Chapter 278 — Tissue Nematodes (Trichinosis, Dracunculiasis, Filariasis) 2943

Management

All people infected with S. stercoralis should be treated with the aim of eradicating the infection. Thiabendazole (Mintezol) is an effective agent that can be given in a dose of 25 mg/kg twice a day for 2 days (maximum of 3 g/day). Alendazole, although currently not approved by the Food and Drug Administration for this purpose, may also be used at a dose of 200 mg/kg/day for 1 to 2 days. In the hypereinfestation syndrome, early diagnosis and treatment for 2 to 3 weeks may be lifesaving, but the mortality is very high despite treatment. Patients with a past history of exposure to S. stercoralis should be thoroughly examined and treated before undergoing any immunosuppressive therapy.

REFERENCES


Chapter 278

Tissue Nematodes (Trichinosis, Dracunculiasis, Filariasis)

DAVID I. GROVE

The tissue-dwelling roundworms constitute a major global health problem. They are widely scattered around the world, especially in the tropics, and infect millions of people. Some are parasites of humans only, whereas others have an animal reservoir. All these parasites have complex life cycles involving arthropod intermediate hosts except for Trichinella spiralis, which is transmitted directly from one host to the next by ingestion of infective larvae. Like most helminths, the adult worms do not multiply within the human host; therefore, the worm load and severity of disease depend in large measure on the intensity and frequency of exposure to the infective forms. The relative pathogenicity of the adult worms versus the larval forms varies according to the species of the infective theory. Definitive diagnosis requires isolation and identification of the parasite, but in some infections this may be difficult. Effective therapy is available for only some of these infections. Some parasites present almost insurmountable control problems, but others can be avoided by simple preventive measures. Infections acquired by ingestion of contaminated food or water are considered first, and then those transmitted by blood-sucking flies are discussed. Historical information concerning all of these parasites, including the circumstances of their discovery and elucidation of their life cycles, together with the clinical illness they cause as well as modes of treatment that have been developed may be found elsewhere.

TRICHINOSIS

Trichinosis develops when undercooked flesh contaminated with infective larvae of Trichinella spp. is eaten. Most infections are asymptomatic, but heavy exposure may lead to diarrhoea, periorbital edema, myositis, fever, and prostration.

T. spiralis is the species that has been recognized for years, but the genus has been revised taxonomically. Five species have now been described on the basis of genetic, biochemical, and biologic data (Table 278–1). In addition, three other phenotypes are acknowledged in the genus, but their taxonomic level is uncertain in the present.2 4

<table>
<thead>
<tr>
<th>Species Name</th>
<th>Code</th>
<th>Distribution</th>
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<tr>
<td>T. spiralis</td>
<td>T1</td>
<td>Worldwide</td>
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<tr>
<td>T. nativa</td>
<td>T2</td>
<td>Arctic, subarctic</td>
<td>Bears, horses, foxes</td>
</tr>
<tr>
<td>T. britovi</td>
<td>T3</td>
<td>Temperate, subarctic</td>
<td>Bears, foxes</td>
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<tr>
<td>T. pseudospiralis</td>
<td>T4</td>
<td>Arctic, Tasmania</td>
<td>Birds, omnivorous mammals</td>
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<td>T. temperate</td>
<td>T5</td>
<td>Tropical</td>
<td>Bears, foxes</td>
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<tr>
<td>T. nelsoni</td>
<td>T7</td>
<td>Southern Africa</td>
<td>Hyenas</td>
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<tr>
<td>T. tropicalis</td>
<td>T8</td>
<td>Tropical Africa</td>
<td>Lions, panthers</td>
</tr>
</tbody>
</table>

TABLE 278–1 Species within the Genus Trichinella
Life Cycle

When raw or inadequately cooked meat containing viable larvae of *Trichinella* spp. is eaten, the organisms are freed from the cyst walls by acid-pepsin digestion in the stomach and pass into the small intestine. Larvae invade the columnar epithelium at the bases of the villi of the small intestine and then develop into adult worms. These are obligate intracellular parasites occupying the cytoplasm of a row of enterocytes. The males are about 1.5 × 0.05 mm and the females 3.5 × 0.06 mm in size. The number of larvae released by a fertilized female varies with the species of both parasite and host. *T. spiralis* probably produces about 500 larvae over a period of 2 weeks and then the fertilized female is expelled in the feces. The newborn larvae seed the skeletal muscles via the blood stream. They burrow into individual muscle fibers and then over the next 3 weeks increase 10 times in length, coil, and become capable of infecting a new host. A cyst wall develops around the larva and may eventually calcify. Larvae may remain viable for several years.

