness, skin atrophy and depigmentation do not improve with treatment. The life expectancy in blind persons is decreased secondary to difficulty coping with activities of daily living.

CONCLUSION

Onchocerciasis is an infection caused by the nematode *Onchocerca volvulus*. Humans acquire onchocerciasis through the bite of *Simulium* blackflies which is the major cause of blindness world wide. Onchocerciasis is commonly found along rivers and is sometimes referred to as river blindness. The infections caused by bite of this nematode causes serious infections such as onchodermatitis, lymphadenopathy etc. Thus the proper preventive majors such as avoiding vector contact with protective clothing and repellants helps us to be far away this infection.

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