Epidemiology

*Trichinella* spp. are distributed throughout the world and are widely spread in nature among a large number of carnivorous animals, humans being an incidental host (see Table 278–1). Most human infections are due to *T. spiralis*; a few are due to *Trichinella britovi, Trichinella nativa,* and *Trichinella nelsoni.* Only one case of human infection with *Trichinella pseudospiralis* has been reported. *T. spiralis* is the only species with good infectivity for swine and rats. For most of the other species, the different reservoir hosts reflect primarily the fauna present in the region. The vast majority of swine in the United States are fed with grain and are generally uninfected. The small proportion fed with garbage may become infected when given uncooked trichinous scraps, usually pig meat, or when the carcasses of infected wild animals such as rats are eaten. In Europe, the fox is the primary reservoir of the sylvatic cycle of *Trichinella* and human infections usually occur in rural areas where traditional swine-rearing practices are used.

Fewer than 100 human cases are usually reported each year in the United States. About three quarters of these are due to inadequately processed pork; most of the rest have been due to ingestion of poorly cooked bear meat, walrus meat, or cougar jerky. Some epidemics in Europe have followed the consumption of infected horse meat and in Canada the ingestion of wild boar meat. Epidemics occur when families or small communities consume trichinous meat from a common source.

**Pathologic Characteristics**

There have been indications that the various species have different pathogenicities for humans and other hosts. For example, trichinosis in the Inuit population in Canada after ingestion of infected walrus seems to be associated with prolonged diarrhea and few muscle symptoms. *T. nativa* produces primarily an enteral illness, whereas *T. britovi* causes few if any intestinal symptoms. *T. nelsoni* is of relatively low pathogenicity in both its enteral and parenteral phases.

During the first 2 to 3 weeks after infection, the small intestine shows a mild, partial villous atrophy and an inflammatory infiltrate of polymorphs, eosinophils, lymphocytes, and macrophages in the mucosa and submucosa. Adult worms may be seen in the epithelial layer near the bases of the villi. The most striking changes are in the skeletal muscles. The fibers become edematous, lose their cross-striations, undergo basophilic degeneration, and their nuclei proliferate. The typical coiled worm, the cyst wall derived from the host cell, and the surrounding lymphocytic and eosinophilic infiltrate may be seen within the muscle fiber. In severe cases, focal interstitial myocarditis, meningitis, and encephalitis may occur.

**Clinical Features**

Most infections are subclinical. The development of symptoms depends mainly on the size of the inoculum of viable larvae. Consequently, the frequencies of the symptoms and signs of trichinosis vary widely from outbreak to outbreak. Their relative frequencies are shown in Table 278–2. Symptoms attributable to adult worms in the intestines may be found during the first week after infection. Diarrhea is the most common symptom, but patients may also complain of abdominal discomfort and vomiting. Patients with extremely heavy worm burdens may develop a fulminating enteritis. Symptoms associated with systemic invasion by larvae are much more common and usually appear during the second week after infection. Fever is frequently present, although it is of variable intensity and duration. Peripheral edema may be associated with subconjunctival hemorrhages and chomosis. Myositis with pain, swelling, and weakness is also common; it usually develops first in the extracutaneous muscles and then involves the masseters, neck muscles, limb flexors, and lumbar muscles. Some patients may complain of headache, cough, shortness of breath, hoarseness, and dysphagia. Occasionally, a rash that may be macular or petechial is observed. Retinal or subungual splinter hemorrhages are sometimes seen. These systemic symptoms usually peak 2 to 3 weeks after infection and then slowly subside, although malaise and weakness may persist for weeks. Occasionally, a patient dies, usually from myocarditis but sometimes from encephalitis or pneumonia. It has been claimed that there may be long-lasting sequelae of infection including muscle aches, eye disturbances, cardiac complaints, and headaches.

**Diagnosis**

*Trichinosis should be suspected in a patient who has any of the cardinal features of peripheral edema, myositis, fever, and eosinophilia. If questioning reveals the recent consumption of poorly cooked meat, particularly pork products, the likelihood of the diagnosis is greatly increased. Further confirmation is provided if others who have eaten the same meat have similar symptoms. An eosinophilia is often found: it begins about the 10th day and may reach very high levels. The erythrocyte sedimentation rate is usually normal. Elevated serum creatine phosphokinase and lactic dehydrogenase levels indicate considerable muscle involvement. Antibodies are not detectable until at least 3 weeks after infection. They may be measured by a variety of techniques including enzyme-linked, immunofluorescent, indirect hemagglutinin, precipitin, and bentonite flocculation assays. A rising titer may help establish the diagnosis. Tests for detection of *Trichinella* DNA in muscle or blood using the polymerase chain reaction are being developed. The skin test for *Trichinella* remains positive for years after exposure; therefore, it does not differentiate between past and recent infections. Muscle biopsy is usually unnecessary; if doubt remains,

<table>
<thead>
<tr>
<th>Table 278–2 Frequencies of Symptoms and Signs of Trichinosis Condensed from Nine Reported Outbreaks</th>
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<tr>
<td>Symptoms or Sign</td>
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</tr>
<tr>
<td>Fever</td>
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<td>Myalgia</td>
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<tr>
<td>Weakness and malaise</td>
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<td>Peripheral edema</td>
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<tr>
<td>Cutaneous rash</td>
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<tr>
<td>Trunk and limb edema</td>
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<td>Nausea</td>
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<tr>
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</tr>
<tr>
<td>Subungual splinter hemorrhages</td>
</tr>
<tr>
<td>Cough</td>
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<tr>
<td>Vomiting</td>
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</tbody>
</table>
a sample taken from a tender swollen muscle may confirm the diagnosis.

The protean manifestations of trichinosis require differentiation of this infection from a large number of other diseases. The gastrointestinal symptoms may mimic those of gastroenteritis. Systemic symptoms may cause confusion with influenza, typhoid fever, sinusitis, dermatomyositis, glomerulonephritis, and angioneurotic edema. The rash may resemble that found in measles, scarlet fever, and typhus.

Treatment

There is no satisfactory treatment for trichinosis. In the rare case that a patient is known to have ingested trichinous meat within a week or so, thiabendazole should be administered in an oral dose of 25 mg/kg/day for 1 week. This drug is active against intestinal worms but has little effect on muscle larvae and has not been shown to alter the course of the disease in established infections. The mainstays of treatment are bed rest and salicylates. Corticosteroids may be used for critically ill patients, but the evidence for benefit is equivocal. It was claimed that mebendazole was effective when given 5 months after the onset of infection; this uncontrolled, single case report must be viewed with some skepticism. Albendazole has been compared with a combination of thiabendazole and flubendazole, and a marginal benefit was claimed for albendazole; however, no untreated control group was available for comparison. A subsequent study suggested that the efficacy of thiabendazole and albendazole is similar but that albendazole is better tolerated. Albendazole may be given in a dose of 400 mg/day for 5 days.

Prevention

The most effective method of killing Trichinella larvae is by proper cooking: the thermal death point is 55°C, so meat should be cooked until there is no trace of pink fluid or flesh. Storage in a home freezer (−15°C) for 3 weeks usually sterilizes meat, but smoking, salting, and drying are unreliable.

DRACUNCULIASIS

Dracunculiasis (dracontiasis, guinea worm infection) develops after drinking water containing crustaceans infected with Dracunculus medinensis. It is characterized by a chronic cutaneous ulcer from which the worm protrudes.

Life Cycle

When water containing infected copepods is drunk, larvae are released in the host stomach, pass into the small intestine, penetrate the mucosa, and reach the retroperitoneum, where they mature and mate. The female worm (1 to 2 mm in diameter and up to 1 m long) migrates to the subcutaneous tissue, usually of the legs, about 1 year later. The overlying skin ulcerates, and a portion of the worm protrudes. On contact with water, large numbers of larvae are released from a loop of uterus prolapsed through either the mouth or a rupture in the body wall. These are in turn ingested by crustaceans, in which they undergo further development whereby the life cycle is continued.

Epidemiology

D. medinensis is now found mostly in tropical Africa. Shallow ponds, cisterns, and wells are the usual habitat of the crustacean intermediate hosts. The disease is prevalent in areas where people bathe or wade in water used for drinking purposes. Manifestations in a community are markedly seasonal. This reflects both the developmental cycle of the parasite, which requires an incubation period of about 1 year, and the influence of climate on the types of water sources used. The disability resulting from infection may be of great economic importance if the timing of clinical manifestations coincides with a busy period of the agricultural year and causes a significant loss of time in school for children.

Clinical Features

There are often no clinical signs until the worm reaches the surface and is ready to discharge larvae. A stinging papule develops at this point, usually on the lower portions of the legs. At this time, some patients may have a generalized reaction with urticaria, nausea, vomiting, diarrhea, and dyspnea. Over the next few days the lesion vesiculates, and then the blister ruptures and forms a painful ulcer within which part of the worm is often visible. If the area is drenched with fluid, a milky fluid containing larvae wells up. Discharge continues intermittently, and the worm is slowly absorbed or extruded over the next few weeks, after which the ulcer heals. Multiple ulcers are common, and secondary infection is frequent. In endemic areas, patients are often bedridden for a month or so. Immunity to reinfection does not develop.

Diagnosis

The clinical picture is characteristic. Larvae can be found on microscopic examination of the discharge fluid.

Treatment

Thiabendazole, 25 mg/kg twice daily for 2 days, and metronidazole, 5 mg/kg twice daily for 1 week, have no effect on the worms themselves but produce resolution of inflammation within several days. This permits easy removal of the worm over a week or so by progressively rolling out the emerging worm onto a small stick. Corticosteroid ointments shorten the time to complete healing, and the addition of topical antibiotics reduces the risk of secondary bacterial infection.

Ivermectin has no effect on prepatent guinea worms. Mebendazole in high dosage is not recommended, because it does not lessen the duration of disease or disability but increases the incidence of nonemerged worms, thus exacerbating the danger of release of larvae into joints. Alternatively, unerupted worms may be removed completely and painlessly in several minutes by surgical means with local anesthesia. Secondary bacterial infection should be treated as necessary.

Prevention

Guinea worm infection can be prevented by boiling or chlorinating drinking water or by sieving it through a cloth. Control on a public health scale requires health education and improved water supplies. In 1986, the World Health Organization initiated a program to eradicate dracunculiasis by 1995. Strategies include documentation of the extent of the disease as a national problem, demonstration that it can be prevented by targeted provision of protected rural water supplies, mobilization of community participation and political support, and then implementation of interventions nationwide.

Although success has not yet been achieved, dramatic progress has been made. The number of cases has fallen from an estimated 4 million in 1981 to 150,000 in 1996, 120,000 of whom were in the Sudan, where civil war was raging. Infection has been eradicated from Kenya and Pakistan, and only nine cases were reported in 1996 in India, once the home of countless cases of dracunculiasis. Guinea worm disease may soon become the second human infection to be eradicated.
BANCROFTIAN AND BRUGIAN FILARIAE

Bancroftian filariasis and brugian (Malayan) filariasis are similar clinical conditions resulting from the transmission of Wuchereria bancrofti, Brugia malayi, and Brugia timori to humans by mosquitoes. Symptomatic patients have acute lymphatic inflammation or the effects of chronic lymphatic obstruction such as hydrocele, elephantiasis of the limbs, and chyluria.

Life Cycle

After the bite of an infected mosquito, infective larvae pass into the lymphatics and lymph nodes, where they mature over the next few months into white, threadlike adult worms, the males being about 40 × 0.1 mm and the females 100 × 0.25 mm in size. The adults live for 5 years or more, and the fertilized females discharge microfilariae approximately 150 × 7 μm in size via the lymphatics into the blood stream. The number of microfilariae found in the peripheral blood varies. There is usually a surge of microfilariae into the blood during the middle of the night, a phenomenon known as nocturnal periodicity. Patients from the South Pacific with W. bancrofti infection have a much less pronounced peak that is maximal during the day. B. malayi infections produce nocturnal peaks of varying intensity. If microfilariae are ingested by a mosquito during feeding, the organisms develop into infective larvae over the next 2 weeks and are ready to repeat the cycle.

Epidemiology

W. bancrofti is distributed widely throughout the tropics and subtropics; B. malayi is restricted to South and Southeast Asia. B. timori is restricted to the eastern Indonesian archipelago. It is estimated that 120 million people are infected with these parasites. There is no animal reservoir for W. bancrofti, but B. malayi has been found in felines and primates. Even in endemic areas, only a small proportion (less than 1%) of mosquito bites are infective. It is probable that patent infections are produced only when a susceptible person receives a large number of infective larvae and that obstructive disease develops only when exposure continues for many years. Filariasis is mainly a disease of adults and is more common in men.22, 23

Pathologic Characteristics

Lymphatics harboring adult worms display endothelial proliferation, fibrin deposition, and a granulomatous inflammatory infiltrate of eosinophils, lymphocytes, and macrophages. Molting and the death of worms probably exacerbate the inflammation, which is succeeded by fibrosis and obstruction of lymph flow. All of these processes are associated with complex immunologic events.

It is possible that a proportion of the population in endemic areas generates protective immunity that may be T cell mediated.24 Secondary bacterial infection may be an important cofactor in the development of elephantiasis.25

Clinical Features

Many patients are asymptomatic despite the presence of a microfilaraemia. Clinical manifestations are due either to acute inflammation or to chronic lymphatic obstruction. Attacks of lymphangitis or lymphadenitis with fever, headache, backache, and nausea occasionally occur. Acute funiculitis, epididymitis, or orchitis may be seen. These acute episodes usually subside after a few days to several weeks but may recur.26 Chronic lymphadenopathy is frequently found and may be the only manifestation of filariasis. In long-standing cases lymphedema may develop. Chronic hydrocele is the most common feature and may cause considerable sexual disability. The lower limbs are involved less frequently; at first there is pitting edema that is most marked pretilially, but eventually nonpitting edema may involve the whole limb. In elephantiasis, the skin of the leg or scrotum becomes thickened, fissured, and warty. Ulceration and secondary infection may occur.27 Occasionally, lymph varices may be seen, especially in the genital region. Chyluria develops when swollen lymphatics burst into the urinary tract.

Diagnosis

The definitive diagnosis of bancroftian filariasis and brugian filariasis depends on demonstration of the parasite. Unfortunately, microfilariae are frequently absent from the blood in both the early and late stages of the disease. A blood sample should be taken around midnight unless the patient is from the South Pacific. The smear is stained and examined for microfilariae (Fig. 278-1). If none is found, a concentration method should be used.

Microfilariae may occasionally be found in hydrocele fluid or chylous urine. Eosinophilia is usually absent except during episodes of acute inflammation. Serologic tests for antibody such as bentonite flocculation, indirect hemagglutination, enzyme-linked immunosorbent assay, and indirect fluorescent antibody tests may be of some help but do not differentiate among the various forms of filariasis or between past and current infection. Immunoassays to measure filarial antigen in serum have been described.28 Polymerase chain reaction tests to detect W. bancrofti in blood are being developed.29

Adult worms can sometimes be found in lymph node biopsy specimens, but this procedure is not generally justified. Microfilariae or worm fragments may be seen with fine-needle aspiration cytology.30 Ultrasonography of the lymphatic vessels in the spermatic cord may reveal motile adult worms in dilated lymphatics.31 Abnormal lymphatic drainage in the legs may be demonstrated by lymphoscintigraphy.32 If microfilariae cannot be found, the diagnosis must be made on clinical grounds by the exclusion of other causes.

Treatment

There is no satisfactory treatment for filariasis. Diethylcarbamazine citrate has been used for 50 years. Given in an oral dose of 6 mg/kg daily for 2 weeks, it reduces the number of microfilariae in the peripheral blood. Diethylcarbamazine kills some adult worms but...
not others. When it does kill worms, it may precipitate acute inflammation that culminates in an exuberant granulomatous process with progressive fibrosis. Ivermectin in a single dose of 200 to 400 μg/kg has been shown to have a microfilaricidal effect similar to that of diethylcarbamazine. Ultrasonography showed that it has no effect on adult worms, and microfilariae often reappear in the peripheral blood after a few months.33 Even if patients remain microfilaremic after diethylcarbamazine or ivermectin treatment, Wuchereria antigens persist in the serum for at least 2 to 3 years.34 Although diethylcarbamazine and ivermectin have no or limited therapeutic value for the individual patient, repeated administration of either or both drugs every 6 to 12 months may reduce transmission in a community.33 Single-dose therapy with ivermectin at 200 to 400 μg/kg plus albendazole at 400 mg may be even more effective.33 Rarely, repeated treatment with diethylcarbamazine has succeeded in eradicating infection. This was achieved in Kinmen Island; acute inflammatory filarial illnesses disappeared but, as expected, chronic obstructive disease persisted for the next 2 decades.36

Acute inflammatory reactions should be treated with anti-inflammatory agents. Mild lymphedema may be controlled with elastic stockings. Surgery is useful in the management of hydrocele but has little place for patients with elephantiasis of the legs. Laparoscopic ligation of lymphatic vessels has been used successfully to treat recalcitrant chyluria.37

Prevention

The most effective preventive measure is avoidance of mosquitoes by the use of screens, nets, and insect repellents.

LOIASIS

Loiasis is caused by *Loa loa* and is transmitted to humans by tabanid flies. It is characterized by transient subcutaneous swellings. Occasionally, the worm is seen migrating through the subconjunctiva or other tissues.

Life Cycle

The white, threadlike adult worms, measuring 30 to 70 × 0.3 mm, migrate through the connective tissues. The sheathed microfilariae, 300 × 8 μm, appear in the blood during the day and may be ingested by tabanid (horse) flies, in which they develop into infective larvae.

Epidemiology

*L. loa* is irregularly distributed in West and central Africa. The vectors are diurnally biting flies (*Chrysops* spp.) that live in the canopy of the rain forest. They are attracted by people moving through open spaces in the jungle. Infection rates in populations and parasite loads in individuals change little over time in endemic areas.38

Clinical Features

Many patients are asymptomatic, although they may have high eosinophil levels in the peripheral blood. Transient swellings of localized subcutaneous edema, called *Calabar swellings*, may develop.39 Usually only one swelling occurs at a time. The onset may be preceded by localized pain and itching for several hours. It is nonerythematous, 10 to 20 cm in diameter, and lasts for several days to weeks. Calabar swellings are commonly seen around joints such as the wrist or the knee and recur irregularly at either the same or different sites. Other patients complain of pruritus or have urticaria. (Occasionally, a worm may be seen passing through the subconjunctiva, where it produces an intense conjunctivitis lasting several days. Worms have also been seen in the penis or around the nipple.) Infected visitors to areas of endemicity may have a hyperreactive state characterized by more frequent recurrences of fugitive swellings, greater eosinophilia, increased debilitation, and more complications, particularly the development of renal disease, either before or after treatment with diethylcarbamazine.40 These features are associated with differences in immunologic responses from those of people living in endemic areas.41

Other complications that may be seen are endomyocardial fibrosis, retinopathy, encephalopathy, peripheral neuropathy, arthritis, pleural effusion, and breast calcification. Pulmonary infiltrates have also been ascribed to loiasis, but it is difficult to differentiate this condition from tropical pulmonary eosinophilia. Splenectomy has been performed on patients with suspected lymphoma that turned out to be granulomas associated with *L. loa* microfilariae.42

Diagnosis

The disease should be suspected in a patient with a typical history who has lived in West or central Africa. The diagnosis is established by finding microfilariae in the daytime blood as described under "Bancroftian and Brugian Filariasis." Failure to find microfilariae does not rule out the diagnosis, and the diagnosis is usually made on clinical grounds. A polymerase chain reaction test has been described that is positive in some amicrofilaremic individuals but is not generally available.43 Occasionally, the adult worm can be extracted from the eye.

Treatment

Diethylcarbamazine eliminates microfilariae from the blood and often does not kill adult worms.44 It is administered as described under "Onchocerciasis." Encephalitis may be precipitated by treatment, especially if microfilarial loads are high.45 Treatment with ivermectin in a single dose of 200 μg/kg decreases microfilarial densities in the peripheral blood.46 Patients with high microfilarial counts (>30,000/mm³) often experience fever, pruritus, headache, and arthralgia within 36 hours of ivermectin therapy.47 Albendazole at 200 mg twice daily for 3 weeks slowly reduced microfilarial levels, possibly as a result of an embryotoxic effect on the adult worms.48

Prevention

Personal protection depends on avoiding places where biting flies are numerous, wearing protective clothing, and using insect repellents. Mass treatment of villages interrupts transmission; diethylcarbamazine is administered in doses of 5 mg/kg/day for 3 consecutive days each month, or ivermectin may be given at 3-monthly intervals.49 Diethylcarbamazine in a dose of 300 mg once weekly is effective in preventing loiasis in persons resident temporarily in endemic regions.50

ONCHOCERCIASIS

Onchocerciasis (river blindness) is caused by *Onchocerca volvulus* and is transmitted to humans by blackflies. It is characterized by an itchy dermatitis, subcutaneous nodules, keratitis, and chorioretinitis.

Life Cycle

After the bite of an infected *Simulium* blackfly, larvae penetrate the skin and migrate into the connective tissues. They develop into white filiform adults, the males being 3 × 0.2 mm and the females 400 × 0.3 mm in size. The worms are often found tangled together in nodules of fibrous tissue, where they may live for years. Each female produces large numbers of unsheathed microfilariae 200 to 300 × 6 to 8 μm in size that migrate through the skin and connective tissues.
The life cycle is continued when they are ingested by female blackflies and develop into infective larvae.

Epidemiology

*O. volvulus* infects 20 million people in West, central, and East Africa and another 1 million people in scattered foci in Central America and South America. There is no known animal reservoir. Onchocerciasis tends to be focal in distribution within areas in which it is endemic. In Africa, the flies breed in fast-flowing streams in both the savannah and rain forest and tend to bite low on the body. In America, the flies breed in small streams on the hillsides and bite more frequently around the head. Heavy parasite loads and severe disease require repeated infection.

Pathologic Characteristics

A granulomatous inflammatory reaction followed by fibrosis develops around the adult worms. The microfilariae in the subcutaneous tissues may produce a low-grade inflammatory reaction, destruction of the elastic fibers, and fibrosis. Different patterns of cell-mediated and humoral immunity are seen in patients with different clinical syndromes and in the presence or absence of microfilaridermia.51

Clinical Features

Early skin lesions produce an itchy, erythematous, papular rash. In severe infections, cutaneous lymphedema with leathery thickening and degeneration may be seen.52 Ultimately, loss of elasticity with chronic lymphedema may produce pendulous sacs containing inguinal and femoral lymph nodes. Firm, nontender, freely movable fibrous nodules that may be several millimeters to centimeters in size and may contain the adult worms may be found. They are more commonly located over bony prominences. In addition, there may be systemic features including weight loss and musculoskeletal pains.53 Impaired visual acuity is the most serious complication. The most common lesion is punctate keratitis followed by pannus formation and corneal fibrosis. Microfilariae can often be seen in the cornea and anterior chamber with a slit lamp. Iridocyclitis, glaucoma, chorioiditis, and optic atrophy may develop.54,55 Not surprisingly, blindness in endemic areas is associated with a three- to fourfold increase in the mortality rate. It has been suggested that onchocerciasis may be associated with an increased prevalence of epilepsy.56

Diagnosis

The diagnosis is made either by demonstrating microfilariae in skin snips or in the cornea or anterior chamber on slit-lamp examination or by finding adult worms in a nodule biopsy specimen. Impalpable nodules can sometimes be demonstrated by ultrasound techniques.57 Bloodless skin snips are taken without anesthesia by raising small cones of skin about 3 mm in diameter with the tip of a needle and then cutting them off with a razor blade. Snips should be taken from over the scapulas and iliac crests and from the buttocks and thighs. They are allowed to stand for half an hour in a drop of 0.9% saline and are then examined under a microscope for microfilariae. Microfilariae are sometimes found in urine. A red-dot card test has been proposed as a useful aid in screening for the presence of optic nerve disease.58 Ultrasound detection of changes in the vitreous humor has been described.59 Eosinophilia is common. Reliable immunodiagnostic tests are not yet generally available, but molecular techniques are under development.60 If the diagnosis is strongly suspected but parasites cannot be found, a single oral test dose of 50 mg of diethylcarbamazine can be given. If an exacerbation of the rash occurs within a few hours, the diagnosis is likely (Mazzotti reaction).

Treatment

Traditionally, patients with skin disease have been treated with diethylcarbamazine. This drug kills microfilariae but has little effect on the adult worm. Severe reactions such as rash, fever, generalized body pains, keratitis, and iritis may occur, so the dose must be built up gradually as follows: day 1, 50 mg; day 2, 50 mg three times; day 3, 100 mg three times; and days 4 to 21, 3 mg/kg three times a day.

In the past few years, many studies have shown that ivermectin is safer and more effective than diethylcarbamazine.53,61 The rates of decrease in numbers of microfilariae in the skin and anterior chamber of the eye and the severity of Mazzotti reactions are less and the duration of the reduction in microfilarial loads is greater with ivermectin than with diethylcarbamazine. Ivermectin is now the drug of choice. Unfortunately, like diethylcarbamazine, ivermectin primarily kills microfilariae but not adult worms. When given in a single dose, it has little effect on the viability or fertility of adult worms, but courses of treatment with 150 µg/kg repeated at 3-month intervals for 2 to 3 years prevent embryogenesis to the microfilarial stage and may cause slow but steady attrition of adult worms.62,63 Both single and repeated courses of treatment result in marked reductions in microfilarial skin densities and the numbers of microfilariae in the anterior chamber of the eye, and there is a significant reduction in transmission of infection. Ivermectin therapy leads to improvement in severe skin disease and regression of early lesions of the anterior segment of the eye, especially iridocyclitis, but posterior segment lesions remain stable.64,65 A practical approach to treatment is to administer ivermectin, 150 µg/kg orally once, and repeat at 3-monthly intervals if there are continuing symptoms or evidence of eye infection. Side effects appear to be relatively mild in patients in endemic areas but may be more severe in infected expatriates, who often develop fever, pruritis, and urticarial rash.66 However, patients with concurrent onchocerciasis and loiasis may develop an encapsulating thread when treated with ivermectin.67 Inadequate administration of ivermectin during pregnancy was not associated with an increased number of birth defects.

Adult worms can be killed by suramin, but this drug is not generally recommended.61 Albendazole does not kill microfilariae but interferes with embryogenesis.68 Amocarazine is a novel drug still under development that appears to have both macro- and microfilaricidal effects. Unfortunately, it does not prevent the evolution of chorioretinitis.69 Surgical removal of nodules should be performed whenever practical. Expert ophthalmologic advice should be sought before the treatment of eye lesions.

Prevention

Personal protection depends on avoiding places where biting flies are numerous or on wearing protective clothing. A major control program is in progress in West Africa. The vector is being attacked by larvicides applied to breeding places; the onchocerciasis-infected population is gradually being replaced by a healthy population.70,71 In 1991 a program was set in motion to eradicate onchocerciasis from the Americas, and there is hope that one of the three major foci of infection will shortly be eliminated.72

**Mansonella Infections**

*Mansonella ozzardi,* transmitted by blackflies and midges, is found in Latin America. Adult worms are found in the visceral fatty issues. Unsheathed microfilariae that are not periodic may be found in the peripheral blood. Most patients are asymptomatic.

*Mansonella perstans,* also transmitted by midges, is found in Africa and South America. Adult worms live in the body cavities. Unsheathed microfilariae may be found in the peripheral blood, especially at night. Most patients are asymptomatic, although some have conjunctival nodules.73 If treatment is required, diethylcarba-
mazine should be tried because ivermectin does not appear to be effective.79 Albendazole may be of some value when given at a dose of
400 mg twice daily for at least 1 month.79
* Mansonella streptocerca* is transmitted to humans by biting
midge. It is found in central Africa and is characterized by derma-
titis. Microfilariae are found in skin snips, and treatment is
with diethylcarbamazine;76 the value of ivermectin is unproved.

**TROPICAL PULMONARY EOSINOPHILIA**

Tropical pulmonary eosinophilia is a disease syndrome caused by
microfilariae in the tissues, especially the lungs. It is probably due
to immunologic hyperresponsiveness to *W. bancrofti* or *B. malayi*. It
is scattered throughout the tropics but is most commonly seen in
southern Asia. Patients have recurrent episodes of a paroxysmal, dry
cough, wheezing, and dyspnea. Malaise, anorexia, and weight loss
are frequently seen. Physical examination often reveals scattered
wheezes and cracks. Some patients may have hepatomegaly and
lymphadenopathy. The symptoms usually fluctuate in severity over
many months. The absence of microfilariae from the blood makes a
definitive diagnosis difficult. Eosinophilia is almost always present,
and often at extremely high levels. Chest radiographs usually reveal
scattered reticulonodular opacities. Antibodies to filarial worms are
found in the serum. A presumptive clinical diagnosis can usually be
made without recourse to lung biopsy, and the diagnosis is estab-
lished by a successful response to therapy. The administration of
diethylcarbamazine orally in a dose of 3 mg/kg three times daily for
2 weeks is an effective treatment. There may be an initial exacerbation
of symptoms, but the eosinophil level falls, and the chest
radiograph clears over a few weeks. A small proportion of patients,
however, have persistent subclinical, radiologic, or functional
abnormalities indicating chronic low-grade alveolitis;77 in such in-
stances, it may be appropriate to repeat the course of treatment with
diethylcarbamazine. The role of ivermectin in the treatment of tropi-
cal pulmonary eosinophilia has not yet been determined.

**REFERENCES**

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